



**Australian
National
University**

**A spatiotemporal epidemiological investigation of the impact
of environmental change on the transmission dynamics of
Echinococcus spp. in Ningxia Hui Autonomous Region, China**

Angela Maria Cadavid Restrepo

**A thesis submitted for the degree of Doctor of
Philosophy of The Australian National University**

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DECLARATION BY THE AUTHOR

I declare that this thesis presents my original work and does not contain, in part or in full, material previously published or written by another person except where it is otherwise acknowledged in the text. I have clearly indicated the contribution by others to all jointly-authored works that I have included in my thesis. The work presented in this thesis is an accurate account of research undertaken during a PhD candidature in the Research School of Population Health at the Australian National University and has not been previously submitted for any other degree or diploma at any university or institution.


Angela Maria Cadavid Restrepo
03/05/2018

LIST OF PAPERS AND STATEMENT OF AUTHORS' CONTRIBUTIONS TO JOINTLY AUTHORED ARTICLES

This thesis by compilation is based on the following papers:

Paper I: Cadavid Restrepo, A.M.; Yang, Y.R.; McManus, D.P.; Gray, D.J.; Giraudoux, P.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Hamm, N.A.S.; Clements, A.C.A. The landscape epidemiology of echinococcoses. *Infectious Diseases of Poverty*. 2015;5(1):13.

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Paper III: Cadavid Restrepo, A.M.; Yang, Y.R.; McManus, D.P.; Gray, D.J.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Hamm, N.A.S.; Clements, A.C.A. Spatiotemporal patterns and environmental drivers of human echinococcoses over a twenty-year period in Ningxia Hui Autonomous Region, China. *Parasites & Vectors*. 2018; 11:108.

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For each publication included in the thesis I was the first author. The contribution to each of the five papers is as follows:

Paper I: ACAC and I conceived the idea for the review. I searched the published work, prepared the first draft of the manuscript and created figures and tables. ACAC, YRY, DPM, DJG, PG, RJSM, TSB, GMW and NASH provided comments. ACAC and I undertook revisions as requested by reviewers and finalized the manuscript. All authors gave final approval of the final version of the manuscript and I managed the submission process.

Paper II: ACAC and I developed the concept of the analysis. I reviewed the literature and collected the data. I conducted the analysis and produced the numerical output, tables and figures. NASH, ACAC and I contributed to the interpretation of the results. I drafted the manuscript and coordinated the input from ACAC, YRY, DPM, DJG, RJSM, NASH, TSB, GMW and DG. ACAC, NASH and I undertook revisions as requested by the reviewers. All authors gave final approval of the final version of the manuscript and I managed the submission process.

Paper III: ACAC and I developed the concept of the analysis. I reviewed the literature, conducted the analysis and produced the numerical output, tables and figures. ACAC and

I contributed to the interpretation of the results. I drafted the manuscript and coordinated the input from ACAC, YRY, DPM, DJG, RJSM, TSB, GMW and NASH. ACAC and I undertook revisions as requested by the reviewers. All authors gave final approval of the final version of the manuscript and I managed the submission process.

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The word count for this thesis is approximately 45,000, excluding the front matter, abstract, tables and figures, references, appendices, and numerical code.


Angela Maria Cadavid Restrepo
03/05/2018

Senior author on behalf of all collaborating authors:

I agree that Angela Maria Cadavid Restrepo made the contribution to the authorship and research of papers on which I am a co-author, as stated in the preceding pages.



Prof Archie Clements
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ABSTRACT

Background: Human echinococcoses are zoonotic parasitic diseases of major public health importance globally. According to recent estimates, the geographical distribution of echinococcosis is expanding and becoming an emerging and re-emerging problem in several regions of the world. Echinococcosis endemicity is geographically heterogeneous and might be affected by global environmental change over time. The aims of my research were: 1) to assess and quantify the spatiotemporal variation in land cover and climate change in Ningxia Hui Autonomous Region (NHAR); 2) to identify highly endemic areas for human echinococcoses in NHAR, and to determine the environmental covariates that have shaped the local geographical distribution of the disease; 3) to develop spatial statistical models that explain and predict the spatiotemporal variation of human exposure to *Echinococcus* spp. in a highly endemic county of NHAR; and 4) to analyse associations between the environment and the spatiotemporal variation of human exposure to the parasites and dog infections with *Echinococcus granulosus* and *Echinococcus multilocularis* in four echinococcosis-endemic counties of NHAR.

Methods: Data on echinococcosis infections and human exposure to *E. granulosus* and *E. multilocularis* were obtained from different sources: 1) A hospital-based retrospective survey of human echinococcosis cases in NHAR between 1992 and 2013; 2) three cross-sectional surveys of school children conducted in Xiji County in 2002–2003, 2006–2007 and 2012–2013; and 3) A cross-sectional survey of human exposure and dog infections with *E. granulosus* and *E. multilocularis* conducted in Xiji, Haiyuan, Guyuan and Tongxin Counties. Environmental data were derived from high-resolution (30 m) imagery from Landsat 4/5-TM and 8-OLI and meteorological reports provided by the Chinese Academy of Sciences. Image analysis techniques and a Bayesian statistical

framework were used to conduct a land cover change detection analyses and to develop regression models that described and quantified climate trends and the environmental factors associated with echinococcosis risk at different spatial scales.

Results: The land cover changes observed in NHAR from 1991 to 2015 concurred with the main goals of a national policy on payments for ecosystem services, implemented in the Autonomous Region, in increasing forest and herbaceous vegetation coverages and in regenerating bareland. Statistically significant positive trends were observed in annual, summer and winter temperatures in most of the region, and a small magnitude change was found in annual precipitation, in the same 25-year period. The south of NHAR was identified as a highly endemic area for cystic echinococcosis (CE; caused by *E. granulosus*) and alveolar echinococcosis (AE; caused by *E. multilocularis*). Selected environmental covariates explained most of the spatial variation in AE risk, while the risk of CE appeared to be less spatially variable at the township level. The risk of exposure to *E. granulosus* expanded across Xiji County from 2002–2013, while the risk of exposure to *E. multilocularis* became more confined in communities located in the south of this highly endemic area. In 2012–2013, the predicted seroprevalences of human exposure to *E. granulosus* and dog infection with this parasite were characterised by similar geographical patterns across Xiji, Haiyuan, Guyuan and Tongxin Counties. By contrast, the predicted high seroprevalence areas for human exposure and dog infection with *E. multilocularis* did not coincide spatially. Climate, land cover and landscape fragmentation played a key role in explaining some of the observed spatial variation in the risk of infection with *Echinococcus* spp. among schoolchildren and dogs in the south of NHAR at the village level.

Conclusions: The findings of this research defined populations at a high risk of human exposure to *E. granulosus* and *E. multilocularis* in NHAR. The research provides

evidence on the potential effects of landscape regeneration projects on the incidence of human echinococcoses due to the associations found between the infections and regenerated land. This information will be essential to track future requirements for scaling up and targeting the control strategies proposed by the National Action Plan for Echinococcosis Control in China and may facilitate the design of future ecosystem management and protection policies and a more effective response to emerging local environmental risks. The predictive models developed as part of this research can also be used to monitor echinococcosis infections and the emergence in *Echinococcus* spp. transmission in the most affected areas.

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LIST OF ACRONYMS AND ABBREVIATIONS

| | |
|---------|--|
| °C | Degree Celsius |
| 95% CrI | 95% credible intervals |
| AE | Alveolar echinococcosis |
| AIC | Akaike information criterion |
| ASTER | Advanced Spaceborne Thermal Emission and Reflection Radiometer |
| CAR | Conditional autoregressive |
| CDR | Climate data record |
| CE | Cystic echinococcosis |
| DALYs | Disability-adjusted life years |
| DIC | Deviance information criterion |
| DNA | Deoxyribonucleic acid |
| ED | Edge density |
| ELISA | Enzyme-linked immunosorbent assay |
| ENVI | Environment for Visualizing Images |
| EROS | Earth Resources Observation and Science |
| ESPA | Center Science Processing Architecture |
| ESRI | Environmental Systems Research Institute |
| EVI | Enhanced vegetation index |
| FNF | Forest/non-forest maps |
| GDEM | Global digital elevation model |
| GEP | Google Earth Pro |
| GGP | Grain for Green Project |
| GIS | Geographic information system |

| | |
|-----------------|---|
| IDW | Inverse distance weighting |
| JAXA | The Japan Aerospace Exploration Agency |
| M | Metre |
| MA | Moving average |
| MPI | Mean shape index |
| MPS | Mean patch size |
| NASA | National Aeronautics and Space Administration |
| NGCC | National Geomatics Center of China |
| NHAR | Ningxia Hui Autonomous Region |
| NHFPC | National Health and Family Planning Commission |
| NUMP | Number of patches |
| OR | Odds ratio |
| OLI/TIRS | Operational Land Imager and Thermal Infrared Sensor |
| PCR | Polymerase chain reaction |
| PD | Patch density |
| ROI | Region of interest |
| RR | Relative risk |
| SD | Standard deviation |
| SMR | Standardised morbidity ratio |
| TM | Thematic Mapper |
| USGS | United States Geological Survey |
| UTM | Universal Transverse Mercator |
| KM ² | Square kilometre |
| WHO | World Health Organization |

WGS84 World Geodetic System 84

CHAPTER 1

Introduction

CHAPTER 1 INTRODUCTION

1.1 Context

Echinococcoses are often severe and potentially lethal zoonotic diseases caused by cestode species of the genus *Echinococcus*. There are three different types of echinococcoses in humans that result from infection with different *Echinococcus* spp.: cystic echinococcosis (CE), alveolar echinococcosis (AE) and neotropical echinococcoses (unicystic and polycystic echinococcoses) (1, 2). This research focused on CE, caused primarily by *Echinococcus granulosus*, and alveolar echinococcosis (AE), which results from infection with *Echinococcus multilocularis*. Both infections are widespread worldwide and cause health conditions with high global public health relevance (3-5). The apparent expansion of the geographical range of *E. granulosus* and *E. multilocularis* in recent decades has raised great interest in examining the potential role of anthropogenic environmental change in influencing the transmission patterns of these parasites (6-10).

China is a country heavily affected by CE and AE (11). Control efforts have markedly contributed to estimated reductions in the national echinococcosis burden in China (11). However, a lack of evidence on echinococcosis risk at local levels indicates that sub-national data and maps of disease distribution are needed to facilitate the progress of interventions for echinococcosis control (11). This information will be essential in gaining a better insight into the local epidemiology of human echinococcoses at finer spatial scales. This Chapter presents the introduction and outlines the major themes of the thesis. The introduction starts with a background about *Echinococcus* spp. and the global disease burden of *E. granulosus* and *E. multilocularis* infections. This is followed by the description of the geographical extent of the parasites, current measures for control and future challenges. Subsequently, a description of the contributions of this thesis, the research goals, specific objectives, approach and methods are presented. Finally, the thesis structure is outlined.

1.2 Background

Human echinococcoses are parasitic diseases caused by the larvae of dog and fox cestode worms of the genus *Echinococcus*. There are currently ten recognised species of *Echinococcus* and among them, the species that cause infection in humans are: *E. granulosus*, *E. multilocularis*, *E. oligarthrus*, *E. vogeli*, *E. orteppi*, *E. canadensis* and *E. intermedius* (2). *E. granulosus*, the main causative agent of CE, and *E. multilocularis*, the etiological agent of AE, are the two species of major global public health importance (3-5). Both have a wide geographic distribution and cause serious and chronic debilitating diseases that if poorly treated or left untreated may be potentially fatal (3-5). Infections with *E. vogeli* and *E. oligarthrus* cause polycystic and unicystic echinococcoses in humans, respectively (2).

Human echinococcoses affect approximately 200,000 people every year with a total of 2–3 million people infected worldwide (12). The latest global estimates of the burden of CE indicate that 188,000 people are infected with *E. granulosus* annually which, measured in terms of Disability-Adjusted Life Years (DALYs), represents a human health burden of 184,000 DALYs lost (12). When underreporting is accounted for, the global burden of CE exceeds 1 million DALYS lost and results in an annual estimated cost of \$760 million (12). The global estimates of AE suggest that there are approximately 18,235 people infected every year and a total of 0.3-0.5 million AE cases diagnosed worldwide. Most of the disease burden of AE occurs in Western China and results in the loss of 666,434 DALYs per annum (13). However, these figures could be underestimates of the real global burden of human echinococcoses due to challenges with the early diagnosis of the infections and the lack of mandatory reporting in several countries (14, 15). Recent epidemiological reports suggest that *Echinococcus* spp. might be expanding their geographical range and becoming an emerging problem in previously unaffected areas and a re-emerging problem in previously endemic areas (5, 16, 17). These new trends in the geographical distribution of the parasites and the limited evidence on the

effectiveness of control and elimination strategies across several regions have raised concerns about the impact of environmental change on the transmission dynamics of *Echinococcus* spp. between definitive and intermediate hosts (18).

1.2.1 *Echinococcus* spp. transmission and clinical course of the infections in humans

Echinococcus spp. are transmitted in complex multi-host systems that include a broad range of animal species as definitive and intermediate hosts. The transmission of *E. granulosus* occurs in domestic settings involving domestic dogs and other canids as typical definitive hosts, and sheep and other ungulates as intermediate hosts (5). *E. multilocularis* is transmitted within semi-domestic and sylvatic predator-prey cycles that involve different species of foxes and small mammals as definitive and intermediate hosts, respectively (5, 19). Foxes are the main source of environmental contamination with *E. multilocularis* eggs in most endemic areas (5). However, this parasite species has also been found in coyotes, wolves, raccoon-dogs and wild cats (20). In China, Central Europe and some areas in North America, high prevalence of *E. multilocularis* has also been detected in domestic dogs (21-23). Therefore, in several regions, domestic dogs are currently recognized as important transmission sources of both, *E. granulosus* and *E. multilocularis*, to the local human population (24, 25).

Transmission of *Echinococcus* spp. takes place when intermediate hosts ingest the parasite eggs. Eggs are produced by the adult worms in the small intestine of definitive hosts and are released in the faeces. Cysts develop in the organs of intermediate hosts and cysts are then ingested by definitive hosts when they feed on the intermediate hosts, completing the cycle (3). Humans usually do not play a role in the transmission of these parasites but can be affected as aberrant intermediate hosts (3).

After the accidental ingestion of the parasite eggs by humans, these infections remain asymptomatic for several months or even years (26). Clinical manifestations and disease courses vary for the different species of the parasite and depend on the organs where the cysts are located. In most patients, the infections affect a single organ and harbours a unique cyst, while in a lower number of cases, infections involve multiple organ systems (27-29). The liver and lungs are the most common organs affected (29). However, cysts can occur in any organ system including bone, heart, brain or muscle (29). The clinical presentation of AE can be compared to the development of an invasive tumor that grows and infiltrates adjacent organs and produces distant metastases (29). Ultrasonography is the method of choice for the diagnosis of abdominal lesions. However, other imaging techniques such as computed tomography, radiography or magnetic resonance imaging may be indicated depending upon the characteristics and location of the cyst(s) (30, 31). Serology is another supportive diagnostic method that can play a confirmative role when the infections are suspected, and it can be used to aid epidemiological surveys of CE and AE in endemic regions (32). However, the specificity of serological tests is limited by cross-reactions due to other helminth infections, liver cirrhosis malignancies and presence of anti-P1 antibodies (33, 34).

Treatment of CE usually depends on the stage, number, size, and location of cysts. Therapeutic options for this infection include the watch-and-wait approach, administration of albendazole and/or surgical intervention (32). Cure of AE can be achieved by radical surgery (32). However, most patients are not candidates for curative surgery at the time of diagnosis and are treated with life-long albendazole (32). The average case fatality rate for patients with CE has been estimated to be approximately 2.2% and for patients with untreated AE 10 and 15 years after diagnosis, 71% and 100%, respectively (3, 35).

1.2.2 Geographical distribution of *E. granulosus* and *E. multilocularis*

Human echinococcoses are among the most geographically widespread zoonoses in the world, and prevalence varies considerably within endemic regions (5). *E. granulosus* in particular has a wide global distribution and occurs in all continents, and in circumpolar, temperate, subtropical and tropical zones (5). Overall, the highest parasite prevalence has been reported from regions in Eurasia (especially in the Mediterranean region, China, the Russian Federation and adjacent independent states), North East Africa, Australia and South America (5). Effective eradication or control of the parasite have been achieved in some countries including Iceland, Cyprus and New Zealand, and in some regions such as Tasmania in Australia and the provinces of Neuquen and Rio Negro in Argentina (18, 26, 32). At the end of the 1980s, there was a limited number of countries that reported cases of AE (5). However, recent epidemiological surveys suggested that *E. multilocularis* has a much wider geographical distribution than previously anticipated and a more diverse range of suitable hosts (17, 20, 36). Since adequate information from early reports of AE cases is not available, it has been difficult to determine if these findings correspond to the expansion of the geographical range of the parasite or the first identification of previously unknown endemic areas (16). Currently, AE is found in non-tropical areas of the northern hemisphere affecting regions in Northern and Central Eurasia, Japan and parts of North America, China and Russia (5). The endemic areas for *E. oligarthrus* and *E. vogeli* are restricted to Central and South America (5).

The current level of human–ecosystem interaction has been responsible for accelerated environmental change (37). The resulting alterations to species assemblages and human/animal/pathogen contact rates have been increasingly recognized as potential drivers of the apparent geographical expansion of *Echinococcus* spp. (38, 39). Land cover and land use determine vegetation patterns and microclimates and therefore, play an important role in facilitating the transmission cycles of these parasites (40). Thus, the understanding of

environmental determinants of human echinococcosis risk has become essential in order to explain the regional gaps and differences observed at different spatial scales (41). Deforestation, afforestation, grazing practices, climate variability and direct or indirect control of intermediate and definitive hosts are currently being studied as potential determinants of the persistence and geographical expansion of *E. multilocularis* (25, 42-46). As a result, this parasite species has been found in countries of Europe that were not previously endemic and discovered in foci of high incidence in Western China and other endemic areas in Central Asia and Siberia (47). In North America, substantial research to establish the epidemiology and transmission patterns of *E. multilocularis* was conducted between the early 1930s and the 1980s (48-51). In following decades, the limited number of reported human echinococcosis cases in this region resulted in a lack of concern regarding the potential public health threat posed by these infections (52). However, the apparent expansion of *E. multilocularis* across areas in Europe and Asia, motivated the scientific community to reconsider the public health risks of this parasite in North America and assess possible species introductions that might have occurred in recent decades (53). Although data have been difficult to compare due to spatial and temporal inconsistencies in the sources, studies suggest that a similar emerging phenomenon may be occurring in the central region of the United States and Canada (44, 53, 54). In the city of Calgary, Alberta, Canada, particularly, *E. multilocularis* infections in *Myodes gapperi* (*Cricetidae*) were detected in 2012 (54). *Myodes gapperi* is a southern red-backed vole that was not recognized previously as an intermediate host for *E. multilocularis* and that can be found in close proximity to, and within metropolitan areas (54). Also, domestic dogs were found to be infected with *E. multilocularis* in the city of Calgary were parasite transmission involving coyotes and rodent intermediate hosts occurs in urban settings (44). Establishment and local transmission of a European-type strain of *E. multilocularis* in wildlife in a forested region of North America have also been reported (55).

Socio-demographic, economic and human behavioural factors also determine the heterogeneous geographical distribution of *Echinococcus* spp. transmission. Some factors associated with high risk of exposure to the parasite include low income, poor hygienic practices, dog ownership and limited education. In contrast, the use of tap water has been identified as a factor that can protect against the disease (56-60). Higher risk of acquiring the infection has been observed in females compared to males (58-60). This observation is likely to be related to greater exposure rather than a different gender predilection. In China, the Buddhist practice of allowing old livestock to die naturally, the unrestricted disposal of animal viscera and the presence of free ranging dogs have been identified as important factors influencing the high prevalence of human CE among Tibetan communities (61). Following the collapse of the Soviet Union in 1991, there was an apparent emergence of human echinococcoses in Central Asia (62, 63). In Kazakhstan, official reports indicated that the number of annual CE cases increased from about 200 to approximately 1000 between 1994 and the beginning of the 21st century (62). This epidemic coincided with local worsening economic conditions and deteriorating health services (63). The Soviet model of health care was centrally planned and provided universal, free access to basic care (64). However, most of the systems that emerged posteriorly were characterised by large inequalities due to affordability (64). Increases in the incidence of human echinococcosis cases were also described in Kyrgyzstan (65), Uzbekistan, Turkmenistan (66) and Tajikistan (67).

1.2.3 Human echinococcoses in China

According to recent estimates, there are approximately 0.6–1.3 million cases of human echinococcoses in China (1/3 are children), especially in western areas, where the highest local prevalence of AE infection has been recorded worldwide (24, 68).

In China, human echinococcoses affect at least twenty of the thirty-three Provinces, Autonomous Regions and Municipalities of the country. The endemic areas cover approximately 87% of the entire national territory (69, 70). However, most of the infection risk tends to occur in Provinces or Autonomous Regions located in Central and Western China such as, Shaanxi, Gansu, Sichuan, and Qinghai Provinces, Ningxia Hui Autonomous Region (NHAR), Xinjiang Uyghur Autonomous Region (XUAR) and Tibet Autonomous Region (TAR) (70). Notably, despite the high national burden of AE, CE is the most frequent form of the disease in China, and the regions with the highest risk of echinococcosis infection are usually co-endemic for both human CE and AE (26). CE occurs in all echinococcosis endemic areas of the country, affecting regions where livestock husbandry practices maintain stable transmission of the parasite between definitive and intermediate hosts (69).

Human AE has been known to occur in Western China since the early 1950s (71). However, this form of the infection was identified as a major public health problem in semi-pastoral and pastoral communities from mountainous areas in Western, Northern, and Central China until recent decades. Currently, human AE is highly endemic in nine Provinces, Autonomous Regions and Municipalities of the country (72). Epidemiological studies have revealed that the Qinghai-Tibetan plateau has the highest rates of human AE ever recorded in the world (73). This region covers most of the Tibet Autonomous Region and the Qinghai Province, and parts of Sichuan, Gansu and Yunnan Provinces and XUAR.

1.2.4 Strategies for prevention and control of human echinococcoses

The One Health concept, proposed by William Osler in 1973 and reintroduced by Calvin W. Schwabe in 1984 (74, 75) and the field of EcoHealth, applied since the 1990s (75), have been increasingly recognized as major components of disease assessments and interventions in recent decades (76). Both emphasize particularly on transdisciplinary collaboration among the

sectors of human, animal, and environmental health to understand better the ecological, socio-economic and epidemiological mechanisms influencing the persistence and emergence of diseases (77). Therefore, One Health/Eco Health approaches provide a holistic framework within which professionals such as clinicians, public health scientists, ecologists, veterinarians and economists join efforts for effective surveillance and control of zoonotic pathogens and elimination or mitigation of their transmission routes (78). Due to the ecological interconnectedness among *Echinococcus* spp. hosts, effective prevention and control of human echinococcoses will only be achieved by such concerted efforts to implement sustained and long-term interventions in highly endemic areas (79).

The most critical component of interventions against *Echinococcus* spp. is aimed at the definitive hosts (dogs and foxes) (18). Such interventions are aimed at reducing or eliminating the population of adult worms, and therefore, the production of parasite eggs, thereby decreasing infection pressure on intermediate hosts (18, 80). Praziquantel is highly effective against *Echinococcus* spp. and is the recommended antiparasitic drug for regular deworming of dogs and foxes (18). However, regular mass treatment of dogs and foxes is usually challenging in most settings (80). Japan and some regions in Europe have decreased the infection pressure with *E. multilocularis* by implementing regular baiting with praziquantel (81-85).

To control human echinococcoses, it is also possible to target the intermediate hosts for *E. granulosus* (18). This involves undertaking classical meat inspection at slaughter houses and can also involve using an infection preventive vaccine (EG95) (80). Strategies to target small mammals are not currently considered as a feasible strategy against AE (80). Pharmacological and/or surgical treatment of human CE and AE cases is a measure that is regarded a public health priority (80). However, treatment of human cases does not have an impact on the transmission of the parasites (80). Reduction in human exposure to parasite eggs

can also be achieved with health education campaigns that promote hygiene and sanitation, appropriate slaughter practices and dog contact, community acceptance and participation in long-term implementation of control programmes (80).

In China, the National Control Programme to prevent and cure echinococcoses was developed by the National Health and Family Planning Commission (formerly the Ministry of Health) in 2005 (86). Aiming to decrease the seropositivity rate in children aged <12 years and reduce infection rates in dogs, the measures that are currently being implemented in endemic areas include: community-based epidemiological surveys involving serological, abdominal ultrasound and chest X-ray screening for early detection, treatment and surveillance of the disease, education campaigns to enhance awareness among local people and health officials, and regular antihelminthic treatment for deworming of dogs (18, 87). To date, the implementation and long-term sustainability of the programme has proven challenging in most endemic regions due to the lack of effective surveillance data, dispersed populations and movement of people and livestock to summer pastures (80). Consequently, the Chinese government is currently trying to identify areas at higher risk for infection, estimate the public health impact of human disease in the country and promote integrated control measures involving multidisciplinary and international cooperation (88).

1.3 Contributions of this thesis

This research was conducted in NHAR, which is an underdeveloped Autonomous Region located in North-western China and a hyper-endemic area for both, CE and AE (89). In NHAR, human echinococcoses represent a severe public health problem that primarily affects communities with low socioeconomic development that depend on subsistence agriculture and livestock herding as the main source of livelihood (89, 90).

Similar to other Provinces/Autonomous Regions in China, NHAR has experienced a considerable population growth in the past five decades. Consequently, the natural landscape and wildlife biodiversity of the region have been transformed by the human population to cope with the high demand for food and natural resources (91). Since the late 1990s, the Chinese government through the "Sloping Land Conversion Program", also called "Grain for Green Project", is attempting to recover the degraded areas of the country by reducing over-grazing on high pastures and reforesting eroded landscapes (92). However, increasing evidence indicates that the landscape rehabilitation process that is taking place near human settlements in rural areas of China has affected the population density and dynamics of various suitable intermediate and definitive hosts of *E. multilocularis*, and therefore, exacerbating the risk of human AE infections (24, 93-95). Currently, little is known about the host-environment interactions that take place at different spatial scales in China to regulate the transmission of *E. granulosus* in domestic settings.

Although previous epidemiological reports provided estimates of the impact of human echinococcoses in NHAR (43, 60, 87, 96) it has been difficult to determine the local distribution of *E. granulosus* and *E. multilocularis* and the changes that may have occurred in the geographical ranges of these parasites as a result of environmental change. Therefore, there was a need to identify highly endemic areas for CE and AE in NHAR, analyse the incidence of both infections over time and identify the role of climatic and land cover factors in determining the local transmission dynamics of the parasites (43, 88). Despite compelling evidence indicating that there is a link between the risk of AE infection and the structure and composition of the landscape (43, 46, 94, 95, 97-100), it is apparent that the association is not consistent across regions. Landscape features may affect predator – prey interactions and the survival of the parasite eggs in the external environment in several different ways (reviewed in Chapter 2). The findings and predictive maps created as part of the work included in this thesis

provide insight into the complex environmental processes underlying the heterogeneous spatiotemporal variation of CE and AE risk in NHAR.

Community screening surveys have contributed notably to providing better estimates of the incidence of CE and AE (or, in the case of serology, exposure to the parasites causing these diseases), and to reducing the impact of the infections by facilitating early detection and treatment of the disease. However, screening is a measure that may be inefficient and resource-intensive if implemented in areas of low prevalence of echinococcoses. Previous experience indicates that targeted screening represents a cost-effective strategy that offers the opportunity to refine prevention and control interventions (43). The research presented in this thesis will be significant in that the findings will offer a scientifically sound basis that may assist local and national initiatives against echinococcoses by providing visual representations of the areas at higher risk of infection. This may lead to an improvement of the cost-effectiveness of echinococcosis programmes by facilitating targeted interventions and a better allocation of resources to those places where they are most required.

Successful echinococcosis strategies designed and implemented in NHAR based on the findings of this work may also be translated into practices that potentially promote effective environmentally based control strategies to reduce the burden of human echinococcoses in China.

The PhD project presents concepts for broader landscape epidemiological studies and research development in other echinococcosis-endemic regions of the world that may also be affected by environmental change.

1.4 Research goal and objectives

The goal of the research presented in this thesis is to quantify climatic and land cover factors impacting on the incidence of echinococcoses in NHAR over the past three decades, and to

predict the spatiotemporal distribution of the risk of infection with *Echinococcus* spp. in NHAR. The research was guided by the following specific objectives:

Objective 1: To quantify and describe the spatial and temporal patterns of climate and land cover change in NHAR from 1980 to 2015, a period of extensive landscape restoration in NHAR.

Objective 2: To identify highly endemic areas for human echinococcoses in NHAR, and to determine and quantify the environmental covariates that shaped their geographical distributions at the township level from 1992 to 2013.

Objective 3: To determine the spatiotemporal distribution of human echinococcoses in Xiji County based on selected demographic and environmental factors, and to produce spatial prediction maps to show the evolving geographical distribution of these infections in 2002–2003, 2006–2007 and 2012–2013.

Objective 4: To predict and compare the spatial distribution of human seropositivity for *E. granulosus* and *E. multilocularis* and infections with these parasites in dogs in four counties located in the south of NHAR, Guyuan, Haiyuan, Tongxin and Xiji, in 2012–2013, and to identify communities where targeted prevention and control efforts are required.

1.5 Approach and methods

The methods used in this thesis are described separately in each research Chapter. This section summarizes the different data sources, statistical software and analytical methods applied throughout the thesis.

Data on echinococcosis infections and human exposure to *E. granulosus* and *E. multilocularis* were obtained from existing and updated epidemiological data sets that were collected as part of a larger echinococcosis research program in NHAR. The sources of the data sets include: first, a hospital-based retrospective survey of human CE and AE cases conducted in NHAR between 1992 and 2013; second, two mass serological screening surveys of randomly-selected children aged 6–18 years conducted in Xiji County in 2002–2003 and 2006–2007; and third, cross-sectional school surveys of human echinococcoses conducted in Guyuan, Haiyuan, Tongxin and Xiji Counties in 2012–2013.

Data on infection status in dogs were collected from cross-sectional surveys, with diagnosis using copro-multiplex PCR assays, undertaken in Guyuan, Haiyuan, Tongxin and Xiji Counties in 2012–2013.

Multiple data sources and analytical software were used to derived environmental data for the analyses: high-resolution (30 m) imagery from Landsat 4-5 Thematic Mapper (Landsat 4-5 TM) and Landsat 8 Operational Land Imager and Thermal Infrared Sensor (Landsat-8 OLI/TIRS) were downloaded for the period 1990 to 2015 for the entire region to estimate enhanced vegetation index (EVI) values and create land cover maps of NHAR using ENVI version 5.3 (101). Also, ArcGIS software version 10.3.1 (102) was used to quantify land cover changes in a spatially explicit way. Monthly averages of temperature and precipitation data for the period January 1 1980 to December 31 2013 were provided by the Chinese Academy of Sciences. Elevation estimates were obtained in a GeoTIFF format at the spatial resolution of 1 arc-second (approximately 30 m) from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) version 2 downloaded from the (103).

A geographic information system (GIS) platform was used to assemble, summarise and extract the data using administrative boundary maps of NHAR. Multivariate spatial regression models were developed based on a Bayesian statistical framework in OpenBUGS software 3.2.3 rev 1012 (104).

1.6 Research and thesis structure

This thesis consists of seven Chapters (Figure 1); an introduction, five Chapters comprising five journal publications (either published or in Press), and a discussion with general conclusions based on the results of the work presented in this thesis. The first publication is a narrative review about landscape epidemiology and its potential applications to characterise patterns of parasite transmission across natural and human-altered landscapes. This is followed by a compilation of four journal papers that present original research work. All of the Chapters commence with a description of context of the paper. References appear at the end of each Chapter.

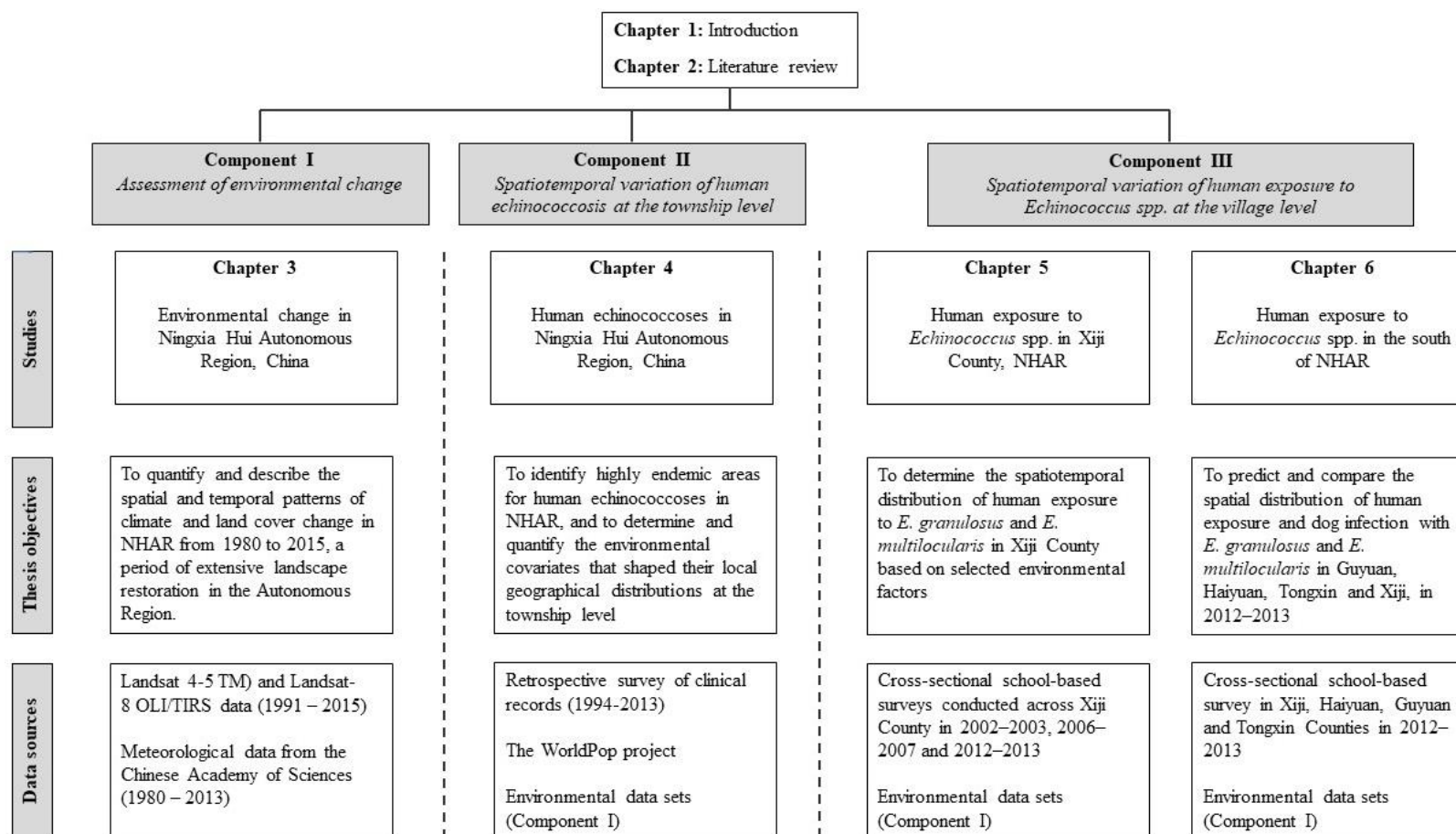


Figure 1 Thesis structure

The details of each Chapter are listed below:

Chapter 1 contains the introduction and outlines the major themes of the thesis. The introduction provides a background about *Echinococcus* spp. and the global disease burden of *E. granulosus* and *E. multilocularis* infections. This is followed by a description of the geographical extent of the parasites, current measures for control and future challenges. This Chapter also outlines the contributions of this thesis, research objectives, a summary of the approaches and methods applied throughout the thesis and the research and thesis structure.

Chapter 2 is a detailed narrative review in which I provide a theoretical background to investigate spatiotemporal variation in echinococcosis risk at different spatial scales. This Chapter describes important epidemiological features of the parasite and discusses the most relevant biophysical environmental factors that can affect the transmission of *E. granulosus* and *E. multilocularis*. Also, this Chapter presents information on how landscape epidemiology may be used to improve the understanding of the transmission dynamics of *Echinococcus* spp. and facilitate targeted allocation of resources for echinococcosis control.

In Chapter 3, I addressed Objective 1 by producing single date land cover maps for NHAR for the years 1991, 1996, 2000, 2005, 2010 and 2015, and quantifying changes in land cover in NHAR from 1991 to 2015. I also describe and present the results of an analysis conducted to identify annual, summer and winter temperature and precipitation trends in the Autonomous Region from 1980 to 2013 (Appendix A). Visual representation of land cover changes is also provided in this Chapter.

In Chapter 4, I addressed the requirements of Objective 2 by exploring and describing the spatio-temporal patterns of human echinococcoses at the township level in NHAR between January 1994 and December 2013. In this Chapter, I also provide

evidence on the potential impact of national landscape regeneration projects on the incidence of AE.

Chapter 5 addresses Objective 3 by exploring and quantifying changes in the predicted prevalence of human exposure to *E. granulosus* and *E. multilocularis* in Xiji County, which is a highly endemic area for human echinococcoses, from 2002 to 2013, a period during which extensive landscape restoration projects were implemented in NHAR and other parts of China.

Chapter 6 presents predicted risk maps of human exposure to *E. granulosus* and *E. multilocularis* and domestic dog infections with these parasites. In this chapter, I extended the work undertaken in Xiji County to other three neighbouring counties, Haiyuan, Guyuan and Tongxin, to address Objective 4. Maps of prediction error are also presented to identify those areas where prediction uncertainty is greatest.

Chapter 7 includes a discussion about the key findings from Chapters three to six. In this Chapter, I placed the findings in the context of other research and observations, present general conclusions and identify future research priorities.

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CHAPTER 2

Literature review

CHAPTER 2 LITERATURE REVIEW

2.1 Context

This literature review highlights the importance of landscape epidemiology in the assessment of global, regional, local and individual vulnerabilities to human echinococcoses based on the environmental processes that underlie the transmission dynamics of *Echinococcus* spp. The main reason to describe and promote the use of landscape epidemiological studies in this review include: first, this approach has proven to be essential for achieving significant advances in the understanding of the role of landscape characteristics in determining the geographical distribution of *E. multilocularis*; second, there is limited evidence on the use of landscape epidemiological studies that examine the impact of anthropogenic environmental change on the transmission of *E. granulosus* in domestic settings; and third, the integrated use of GIS, RS and spatial modelling techniques may help to identify the environmental conditions that favour the persistence, emergence and re-emergence of both of echinococcoses in different regions of the world. Landscape epidemiology allows the application of novel technologies and analytical methods to target appropriate surveillance and response interventions where they are most required.

In general, this Chapter attempts to provide a theoretical framework within which the influences of the environment on parasite transmission might be studied at global, regional and local contexts.

In this Chapter I presented the principles of landscape epidemiology. Then, I introduced and described in detailed two conceptual diagrams that were created to

represent the environmental factors that may influence the patterns of *E. granulosus* and *E. multilocularis* transmission at different spatial scales. Finally, the review identifies limitations, challenges and gaps in the current evidence and proposes research priorities to support the surveillance of human echinococcoses in highly endemic areas, and guide the implementation of appropriate intervention strategies for prevention and control.

2.2 The landscape epidemiology of echinococcoses

Cadavid Restrepo, A.M.; Yang, Y.R.; McManus, D.P.; Gray, D.J.; Giraudoux, P.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Hamm, N.A.S.; Clements, A.C.A. The landscape epidemiology of echinococcoses. *Infectious Diseases of Poverty*. 2015;5(1):13.

SCOPING REVIEW

Open Access



The landscape epidemiology of echinococcoses

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Abstract

Echinococcoses are parasitic diseases of major public health importance globally. Human infection results in chronic disease with poor prognosis and serious medical, social and economic consequences for vulnerable populations. According to recent estimates, the geographical distribution of *Echinococcus* spp. infections is expanding and becoming an emerging and re-emerging problem in several regions of the world. Echinococcosis endemicity is geographically heterogeneous and over time it may be affected by global environmental change. Therefore, landscape epidemiology offers a unique opportunity to quantify and predict the ecological risk of infection at multiple spatial and temporal scales. Here, we review the most relevant environmental sources of spatial variation in human echinococcosis risk, and describe the potential applications of landscape epidemiological studies to characterise the current patterns of parasite transmission across natural and human-altered landscapes. We advocate future work promoting the use of this approach as a support tool for decision-making that facilitates the design, implementation and monitoring of spatially targeted interventions to reduce the burden of human echinococcoses in disease-endemic areas.

Keywords: Landscape epidemiology, Helminth infection, Human echinococcosis, *Echinococcus* spp, Environmental change, Geographic information systems, Remote sensing, Geostatistics

Multilingual abstracts

Please see Additional file 1 for translations of the abstract into the six official working languages of the United Nations.

Introduction

Landscape epidemiology is the study of the spatial variation in disease risk, in strong connexion with landscape characteristics and relevant environmental factors that influence the dynamics and distribution of host, vector and pathogen populations. The fundamental concepts of landscape epidemiology were formalised and introduced by the Russian parasitologist, Pavlovsky, in 1966 [1]. According to Pavlovsky, landscape epidemiology is based on three observations: first, diseases tend to be limited geographically; second, the spatial variation in the distribution of a disease is determined by variations of

physical and/or biological conditions that support a pathogen, its vectors and reservoirs; and third, the contemporaneous and future risk of a disease can be predicted if those conditions are mapped [2]. This conceptual framework has been developed and extended progressively to integrate concepts and approaches from multidisciplinary studies, including landscape ecology, for a better understanding of the complex composition of the landscape and its relationship with the transmission processes and geographical distribution of a disease [3–5]. The current principles of landscape epidemiology have been recently summarised in a set of propositions outlined by Lambin and colleagues (Table 1) [6].

Most modern landscape epidemiological studies use Earth observation (EO) to obtain remotely sensed (RS) and in situ data about the environment [5]. Geographic information systems (GIS) are used to capture, store, analyse and display geo-referenced data that may be exported to various analytical and statistical platforms [5]. The integrated use of these technologies and the application of spatiotemporal statistics allow investigators

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Table 1 The 10 principles of landscape epidemiology proposed by Lambin and colleagues

| Principle | Description |
|-----------|---|
| 1 | Landscape attributes may influence the level of transmission of an infection |
| 2 | Spatial variations in disease risk depend not only on the presence and area of critical habitats but also on their spatial configuration |
| 3 | Disease risk depends on the connectivity of habitats for vectors and hosts |
| 4 | The landscape is a proxy for specific associations of reservoir hosts and vectors linked with the emergence of multi-host disease |
| 5 | To understand ecological factors influencing spatial variations of disease risk, one needs to take into account the pathways of pathogen transmission between vectors, hosts, and the physical environment |
| 6 | The emergence and distribution of infection through time and space is controlled by different factors acting at multiple scales |
| 7 | Landscape and meteorological factors control not just the emergence but also the spatial concentration and spatial diffusion of infection risk |
| 8 | Spatial variation in disease risk depends not only on land cover but also on land use, via the probability of contact between, on one hand, human hosts and, on the other hand, infectious vectors, animal hosts or their infected habitats |
| 9 | The relationship between land use and the probability of contact between vectors and animal hosts and human hosts is influenced by land ownership |
| 10 | Human behaviour is a crucial controlling factor of vector-human contacts, and of infection. |

to explore in detail the landscape patterns that influence the transmission dynamics of an infectious disease at different spatiotemporal scales. EO, GIS and the use of innovative analytical methods also provide the opportunity to visualise and predict the geographical variations in disease risk in response to shifting environmental patterns [7, 8]. In this way, landscape epidemiology may offer a feasible and acceptable framework to reduce disease burdens by allowing a more precise estimation of populations at high risk and the identification of priority areas where allocation of disease control resources is most required [9].

To date, landscape epidemiology has been mainly applied to examine associations between the environment and the transmission dynamics of mosquito-borne diseases such as malaria, dengue, leishmaniasis, filariasis and trypanosomiasis [10–13]. However, with the advent of global environmental change, there has been an increasing interest in conducting studies centred on the understanding of the landscape epidemiological aspects of non-mosquito-borne helminth infections, such as schistosomiasis [14–16]. This approach has been successful in providing valuable information to enhance the implementation of strategies for surveillance, control and elimination of helminth infections in various settings [17–19].

Echinococcoses are zoonotic parasitic diseases caused by larval stages of taeniid cestodes of the genus *Echinococcus*. Currently, there are nine recognised species within the genus and six of these species cause infection in humans, *E. granulosus*, *E. multilocularis*, *E. canadensis*, *E. ortleppi*, *E. vogeli* and *E. oligarthrus* [20, 21]. Among them, *E. granulosus*, the main aetiological agent of cystic echinococcosis (CE), and *E. multilocularis*, the causative agent of alveolar echinococcosis (AE), are the species of major public health importance globally [22].

Both have a wide geographic distribution and cause severe disease in humans that can be fatal if left untreated [23–25]. The other two less common forms of human infection are polycystic echinococcosis and unicystic echinococcosis caused by *Echinococcus* species restricted to Central and South America [25].

There are approximately 200,000 new cases of human CE or AE cases diagnosed every year and a total of 2–3 million people infected worldwide [26, 27]. According to the *Office International des Epizooties* databases and published case reports, the estimated human burden of CE measured in terms of Disability-Adjusted Life Years (DALYs) lost is 285,407. When underreporting is accounted for, the global burden of this form of infection exceeds 1 million DALYs, which results in an annual estimated cost of \$760 million [26]. Global estimates of AE suggest that there are approximately 18,235 people infected every year and a total of 0.3–0.5 million AE cases diagnosed worldwide. Most of the disease burden of AE is focused on Western China and results in the loss of 666,434 DALYs per annum [28]. Although these reports may be underestimates due to challenges with the early detection of the diseases and lack of mandatory reporting in most countries, it is apparent that the burden of echinococcoses has increased in recent years and human infection is becoming an emerging or re-emerging problem in several regions in the world [29–36]. Consequently, landscape epidemiological approaches have been incorporated progressively into echinococcosis research to identify the environmental mechanisms underlying the variation in disease risk and the most plausible drivers of parasite dispersion [37–43].

This review aims to describe the potential applications of landscape epidemiological studies to establish, quantify and predict the geographical distribution of human echinococcoses and as a decision-making tool to

enhance the implementation of spatially targeted interventions against the disease. First, the review describes important epidemiological features of the parasite and discusses some of the most relevant biophysical environmental factors that may affect the distribution of echinococcosis risk at different spatial scales. Next, the review describes how landscape epidemiology may use geospatial resources and techniques to improve the understanding of the transmission dynamics of *Echinococcus* spp., and facilitate the strategic allocation of resources for interventions to the appropriate geographic locations. Finally, challenges and gaps in the current evidence are identified and research priorities to support the surveillance and control of human echinococcoses are proposed.

Search strategy

A search was conducted of literature including all relevant articles that were published until September 2015, identified from Medline, Google Scholar, PubMed and Web of Knowledge. The key terms used in the search strategy included one word and/or phrase from each of the following three categories: first, terms related to the disease, including zoonoses, parasitic disease, helminth infections, human hydatidosis, hydatid cyst, cystic echinococcosis and alveolar echinococcosis; second, terms related to risk factors for parasite transmission, including environmental influences, climate change, anthropogenic environmental factors, and landscape; and third, terms related to the analytical approach, including landscape epidemiology, risk mapping, geographic information systems, remote sensing, Bayesian analysis, geostatistics and geospatial techniques and/or methods. Additionally, secondary searches were conducted in reference lists of peer-reviewed studies. The language of the literature was restricted to English.

Environmental determinants of the multi-spatial variation in human echinococcosis risk

Echinococcus spp. have complex domestic and sylvatic life cycles that involve a wide range of intermediate and definitive hosts. Therefore, echinococcosis transmission can take place in different landscape types in which a variety of physical and biological factors combine to determine the transmission intensity of the parasite [25]. Although these factors remain poorly understood, it is apparent that the environment plays an important role in the life cycle of *Echinococcus* spp. Climate and landscape structure influence particularly human behaviour, animal population dynamics, spatial and temporal overlap of intermediate and definitive hosts and the survival of the parasite eggs [41, 44–47]. Humans, who become infected by ingesting the parasite eggs directly through contact with definitive hosts or indirectly from a

contaminated environment, are regarded as accidental intermediate hosts who do not usually contribute to the developmental cycle of the parasite. However, reports from hyperendemic areas in north-western Kenya indicate that humans may act as intermediate hosts in the life cycle of the parasite under unique circumstances. The close human-dog relationship and the absence of burial customs among the Turkana people in this region, seem to have made possible the transmission of *E. granulosus* from tribesmen to dogs or wild carnivores which are able to access and scavenge potentially infected human remains [48]. Comprehensive reviews of the parasite life cycle, environmental factors influencing parasite transmission, clinical manifestations, diagnosis and management of the disease are available [22, 25, 44, 49].

There is an important spatial dimension in the relationship between the risk of echinococcosis infection and environmental factors that influence both the distribution of the hosts and the rate of development of the parasite [45, 50]. Despite the extent of epidemiological variations within the genus *Echinococcus*, a general framework may be used to describe factors driving the transmission of the parasite at the continental, sub-continental and local spatial scales. At the continental level, echinococcosis risk may be related to the phyllogeography (biogeography) of animal communities and to variations in climatic conditions that control the presence/absence of host species within a particular landscape type [41]. At the sub-continental level, the spatiotemporal patterns of echinococcosis risk depend upon animal population dynamics, predator–prey interactions and parasite free living stage survival. Thus, at this spatial scale, the infection is likely to be associated with landscape characteristics, such as composition (variety and abundance of patch types in the landscape), and configuration (spatial arrangement and complexity of patches present in the landscape) that together with climatic factors determine the seasonal and interannual variation in population density of the hosts, parasite free stage survival, and subsequently the geographical distribution of *Echinococcus* spp. [50].

To date, most studies conducted at sub-continental spatial scale have focused on describing the role of landscape composition in determining the risk of infection with *E. multilocularis* in wildlife [41–43, 51–55]. In eastern France, high population densities of *Microtus arvalis* and *Arvicola terrestris*, vole species that are key intermediate hosts for *E. multilocularis*, were identified in areas where ploughed fields were converted into permanent grassland as a result of the local specialisation in milk production in the 1960s and 1970s [41, 56]. In addition, significant positive relationships between percentage of area covered by grassland and *E. multilocularis* infection in humans and foxes have also been

reported in the same region [39, 41, 57]. Studies conducted in Zhang County, Gansu Province, China, indicated that the transmission of *E. multilocularis* may be related to the transient augmentation of grassland/shrubland following a period of deforestation. In this hyperendemic area for AE, land cover change favoured the creation of optimal peri-domestic habitats for AE intermediate host species, and the development of a peri-domestic cycles involving dogs [41, 58]. In AE-endemic areas from the north-western part of Sichuan Province on the Tibetan Plateau, private partial fencing has been common among Tibetan pastoral communities since the 1980s. This practice allows the creation of private grazing areas to support livestock during the winter period and early spring. Although fenced pasture has reduced grazing pressure in private areas, it has also exacerbated overgrazing in common lands and has improved suitability of habitats for various rodent species that are vulnerable to the parasite. As a result, the risk of AE has also increased in the region [54, 59, 60]. By contrast, in northern Japan, grey-sided voles form large populations in dense bamboo undergrowth of forest. Since this land cover is natural vegetation, AE prevalence in this part of the country appears to be not related to anthropogenic landscape changes [61, 62].

Despite compelling evidence supports the association of the environment with the spatial variation of *E. multilocularis* infection in sylvatic systems [41, 43, 51–55, 63], little is known about the host-environment interactions that take place at sub-continental levels to regulate the transmission of *E. granulosus* in domestic settings, where dogs are identified as typical definitive hosts, and sheep and other ungulates, as intermediate hosts [25]. Livestock like any other animal system can be influenced by climate and landscape resources that shape animal feeding behaviour, growing rates, reproductive efficiency and immunological mechanisms that protect against pathological and non-pathological stressors [64]. Heat stress, particularly, declines feeding intake, conception rates and the immune response to infectious diseases in sheep and cattle [64, 65]. Therefore, climate change and landscape transformation, together with high level of environmental contamination with parasite eggs have the potential to affect parasite transmission intensity not only in wildlife but also in urban settings, and consequently increase the risk of human CE. Reports from abattoir meat inspections suggested seasonal variations in the prevalence of *E. granulosus* infection in Iran and Saudi Arabia [66, 67]. Additionally, high altitudes and annual rainfall were associated with high infection rates of CE in livestock from hyperendemic regions for this infection in north-central Chile and Ethiopia [68, 69]. The observations from these countries were explained by factors such as sources of slaughtered animals,

different animal age-structures among seasons, changes in agricultural management practices and environmental factors. The geographical location of livestock farms and the animal spatial structure also appeared to have an important effect on the prevalence of CE in the Campania region of southern Italy. Using geo-referenced data, a survey conducted in this region suggested that the significantly higher prevalence of CE on cattle farms compared to water buffalo farms was associated with their closer distance to potentially infected sheep [70].

At local or community spatial scales, microclimate is one of the most significant factors underlying the variation in the risk of echinococcosis infection [46, 47]. Temperature and moisture/humidity, particularly, are major determinants of the survival and longevity of the parasite eggs in the external environment [46, 47]. Although the optimal temperature range for egg survival has been estimated to be between 0 and 10 °C, the tolerance of the eggs to external environmental conditions varies between parasite species and strains [46, 47]. For *E. multilocularis* eggs, temperatures of 4 and of –18 °C were found to be well tolerated, with survival times of 478 and 240 days, respectively [46]. In addition, a recent study showed that *E. multilocularis* eggs are more resistant to heat if suspended in water compared to eggs exposed to heat on a filter paper at 70 % relative humidity. Eggs suspended in water can remain infectious for up to 120 min if exposed to temperatures of 65 °C [71]. In vivo studies also revealed that the eggs of *E. granulosus* remain viable and infective after 41 months of exposure to an inferior arid climate, which is characterised by large thermal amplitude (from –3 to 37 °C), with warm summers, cold winters and low precipitation (under 300 mm/year) [47].

At the local level, human behavioural changes, driven in large part by population growth and economic and technological development, have been associated with the creation of novel interactions between humans, domestic animals and wildlife [72]. This new human-environment interplay also appears to be altering human exposure to *Echinococcus* spp. by facilitating the establishment and introduction of competent intermediate and definitive hosts in the life cycle of the parasite [73, 74]. Foxes, the primary definitive host of *E. multilocularis*, take advantage of the most accessible and abundant resources of water and food. Therefore, the reported movement of foxes towards urban areas, where the transformed landscapes provide optimal conditions for surges of small mammal species, have explained the observed higher circulation of the parasite within local urban landscapes [73]. In addition, the role of dogs in semi-domestic life cycles of *E. multilocularis* appears to be the result of human-related activities in certain communities where dog ownership and close association between humans and dogs were identified as significant

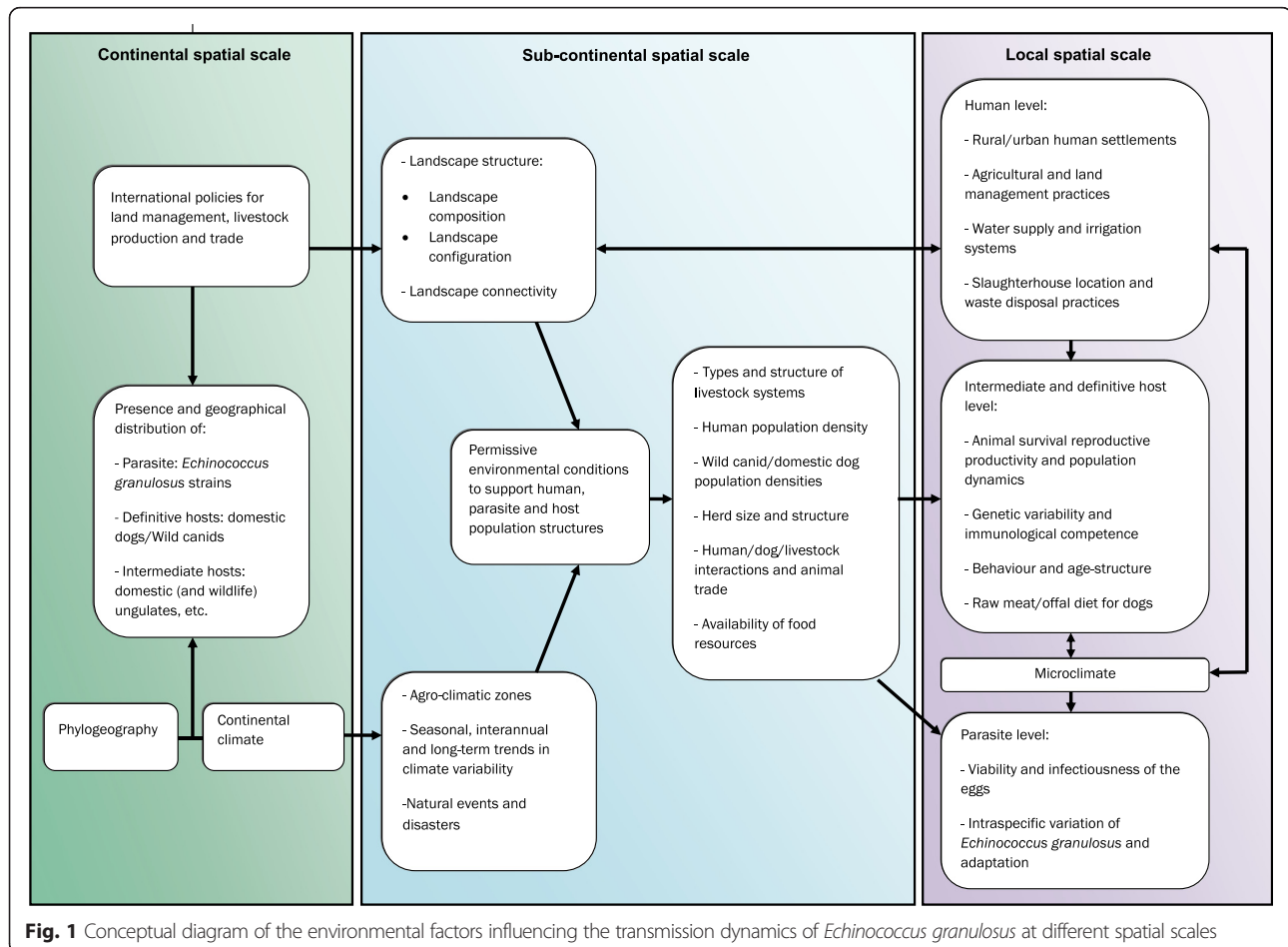
predictors of human AE risk. [75–77]. Similarly, reports have revealed that urban coyotes are currently playing a key role in the maintenance of the life-cycle of *E. multilocularis* within North American urban settings [78].

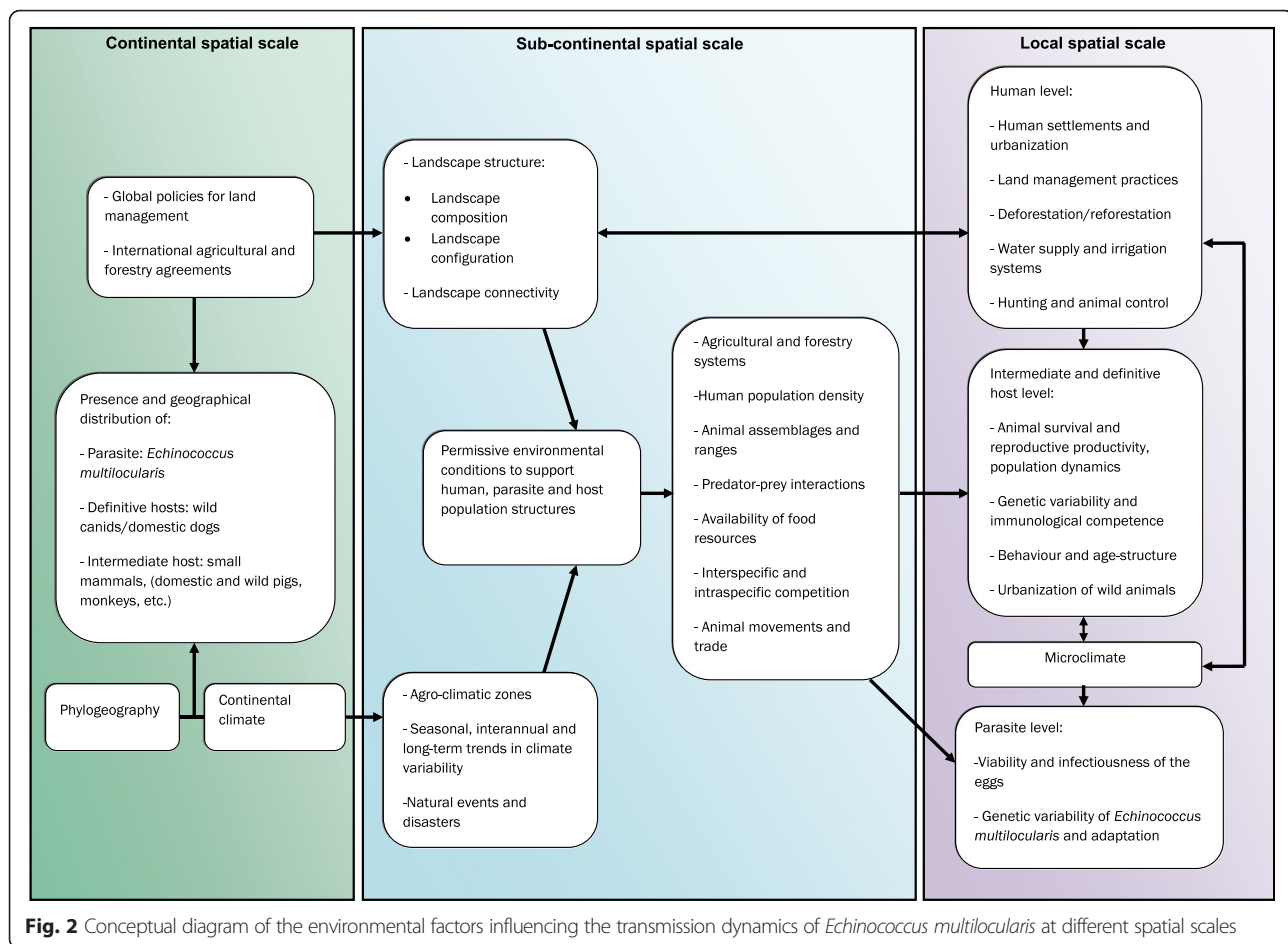
Genetic factors and immunological interactions between the parasite and hosts are also associated with echinococcosis risk at local and community levels. These factors affect the development of the adult parasite in the intestine of definitive hosts and determine the time course of the production and viability of the eggs [79]. Genetic and immunological factors also govern differences in the reproductive potential of the hosts and influence the susceptibility/resistance of humans and animals to the infection [80]. Patients with impaired immune response appear to have increased susceptibility to *E. granulosus* and *E. multilocularis* infections, and are more prone to develop severe disease [81–83]. Similarly, an increase risk of infection with *E. multilocularis* has been observed in experimental immunosuppressed animals [80]. Figures 1 and 2 show a conceptual diagram of the environmental factors influencing the transmission dynamics of *E. granulosus* and *E. multilocularis*, respectively, at different spatial scales.

The use of landscape epidemiological approaches to understand the transmission dynamics of *Echinococcus* spp.

The inherently multi-scale nature of the life cycle of *Echinococcus* spp. has represented a challenge to comprehensively understand the mechanisms that govern parasite transmission and the subsequent variation in disease risk [79, 84]. However, over the past decade, advances in EO, that have led to the increased availability of high-quality environmental data, and developments in GIS and methods for spatial analysis have improved the ability of investigators to explore and predict the spatio-temporal dynamics of echinococcosis infections.

Much progress has been made in the use of geospatial technologies to map the prevalence of infection with *Echinococcus* spp. and identify space-time clusters of human disease in various settings [58, 70, 85–88]. With global environmental change, there has been a growing interest in determining the role of climatic factors and the process of landscape transformation in the recent observed patterns of parasite transmission. Thus, deforestation, grazing practices, climate variability and direct or indirect control of intermediate and definitive hosts





are currently being studied as potential environmental factors that have favoured the persistence and geographical expansion of the parasite [41, 43, 61, 75].

Landscape epidemiology uses a wide variety of data and statistical techniques [5]. Accurate data, both in space and time, are required to develop statistical models that describe the complex associations between the environment and the transmission of the parasite [89]. Data collected at a specific geographic location can be geo-referenced using spatial coordinates, such as those obtained from global positioning systems (GPS). By contrast, data collected from a defined spatial region, such as clinical surveillance data for an administrative area, are geo-referenced by specifying the administrative boundaries, with some associated limitations for subsequent spatial analysis [89]. Because reporting of echinococcosis infections is not mandatory in most countries, epidemiological data are usually fragmented and scarce. In most endemic areas, human cases are primarily identified through clinical case reports, hospital records or mass screening surveys that usually combine questionnaires based-interviews, abdominal ultrasound and specific serology tests [90–93]. These initiatives have

resulted in a valuable source of geospatial data for the estimation of echinococcosis risk at local and regional spatial scales, and at certain points in time in several endemic regions. However, these represent inefficient measures that are difficult to sustain in the long term [43]. The European Echinococcosis Registry (EurEchinoReg) Project was the first attempt to establish a continent-wide database for echinococcosis, with the aim being to estimate the impact of AE in western and central Europe. However, the routine collection of data by individual countries has been heterogeneous in terms of completeness and reliability across regions [94]. Since the beginning of the project, Austria, France, Germany and Switzerland are among the few countries that have maintained population-based human AE data registries that can be used to analyse patterns of this form of disease at various spatial scales [94–96].

In addition to data on human echinococcosis cases, data on environmental factors and survey data to determine the presence of echinococcosis host species and their infection status may also be combined in landscape epidemiological studies [45]. Although infection in definitive and intermediate hosts are key indicators of the

presence of the parasite in the environment, the identification of infected animals does not directly reflect transmission pressures of *Echinococcus* spp. to human populations. Nevertheless, it can be assumed that environmental processes that support variation in host population densities are also likely to influence the risk of human infection [31, 41]. Sources of EO for environmental data include satellite remote sensing and spatially distributed in situ sensors, such as meteorological stations [97]. EO and its derived products provide extensive coverage of vast areas of the earth at periodic intervals. In the case of in situ data, interpolation methods can be applied to obtain data for those locations where there are no meteorological observations locally available [98, 99]. Currently, a wide range of high-quality environmental datasets are freely available and can be used to identify continental, sub-continental or local environmental variability [97]. The International Union for Conservation of Nature has also created databases for mapping the distribution of animal species, including most definitive and intermediate hosts of *Echinococcus* spp. [100]. The environmental variables most commonly used in echinococcosis research include altitude, temperature, precipitation, land cover, land use, vegetation indices and geographical distribution of the hosts [44, 75].

The characterisation and prediction of echinococcosis risk using landscape epidemiology can be achieved by using geospatial resources and spatial analysis methods that allow visualisation, exploration and modelling of multi-source geo-referenced data. Among them, GIS mapping and cluster detection techniques are useful tools that have been widely applied in echinococcosis research to prioritise areas for further studies and plan preventive and control interventions [70, 95, 101–103]. In general, these methods have indicated that echinococcosis infections have a focal spatial distribution, with defined areas at high risk for parasite transmission between definitive and intermediate hosts, in which the prevalence or incidence of human disease may be higher than in surrounding areas. Examples include studies undertaken in France, Japan and China, countries heavily affected by AE. In these countries, the evidence has suggested that the number of human cases of AE is a nested hierarchy of spatial aggregates in the eastern part of France. Aggregative distribution has also been shown in the northern island of Hokkaido, Japan, and in provinces located in the central and western part of China, where the Qinghai-Tibetan plateau has been identified as the geographic area with the highest rates of human AE recorded globally [41, 104, 105]. Similarly, epidemiological studies in north-western China revealed much higher prevalence of CE among local communities from the Tibet Autonomous Region, Xinjiang Uygur Autonomous

Region, Ningxia Hui Autonomous Region (NHAR), and Sichuan and Qinghai Provinces [106]. Demographic, socio-economic and human behavioural factors are also variables that have been commonly explored as potential factors interacting with the environment to determine the heterogeneous spatial distribution of echinococcoses in several endemic regions. The Buddhist doctrine among pastoral communities that allows old livestock to die naturally, coupled with the practice of unrestricted disposal of animal viscera and the presence of free ranging dogs have been identified as factors influencing the high prevalence of human CE in Tibetan communities in China [106]. Significant difference in prevalence rates of human infection has also been observed between males and females. Women are more likely to be exposed to *E. granulosus* and *E. multilocularis* as a result of their daily family activities such as feeding dogs, herding livestock and collecting yak dung for fuel [85, 107, 108]. Additional risk factors found to be related to high risk of exposure to both parasite species include dog ownership, poor hygienic practices, low income and limited education. In contrast, the use of tap water has been identified as a factor that can protect against the disease [85, 93, 101, 107–109].

As a result of the apparently expanding geographical distribution of *Echinococcus* spp. [29–35], particular emphasis has recently been placed on the implementation of landscape epidemiological approaches that use spatial statistical techniques to identify environmental conditions that may be affecting the habitat suitability for sustaining the sylvatic life cycle of the parasite [42, 43, 53, 75, 110]. Spatial statistics are statistical methods that can be applied to explore geographically referenced data and investigate associations between the observed number of human cases and the most plausible factors that underlie the transmission dynamics of the parasite. On the basis of the information provided by this approach, traditional or spatially explicit statistical models can also be constructed to predict the spatial distribution of disease based on environmental variables. Of note, the statistical methods applied in epidemiology that fail to account for spatial autocorrelation in the variables used to model and predict disease risk, may possibly lead to erroneous statistical inference [111]. Thus, spatially explicit models that incorporate information on spatial autocorrelation, obtained using Bayesian methods are increasingly incorporated in landscape epidemiological research. Bayesian methods are sufficiently flexible to allow the development of complex hierarchical spatio-temporal models that quantify uncertainty in the analysis of disease risk by assuming that parameter values, including spatial predictions, vary as random quantities [112]. Predictive risk maps of echinococcoses that account for uncertainty estimates can be essential to inform decision-makers

about the uncertainty and implications of the interventions against these infections [14, 113]. A Bayesian statistical framework was used in Xiji County, NHAR, China, for risk mapping and transmission modelling of human AE [43]. The study indicated that the landscape characteristics favouring *E. multilocularis* transmission in Xiji County differed from the previous observations in Zhang County located in the neighbouring Gansu Province. While grassland around villages did not correlate with the prevalence of human AE, abundance of degraded lowland pastures was associated with higher prevalence of the disease in Xiji County. From the results, it was possible to infer that *E. multilocularis* can sustain transmission through a diversity of host communities in China [43]. A similar Bayesian approach was carried out in Tibetan plateau communities, which led to confirm and predict human disease hotspots over a 200,000 km² region and showed that human AE risk was better predicted from landscape features [75].

Applications to surveillance, prevention and control programmes

Landscape epidemiology has been applied progressively in echinococcosis research, particularly AE research, in order to identify the environmental determinants of echinococcosis risk. However, there is still limited guidance on the practical implementation of this approach to improve echinococcosis surveillance and maximise the impact of prevention and control efforts.

Most of the evidence in the use of landscape epidemiology to support the effective implementation of interventions against infectious diseases has been obtained from studies of mosquito-borne diseases [10, 11, 13], and non-mosquito-borne helminth infections, particularly schistosomiasis and soil-transmitted helminthiasis [17–19]. At the global scale, atlases have been developed that may potentially guide international priority setting for investments in disease control and elimination [114–116].

In the context of echinococcosis surveillance and control, mass screening surveys of echinococcoses have provided valuable data to help reduce the medical, social and economic burden of the infection by ensuring early detection and prompt treatment of human cases. However, this measure may be inefficient and resource intensive if implemented in areas of low prevalence of the disease. Echinococcoses affect particularly remote pastoral communities with low socio-economic development that may have limited access to health care [108, 117]. Therefore, landscape epidemiological studies have the potential to assist local and national initiatives against echinococcoses such as the one launched by the Chinese government to reduce the impact of these infections in 217 endemic

counties in western China [23, 118]. Such studies generate both quantitative evidence and visual representation of the geographical distribution of these diseases and allow a more precise estimation of populations at high risk. Updated maps of echinococcoses and accurate information about individuals and households at high risk may allow decision makers to optimally target resources and interventions for prevention and control.

In China, particularly, the current measures adopted against echinococcoses include community-based epidemiological surveys, patient treatment and monitoring, health education campaigns, and regular antihelminthic treatment for dog deworming [23, 118]. Under the strategic and operational context of these interventions and other potential strategies that may help reduce the burden of these infections in endemic regions, landscape epidemiological approaches represent a cost-effective measure not only to prioritise geographical areas at high risk, but also to identify the type of parasite control activity that is most required in specific locations. Deworming of wild foxes using baits with antihelminthic treatment is being established in some countries as a preventive technique against environmental contamination with *E. multilocularis* eggs [119–121]. In order to improve the cost-benefit performance of these efforts, spatial models were developed in Hokkaido, Japan, and in eastern France to identify the environmental factors that determine the most suitable micro-habitats for delivering the baits. The outcomes of these studies suggested that baiting programmes should be adapted to the local environmental characteristics of domestic and urban settings [119, 122].

Many of the relationships that have been explored in the studies outlined above have provided compelling evidence about the environmental conditions that together with socio-economic and demographic factors support the transmission of *Echinococcus spp.* in endemic regions. However, they fall short of allowing resource managers and policy makers to understand and anticipate the real impact of the infections, and the economic and medical implications of their decisions. Thus, approaches that incorporate the use of geospatial resources and spatial analysis to identify environmental drivers of echinococcoses can be applied as decision-making tools for the design of effective surveillance and response systems. In this way, landscape epidemiological studies may help monitor and predict parasite transmission based on changing environmental factors, and in response to the implementation of interventions for disease control. Most importantly, these approaches have the potential to guide echinococcosis control programmes in those regions with limited availability of surveillance data on echinococcoses [123].

The understanding of the landscape epidemiological aspects of echinococcoses may also provide scientific evidence that can be used to support environmental policy-making and landscape planning processes in hyperendemic areas for these diseases. Thus landscape epidemiology may also prove useful to promote environmentally-based strategies that have minimal impact on the transmission dynamics of the different *Echinococcus* spp. This is particularly relevant in regions where climate variability and landscape transformation may be facilitating the transmission of the parasite.

Previous studies conducted in echinococcosis-endemic regions have provided valuable insight into the landscape processes underlying the transmission of *E. multilocularis* at various spatial scales. However, most of these analyses involved environmental data collected at a single point in time and did not capture major environmental changes over time [50]. Because human echinococcoses may be the result of cumulative events that occurred over many years prior to the detection of the disease, the use of multi-temporal Earth observation datasets to identify environmental change will be necessary in order to conduct a meaningful landscape epidemiological analysis of the forms of human echinococcosis infections. Therefore, we advocate future research that incorporates time-series analyses of environmental data for the identification of the long-term trends in climatic and landscape conditions that may be facilitating the persistence and spread of *Echinococcus* spp. across heterogeneous landscapes.

Despite the potential applications of landscape epidemiology in echinococcosis research, it is evident that work is still necessary to address the limited availability of human echinococcosis data. Thus, further advances are required to improve long-term and multi-scale monitoring of these infections. We believe that the design and implementation of systematic and standardised protocols for the diagnosis, collection and recording of human cases may help to better estimate and monitor the prevalence of these infections in endemic areas, and also to increase awareness among all actors involved in the control of these infections. In addition, we also recommend the development of national and sub-national data collection systems to record all confirmed cases of echinococcoses identified through mass screening surveys or clinical and laboratory reports. Systematic surveillance systems may be used as efficient, reliable and secure data sources for the implementation of clinical and landscape epidemiological studies. Because echinococcoses are complex diseases that involve animal and human hosts, as well as ecological and environmental factors, integrated multisectoral efforts are clearly required to monitor the interactions between the landscape and parasite, hosts and human diseases. The availability of data on annual infection rates in humans, definitive and

intermediate hosts in hyperendemic areas combined with annual averages of climate data and land cover change may be particularly useful to improve cost-effectiveness of small-scale campaigns and reduce local risk. These data are essential to establish pre-intervention baseline, monitor the efficacy of interventions and inform the strategic planning of future control measures.

Factors that need to be considered for the routine implementation of these approaches include the availability of resources for collecting, processing, and modelling geospatial data at various spatial scales, training of personnel on the use of these technologies and the proper interpretation of results, and the continuous availability of high quality environmental data. It should be emphasized that the allocation of resources for the implementation of these novel techniques should not come at the cost of preventive and control efforts against the infections. Co-endemicity and polyparasitism are common in several regions of the world [124]. Therefore, initiatives to combine control strategies against human echinococcoses with other zoonotic diseases could potentially help to optimise resources, ensure sustainability of interventions and improve awareness among local people [124]. Major integrated programmes to map the distribution and enhance control strategies against some neglected tropical diseases such as onchocerciasis, lymphatic filariasis, soil-transmitted helminthiasis and schistosomiasis are currently being implemented successfully in various regions [125]. In the context of echinococcoses, integrated dog control/deworming and health promotion may be proposed as a cost-effective measure to reduce the impact of these infections in highly endemic areas.

Conclusion

This review demonstrates the potential of landscape epidemiology to explore the complex life cycle of *Echinococcus* spp. that involves time-dependent interactions of multiple definitive and intermediate hosts at different spatial scales. Landscape epidemiology has also proven helpful in characterising the geographical distribution of human AE risk and in determining the association between the geographical patterns of infection and environmental factors. Therefore, the implementation of this approach together with the recent advances in geospatial technologies and spatial analysis techniques provide a unique opportunity to explore the causes of persistence, emergence and re-emergence of some parasite species in several regions, and a better guidance for the design, implementation and monitoring of preventive and control interventions.

Additional file

Additional file 1: Multilingual abstracts in the six official working languages of the United Nations. (PDF 336 kb)

Abbreviations

EO: Earth observation; GIS: geographic information systems; RS: remote sensing; CE: cystic echinococcosis; AE: alveolar echinococcosis; DALYs: disability-adjusted life years; GPS: global positioning systems; EURECHINREG: the European Echinococcosis Registry; NHAR: Ningxia Hui Autonomous Region.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AMCR and ACAC conceived the idea for the review. AMCR prepared the first draft of the manuscript. ACAC, YRY, DPM, DJG, PG, RJSM, TSB, GMW and NASH provided critical comments and helped in drafting subsequent revisions. AMCR and ACAC finalized the manuscript. All authors read and approved the final manuscript.

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CHAPTER 3

Environmental change in Ningxia Hui Autonomous Region, China

CHAPTER 3 ENVIRONMENTAL CHANGE IN NINGXIA HUI AUTONOMOUS REGION, CHINA

3.1 Context

Climate and land cover are important components of the environment that play a key role in the transmission of *Echinococcus* spp, as outlined in Chapter 2. Climatic and land cover factors can act independently or synergistically to influence: 1) the dynamics of definitive host populations; 2) the dynamics of the intermediate host populations; 3) predator–prey interactions between definitive and intermediate hosts; and 4) the viability and longevity of parasite eggs in the external environment.

China is currently implementing a series of landscape regeneration projects that have significant potential impact on ecosystems, agriculture and public health. Previous spatially explicit models of *E. multilocularis*, developed in highly endemic areas in the country, have indicated that the spatial aggregation of this parasite is partially explained by the structure and composition of the landscape. Therefore, it is essential to establish evidence for the impact of landscape regeneration projects on the local environment, not only to facilitate future landscape planning and ecosystem management and protection, but also for a better understanding and effective response to the risk of human echinococcoses for the local population.

In addition to the direct effects of the implementation of landscape regeneration projects on land cover, in NHAR, these initiatives have also helped farmers to shift their income structure. In the Autonomous Region, the young population particularly, has moved from agricultural and livestock production practices to other economic activities such as industry, construction and transportation. The number of labourers who migrate to the cities has risen with urban population increasing more rapidly than the rural

population. As in many other areas in China, in NHAR, population growth and urbanization are identified as major sources of landscape transformation

This Chapter focuses on describing the results of an analysis that was conducted to examine and quantify land cover change in NHAR over the past decades. In this Chapter, I describe the process of land cover classification and validation of the first land cover maps created for NHAR for the period 1990 to 2015 at five-year intervals. Also, I report and discuss the main changes in land cover at six different time intervals 1991–1996, 1996–2000, 2000–2005, 2005–2010, 2010–2015 and 1991–2015. The results suggest that land cover transformation in NHAR from 1991 to 2015 concur with the main goals of a national policy implemented in China to recover degraded landscapes. Previous evidence on the association of echinococcoses and the environment, and the findings presented in this Chapter suggest that anthropogenic land cover change in NHAR may have been affecting the transmission dynamics of *Echinococcus* spp. in NHAR in past decades.

As part of the study of environmental change in NHAR, an analysis of meteorological data that were provided by the Chinese Academy of Sciences was conducted to quantify and map temperature and precipitation trends for the period 1980 to 2013. The analysis is provided in Appendix A. The findings were presented in the context of the Grain for Green Project (GGP), also called the Sloping Land Conversion Program, the largest ecosystem service payment project that has been implemented in China. The outputs of this Chapter (including Appendix A) provided variables that were used as covariates in Chapters 4–6.

3.2 Land cover change during a period of extensive landscape restoration in Ningxia Hui Autonomous Region, China

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Supplementary material for this paper is provided in Appendix B.



Land cover change during a period of extensive landscape restoration in Ningxia Hui Autonomous Region, China



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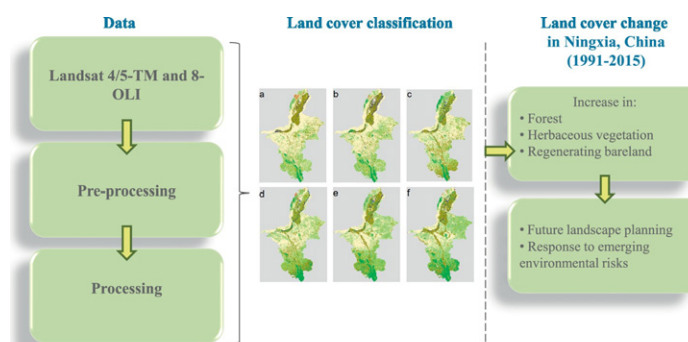
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HIGHLIGHTS

- We found an increase in forest, herbaceous vegetation and in regenerating bareland.
- The largest relative change for the period 1991–2015 was observed in the area covered by forest.
- The increase in forest resulted mainly from conversion of cultivated land and herbaceous vegetation.
- Forest growth primarily occurred in the north and south of the province.

GRAPHICAL ABSTRACT



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ABSTRACT

Environmental change has been a topic of great interest over the last century due to its potential impact on ecosystem services that are fundamental for sustainable development and human well-being. Here, we assess and quantify the spatial and temporal variation in land cover in Ningxia Hui Autonomous Region (NHAR), China. With high-resolution (30 m) imagery from Landsat 4/5-TM and 8-OLI for the entire region, land cover maps of the region were created to explore local land cover changes in a spatially explicit way. The results suggest that land cover changes observed in NHAR from 1991 to 2015 reflect the main goals of a national policy implemented there to recover degraded landscapes. Forest, herbaceous vegetation and cultivated land increased by approximately 410,200 ha, 708,600 ha and 164,300 ha, respectively. The largest relative land cover change over the entire study period was the increase in forestland. Forest growth resulted mainly from the conversion of herbaceous vegetation (53.8%) and cultivated land (30.8%). Accurate information on the local patterns of land cover in NHAR may contribute to the future establishment of better landscape policies for ecosystem management and

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1. Introduction

Changes in land use and land cover (LULC) are fundamental components of environmental change, and are major determinants of sustainable development and human adaptation to global change (Turner et al., 2007; Turner et al., 1993). Land cover (biophysical cover of the Earth's surface) and land use (description of how humans use the land) are of great significance in maintaining the structure and productivity of ecological systems (Lambin et al., 2001). LULC change influences the climate system through effects on the Earth's surface albedo (the fraction of incident electromagnetic radiation reflected by the land surface) and the exchange of greenhouse gases between the soil and the atmosphere (Foley et al., 2005; Pielke et al., 2002). Thus, land cover change has the potential to impact on climate change at local and regional scales (de Noblet-Ducoudré et al., 2012; Kalnay and Cai, 2003) and also at a global scale (Foley et al., 2005). Some extensive LULC changes may also contribute to diminish or accelerate soil erosion, homogenization of the agricultural landscape and subsequent loss or fragmentation of natural habitats (Blaikie and Brookfield, 2015; Bommarco et al., 2013). These effects have the potential to alter biodiversity (Newbold et al., 2015; Sala et al., 2000) to such an extent that the well-being and vulnerability of humans to social and environmental stressors may be positively or negatively affected (Carpenter et al., 2006).

Human population growth and economic expansion are widely recognised as major anthropogenic drivers of LULC change (Vitousek et al., 1997). Approximately one-third to one-half of the Earth's land surface has already been modified considerably by human activities (Vitousek et al., 1997), and the extent of this transformation may increase to compensate for the growing demand for food and natural resources (Bommarco et al., 2013). In response to the concerns about human capability to adapt to a changing environment, interdisciplinary assessments of LULC status and change have become increasingly important subjects of environmental change research (Verbarg et al., 2009).

Since the start of economic reforms in China in 1978, the country has sustained accelerated economic growth and urban expansion. The total population grew from about 980 million people in 1980 to 1.36 billion people in 2013 (National Bureau of Statistics of China, 2014). Resultant social restructuring processes have led to an environmental transformation of unprecedented proportions (Liu and Diamond, 2005). Projects such as the Three-Gorges Dam across the Yangtze River, designed to promote infrastructure and economic development in the country, have been associated with alterations to biodiversity and ecosystem properties in several regions (Xu et al., 2013). To mitigate the adverse impacts of socio-economic and demographic changes, the Chinese government has responded by implementing a series of land reform policies and incentive programs to reduce land degradation and promote sustainable development in rural China (The University of Nottingham, 2010).

The Grain for Green Project (GGP), also called the Sloping Land Conversion Program, implemented since 2002 after a short pilot between 1999 and 2001, is the largest ecosystem service payment project in the country (Liu et al., 2008; Wang et al., 2007). Under the GGP, the government offers farmers annual grain and cash subsidies as well as free seeds or seedlings per area of converted land to reduce soil erosion (Yin and Yin, 2010). The project focuses primarily on the reduction of cropland on steep slopes by promoting three types of land conversions: cropland to forest, cropland to grassland, and sandy land that cannot be used for arable production to forest (The University of Nottingham,

2010; Zhou et al., 2012). The GGP also advocates for prohibition of enclosures for grazing, and sand storm prevention and control (Wang et al., 2007). Some of the immediate ecological benefits of the land restoration program include increased forest coverage, control of soil erosion, and reduced water surface runoff and spread of wind-blown dust (Fan et al., 2015). However, work is still required to explore the additional ecological, climatic and public health consequences that can result from the long-term implementation of the GGP and other similar environmental initiatives (Liu et al., 2008; Pielke, 2005). NHAR is a province located in arid and semi-arid areas across the Loess Plateau and the Yellow River plains which are priority regions for the implementation of the GGP (Liu et al., 2008; The University of Nottingham, 2010). The high local poverty rates, the difficult natural environmental conditions and the over-exploitation of natural resources in NHAR have contributed to the deterioration of the local ecological environment in past decades.

Earth observation (EO) data collected using satellite remote sensing and in situ observations, have been used extensively to characterize and monitor LULC change (Broich et al., 2014; Carreiras et al., 2014; Hamm et al., 2015; Shalaby and Tateishi, 2007; Turner et al., 2007; Yuan et al., 2005). Recently, the wide availability of very fine- (<10 m) and fine- (10 to 100 m) resolution imagery from satellite sensors such as Landsat, QuickBird and IKONOS, have provided new opportunities to represent more accurately LULC at finer spatial resolutions (J. Chen et al., 2015; Hamm et al., 2015; Raj et al., 2013; Sawaya et al., 2003). EO data and geographic information systems (GIS) have been applied in China to guide scientific activities that focus on the assessment and monitoring of the short- and long-term effects of different land use and management practices implemented at various administrative levels (Fan et al., 2015; Liu et al., 2014; Weng, 2002).

This study aims to quantify and describe the spatial and temporal patterns of land cover change in NHAR during a period of extensive landscape restoration. Maps that document accurately the local patterns of land cover change in this province can form the basis for future landscape planning and ecosystem management and protection. This spatially explicit information on land cover change may also help to understand and respond rapidly and effectively to emerging environmental risks such as natural disasters, infectious diseases and food insecurity for the local population.

2. Materials and methods

2.1. Study area

NHAR is a small province located on the upper reaches of the Yellow River in northwest China between latitudes 35°26' N and 39°30' N, and between longitudes 104°50' E and 107°40' E. NHAR shares borders with the Inner Mongolia Autonomous Region in the north, Gansu Province in the south and west and Shaanxi Province in the east. From north to south, the provincial territory stretches 465 km, and from east to west between 45 km and 250 km, with a total area is 66,400 km². NHAR consists of five prefectures that are subsequently subdivided into counties, townships and villages. By the end of 2014, the total population amounted to 6.6 million people of which 53.6% were living in urban areas and 46.4% in rural areas (Li et al., 2008; Statistical Bureau of Ningxia Hui Autonomous Region, 2014).

NHAR lies at ~1000 m above sea level. The territory is geographically diverse and consists of three major natural regions that have distinct agricultural production systems: the northern Yellow River Irrigated District (irrigated agricultural system), the central desertified district (a mix of rainfed and irrigated areas with extensive grazing) and the

southern mountainous and loess hilly district (with a rainfed agricultural system). These regions cover 23.7%, 45% and 31.3% of the NHAR territory, respectively (Li et al., 2008; Li et al., 2013). Elevation increases from north to south with the highest peak at 3556 m. In general, the province has a temperate continental monsoon climate and four distinct seasons. Temperature varies from 24 °C in July to −9 °C in January with an annual average of 9.5 °C. Rainfall varies from 180 to 800 mm year^{−1} increasing from north to south. Most rainfall occurs during the summer and autumn months (80% of the total precipitation in the entire region). The annual average rainfall is 289 mm year^{−1} (Li et al., 2008) (Fig. 1).

2.2. Environmental data

2.2.1. Remotely sensed data

The Landsat Surface Reflectance Climate Data Record (Landsat CDR) was the main source of the data used for land cover classification and change detection analyses. Landsat CDR data sets, also called Landsat level 2A products, are high-level data products that were generated by applying atmospheric correction routines to Landsat Level 1 scenes (Department of the Interior - The United States Geological Survey (USGS), 2016a; Department of the Interior - The United States Geological Survey (USGS), 2016b). The Landsat CDR uses the Universal Transverse Mercator (UTM) projection (48N for NHAR). For the study, time series of Landsat CDR data sets processed from Landsat 4–5 Thematic Mapper (Landsat 4–5 TM) and Landsat 8 Operational Land Imager and Thermal Infrared Sensor (Landsat-8 OLI/TIRS) were downloaded for the period 1990 to 2015 at five-year intervals. This time period was selected due to the increased availability of cloud-free data. Images were acquired from the Earth Explorer website (The United States Geological

Survey (USGS)). For most years, four scenes were required to cover the entire territory. However, due to the presence of clouds in most of the available images from 1990 and 1995, Landsat data from the years 1991 and 1996 were obtained and used for classification (Table 1). Also for the years 1996 and 2000, a fifth scene was required to fill the missing data. The primary scene selection criteria were based on acquisition dates. To the extent possible, images were collected from the period June to November each year which corresponds to the summer and autumn growing seasons in NHAR. However, actual image acquisition dates varied depending on the availability of the data. When there were no scenes available for the selected months, the closest-in-time and most cloud-free scenes available were downloaded for the analyses (Table 1).

2.2.2. Elevation data

Topographic correction was performed to reduce terrain illumination effects on the retrieved data. To apply the topographic correction algorithm, information on solar position according to the acquisition time of the images, and on the slope and aspect of the terrain are required. Therefore, in addition to the Landsat metadata files, the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) version 2 was downloaded from the USGS Earth Explorer website (The National Aeronautics and Space Administration (NASA) and Ministry of Economy Trade and Industry (METI), 2011; The United States Geological Survey (USGS)). It was necessary to project the ASTER DEM to match the Landsat imagery. Using nearest-neighbour resampling, the GDEM data were projected to the Universal Transverse Mercator (UTM) coordinate system zone 48N and resampled to a 30 m spatial resolution using ArcGIS software version 10.3.1 (ESRI, 2015).

2.2.3. Reference data for image classification

Due to the lack of reference information on land cover information for NHAR during the study period, multiple data sources were required to produce reference data sets for land cover classification (training). Training data for the years 2000 and 2010 were obtained from random sampling of a combination of relatively fine-scale global maps, the Globeland30 and the global forest/non-forest maps (FNF) (Japan

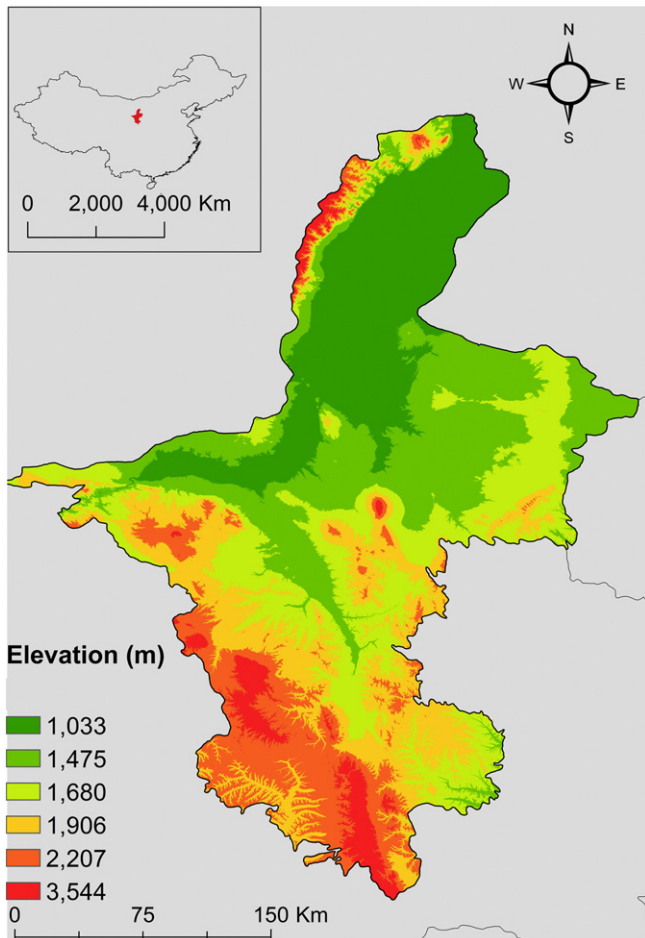


Fig. 1. Map and elevation of NHAR and location of the province within China (inset).

Table 1

Specifications for the Landsat scenes used for land cover classification and change detection analyses in Ningxia Hui Autonomous Region from 1991 to 2015.

| Year | Data type | Landsat scene | Path/row | Date acquired |
|------|--|-----------------------|----------|---------------|
| 1991 | Landsat 4–5 Thematic Mapper | LT51290331989236BJC00 | 129/033 | 24/08/1989 |
| | | LT51290341991242BJC00 | 129/034 | 30/08/1991 |
| | | LT51290351991242BJC00 | 129/035 | 30/08/1991 |
| | | LT51300341993158CLT00 | 130/034 | 07/06/1993 |
| 1996 | Landsat 4–5 Thematic Mapper | LT51290331995253CLT00 | 129/033 | 10/09/1995 |
| | | LT51290341996128CLT00 | 129/034 | 07/05/1996 |
| | | LT51290351996112CLT00 | 129/035 | 21/04/1996 |
| | | LT51300341996215BJC00 | 130/034 | 02/08/1996 |
| | | LT51300341996023CLT00 | 130/034 | 23/01/1996 |
| 2000 | Landsat 4–5 Thematic Mapper | LT51290332000235BJC00 | 129/033 | 22/08/2000 |
| | | LT51290342000235BJC00 | 129/034 | 22/08/2000 |
| | | LT51290352001141BJC00 | 129/035 | 21/05/2001 |
| | | LT51300332000258BJC00 | 130/033 | 14/09/2000 |
| | | LT51300342000242BJC00 | 130/034 | 29/08/2000 |
| 2005 | Landsat 4–5 Thematic Mapper | LT51290332005296BJC00 | 129/033 | 23/10/2005 |
| | | LT51290342005280BJC00 | 129/034 | 07/10/2005 |
| | | LT51290352005280BJC00 | 129/035 | 07/10/2005 |
| | | LT51300342005303BJC00 | 130/034 | 30/10/2005 |
| 2010 | Landsat 4–5 Thematic Mapper | LT51290332010182IKR00 | 129/033 | 01/07/2010 |
| | | LT51290342010198IKR00 | 129/034 | 17/07/2010 |
| | | LT51290352010198IKR00 | 129/035 | 17/07/2010 |
| | | LT51300342010253IKR00 | 130/034 | 10/09/2010 |
| 2015 | Landsat 8 Operational Land Imager and Thermal Infrared Sensor | LC81290332015244LGN00 | 129/033 | 01/09/2015 |
| | | LC81290342015244LGN00 | 129/034 | 01/09/2015 |
| | | LC81290352015196LGN00 | 129/035 | 15/07/2015 |
| | | LC81300342015187LGN00 | 130/034 | 06/07/2015 |

Aerospace Exploration Agency (JAXA); National Geomatics Center of China, 2014). Although GlobeLand30 was only released in 2014 it has been applied extensively at national and regional levels in various countries with high levels of accuracy (Brovelli et al., 2015; Jokar Arsanjani et al., 2016a; Jokar Arsanjani et al., 2016b; Manakos et al., 2014; Shi et al., 2016; Walker et al., 2010) and evaluation is ongoing. The GlobeLand30 is a Landsat-based product generated by the National Geomatics Center of China (NGCC) (J. Chen et al., 2015). This product represents the first attempt to create global land cover maps for the years 2000 and 2010 at 30 m resolution (J. Chen et al., 2015). The Japan Aerospace Exploration Agency (JAXA) produced the FNF data sets by classifying 25 m resolution satellite images into forest and non-forest areas. FNF data sets are available for the years 2007, 2008, 2009 and 2010 (Japan Aerospace Exploration Agency (JAXA) and Earth Observation Research Center (EORC)).

The ArcGIS software (ESRI, 2015) was used to generate random samples of training points from the GlobeLand30 and FNF data sets for the years 2000 and 2010. A total of approximately 500 training sites were selected for each year. In this way, it was possible to ensure that all land cover categories were adequately represented in the training statistics. Training data for these two years were not limited to the global land cover and FNF products. All the selected training points were cross-checked against historical imagery from Google Earth Pro (GEP) version 7.1.5.1557 (Google Inc., 2015). Google Earth archives display different forms of imagery obtained from multiple sources such as Landsat and QuickBird satellite sensors and various providers of digital photographs (Lemmens, 2011). GEP software is a widely-used platform for the collection of high resolution geo-referenced information on land cover, and also for the validation of land cover classification maps (Cha and Park, 2007; H. Chen et al., 2015; Q. Hu et al., 2013; Lu et al., 2015). GEP images from 2001, which is the earliest time point from which data are available for NHAR, and 2010 were used to evaluate the reference data. Training points that were located in indistinct areas in the GEP imagery or in areas that were covered by clouds were removed from the reference data sets.

The training data for 2000 and 2010 were also checked against GEP historical images from 2005 and 2015, respectively. Both, data sets and images were used to determine visually if land cover had changed between the periods 2000–2005 and 2010–2015. Training points from land areas that changed were discarded to locate and define training signatures for 2005 and 2015.

There were no historical records available for NHAR for the years 1991 and 1996 in GEP. Therefore, training data points for these years were derived from the reference data collected for 2000. Training sites from areas that were likely to remain unchanged based on previous visual interpretation of the GEP historical imagery were selected. In addition, the 1 km spatial resolution land use maps of China produced and provided by the Chinese Academy of Sciences for the 1980s, 1995 and 2000 served as supplementary information to define land cover features in the region.

For all images, visual interpretation of the Landsat data was also implemented to improve image classification. Visual comparisons of multiple sets of three spectral band combinations were conducted using ENVI software version 5.3 (Exelis Visual Information Solutions, 2015). This approach was used to better distinguish the different categories of the land cover scheme.

2.2.4. Reference data for validation

Reference validation data sets for accuracy assessment were created by collecting space- and time-referenced data uploaded to the website Panoramio (Google Inc.). The website is a photo-sharing service that contains geo-tagged photos from around the world. Web-based photo-sharing platforms, like Panoramio, are becoming an important data source with potential applications in multiple research contexts (Dong et al., 2014; Yu et al., 2014; Zhou et al., 2012).

Sets of photos for each year were downloaded and labelled manually based on visual interpretation and using the GlobeLand30 land cover classification scheme. Data were imported into ArcGIS to be projected to the same UTM zone used for the satellite images (ESRI, 2015). Reference points were buffered by 15 m to generate the training site polygons that were used to assess classification accuracy. Although most polygons were effective in distinguishing among different land cover types, the use of this type of data may introduce a level of uncertainty into the analyses (Fonte et al., 2015). Therefore, all polygons of each validation class were checked against historical satellite imagery from GEP. Reference data located in areas where land cover type was questionable were excluded from the analyses.

Although different data sources were used to create data sets for training and validation, from the total number of reference points selected, 425 (89.4%), 451 (90.0%), 486 (90.6%), 478 (90.5%), 500 (90.9%), 456 (90.1%) reference sites were used for training for the years 1996, 2001, 2005, 2010 and 2015, respectively. The reference data sets used for accuracy assessments included 50 polygons with approximately 2–3 pixels each.

2.3. Data analysis

2.3.1. Image classification

Pre-processing of the Landsat data was performed using the Landsat package (version 1.08) (Goslee, 2011) in the R language and environment for statistical computing (R Core Team, 2016). The Minnaert topographic correction method was applied independently to each spectral band to improve image comparability between dates. The spectral bands were stacked together and saved as a multiband image in TIFF format. To reduce the effects of clouds, cloud and cloud shadow removal were performed. The Landsat scenes for each date were mosaicked together and classified using ENVI version 5.3 (Exelis Visual Information Solutions, 2015). The maximum likelihood algorithm was the selected method for the process of supervised classification (Supplementary material Table A.1). Assuming a normal distribution of the data, this algorithm considers both the variance and covariance of class signatures to assign unknown pixels to a specific land cover class (Lillesand et al., 2014; Strahler, 1980).

The land cover classes were grouped into seven categories according to the spectral reflectance values and the objectives of the study. Because the reference data for classification was derived primarily from GlobeLand30, the classification scheme adopted was based on the land cover classification system established by the NGCC (Table 2).

Post-classification refinements were applied to reduce errors in the process of classification. Due to significant spectral confusion among the classes, artificial surfaces and bare or sparsely vegetated areas, these two classes were merged and represented as a single category in the maps and subsequent analyses.

Using the ENVI software, confusion matrices were calculated to assess the accuracy of the land cover classification maps. A confusion matrix is a simple cross-tabulation of each mapped class vs. the reference information (Foody, 2002; Lillesand et al., 2014). The overall accuracy of the classification, Kappa coefficient and user's and producer's accuracy were derived from the confusion matrices. The Kappa statistic reflects the difference between actual agreement between reference data and the classified maps and the agreement expected by chance. A Kappa value of 1 indicates perfect agreement, while a value of 0 indicates no agreement (Foody, 2002). User's accuracy provides an estimate of the probability that a pixel from the land cover map matches the same category in the reference data (it measures errors of commission), whereas the producer's accuracy estimates the probability that a reference pixel has been mapped correctly (it measures errors of omission) (Foody, 2002; Lillesand et al., 2014).

Table 2
Land cover classification scheme and definitions.

| Land cover type | Description | Content |
|----------------------------------|--|--|
| Water bodies | All areas of water | Streams and canals, lakes, reservoirs, bays and estuaries |
| Artificial surfaces | Land modified by human activities | Residential areas, industrial and commercial complexes, transport infrastructure, communications and utilities, mixed urban or built-up land and other built-up land |
| Bare or sparsely vegetated areas | Areas with little or no “green” vegetation present | Dry salt flats, sandy areas, bared exposed rock and mixed barren land |
| Herbaceous vegetation | Areas characterized by natural or semi-natural vegetation | Grasses and forbs |
| Cultivated land | Areas where the natural vegetation has been removed/modified and replaced by other types of vegetative cover that have been planted for specific purposes such as food, feed and gardening | Cropland and pasture, orchards, groves, vineyards, nurseries and ornamental horticultural, other cultivated land |
| Shrubland | Natural or semi-natural woody vegetation with aerial stems <6 m tall | Evergreen and deciduous species of true shrubs and trees or shrubs that are small or stunted |
| Forest | Areas characterized by tree cover or semi-natural woody vegetation >6 m tall | Deciduous forest, evergreen forest and mixed forest |

2.3.2. Land cover change detection analysis

A post-classification change detection technique was performed using ENVI software (Exelis Visual Information Solutions, 2015). Cross-tabulation analyses were conducted to identify changes in land cover between 6 different time intervals 1991–1996, 1996–2000, 2000–2005, 2005–2010, 2010–2015 and 1991–2015. These tables indicate the number of pixels of a given class at time t_1 that are classified as the same or different class at time t_2 (from-to). This supports identification of changes in land cover as well as the identification of areas that have not changed.

3. Results

3.1. Land cover classification and change detection analysis

Confusion matrices showed that the overall classification accuracies were higher or equal to 80% and the total Kappa coefficients were >0.7. These results represent a substantial agreement between the reference data sets and the classified maps (Landis and Koch, 1977). The Kappa coefficients for 1991, 1996, 2000, 2005, 2010 and 2015 were 0.83, 0.83, 0.78, 0.72, 0.74 and 0.80, respectively. Most user's and producer's accuracies of individual classes were also generally high, ranging from 60% to 100% (Table 3).

Table 3
Summary of Landsat classification accuracies (%) for 1991, 1996, 2000, 2005, 2010 and 2015.

| Land cover class | 1991 | | 1996 | | 2000 | | 2005 | | 2010 | | 2015 | |
|----------------------------------|------------|--------|------------|--------|------------|--------|------------|--------|------------|--------|------------|--------|
| | Producer's | User's | Producer's | User's | Producer's | User's | Producer's | User's | Producer's | User's | Producer's | User's |
| Bareland and artificial surfaces | 100.0 | 85.7 | 100.0 | 60.1 | 66.6 | 100.0 | 84.4 | 84.4 | 89.2 | 60.1 | 100.0 | 82.6 |
| Cultivated land | 100.0 | 66.7 | 100.0 | 100.0 | 100.0 | 60.0 | 71.4 | 74.1 | 74.1 | 78.4 | 77.2 | 89.4 |
| Herbaceous vegetation | 66.6 | 100.0 | 60.0 | 100.0 | 100.0 | 60.1 | 66.7 | 69.7 | 75.0 | 85.7 | 80.0 | 92.3 |
| Shrubland | 100.0 | 80.0 | 100.0 | 100.0 | 100.0 | 100.0 | – | – | – | – | – | – |
| Forest | – | – | – | – | – | – | 66.6 | 60.2 | 80.0 | 88.8 | 100.0 | 61.5 |
| Water | 81.3 | 100.0 | 81.2 | 100.0 | 83.3 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 66.7 | 100 |
| Overall accuracy | 87.7 | | 84.8 | | 85.3 | | 80.0 | | 80.0 | | 84.2 | |
| Kappa statistic | 0.8 | | 0.7 | | 0.7 | | 0.7 | | 0.7 | | 0.8 | |

Single date land cover maps were produced for each study year to show the spatial distribution of six land cover types in NHAR (Fig. 2). The geographic area covered by each individual class for all data products and the change statistics for 1991 and 2015, which were the temporal extremes of the project were calculated (Table 4 and Fig. 3).

From 1991 to 2015, herbaceous vegetation, cultivated land and forest increased by approximately 708,600 ha (12.2% of the study area), 164,300 ha (2.9%) and 410,200 ha (7.1%), respectively. Shrubland decreased by 22,000 ha (0.4%) and water decreased by 10,300 ha (0.2%). The largest relative change for the period 1991–2015 was observed in the area covered by forest, which increased by 273.1%. Forest expanded consistently in all periods, with the greatest increase occurring between 2010 and 2015. The change in forest was followed by the increase in herbaceous vegetation, 49.8%, and in cultivated land, 12.3%. Shrubland and water decreased, respectively, 66.7% and 22.2%. Although the extent of water and shrubland may have changed from year to year due to annual variability in precipitation and temperature, the minor changes observed in this category are likely to be partially explained by classification errors. Because artificial surfaces and bareland were merged into one a single class, it is difficult to interpret the changes observed in this land cover category over time.

To further evaluate the results of the different types of land cover conversions, cross-tabulation of the pair of maps 1991 and 1996, 1996 and 2000, 2005 and 2010, 2010 and 2015 were created (Table 5). In Table 5, the categories of the first map (vertical) are compared with those of the second map (horizontal) and tabulation is kept of the number of cells in each combination.

The results suggest that the area covered by herbaceous vegetation increased in all periods except in the interval 1996–2000 when it decreased by 88,900 ha. Although cultivated land increased over the whole study period, it experienced a decrease in the first five years of the study and between 2000 and 2010.

In 1991, forest, herbaceous vegetation and cultivated land covered an area of approximately 147,600 ha, 1,409,200 ha and 1,356,100 ha, respectively. In 2000, prior to the implementation of the GGP, the extent of land covered by these land cover types was 1,455,755 ha and 1,628,894 ha, respectively. By 2015, forest and herbaceous vegetation extended to 557,807 ha and 2,117,812 ha, while cultivated land was reduced to 1,520,435 ha.

The increase in forest resulted mainly from conversion of cultivated land and herbaceous vegetation in the twenty-five-year period. Of the 410,200 ha of total growth in forest between 1991 and 2015, 53.8% was converted from herbaceous vegetation and 30.8% from cultivated land. Although it is not possible to estimate the amount of land conversion, the increase in herbaceous vegetation came mainly from bareland and artificial surfaces.

The matrix created to show the land cover changes in NHAR during the whole study period (1990 to 2015) indicates that the decrease in water bodies (9300 ha) resulted mainly from conversion of cultivated land (Table 5f). This finding was also observed in the matrices developed for the 5-year periods. In NHAR, wetlands are mainly distributed in the irrigated plains of cultivated land. Therefore, the magnitude and location of the changes in the Yellow River Irrigated District suggest

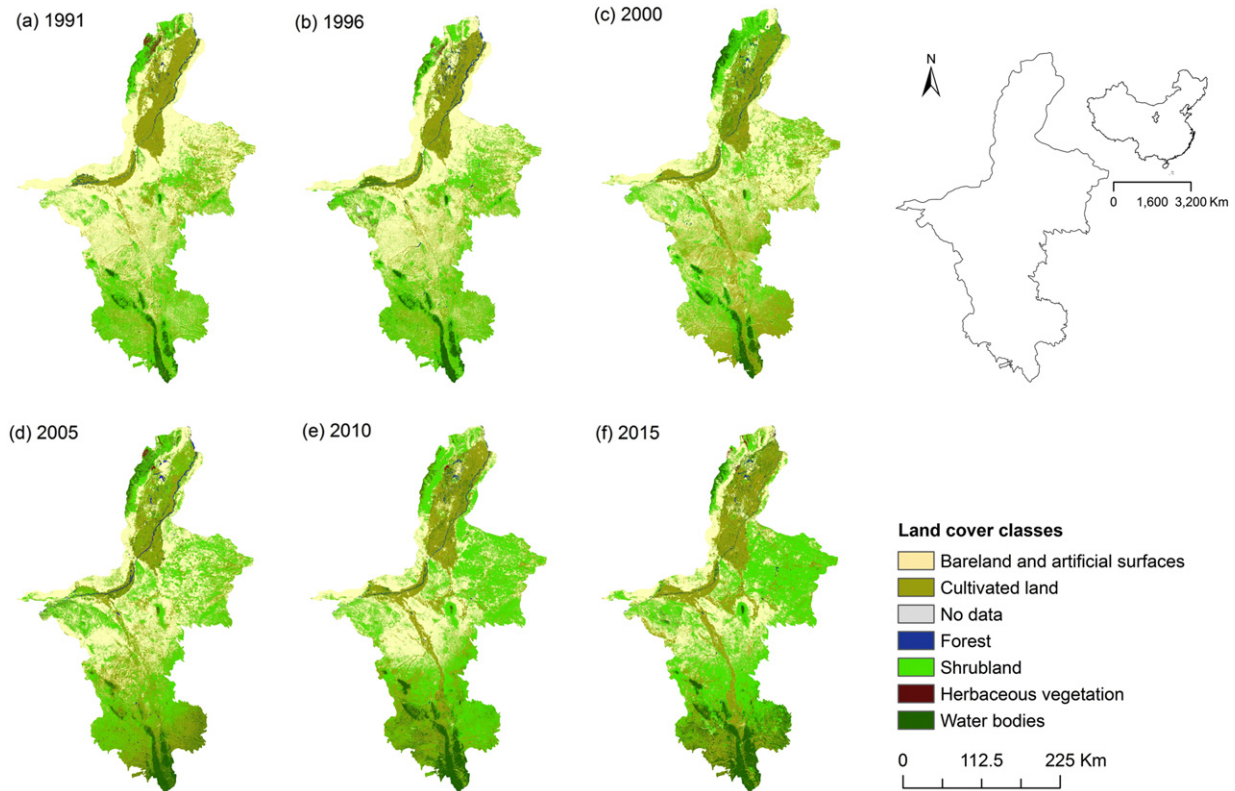


Fig. 2. Land cover classification maps for NHAR from (a) 1991, (b) 1996, (c) 2000, (d) 2005, (e) 2010, (f) 2015 and map of the location of the province in China.

that the results are most likely to be related to omission and commission errors in the Landsat classifications change map.

The changes in land cover that occurred in NHAR between 1991 and 2015 were not spatially homogeneous. The six land cover maps produced in the study reveal that land cover changes varied among the three different geographical regions. In general, the central desertified district and the southern mountainous and loess hilly district were the most transformed. Forest growth primarily occurred in the north and south of the province, in areas of the Helan and Liupan mountains in the north and south, respectively. The increase in herbaceous vegetation was mainly distributed in the central arid area of the province, and around the margin of forestland. Cultivated land dominated the landscape on the big plains of the northern Yellow River Irrigated District with a progressive linear expansion in the central area.

4. Discussion

The results of the present study are consistent with previous environmental assessments conducted in western China to describe the land cover changes that have occurred in regions where ecological restoration policies were adopted (Cao et al., 2009; Fan et al., 2015; Zhao et al., 2010). According to national estimates, by 2006, the GGP policy was responsible for the conversion of almost 9 million ha of cultivated

land into forest and herbaceous vegetation, and the afforestation of 11.7 million ha of barren land (Liu et al., 2008). In the Loess Plateau, a region commonly characterized by drought, desertification and soil erosion, a rapid increase in vegetation cover was reported in the early 2000s after the implementation of the pilot phase of the program (Fan et al., 2015; Xin et al., 2008). The land cover changes observed in NHAR are in agreement with the key environmental goals of the GGP and previous short-term (ten years or less) land cover assessments conducted in the province using remote sensing or official national reports (Li et al., 2008; Qi et al., 2003; Wang et al., 2014; Zhang et al., 2008). In this study, forest, herbaceous vegetation and cultivated land coverages increased between 1991 and 2015. Similar findings were reported in other provinces such as Shaanxi located at the middle reaches of the Yellow River Basin (H. Chen et al., 2015), and Sichuan Province, located at the upper reaches of the Yangtze River (Yan-qiong et al., 2003). Reduction of surface runoff and soil erosion as a result of the implantation of the GGP in Hunan Province (2000–2005) was also reported (Li et al., 2006). However, these land cover changes were reported by researchers as positive or negative effects on the local environment based on the environmental needs of these regions.

As a consequence of rapid human population growth in NHAR, extensive areas of natural grassland were converted to cultivated land (Zhang et al., 2008). The overexploitation of land, together with

Table 4
Summary statistics of land cover maps from Ningxia Hui Autonomous Region by area (1000 ha).

| Land cover class | 1991 Area (%) | 1996 Area (%) | 2000 Area (%) | 2005 Area (%) | 2010 Area (%) | 2015 Area (%) | Relative change 1991–2015 (%) |
|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|----------------------------------|
| Water bodies | 53.1 (0.9) | 84.6 (1.5) | 59.3 (1.0) | 47.9 (0.8) | 43.6 (0.8) | 42.8 (0.7) | –22.2 |
| Herbaceous vegetation | 1409.2 (24.5) | 1543.2 (26.8) | 1455.7 (25.2) | 1687.7 (29.3) | 2022.3 (35.1) | 2117.8 (36.7) | +49.8 |
| Cultivated land | 1356.1 (23.5) | 1257.7 (21.9) | 1628.8 (28.3) | 1543.3 (26.8) | 1504.4 (26.1) | 1520.4 (26.4) | +12.3 |
| Shrubland | 35.4 (0.6) | 27.0 (0.5) | 0.3 (0.004) | 33.9 (0.6) | 7.8 (0.1) | 13.4 (0.2) | –66.7 |
| Forest | 147.6 (2.6) | 227.8 (4) | 290.4 (5.1) | 380.4 (6.6) | 455.1 (7.9) | 557.8 (9.7) | +273.1 |
| Bareland and artificial surfaces | 2757.9 (47.8) | 2611.7 (45.4) | 2321.9 (40.3) | 2066.1 (35.9) | 1726.1 (30) | 1507.1 (26.2) | –45.2 |

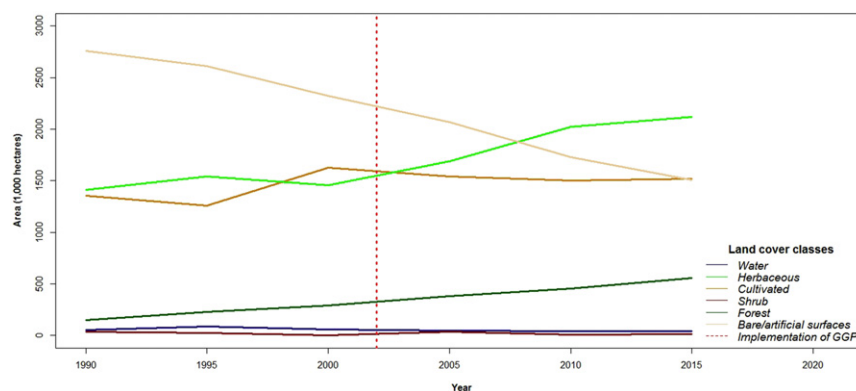


Fig. 3. Summary statistics of land cover maps from Ningxia Hui Autonomous Region by area (1000 ha).

intensive grazing of domestic animals contributed to the degradation of the local environment (Zhang et al., 2008). As part of the efforts to recover the landscape, including the implementation of the GGP, growth of artificial grass was promoted in the province while fencing natural grassland and applying grazing bans (Wang et al., 2014). Therefore, it may be possible that some of the policies implemented to improve ecological conditions may have led to the expansion of herbaceous vegetation and the more discrete increase in cultivated land.

The spatial variation in the distribution of the six land cover types and changes in NHAR between 1991 and 2015 can be explained partially by the contrasting climatic and topographic characteristics of the three geographical regions of the province. However, there are also other local environmental and socio-economic factors that may influence the local land use practices and lead to land cover change. NHAR is vulnerable to numerous meteorological hazards that have the potential to damage the land surface (Li et al., 2013). Drought, floods, torrential rain and high and low temperature stresses are particularly frequent in the region (Li et al., 2013). Between 2004 and 2006, a severe drought affected the region causing an important reduction in the availability of water for industrial and agricultural purposes (Li et al., 2013; Yang et al., 2015). This meteorological event had important environmental and economic consequences for the province, some of which were evident in this study. Decreases of 126,200 ha of cultivated land and 15,800 ha of water were observed between 2000 and 2010, particularly in the northern and the central part of the province, where irrigation water is mainly diverted from the Yellow River. These findings are in agreement with those mentioned previously in a report that promotes better adaptation strategies to minimise the effects of future environmental hazards (Yang et al., 2015).

NHAR is currently undergoing economic transition processes that also affect the use of land directly and indirectly (Wang et al., 2011). Land conversion is linked directly to socioeconomic development due to the effects of economic growth on urban expansion and exploitation of natural resources (Wang et al., 2011). Economic growth also influences positively the spatial structure of land use patterns by improving income opportunities from non-agricultural sectors, causing income diversification and promoting rural-urban migration (Peng, 2011). Population growth in NHAR has also been a dominant factor driving urban development processes, particularly in the north (Wu, 2002). Consequently, some cultivated land has been transformed rapidly into rural and urban built-up areas such as cities, roads, factories and mining infrastructure in past decades (Wu, 2002). Therefore, it is reasonable to conclude that most of the decrease in land area covered by the merged land cover class “bare or sparsely vegetated areas” and “artificial surfaces” corresponded to a reduction in bare and sparsely vegetated areas. In the present study important changes in land cover were identified in NHAR between 1991 and 2015. These findings raise the need for further studies to determine the association of the GGP and other potential drivers of land cover change with the observed increases in forest

cover, herbaceous vegetation and cultivated land. While current evidence recognises the role of national ecological rehabilitation projects in China, there is still a need for more holistic and rational approaches that examine the contributions of other economic and social factors in the process of landscape restoration in the country.

Ecological restoration policies, if implemented appropriately, can be effective measures to address pressing environmental concerns (Liu et al., 2008; Melillo et al., 2016; Nepstad et al., 2014). However, the mixture of natural and artificially modified landscapes has also important implications for the structure and function of ecosystems and human health. Environmental change has the potential to compromise food security by influencing food availability, accessibility, utilization and systems stability (Ingram et al., 2012). In addition, alterations to the climate and landscape features have been increasingly associated with variations in human disease patterns. This is particularly important for infectious diseases, where environmental change impacts on the geographic range of various mosquito-borne diseases such as malaria, dengue and leishmaniasis (Caminade et al., 2014; Colón-González et al., 2013; González et al., 2014) and non-mosquito-borne helminth infections, such as schistosomiasis and echinococcosis (Giraudoux et al., 2013; Gomes et al., 2012; Y. Hu et al., 2013). Quality evaluated land cover maps derived from remote sensing are important for such studies (Danson et al., 2004; Hamm et al., 2015; Navas et al., 2016; Pleydell et al., 2008). In hyper-endemic areas for echinococcosis in western China the geographical patterns of alveolar echinococcosis infection have been associated with the recent implementation of land reform policies in the region (Giraudoux et al., 2013; Pleydell et al., 2008). Land cover transformations that result from land reforms are likely to alter the transmission of *Echinococcus* spp. by influencing human behaviour, animal population dynamics, spatial and temporal overlap of intermediate and definitive hosts and the survival of the parasite eggs in the external environment (Cadavid Restrepo et al., 2015). Further studies may need to be conducted to test the association between land cover change and infection patterns of human echinococcosis.

Although some effects of global environmental change can be anticipated, most of the impacts depend on local vulnerabilities and the implementation of effective strategies for adaptation (McCarthy, 2001). Accurate predictions of LULC can only be estimated when there is an adequate availability of local socio-economic and baseline data (Lambin and Geist, 2008). This study allowed us to identify spatial and temporal patterns in land cover change trends in NHAR in the last 30 years. The findings provide accurate information, in space and time, and visual representations of the areas that are most affected by land cover change. Therefore, these results are a reasonable starting point from which to conduct future research in NHAR to explore, monitor and predict future environmental change and its short- and long-term effects on the well-being of the population.

The main challenges of the study include the limited availability of historical satellite and reference data to train the classifier and validate

Table 5

Matrices of land cover changes (1000 ha) from 1991 to 2015.

| a. Period 1991–1996 | | | | | | | |
|----------------------------------|--------------|-----------------------|-----------------|-----------|--------|------------------------------|------------|
| 1996 | 1991 | | | | | | 1996 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 40.0 | 3.1 | 33.8 | 0.3 | 0.1 | 7.0 | 84.3 |
| Herbaceous vegetation | 0.8 | 1104.5 | 211.6 | 17.5 | 10.8 | 198.0 | 1542.0 |
| Cultivated land | 6.7 | 92.5 | 1024.5 | 0.6 | 5.1 | 128.2 | 1257.6 |
| Shrubland | 0.2 | 10.5 | 0.4 | 10.1 | 0.0 | 5.7 | 27.0 |
| Forest | 3.8 | 54.1 | 35.8 | 1.7 | 131.0 | 0.6 | 227.0 |
| Bareland and artificial surfaces | 0.8 | 142.7 | 49.9 | 5.1 | 0.1 | 2411.9 | 2610.5 |
| Difference | 32.0 | 134.6 | −98.4 | −8.4 | 80.0 | −140.9 | |
| 1991 total | 52.3 | 1407.4 | 1356.0 | 35.4 | 147.0 | 2751.4 | 5748.0 |
| b. Period 1996–2000 | | | | | | | |
| 2000 | 1996 | | | | | | 2000 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 33.6 | 2.4 | 15.2 | 0.4 | 1.7 | 5.8 | 59.3 |
| Herbaceous vegetation | 18.6 | 634.7 | 226.9 | 15.5 | 44.4 | 513.1 | 1453.1 |
| Cultivated land | 21.1 | 387.3 | 685.5 | 0.2 | 43.6 | 490.8 | 1628.4 |
| Shrubland | 0.0 | 0.1 | 0.0 | 0.1 | 0.0 | 0.1 | 0.3 |
| Forest | 3.7 | 59.8 | 77.1 | 5.3 | 133.6 | 10.9 | 290.3 |
| Bareland and artificial surfaces | 7.5 | 457.8 | 252.8 | 5.5 | 3.7 | 1589.7 | 2317.1 |
| Difference | −25.2 | −88.9 | 370.8 | −26.7 | 63.3 | −293.3 | |
| 1996 total | 84.5 | 1542.0 | 1257.6 | 27.0 | 227.0 | 2610.4 | 5748.0 |
| c. Period 2000–2005 | | | | | | | |
| 2005 | 2000 | | | | | | 2005 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 27.5 | 8.1 | 5.7 | 0.0 | 2.2 | 4.0 | 47.5 |
| Herbaceous vegetation | 10.3 | 687.5 | 373.8 | 0.1 | 47.7 | 566.0 | 1685.4 |
| Cultivated land | 7.8 | 326.1 | 786.9 | 0.005 | 83.3 | 338.0 | 1542.1 |
| Shrubland | 1.0 | 17.9 | 1.7 | 0.1 | 9.9 | 3.2 | 33.8 |
| Forest | 5.8 | 82.8 | 133.3 | 0.0 | 139.6 | 17.5 | 379.0 |
| Bareland and artificial surfaces | 6.9 | 330.0 | 327.0 | 0.0 | 7.5 | 1389.0 | 2060.4 |
| Difference | −11.8 | 233.0 | −88.3 | 33.6 | 88.8 | −257.3 | |
| 2000 total | 59.3 | 1452.4 | 1628.4 | 0.2 | 290.2 | 2317.7 | 5748.0 |
| d. Period 2005–2010 | | | | | | | |
| 2010 | 2005 | | | | | | 2010 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 25.5 | 5.3 | 5.4 | 0.1 | 1.7 | 5.5 | 43.5 |
| Herbaceous vegetation | 2.1 | 922.0 | 460.8 | 21.8 | 72.9 | 542.7 | 2022.3 |
| Cultivated land | 9.9 | 386.1 | 753.8 | 2.1 | 95.5 | 257.2 | 1504.6 |
| Shrubland | 0.2 | 1.4 | 0.2 | 3.4 | 0.7 | 1.8 | 7.7 |
| Forest | 3.8 | 82.2 | 168.3 | 1.0 | 193.0 | 6.8 | 455.1 |
| Bareland and artificial surfaces | 6.0 | 289.0 | 154.0 | 5.5 | 15.0 | 1245.0 | 1714.5 |
| Difference | −4.0 | 1100.3 | −37.9 | −26.2 | 76.1 | −345.5 | |
| 2005 total | 47.5 | 1686.0 | 1542.5 | 33.9 | 379.0 | 2060.0 | 5748.0 |
| e. Period 2010–2015 | | | | | | | |
| 2015 | 2010 Total | | | | | | 2015 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 26.8 | 1.4 | 5.6 | 0.3 | 3.1 | 5.5 | 42.8 |
| Herbaceous vegetation | 1.0 | 1294.2 | 276.6 | 0.4 | 45.7 | 500.0 | 2117.2 |
| Cultivated land | 10.8 | 235.5 | 963.9 | 0.2 | 129.5 | 180.0 | 1519.0 |
| Shrubland | 0.0 | 6.7 | 0.3 | 2.8 | 0.3 | 3.3 | 13.4 |
| Forest | 0.8 | 123.9 | 152.4 | 1.2 | 271.0 | 8.4 | 557.7 |
| Bareland and artificial surfaces | 3.9 | 360.5 | 105.5 | 2.9 | 5.6 | 1017.5 | 1496.0 |
| Difference | −0.6 | 95.2 | 15.0 | 5.6 | 102.5 | −218.7 | |
| 2010 total | 43.4 | 2022.0 | 1504.3 | 7.8 | 455.2 | 1714.7 | 5748.0 |
| f. Period 1991–2015 | | | | | | | |
| 2015 | 1991 | | | | | | 2015 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Water bodies | 15.9 | 2.9 | 14.7 | 0.1 | 0.3 | 8.9 | 42.8 |
| Herbaceous vegetation | 2.4 | 689.4 | 307.0 | 12.5 | 9.9 | 1096.0 | 2117.2 |

Table 5 (continued)

| f. Period 1991–2015 | | | | | | | |
|----------------------------------|--------------|-----------------------|-----------------|-----------|--------|------------------------------|------------|
| 2015 | 1991 | | | | | | 2015 total |
| | Water bodies | Herbaceous vegetation | Cultivated land | Shrubland | Forest | Bareland/artificial surfaces | |
| Cultivated land | 27.5 | 279.9 | 724.6 | 1.7 | 16.1 | 470.0 | 1519.8 |
| Shrubland | 0.1 | 5.2 | 0.6 | 2.4 | 0.01 | 5.1 | 13.4 |
| Forest | 2.8 | 230.5 | 142.5 | 1.9 | 120.7 | 59.3 | 557.7 |
| Bareland and artificial surfaces | 3.4 | 199.0 | 166.7 | 16.7 | 0.6 | 1110.4 | 1496.8 |
| Difference | −9.3 | 710.2 | 163.7 | −22.0 | 410.1 | −1253.2 | |
| 1991 total | 52.1 | 1407.0 | 1356.1 | 35.4 | 147.6 | 2750.0 | 5748.0 |

the land cover maps. When analysing time-series data sets, quality and consistency in the data are essential to identify the real changes that occur in the environment (Hamm et al., 2015; Stehman, 2009). In this study, part of the disagreement between the Landsat scenes and the reference training data sets may be attributed to the fact that there were no images for the specified period in some locations. For some years it was necessary to derive data from different growing seasons. In addition, the use of Globeland30 and the FNF maps may have introduced some uncertainty into the analysis because they are also land cover products that may contain classification errors that by default were included in the analyses. Although the reference training data obtained from these maps allowed us to classify the satellite images with good accuracy, a more traditional approach that incorporates different data sources and a combination of field studies would be preferred (Stehman, 2009). The land cover classification scheme used in the study was derived from the land cover classification system established by the NGCC. Although the use of this legend allowed comparability between land cover datasets, the interpretation of the land cover changes found in the study with respect to the GGP goals also represented a challenge (Fritz and See, 2008; Tchuente et al., 2011). Based on similarities of definitions, the changes found in herbaceous vegetation and cultivated land were compared to the project goals with respect to grasslands and croplands, respectively.

5. Conclusions

The present study explores and quantifies the changes in land cover that occurred in NHAR during a period of extensive landscape regeneration. The results of the analysis of land cover change conducted in this study concur with the large-scale impact of the GGP in increasing forest and herbaceous vegetation coverage and in regenerating bareland area. These results provide evidence that may help facilitate future landscape planning, management and decision making in the province. In addition, this assessment of land cover change may help to explain and respond effectively to emerging environmental risks in NHAR.

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CHAPTER 4

Human echinococcoses in Ningxia Hui Autonomous Region, China

CHAPTER 4 HUMAN ECHINOCOCCOSES IN NINGXIA HUI AUTONOMOUS REGION, CHINA

4.1 Context

Evidence of *E. granulosus* and *E. multilocularis* emergence and re-emergence in several regions of the world creates an increasing need to monitor and map the risk that CE and AE pose for human populations. Land cover change and climatic variations have been identified as potential environmental processes determining the emergence or re-emergence of these parasites in areas that were not previously endemic.

The process of landscape transformation in NHAR over the past decades may have led to an increasing human disease burden. Therefore, there was a need to identify highly endemic areas for human echinococcoses in NHAR and establish evidence on the association of local human echinococcosis risk with environmental change to facilitate the surveillance and targeting of essential control strategies.

Spatial epidemiological studies conducted in echinococcosis-endemic regions in Western China, including NHAR, have provided valuable insight into the landscape processes underlying echinococcosis transmission at local spatial scales. However, most of those previous approaches involved environmental data collected at a single time-point that did not allow capture of major environmental changes over time. In this Chapter, I present the result of a retrospective study of clinical records conducted in NHAR to assess the relationship between the changes in local environmental features (described in Chapter 3) and the spatiotemporal variation in CE and AE risk at the township level between January 1994 and December 2013.

4.2 Spatiotemporal patterns and environmental drivers of human echinococcoses over a twenty-year period in Ningxia Hui Autonomous Region, China

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Supplementary material for this paper is provided in Appendix C.

Spatiotemporal patterns and environmental drivers of human echinococcoses over a twenty-year period in Ningxia Hui Autonomous Region, China

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Abstract

Background: Human cystic (CE) and alveolar (AE) echinococcoses are zoonotic parasitic diseases that can be influenced by environmental variability and change through effects on the parasites, animal intermediate and definitive hosts, and human populations. We aimed to assess and quantify the spatiotemporal patterns of human echinococcoses in Ningxia Hui Autonomous Region (NHAR), China between January 1994 and December 2013, and examine associations between these infections and indicators of environmental variability and change, including large-scale landscape regeneration undertaken by the Chinese authorities.

Methods: Data on the number of human echinococcosis cases were obtained from a hospital-based retrospective survey conducted in NHAR for the period 1 January 1994 through 31 December 2013. High-resolution imagery from Landsat 4/5-TM and 8-OLI was used to create single date land cover maps. Meteorological data were also collected for the period January 1980 to December 2013 to derive time series of bioclimatic variables. A Bayesian spatio-temporal conditional autoregressive model was used to quantify the relationship between annual cases of CE and AE and environmental variables

Results: Annual CE incidence demonstrated a negative temporal trend and was positively associated with winter mean temperature at a 10-year lag. There was also a significant, nonlinear effect of annual mean temperature at 13-year lag. The findings also revealed a negative association between AE incidence with temporal moving averages of bareland/artificial surface coverage and annual mean temperature calculated for the period 11–15 years before diagnosis and winter mean temperature for the period 0–4 years. Unlike CE risk, the selected environmental covariates accounted for some of the spatial variation in the risk of AE.

Conclusions: The present study contributes towards efforts to understand the role of environmental factors in determining the spatial heterogeneity of human echinococcoses. The identification of areas with high incidence of CE and AE may assist in the development and refinement of interventions for these diseases, and enhanced environmental change risk assessment.

Keywords: Echinococcosis, Cystic echinococcosis, Alveolar echinococcosis, Spatial analysis, Environmental change, Remote sensing

Background

Cystic (CE) and alveolar (AE) echinococcoses, caused by *Echinococcus granulosus* and *E. multilocularis*, respectively, are the two forms of human echinococcosis of major public health importance worldwide [1]. Both diseases are distributed widely and potentially life threatening if left untreated [2–4]. Within China, *E. granulosus* and *E. multilocularis* are responsible for approximately 0.6–1.3 million human cases, with transmission occurring predominantly in central and western areas. Based on reports from the Chinese Ministry of Health, more than 98% of patients with human echinococcoses originate from Gansu, Qinghai and Sichuan Provinces and from Xinjiang Uygur, Ningxia Hui and Inner Mongolia Autonomous Regions [5]. Although these regions constitute highly endemic areas for these diseases in East Asia, significant differences in parasite prevalences have been demonstrated at regional and local levels [6–8]. On the Qinghai-Tibet Plateau, where there is high transmission of *Echinococcus* spp., the prevalence of both CE and AE ranges between 0.4–9.5%, being higher in communities where pastoralism and poor socio-economic conditions are predominant [9, 10]. The patchy AE endemicity distribution has been associated with landscape characteristics and climatic factors that determine habitat suitability for the definitive and intermediate hosts [11–17]. Hence, understanding how environmental and social factors interact to determine parasite transmission is essential for the design and implementation of effective strategies against echinococcosis, and to target resources to the communities most in need.

Echinococcus spp. are maintained primarily through complex domestic and sylvatic life-cycles that involve a wide range of intermediate and definitive hosts and a free-living egg stage. Humans are accidental hosts, that acquire the infection through direct contact with definitive hosts or through a contaminated environment [2]. In the sylvatic and semi-domestic (*E. multilocularis*) and domestic (*E. granulosus*) life-cycles

of the parasites, distinct socio-demographic and environmental factors modulate the parasite-host-human interplay at different spatial scales [18, 19]. Therefore, different processes of environmental change have the potential to modify the transmission pathways of these parasites [18].

Various land reform policies and incentive programmes have been developed in China to recover degraded lands and promote sustainable development in rural areas [20]. The Grain for Green Project (GGP), also called the Sloping Land Conversion Programme, implemented since 1999, is one of the largest payment for ecosystems services schemes in China [21]. The main focus of the programme is to rehabilitate the ecological environment by promoting three different types of land conversion on steep slopes: cropland to grasslands, cropland to forest and wasteland to forest [21]. The GGP also advocates for small ruminant enclosure and grazing prohibition. In highly endemic areas for echinococcoses, the anthropogenic-driven land cover modifications that resulted apparently from the implementation of the GGP and other reforestation programmes might have favoured the transmission of *E. multilocularis*. Evidence on the impact of deforestation [13, 22], afforestation [11] and fencing/agricultural practices [23–25] on the population density and distribution of small mammals is increasing.

Recognizing the public health and economic significance of human echinococcoses, and the potential risk of parasite range expansion, the National Health and Family Planning Commission (NHFPC) launched a national action plan for echinococcosis control in 2005 [26]. This initiative aims to decrease the seropositivity rate in children aged < 12 years and to reduce infestation rates in dogs. To achieve these goals, five interventions were designed to reduce the impacts of these infections in 217 endemic counties: community-based epidemiological surveys involving serological, abdominal ultrasound and chest X-ray screening for early detection of cases; treatment

and surveillance of patients diagnosed with the disease; education campaigns to enhance awareness among local people and health officials; regular anti-helminthic treatment for deworming of dogs; and improved control of slaughter practices [27]. In general, the coordination of these efforts has proven difficult, especially in rural areas [26, 27]. In order to improve the establishment and monitoring of realistic targets for control, it is necessary to estimate the real impact of these infections and the permissive factors for transmission at local and regional scales [28].

Using geographical information systems (GIS), Earth observation data and a Bayesian statistical framework, the present study describes the spatio-temporal patterns of CE and AE in NHAR between January 1994 and December 2013. The aims were to identify highly endemic areas for these infections in the autonomous region, and to determine the environmental covariates that are shaping their local geographical distributions, in particular those that may be indicators of the potential impact of the GGP on the NHAR land cover profile. The findings may help the targeting of resources to communities most in need of echinococcosis control, and by contributing to environmental risk assessments of major landscape regeneration programmes such as the GGP.

Methods

Study area

NHAR is a province-level autonomous region located in Northwest China between latitudes 35°26'N and 39°30'N, and between longitudes 104°50'E and 107°40'E. The provincial territory covers an area of 66,400 km² and is bordered by the Inner Mongolia Autonomous Region to the North, Gansu Province to the South and West and Shaanxi Province to the East. Administratively, NHAR is divided into 5 prefectures that are

subsequently subdivided into counties/districts/county-level cities, townships and villages (Additional file 1). The population reached about 6.6 million people in 2014, of whom the majority were living in urban areas (53.6%) compared to rural areas (46.4%) [29]. From those living in rural areas, 54.7% belonged to the Hui minority ethnic group and 45.3% were Han Chinese [29]. Internal migration, movement of people from one area (a province, prefecture, county or township) to another within one country [30], is particularly high in NHAR with 54.6% of households reporting at least one migrant in 2001 [31]. Also, a report from the Beijing Normal University and Hitotsubashi University in 2009 indicated that internal migration in NHAR increased from 17.2% in 2002 to 28.3% in 2008, among the working-age population (aged between 16 and 65 years) who participated in the GGP (participation period between 3 and 6 years), and decreased from 24% in 2002 to 17.6% in 2008 among people who did not participate in the programme [32]. The report also demonstrated that migration decision depends on various demographic and socioeconomic factors. In NHAR, most migrants are young men with an education level of about 6–9 years, which coincides with the population with high tendency towards migration in China [33]. Variations in migration propensity between Han and Hui nationality groups or between married and non-married people were not found [32].

NHAR lies in a temperate continental monsoon climate zone that is characterized by large seasonal variation in temperature, rainfall and humidity. About 80% of the annual rainfall occurs during the summer and autumn months and generally increases from North to South. Elevation increases from North to South with the highest peak at 3556 meters (Fig. 1) [16].

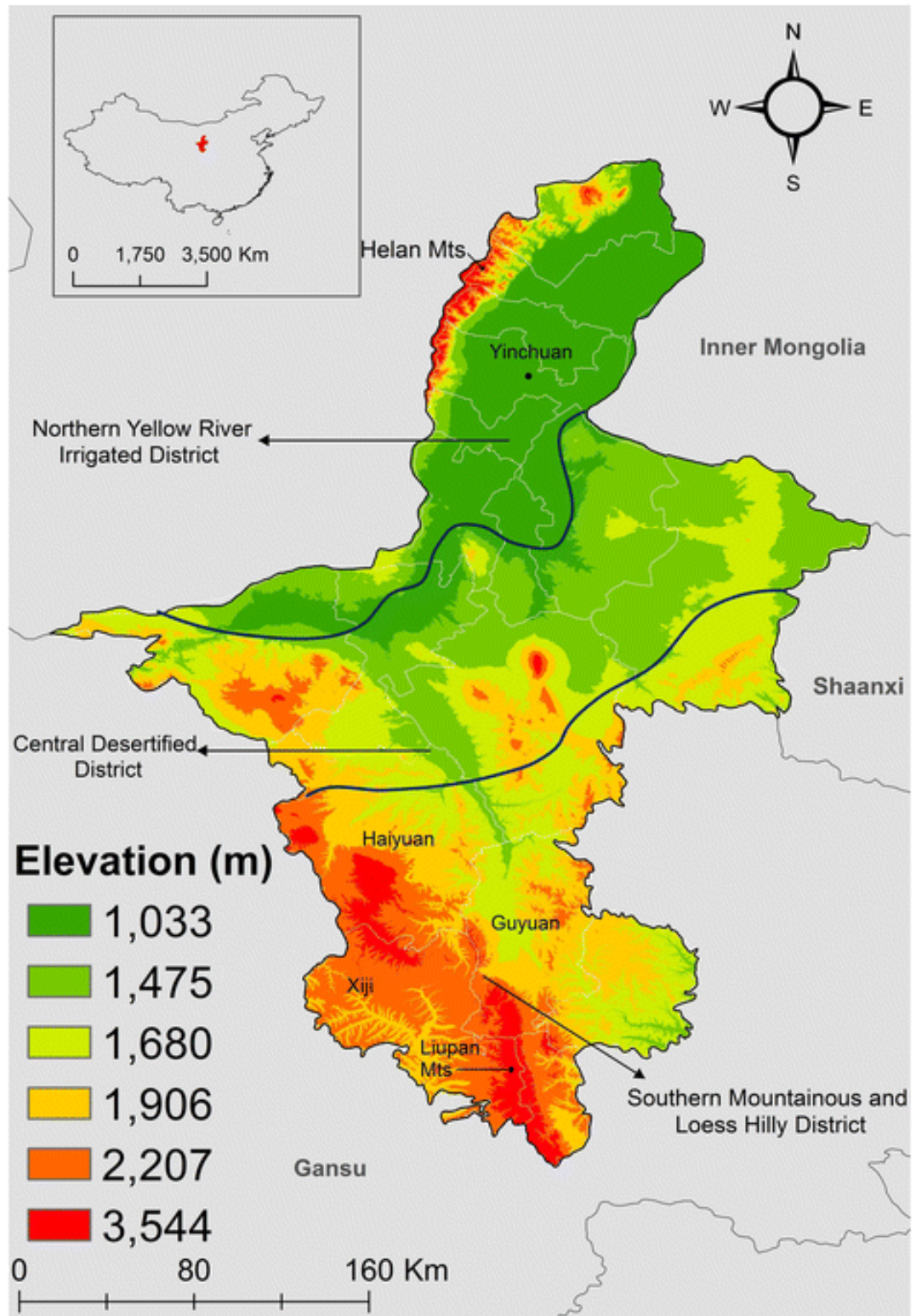


Fig. 1 Map and elevation of NHAR and location of the province within China (insert). The blue lines divide the three major natural regions

Data on human CE and AE

Data on the number of human CE and AE cases were derived from a hospital-based retrospective survey. Hospital medical records for the period between January 1 1992 and December 31 2013 were reviewed in 25 public hospitals in NHAR: 1 hospital from each county ($n = 21$), three hospitals from the capital city, Yinchuan, and 1 hospital from Guyuan Prefecture. Data collection was conducted during two different time periods, 2002–2003 and 2012–2013 and both involved the same number of hospitals. These hospitals were selected because they provide clinical and surgical care for most echinococcosis patients from rural and urban areas in the province. When patients with a presumptive echinococcosis diagnosis are admitted to local rural medical centres, they are usually referred to the county hospital for confirmation, treatment and follow-up examination. All patients whose diagnoses of CE and AE infection were established during the study period were included in the analysis. Inclusion criteria required that the diagnosis of a CE or AE case was confirmed based on imaging, serological, surgical and/or histopathologic findings. The classification scheme proposed by the World Health Organization was used to diagnose and categorise CE and AE [73]. A standard form was used to extract individual information on relevant clinical, pathological and demographic data for all confirmed cases. Data were geo-referenced to the township in which each patient resided: this was assumed to be the geographical area where the infection occurred. The day of diagnosis was considered to be the date of primary surgical and confirmatory procedures. If a confirmed case was readmitted to hospital with the same diagnosis, only the initial admission was included in the analysis. The design and methods of the hospital survey for the period 1992–2002 have been described in detail elsewhere [34, 35]. The review of medical records for the period 2003–2013 followed the same protocol.

Because the data collected between 1992 and 1993 had considerable gaps, the CE and AE cases derived from these years were excluded from the analysis. For the purpose of our analyses the time period for the study was set from January 1 1994 to December 31 2013. To conduct the analysis, CE and AE cases were aggregated by township and year.

Population data

Data on population for the year 2010 were downloaded from the WorldPop Project website [36]. A grid (i.e. raster surface) was available for the area of China at the resolution of 100 m. Population counts were extracted for each township using the ArcGIS software [37] and an administrative map of NHAR. In addition, data on population at the prefecture level were also obtained for the years 1990 and 2000 from the national censuses [38]. These data were used to calculate an average annual population growth rate for each prefecture between the years as follows: $r = (P_2 - P_1 / P_1) / t$; where r is the average rate of growth, P_1 and P_2 are the population totals for the first and second reference years, respectively, and t is the number of years between the two census counts. Applying a Taylor series approximation to remove non-linear terms [39], the growth rate estimates were then used to calculate population counts for each township and year based on the 2010 population values derived from the WorldPop grid, ($P_2 = P_1 e^{(rt)}$) [40]. However, it should be noted that the approximation becomes increasingly erroneous as t increases (Additional file 2) [39].

Climate and physical environment data

The independent variables included in the analysis were derived from the following datasets: land cover maps, elevation, monthly mean temperature and precipitation.

Because data on human echinococcoses were collected for the period 1994–2013, the environmental datasets were derived from 1980 to 2013 to investigate different lag periods of environmental variables between exposure and disease (the incubation period of echinococcosis infections is 5–15 years) [41].

Single date land cover maps were created for the years 1991, 1996, 2000, 2005, 2010 and 2015. The scientific background and processing steps have already been published [9] so are only outlined in brief here. These maps were produced using images retrieved from the Landsat Surface Reflectance Climate Data Record available in Earth Explorer [42]. Four scenes processed from Landsat 4-5 Thematic Mapper and Landsat 8 Operational Land Imager and Thermal Infrared Sensor were collected for each year. Most scenes were retrieved from the summer and autumn season that correspond to the period June to November [43, 44]. When there were no scenes available for the selected months, the closest-in-time and most cloud-free scenes available were downloaded for the analyses. Minnaert topographic correction, cloud and cloud shadow removal were performed using the *Landsat* package in the R language and environment for statistical computing [45, 46]. Images were mosaicked and classified by applying the maximum likelihood algorithm in ENVI version 5.3 [47]. Reference datasets for land cover classification (training) were produced by random sampling of a combination of relatively fine-scale global maps, the GlobeLand30 and the global forest/non-forest maps (FNF) [48, 49] using the ArcGIS software version 10.3.1 [37]. Six land cover classes were identified: water bodies, artificial surfaces, bare or sparsely vegetated areas, herbaceous vegetation, cultivated land, shrubland and forest. Due to substantial similarities between the spectral values of artificial surfaces and bare or sparsely vegetated areas, these two classes were merged and represented as a single land cover category called bareland/artificial surfaces (Table 1).

Table 1 Land cover classification scheme and definitions

| Land cover type | Description | Content |
|----------------------------------|--|--|
| Water bodies | All areas of water | Streams and canals, lakes, reservoirs, bays and estuaries |
| Artificial surfaces | Land modified by human activities | Residential areas, industrial and commercial complexes, transport infrastructure, communications and utilities, mixed urban or built-up land and other built-up land |
| Bare or sparsely vegetated areas | Areas with little or no ‘green’ vegetation present | Dry salt flats, sandy areas, bared exposed rock and mixed barren land |
| Herbaceous vegetation | Areas characterized by natural or semi-natural vegetation | Grasses and forbs |
| Cultivated land | Areas where the natural vegetation has been removed/modified and replaced by other types of vegetative cover that have been planted for specific purposes such as food, feed and gardening | Cropland and pasture, orchards, groves, vineyards, nurseries and ornamental horticultural, other cultivated land |
| Shrubland | Natural or semi-natural woody vegetation with aerial stems less than 6 m tall | Evergreen and deciduous species of true shrubs and trees or shrubs that are small or stunted |
| Forest | Areas characterized by tree cover or semi-natural woody vegetation greater than 6 m tall | Deciduous forest, evergreen forest and mixed forest |

Sets of space- and time-referenced photographs from the website Panoramio [50] were downloaded for each year to produce datasets for accuracy assessments of the land cover classes. In order to reduce the level of uncertainty due to the use of this type of data [51], all selected photographs were labelled manually based on visual interpretation, and cross-checked against historical imagery from Google Earth Pro (GEP) version 7.1.5.1557 [52]. The overall classification accuracies of all maps were higher or equal to 80% and the total Kappa coefficients were greater than 0.7. These results represent a substantial agreement between the reference datasets and the classified maps. The six land cover maps and more specific and detailed information about the process of land cover classification and validation is available elsewhere [53].

Monthly averages of temperature and precipitation data for the period January 1 1980 to December 31 2013 were provided by the Chinese Academy of Sciences. Data were first collected from 16 local weather stations and interpolated using the Inverse Distance Weighting (IDW) method. ESRI grids including the monthly data were obtained at the resolution of 1 km (approximately 30 arc-seconds) grid (Additional files 3–5).

Elevation data from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) version 2 were downloaded from the USGS Earth Explorer website [54]. The ASTER GDEM is available globally in GeoTIFF format at the resolution of 1 arcsecond (approximately 30 m) (Fig. 1).

Data analysis

A township-level shapefile (boundary map) of NHAR was produced using MapInfo Pro software version 15.0 [55] and a scanned and geo-referenced administrative map of NHAR provided by the Bureau of Geology and Mineral Resource. The administrative

boundary map included 227 township-level areas. The small area of the townships (median 154 km², interquartile range 73.5–297.5 km²) permitted an analysis of human echinococcoses at a high level of spatial disaggregation.

The spatial datasets including human echinococcosis cases, demographic and environmental data were imported into the ArcGIS software [37] and projected to the Universal Transverse Mercator (UTM) coordinate system zone 48N. The datasets were linked according to location to the administrative boundary map of NHAR to summarise and extract the data by township area and define parameters for subsequent statistical analyses.

The spatial mean values of elevation (average elevation calculated from pixel values) and the spatial extent (as percentage of area) of each land cover class for the years 1991, 1996, 2000, 2005, 2010 and 2015 were calculated for all the townships. Because there were only six land cover maps, data extracted by class were then used to impute change rates at the township level for the periods 1991–1996, 1996–2000, 2000–2005, 2005–2010, and 2010–2015. In this way, it was possible to estimate the spatial extent of all land cover classes in each township for all years between 1980 and 2015.

Annual series of bioclimatic variables were calculated at the township level from the climate datasets. Monthly temperature and precipitation records were summed in the GIS to provide annual, summer (June–August) and winter (December–February) averages. Other variables that were calculated include maximum, minimum, standard deviation, range values and precipitation of the driest and wettest quarters of each year.

Crude standardised morbidity ratios (SMRs) for each administrative area were calculated for the periods 1994–1998, 1999–2003, 2004–2008 and 2009–2013. SMRs were computed by dividing the observed number of cases by the expected number of

cases in the study population (overall incidence rate of human echinococcoses for the whole province from 1994 to 2013 multiplied by the population of each township).

To account for the long incubation period of CE and AE, temporal lags in the effects of land cover and bioclimatic variables were incorporated in the analysis by calculating cross-correlation coefficients between the CE and AE counts in a given year and the value of each environmental predictor at time t ($t-0, t-1, t-2 \dots t-34$ years). From each bivariate time-lagged correlation, only the lag with the highest correlation value was selected for the analysis. A moving average (MA) technique was also applied to generate temporally smoothed estimates of the land cover and climate data. In this way, it was possible to capture the interplay between the parasite, hosts and the environment over an extended period of time rather than at a single point in time. In order to examine different short-, intermediate-and long-term exposure windows, the MAs were calculated by aggregating the environmental data in 5-year lagged periods as follows:

- MA 1 ($t-0, t-1, t-2, t-3, t-4$)
- MA 2 ($t-1, t-2, t-3, t-4, t-5$)
- MA 3 ($t-5, t-6, t-7, t-8, t-9$)
- MA 4 ($t-10, t-11, t-12, t-13, t-14$)
- MA 5 ($t-6, t-7, t-8, t-9, t-10$)
- MA 6 ($t-11, t-12, t-13, t-14, t-15$)

Univariate Zero-inflated negative binomial regression models were developed using the R software version 3.2.2. [45]. In this way, it was possible to assess separately the association of the response variables, CE and AE counts, with the environmental factors with the highest lagged correlation and all MAs. Zero-inflated negative binomial

regression models were preferred over Poisson, negative binomial and zero-inflated Poisson models based on the results of the Vuong test [56]. Pearson correlation analyses were applied to assess collinearity among all environmental predictors. If the correlation coefficient between a pair of variables was > 0.9 , the variable with the highest value of the Akaike information criterion (AIC) in the univariate regression model was excluded from the multivariate analysis. Nonlinear associations between all environmental covariates and CE/AE counts were also examined using quadratic terms (Fig. 2).

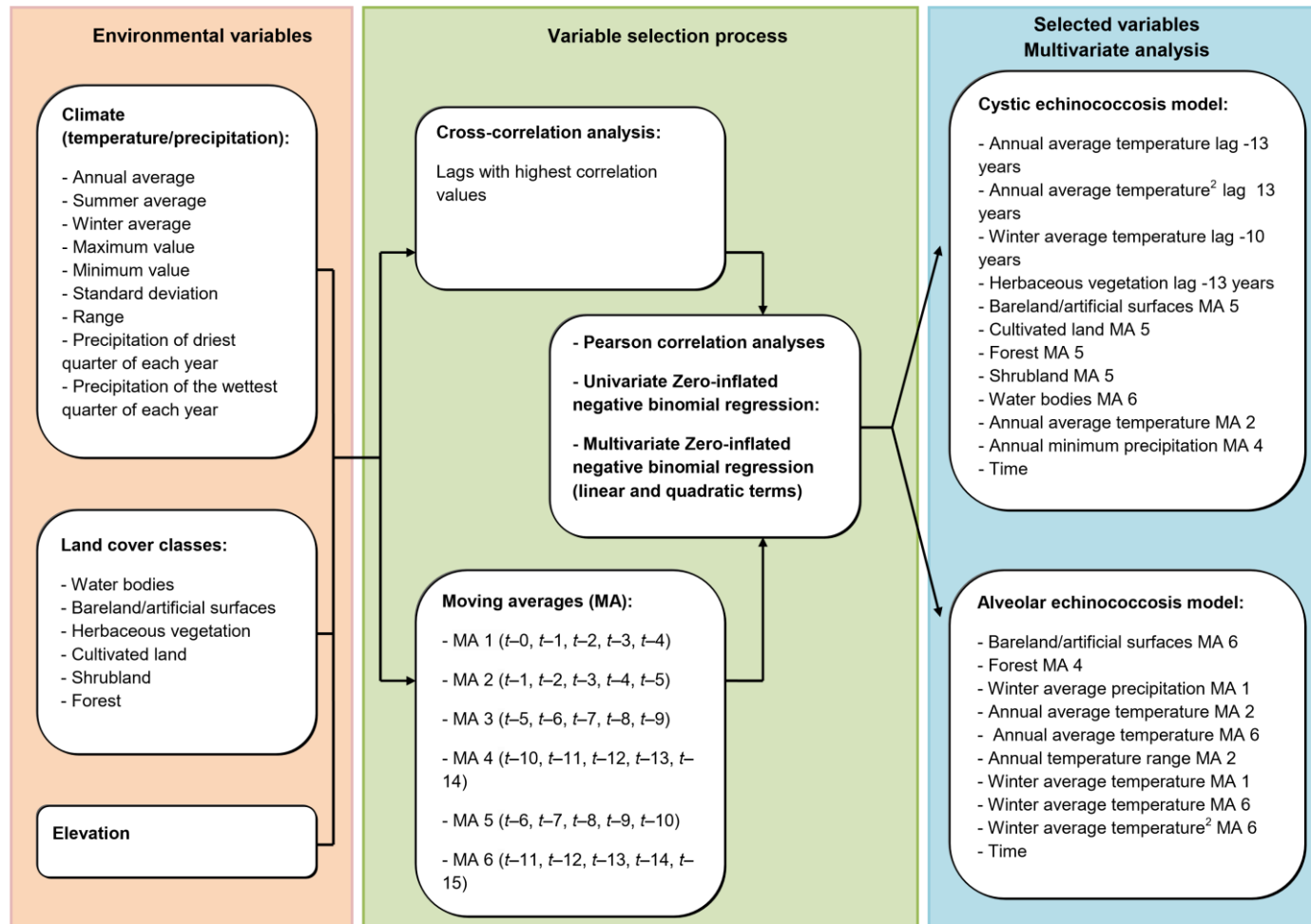


Fig. 2 Environmental variables and variable selection process for the spatiotemporal analysis of human echinococcosis in NHAR for the period 1 January 1994 to 31 December 2013

A Bayesian framework was used to construct three different Poisson regression models of the observed incidence data of CE and AE using the OpenBUGS software 3.2.3 rev 1012 [57]. The first model (Model I) was based on the assumption that spatial autocorrelation was not present in the relative risk of these infections. This model was developed incorporating time in years, the selected explanatory variables and an unstructured random effect for township; the second model (Model II) included the explanatory variables and a spatially structured random effect; the third model (Model III) was constructed without explanatory variables and incorporating only a spatially structured random effect (enabling an assessment of the degree to which the explanatory variables characterised spatial clustering of infections).

The mathematical notation for Model II is provided below, and contains all of the components of Model I and Model III. Model II, assumed that the observed counts of the infection (CE or AE), Y , for the i th township ($i = 1 \dots 227$) in the j th year (1994–2013) followed a Poisson distribution with mean (μ_{ij}), that is,

$$Y_i \sim \text{Poisson}(\mu_{ij})$$

$$\log(\mu_{ij}) = \log(\text{Exp}_{ij}) + \theta_{ij}$$

$$\theta_{ij} = \alpha + \text{Year}_j \times \gamma + \sum_{z=1}^Z \beta_z \times \lambda_{zij} + s_i$$

where Exp_{ij} is the expected number of cases in township i in year j (acting as an offset to control for population size) and θ_{ij} is the mean log relative risk (RR); α is the intercept, γ is the coefficient for temporal trend, β is a vector of z coefficients, λ is a matrix of z environmental covariates, and s_i is the spatially structured random effect with mean zero and variance σ_s^2 . Standardization of environmental variables was used to allow comparability of the effects and provide a more meaningful interpretation on the results. Standardization, involved subtracting the mean from each environmental variable and the

difference was divided by the standard deviation, which resulted in a standard deviation of one.

The spatially structured random effect (Models II and III) was modelled using a conditional autoregressive (CAR) prior structure [58]. This approach uses an adjacency weights matrix to determine spatial relationships between townships. If two townships share a border, it was assumed the weight = 1 and if they do not, the weight = 0. The adjacency matrix was constructed using the ‘Adjacency Tool’ of the OpenBUGS software 3.2.3 rev 1012 [57]. A flat prior distribution was specified for the intercept, whereas a normal prior distribution was used for the coefficients (with a mean = 0 and a precision = 0.001). The priors for the precision ($1/\sigma_i^2$) of spatially structured random effects were specified using non-informative gamma distributions (0.5, 0.0005) (Additional files 6 and 7).

The first 1000 iterations were run as a burn-in period and discarded. Subsequent sets of 20,000 iterations were run and examined for convergence. Convergence was determined by visual inspection of posterior density and history plots and by examining autocorrelation plots of model parameters. Convergence occurred at approximately 100,000 iterations for each model. The last 20,000 values from the posterior distributions of each model parameters were stored and summarised for the analysis. The deviance information criterion (DIC) was used to compare the goodness-of-fit between models, where lower DIC indicates a better model fit. An α -level of 0.05 was used in all analyses to indicate statistical significance (as indicated by 95% credible intervals (95% CrI) for relative risks (RR) that excluded 1).

Choropleth maps were created using the ArcGIS software [37] to visualise the geographical distribution of crude SMRs for the 227 townships in NHAR. The relative

risks of infection were expressed as a percentage by multiplying by 100. The posterior means of the random effects obtained from the models were also mapped.

Results

Descriptive analysis

Summary statistics for annual mean numbers of human echinococcoses in NHAR for the period 1 January 1994–31 December 2013 were calculated (Table 2). A total of 4472 cases were diagnosed in the hospitals during the study period. From the total number of cases, 4402 cases (98.4%) were CE and 72 (1.6%) were AE. Two patients were diagnosed with both diseases. The number of annual cases of CE increased slightly from 1994 to 2013 (Additional file 8). Apart from the peak in the annual number of AE cases in 2007 and 2008, the annual human echinococcosis cases remained relatively stable during the study period (Additional file 9). While the number of annual CE cases by township ranged between 0–32 with a mean of 0.9 (standard deviation (SD), 2.1), the annual number of AE cases ranged between 0–5 with a mean of 0.02 (SD, 0.2). Annual maximum and minimum temperatures for the townships in NHAR were 26.3 °C and -13.9 °C, respectively, with a mean of 8.7 °C (SD, 0.98 °C) between 1980 and 2013. In the same period, annual maximum precipitation was 19,981.3 mm and annual minimum precipitation was 0.01 mm with a mean of 255.6 mm (SD, 131.1 mm) (Additional files 10, 11). The mean elevation of the administrative areas was 1506.3 m above sea level (SD, 374.9 m). Township area covered by each land cover class in NHAR for the period 1 January 1980 to 31 December 2013 is presented in Additional file 12.

Table 2 Numbers of total echinococcosis cases in Ningxia Hui Autonomous Region by year from 1994 to 2013

| Year | Frequency total (CE/AE) | Percent of total cases (CE/AE) in the period (%) | Cumulative frequency total (CE/AE) | Cumulative percent total (CE/AE) |
|-------------|--------------------------------|---|---|---|
| 1994 | 141 (139/2) | 3.2 (3.1/2.8) | 141(139/2) | 3.2 (3.1/2.8) |
| 1995 | 208 (205/3) | 4.7 (4.6/4.2) | 349 (344/5) | 7.8 (7.7/7.0) |
| 1996 | 244 (240/4) | 5.5 (5.4/5.5) | 593 (584/9) | 13.3 (13.1/12.5) |
| 1997 | 270 (266/4) | 6.0 (6.0/5.5) | 863 (850/13) | 19.3 (19.1/18.0) |
| 1998 | 244 (239/5) | 5.5 (5.4/6.9) | 1107 (1089/18) | 24.8 (24.6/24.9) |
| 1999 | 249 (243/6) | 5.6 (5.5/8.3) | 1356 (1332/24) | 30.3 (30.1/33.2) |
| 2000 | 275 (268/7) | 6.1(6.1/9.7) | 1631 (1600/31) | 36.5 (36.2/42.9) |
| 2001 | 195 (192/3) | 4.4 (4.3/4.2) | 1826 (1792/34) | 40.8 (40.5/47.1) |
| 2002 | 215 (214/2) | 4.5 (4.8/2.8) | 2041 (2006/36) | 45.6 (45.3/49.9) |
| 2003 | 186 (184/2) | 4.2 (4.2/2.8) | 2227 (2190/38) | 49.8 (49.5/52.7) |
| 2004 | 213 (211/2) | 4.8 (4.8/2.8) | 2440 (2401/40) | 54.6 (54.3/55.5) |
| 2005 | 223 (221/2) | 5.0 (5.0/2.8) | 2663 (2622/42) | 59.5 (59.3/58.3) |
| 2006 | 189 (188/1) | 4.2 (4.3/1.4) | 2852 (2810/43) | 63.8 (63.6/59.7) |
| 2007 | 214 (201/13) | 4.8 (4.6/18.1) | 3066 (3011/56) | 68.6 (68.2/77.8) |
| 2008 | 255 (246/9) | 5.7 (5.6/12.5) | 3321(3257/65) | 74.3 (73.8/90.3) |
| 2009 | 283 (279/5) | 6.3 (6.3/6.9) | 3604 (3536/70) | 80.6 (80.1/97.2) |
| 2010 | 218 (218/0) | 4.9 (4.9/0.0) | 3822 (3754/70) | 85.5 (85.0/97.2) |
| 2011 | 205 (204/1) | 4.6 (4.6/1.4) | 4027 (3958/71) | 90.0 (89.6/98.6) |
| 2012 | 249 (249/0) | 5.6 (5.6/0.0) | 4276 (4207/71) | 95.6 (95.2/98.6) |
| 2013 | 196 (195/1) | 4.4 (4.4/1.4) | 4472 (4402/72) | 100 (100/100) |
| Total | 4472 (4402/72) | 100 (100/100) | — | — |

The maps of SMRs for the number of CE infections by township in the four time periods show some degree of spatial variability across the province (Fig. 3). In general, higher incidence rates of CE were observed in townships located in the northern Yellow River Irrigated District and the southern mountainous and loess hilly district, whereas lower incidence rates were recorded in the central desertified district of NHAR. The maps of AE incidence show that this infection was mainly distributed in the South with occasional foci identified in the North (Fig. 4).

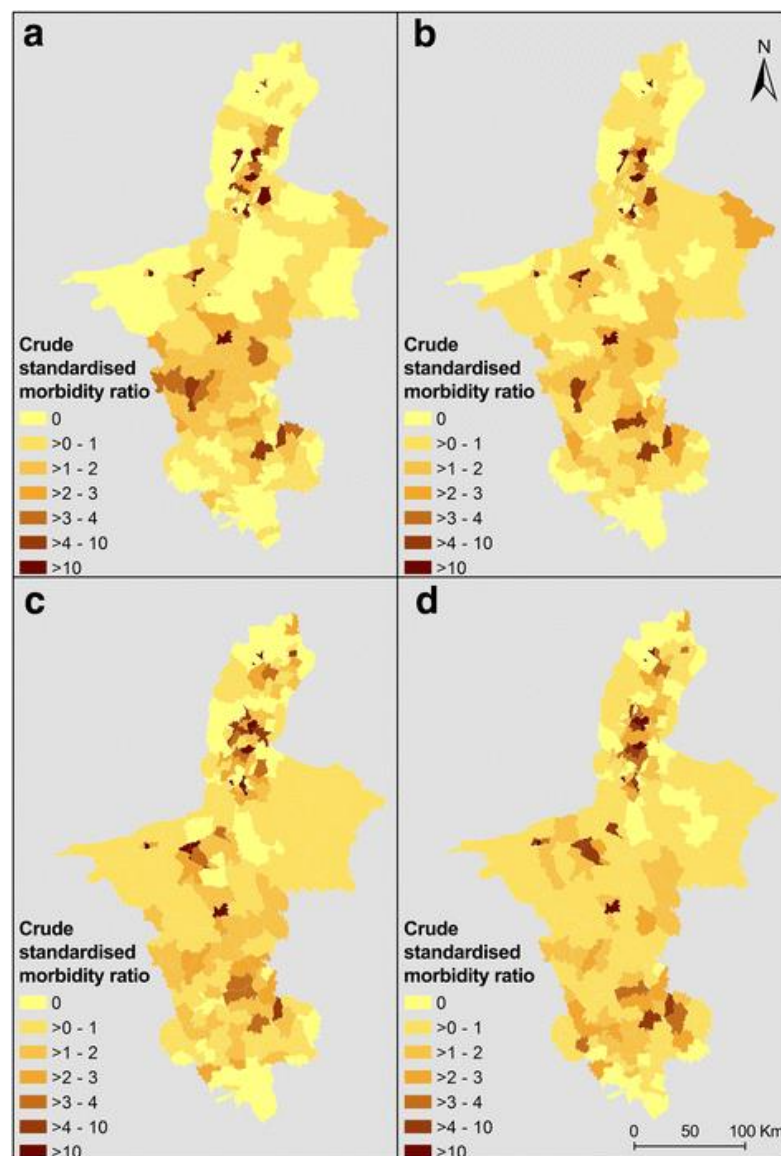


Fig. 3 Crude standardised morbidity ratios for cystic echinococcosis by township in NHAR for four different periods: a 1994–1998; b 1999–2003; c 2004–2008; d 2009–2013

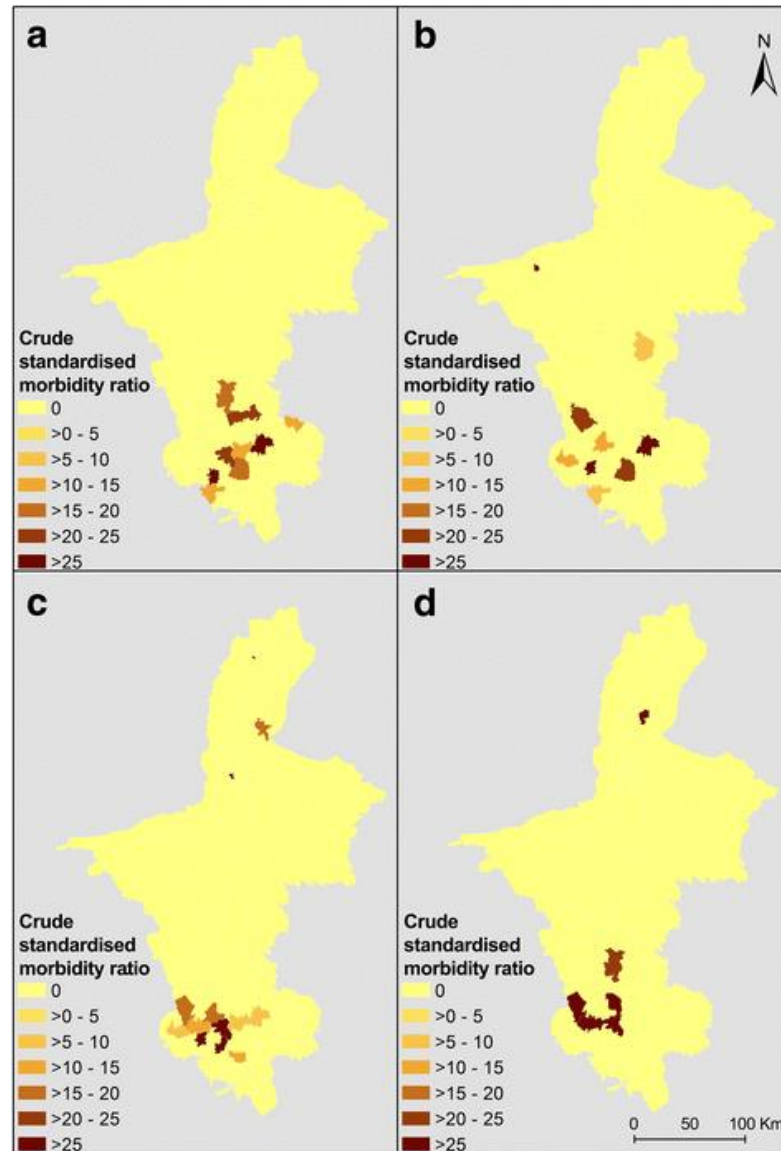


Fig. 4 Crude standardised morbidity ratios for alveolar echinococcosis by township in NHAR for four different periods: a 1994–1998; b 1999–2003; c 2004–2008; d 2009–2013

Bayesian spatio-temporal models of human CE and AE

Based on the DIC estimates, Models II of CE and AE had the best parsimonious characterization of the data among all the models examined (Tables 3, 4). The higher DIC for Model I and III than Model II indicates that the addition of spatial structure to the random effects improved model fit. In model II of CE, winter mean temperature at 10-year lag had a statistically significant association with the incidence of cases (Additional

file 13). There was an estimated increase of 15.0% (95% CrI: 10.8–19.3%) in the risk of CE for a 1 °C increase in winter mean temperature 10 years prior to the diagnosis of the infection. Conversely, there was a decrease of 2.2% (95% CrI: 1.2–3.4%) in the risk of CE for every year during the study period. The quadratic term for annual mean temperature was also significant, indicating that the association between this variable and the outcome was nonlinear (Additional file 14). The MA2 of annual mean temperature, the MA4 of annual mean precipitation and the MAs calculated for the percentage of township area covered by the land cover types were not significant. The difference in the variance of the spatially structured random effect between Model III (9.1; 95% CrI: 7.4–11.6) and Model II (8.9; 95% CrI: 7.1–11.1) indicates that the covariates accounted for only a small proportion of the spatial variability in the data (Table 3 and Fig. 5a, b).

Model II of AE showed that the MA1 of winter mean temperature (Additional file 15), the MA6s of annual mean temperature (Additional file 16) and the percentage of township area covered by bareland/artificial surfaces, had a significant negative association with AE cases. There was a decrease of 65.7% (95% CrI: 19.6–85.4%) in the risk of AE for a 1 °C increase in the average of winter temperature calculated for the 5-year period previous to the diagnosis of the disease (0–4 years). Also, the decrease in the risk of AE was 97.4% (95% CrI: 70.8–99.8%) and 5.0% (95% CrI: 0.9–9.3%) for an increase of 1 °C in annual mean temperature and 1% increase in MA6 of township area covered by bareland/artificial surfaces, respectively. There was a statistically significant increasing temporal trend in the risk of AE. The difference between the DIC of Model II, 184.8, and that of model III, 486.7, indicates that the inclusion of the environmental covariates improved model parsimony. The variance of the spatially structured random effect decreased from 10.6 (95% CrI: 5.5–25.0) in Model III to 9.5 (95% CrI: 4.6–23.8) in Model II. These results may suggest that, unlike the findings in the model of CE, the

selected environmental covariates characterised a higher proportion of the spatial variation in the risk of AE (Fig. 5c, d).

The maps of the residual spatial variation of CE, before (Model III) and after (Model II) accounting for the environmental covariates, show almost identical spatial patterns without clear evidence of disease clustering (Fig. 5a, b). Conversely, the maps of the distribution of the residual spatial variation of AE risk demonstrated evidence of clustering when the model did not incorporate the environmental covariates (Model III). The degree of clustering decreased when the effect of these variables was included (Model II), suggesting that the covariates contributed to clustering in the south of NHAR (Fig. 5c, d). Maps of the raw relative risks were generated for CE and AE by township and year (Additional files 17, 18). These maps show that the risk of CE was distributed across all geographic regions in NHAR during the entire study period, while the risk of AE was confined to the south. However, based on the environmental factors associated with AE risk in NHAR, it was also possible to identify an area at high risk of AE in the northeastern part of the central desertified district (Additional file 18).

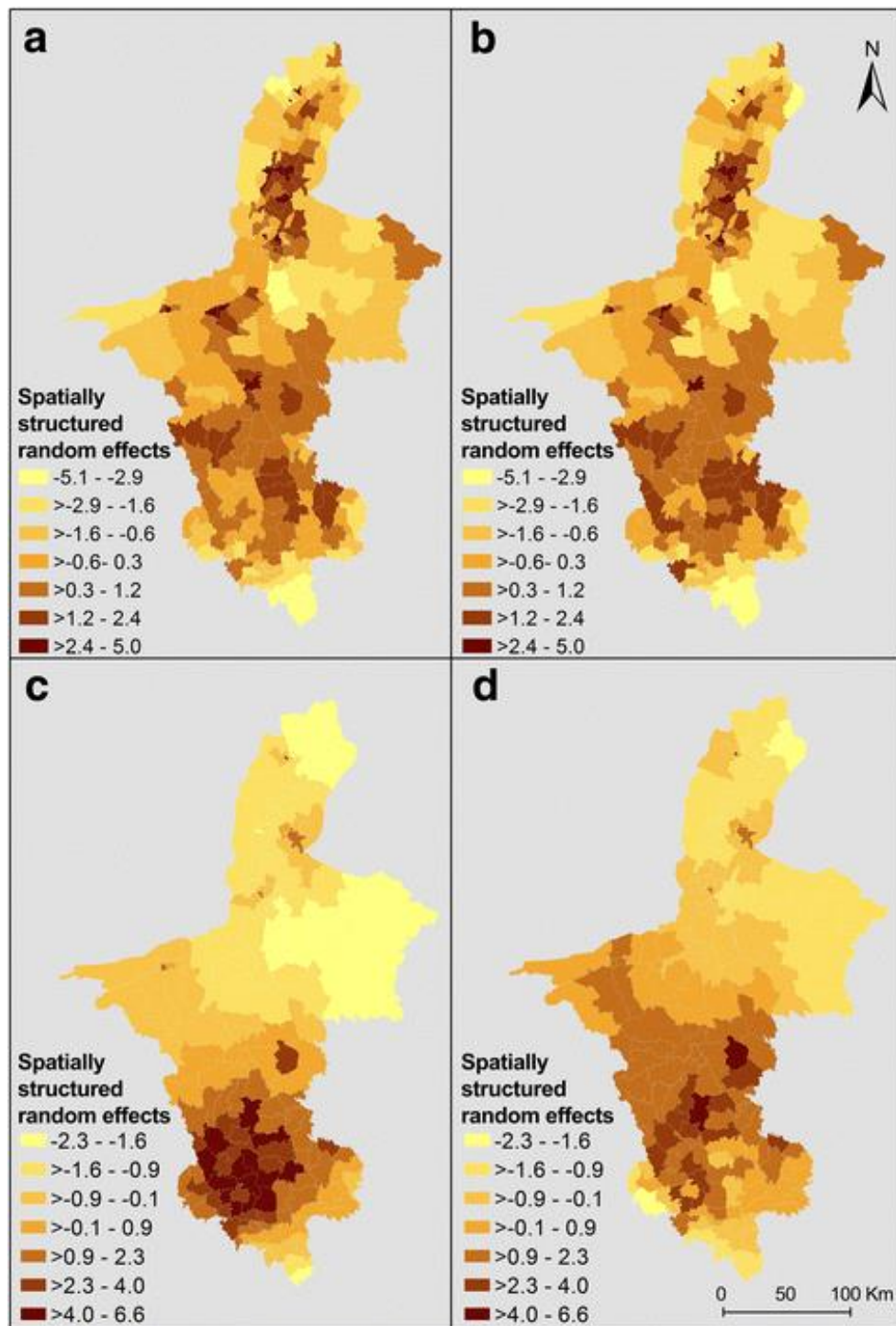


Fig. 5 Spatial distribution of the posterior means of random effects for cystic and alveolar echinococcoses in NHAR. Spatially structured random effects of Models II (a) and III (b) of cystic echinococcosis, and spatially structured random effects of Models II (c) and III (d) of alveolar echinococcosis

Table 3

Regression coefficients, RRs and 95% CrI from Bayesian spatial and non-spatial models for cystic echinococcosis in NHAR from 1 January 1994 to 31 December 2013

| | Model I | | Model II | | Model II |
|---|--|--------------------------------------|--|--------------------------------------|--|
| Variable | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) |
| α (Intercept) | -0.38 (-0.01– -0.38) | – | -0.40 (-0.56– -0.25) | – | -0.67 (-0.78– -0.60) |
| 1. Annual mean temperature (°C) lag-13 years | 0.04 (4.55×10^{-4} –0.04) | 1.04 (1.00–1.04) | 0.04 (-0.03–0.11) | 1.04 (0.97–1.12) | – |
| 2. Annual mean temperature ² (°C) lag-13 years | -0.05 (-0.05– 1.56×10^{-4}) | 0.95 (0.95–1.00) | -0.05 (-0.08– -0.02) | 0.95 (0.92–0.98) | – |
| 3. Winter mean temperature (°C) lag-10 years | 0.14 (1.93×10^{-4} –0.14) | 1.15 (1.00–1.15) | 0.14 (0.10–0.18) | 1.15 (1.11–1.19) | – |
| 4. Herbaceous vegetation lag-13 years | -0.01 (-0.01– 7.08×10^{-5}) | 0.99 (0.99–1.00) | -0.01 (-0.01– 2.86×10^{-4}) | 0.99 (0.98–1.00) | – |

| | Model I | | Model II | | Model II |
|---|---|--------------------------------------|--|--------------------------------------|--|
| Variable | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) |
| 5. Bareland/artificial surfaces (%) MA5 | 0.01 (6.21×10^{-5} –0.01) | 1.01(1.00–1.01) | 4.89×10^{-3} (-1.31×10^{-3} –0.01) | 1.00 (0.99–1.01) | – |
| 6. Cultivated land (%) MA5 | 2.79×10^{-3} (5.02×10^{-5} – 2.79×10^{-3}) | 1.01 (1.00–1.01) | 2.83×10^{-3} (-2.38×10^{-3} – 8.08×10^{-3}) | 1.00 (0.99–1.01) | – |
| 7. Forest (%) MA5 | 4.09×10^{-4} (5.26×10^{-5} – 4.4×10^{-4}) | 1.01 (1.00–1.01) | 5.52×10^{-3} (-3.93×10^{-3} –0.01) | 1.00 (0.99–.01) | – |
| 8. Shrubland (%) MA5 | -0.02 (-0.02– 9.85×10^{-5}) | 0.98 (0.98–1.00) | -0.02 (-0.05–0.01) | 0.98 (0.95–1.01) | – |
| 9. Water bodies (%) MA6 | -1.84×10^{-3} (-1.81×10^{-3} – 2.72×10^{-5}) | 0.99 (0.99–1.00) | -2.06×10^{-3} (-0.01– 4.71×10^{-3}) | 0.99 (0.99–1.00) | – |
| 10. Annual mean temperature (°C) MA2 | -0.01 (-0.01– 8.81×10^{-5}) | 0.99 (0.99–1.00) | -0.01 (-0.02– 8.15×10^{-3}) | 0.99 (0.98–1.01) | – |
| 11. Annual minimum precipitation (mm) MA4 | -0.07 (-0.07– 5.3×10^{-4}) | 0.93 (0.93–1.00) | -0.06 (-0.15–0.03) | 0.94 (0.86–1.03) | – |

| | Model I | | Model II | | Model II |
|----------------------------|--|--------------------------------------|--|--------------------------------------|--|
| Variable | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) |
| 12. Time (year) | -0.02 (-0.02– 1.13×10^{-4}) | 0.98 (0.98–1.00) | -0.02 (-0.03– -0.01) | 0.97 (0.96–0.98) | – |
| Heterogeneity unstructured | 2.77 (2.79–2694.70) | – | – | – | – |
| Heterogeneity structured | – | – | 8.98 (7.14–11.11) | – | 9.14 (7.37–11.59) |
| DIC | 9610 | – | 9396 | – | 9529 |

Abbreviations: RRs relative risks, 95% CrI 95% credible interval

Table 4

Regression coefficients, RRs and 95% CrI from Bayesian spatial and non-spatial models for alveolar echinococcosis in NHAR from 1 January 1994 to 31 December 2013

| | Model I | | Model II | | Model III |
|---|--|--------------------------------------|--|--------------------------------------|--|
| Variable | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) |
| α (Intercept) | -4.9 (-7.78– -2.81) | – | -5.33 (-7.97– -3.08) | – | -2.83 (-4.36– -1.76) |
| 1. Bareland/artificial surfaces (%) MA6 | -0.03 (-0.07– 1.3×10^{-3}) | 0.97 (0.93–1.00) | -0.05 (-0.09– -0.01) | 0.95 (0.91–0.99) | – |
| 2. Forest (%) MA4 | -0.04 (-0.11–0.03) | 0.96 (0.89–1.03) | -0.06 (-0.14–0.01) | 0.94 (0.87–1.01) | – |
| 3. Winter mean precipitation (mm) MA1 | -0.01 (-0.05–0.02) | 0.99 (0.95–1.02) | -0.01 (-0.06–0.02) | 0.99 (0.94–1.02) | – |
| 4. Annual mean temperature (°C) MA2 | 1.18 (-0.31–2.65) | 3.26 (0.73–14.18) | 1.33 (-0.23–2.91) | 3.79 (0.80–18.45) | – |
| 5. Annual mean temperature (°C) MA6 | -3.63 (-6.07– -1.36) | 0.02 (2.31×10^{-3} –0.26) | -3.63 (-6.20– -1.23) | 0.03 (2.03×10^{-3} –0.29) | – |

| | Model I | | Model II | | Model III |
|--|--|--------------------------------------|--|--------------------------------------|--|
| Variable | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) | RRs, posterior mean (95% CrI) | Coefficient, posterior mean (95% CrI) |
| 6. Annual temperature range (°C) MA2 | -0.34 (-1.04–0.40) | 0.71 (0.35–1.49) | -0.20 (-0.98–0.60) | 0.82 (0.37–1.81) | – |
| 7. Winter mean temperature (°C) MA1 | -1.03 (-1.86– -0.18) | 0.36 (0.16–0.84) | -1.07 (-1.92– -0.22) | 0.34 (0.15–0.80) | – |
| 8. Winter mean temperature (°C) MA6 | 0.42 (-0.68–1.51) | 1.52 (0.51–4.52) | 0.32 (-0.92–1.53) | 1.38 (0.40–4.62) | – |
| 9. Winter mean temperature ² (°C) MA6 | -0.47 (-1.14–0.11) | 0.62 (0.32–1.12) | -0.50 (-1.18–0.11) | 0.61 (0.30–1.12) | – |
| 10. Time (year) | 0.17 (0.05–0.30) | 1.20 (1.06–1.35) | 0.18 (0.05–0.32) | 1.20 (1.05–1.37) | – |
| Heterogeneity unstructured | 3.51 (1.66–9.27) | – | – | – | – |
| Heterogeneity structured | – | – | 9.47 (4.60–23.82) | – | 10.63 (5.54–25.01) |
| DIC | 485.2 | – | 184.8 | – | 486.7 |

Abbreviations: RRs relative risks, 95% CrI 95% credible interval

Discussion

The results indicate that winter mean temperature and annual mean temperature, 10 and 13 years prior to diagnosis, respectively are associated with the incidence of *E. granulosus* at the township level in NHAR. Temperature is a major determinant of the survival and longevity of *Echinococcus* spp. eggs in the external environment [59, 60]. In vivo studies have concluded that the eggs of *E. granulosus* remain viable and infective after 41 months of exposure to an inferior arid climate, which is characterised by large thermal amplitude (from -3 to 37 °C) and low precipitation (under 300 mm/year) [59]. The present study revealed a positive association of CE cases with winter temperature at 10-year lag and a non-linear association with annual mean temperature at 13-year lag. These findings indicate that the number of CE cases may have increased progressively when eggs were exposed to optimal temperatures but decreased with extreme temperatures that fell outside the optimal range. The relationship between *E. granulosus* infection and these two variables was significant after a time lag of more than 10 years. This is in agreement with the long incubation period of this parasite that has been reported to be between 5 and 15 years [41]. Of note, we do not suggest that the specific lag periods for each variable are important, but that the general pattern of lags indicate environmental conditions in the range of 10 to 15 years previously influence current patterns of disease.

CE cases were distributed across all the three biogeographical areas of NHAR: the northern Yellow River Irrigated District, the central desertified district and the southern mountainous and loess hilly district (Fig. 1). A higher risk of infection was observed in townships located in the North in close geographical proximity to Yinchuan. Urban areas may provide better job prospects and higher salaries for rural migrants who were exposed in their home township. In the cities, people who contracted the infection in their rural areas of origin may have had an improved access to healthcare services and

the confirmation of the diagnosis of echinococcosis and management [61]. These findings raise the need for further studies to determine how access to healthcare may affect the incidence of the infection. The risk of CE was found to be higher in townships from the southern mountainous and loess hill district. This part of NHAR is one of the three poorest areas in China where almost half the population belong to the Hui minority ethnic group [16]. Livestock and arable farming, which are common practices among these communities, represent higher risk of exposure to *Echinococcus* spp. [62, 63]. The Provincial technical standards for livestock slaughtering and antemortem and *post-mortem* meat inspection in NHAR are in agreement with the recommendations proposed by Food and Agriculture Organization of the United Nations [64, 65]. However, government-run abattoirs in NHAR are scarce, particularly in the South, where livestock slaughter is carried out mostly at rural market places or in domestic environments that are not legally compliant [66]. Unrestricted post-slaughter offal disposal is common in the region and has been identified as a potential local factor increasing the risk of CE [67]. Under similar circumstances in Qinghai Province, previous studies have suggested that domestic dogs may have a higher probability of access to livestock viscera in early winter and spring [68]. The prevalence of CE in sheep was estimated to be 52% in NHAR in 2008, and between 0–9% according to more recent reports of studies conducted at small spatial scale (no larger than county level) [66, 69, 70]. The variance in these prevalence estimates may be related to local or individual conditions that favour hotspots of high transmission within discrete patches of CE endemicity. Also, in the Autonomous Region, 3% of goats, 81% of cattle, 24% of pigs and 19% of camels were reported infected with *E. granulosus* in 2008 [71]. Although there is evidence of spatial clustering within the central desertified district, lower risk of CE was observed in this biogeographical area where communities are more scattered in isolated settlements.

The environmental covariates accounted for a relatively small proportion of the spatiotemporal variation in CE risk in NHAR. These findings suggest that there may be other local unmeasured factors that are associated with the spatial distribution of *E. granulosus* in the province. Some local socio-economic and behavioural drivers that have also been found to be positively related to CE in this hyperendemic area include low income, limited education, poor hygiene practices, female gender and Hui ethnicity. In contrast, tap water consumption has been identified as a factor that can protect against *E. granulosus* infection [35]. Although infection control in dogs has been identified as a key measure against echinococcoses in China, dog ownership still remains as an important risk factor for the infection in NHAR [35, 72]. The western China echinococcosis control programme recommends supervised treatment of all owned dogs four to eight times a year with praziquantel [73]. However, this is a measure that has been hard to apply, monitor and sustain in the remote-settled communities of the Autonomous Region [74].

The findings of the model of AE concur with previous studies conducted in different regions in echinococcosis-endemic countries that indicated that *E. multilocularis* has a focal spatial distribution [6–8]. The study also concurs with previous evidence that indicates that land cover and temperature are associated with AE incidence [22, 60, 75]. AE risk was spatially clustered in an area covered by Xiji, Guyuan and Haiyuan Counties, located in the southern mountainous and loess hill district (Fig. 1). This part of NHAR has been greatly transformed by the implementation of the GGP. Forest growth has primarily occurred in the northern and southern parts, in the Helan and Liupan mountains in the North and South, respectively (Fig. 1) [76, 77]. An increase in herbaceous vegetation has also been described in the central arid area of NHAR, and around the margin of the forestland [76, 77]. Hence, the distribution of AE risk observed

in the current study concurs with the spatial patterns of the GGP land conversion processes that have been described in this autonomous region.

Echinococcus multilocularis is transmitted in semi-domestic and sylvatic life cycles that involve dogs and foxes as main definitive hosts, respectively, and small mammals as intermediate hosts [6, 78]. It has been demonstrated that landscape structure may influence the transmission patterns of this parasite by influencing the suitability and location of ecological habitats for its hosts [11]. With regards to land cover, it was found that the merged category of bareland/artificial surfaces was not associated with the transmission of *E. multilocularis* at the township level in NHAR. This observation suggests that the life-cycle of the parasite is supported in vegetated areas (i.e. forest, shrubland and cropland). These findings raise the need for further studies to determine the association of the GGP and other potential drivers of land cover change with the risk of human AE.

The impact of forest fragmentation on small mammals assemblages has now been demonstrated and explained by the interaction between forest patch metrics and small mammal species richness, abundance and composition [21, 31, 79–81]. In Xiji County, in the South of NHAR, a previous study indicated that the abundance of degraded lowland pasture was related to higher prevalence of AE in humans [14]. In the same area, a small-mammal survey conducted in relation to different land cover types at the community level revealed the presence of 16 species of small mammals [11]. That study indicated that in areas that experienced afforestation, the diversity of assemblages was lower than that of assemblages in areas where deforestation occurred [11]. However, species richness did not seem to be affected by these land conversion processes [11]. Trapping success of potential *E. multilocularis* intermediate hosts such as, *Cricetulus longicaudatus* and *Ochotona daurica*, was higher in recently afforested set-aside fields and abandoned

grasslands, and *Spermophilus alashanicus/dauricus* in young plantations [11]. Therefore, it can be assumed that landscape transformation process that is taking place in NHAR may have disturbed rodent assemblages, and therefore affect the risk of *E. multilocularis* transmission. In Zhang County, Gansu Province, a study revealed that the process of land cover change that occurred in this endemic area affected the transmission dynamics of the parasite. There, the increase in grassland/shrubland that followed a process of deforestation favoured the creation of peri-domestic habitats of intermediate host species, and the development of peri-domestic cycles involving dogs [13, 82]. Similarly, the percentage of area covered by grassland and *E. multilocularis* infection in humans and foxes had a positive relationship in Eastern France [13, 83, 84]. In this area various studies also reported regular outbreaks of *Microtus arvalis* and *Arvicola terrestris*, key intermediate hosts for *E. multilocularis* [13, 17]. However, the picture is complex, given that in Sichuan Province, a negative cross-sectional association was observed between *Ochonta* spp. and Enhanced Vegetation Index, and previous evidence showed that this recognised intermediate host of *E. multilocularis* is more common in areas with low vegetation cover [16, 85, 86].

The negative association between AE cases and winter temperatures may be due to the influence of temperature exposure on eggs of *E. multilocularis*, and potentially the influence of temperature on small mammal population dynamics and fox/dog/small mammal predator-prey relationships [60, 87]. Evidence indicates that temperature affects the geographical range and changes the composition of small mammal communities [88, 89]. Also, climate has been identified as a factor contributing to changes in the distribution and abundance of the red and Arctic foxes, which are sylvatic definitive hosts for *E. multilocularis* in Arctic Canada [90, 91]. Reports of infection with *E. multilocularis* in red foxes in NHAR are only available for the mid-1980s [92]. At that time, 15% of

trapped red foxes were infected with *E. multilocularis* in Xiji and Guyuan Counties [92]. Although there is not current evidence on how the local environment fluctuations influence the ecology of this type of vertebrates in the Autonomous Region, it can be thought that variations in climate and land cover have the potential to affect the dynamics and predator-prey interactions of potential hosts for *E. multilocularis* in NHAR. Also, climate and the landscape may favour the presence of other potential definitive hosts for this parasite in NHAR. Infection with *E. multilocularis* has also been detected in wolves (*Canis lupus*) and corsac foxes (*Vulpes corsac*) in other parts of the P.R. China [82].

Since the latent phase of AE in humans has been estimated to be between 5–15 years, the associations between AE incidence and land cover and temperature are plausible [93]. However, in this study there was also a significant association between AE cases with the average of winter temperature for the years 0, 1, 2, 3 and 4 prior to diagnosis. This finding may suggest other effects of temperature on the health-seeking behaviour of the inhabitants of NHAR, rather than on exposure to, or infection with the parasite. The high cost of medical care and the lack of health insurance have been identified previously as primary factors for the under-utilization of health care services in China [94, 95]. Therefore, seasonal rural-urban migration and temporary employment in NHAR could be related to this association between winter temperature and the risk of human AE.

As initiatives to address the high burden of human echinococcoses in China have already been established [27], there is a current need to identify high-risk areas for undetected infection to provide guidance to local authorities in implementation of the surveillance and control interventions [27]. The present study provides important evidence that indicates that populations living in southern mountainous and loess hilly district of NHAR were at greatest risk of acquiring CE or AE during the study period.

Hence, these findings can be used to inform a decision to prioritise screening surveys in communities from Xiji, Guyuan and Haiyuan Counties which areas heavily affected by both forms of the infection. In this way, it will be possible to provide better estimates of the real impact of human echinococcoses in the autonomous region and to monitor the patterns of *E. granulosus* and *E. multilocularis* transmission [96]. To further improve the predictive performance of our models, particularly in remote areas with limited access to health services, the surveillance data should be analysed with other socio-demographic data [18]. The use of GIS technologies, Earth observation data and spatial statistical analysis for the study of the spatio-temporal dynamics of CE and AE cases may help to monitor trends in echinococcosis occurrence in hyperendemic regions. This information is relevant particularly in areas where ecological projects that alter local ecosystems are currently being implemented. Therefore, these technologies may be used to estimate future requirements for scaling up and targeting of essential control strategies, and to provide risk assessments for future landscape planning and ecosystem management and protection initiatives [19].

The limitations of this study include that it relied mainly on data collected from selected county hospitals, which overlooks the contribution of CE and AE cases that were not referred to these health care institutions for confirmation of diagnosis treatment and follow-up. Human echinococcoses are not legally notifiable diseases in China. Most patients are commonly identified in clinical records and mass screening surveys conducted in the most affected areas to help reduce the medical, social and economic burden of the infections. Therefore, further work needs to be carried out to evaluate and improve the surveillance and provide real estimates of the number echinococcosis cases in the country. Also, in this study, data on the number of patients who were immunosuppressed at the time of diagnosis were not available. Among these patients, CE

and AE behave differently and may develop during a relatively short period of time [97]. Therefore, it is recommended that future studies to identify environmental risk factors for transmission also involve indices of individual biological condition that may be associated with progression and times of infection and diagnosis of the disease. In the study, the township in which patients resided at the time of diagnosis was assumed as the place where acquisition of infection occurred. Although the patient's place of residence may be a reliable indicator for establishing the geographical origin of the infections, this may not apply for all cases. The human labour migration that has characterised NHAR in past decades may have had an impact on the observed trends of infection and results need to be interpreted with caution. Here, we explored the spatio-temporal patterns of echinococcosis infection in NHAR, and the association of environmental variables with the transmission of *Echinococcus* spp. at the township level. Hence, the results do not allow for inferences to be made about the risk of human echinococcoses at the commune or individual levels. More detailed information about the local structure of these infections may be further included to improve the CE and AE models. The impact of the GGP and other ecological restoration projects was not formally tested in this study. Therefore, it is necessary to establish evidence for the impact of such projects to facilitate environmental risk assessments of future ecosystem management and protection programmes. [98]. The use of interpolated surfaces for the estimation of climatic and land cover variables also represented a challenge for the interpretation of the findings. The precision of the interpolated values at point locations may vary considerably over time and over the entire study area. Also, the IDW interpolation method used by the Chinese Academy of Sciences is a simple and intuitive deterministic method based on the assumption that sample values closer to the prediction location have more influence on prediction value than sample values farther apart. However, IDW has sensitivity to

outliers or sampling configuration and does not allow the incorporation of ancillary data [99, 100]. We believe that a meaningful assessment of the associations between human echinococcosis risk and the environment can only be achieved with the use of consistent and long-term climate and land cover records that allow to capture significant spatial variability.

Conclusions

In this study, maps of the geographical distribution of CE and AE for a highly endemic area of China (NHAR) have been produced, and some of the environmental factors that are associated with the transmission patterns of *E. granulosus* and *E. multilocularis* at the township level were quantified. Selected environmental covariates characterised a large proportion of the spatiotemporal variation in the risk of AE. However, the CE appears to be less spatially variable and the geographical distribution is likely determined by other unmeasured factors. Evidence on the potential effects of the GGP on the risk of AE was presented due to the association with vegetated areas and a decrease in bareland. By mapping the distribution of the risk of these infections, we provide evidence that can be used to scale-up and target essential control strategies, and to inform risk assessment of large-scale landscape regeneration initiatives.

Additional files (Appendix C)

Additional file 1: Administrative map of NHAR at the (a) county, (b) prefectural and (c) township level.

Additional file 2: Percent population change in NHAR for the periods 1980–1990, 1991–2001 and 2002–2013.

Additional file 3: Spatial distribution of the average annual mean temperature in °C in NHAR for the period 1980–2013.

Additional file 4: Spatial distribution of the average annual mean precipitation in mm in NHAR for the period 1980–2013.

Additional file 5: Maps of the spatial distribution of **a** annual, **b** summer and **c** winter temperature trends, and **d** annual, **e** summer and **f** winter precipitation trends in NHAR for the period 1 January 1980 to 31 December 2013. Note, the values presented in the figure are relative to the provincial average per decade.

Additional file 6: OpenBUGS code used to develop the Bayesian spatial model (Model II) for cystic echinococcosis in NHAR from 1 January 1994 to 31 December 2013.

Additional file 7: OpenBUGS code used to develop the Bayesian spatial model (Model II) for alveolar echinococcosis in NHAR from 1 January 1994 to 31 December 2013.

Additional file 8: Number of observed and expected number of CE cases by year (1994–2013) in NHAR for the period 1 January 1994 to 31 December 2013.

Additional file 9: Number of observed and expected number of AE cases by year (1994–2013) in NHAR for the period 1 January 1994 to 31 December 2013.

Additional file 10: Annual temperature in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013.

Additional file 11: Annual precipitation in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013.

Additional file 12: Township area covered by each land cover class in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013.

Additional file 13: Scatterplots of number of CE cases by township against winter mean temperature at a 10-year lag.

Additional file 14: Scatterplots of number of CE cases by township against annual mean temperature at 13-year lag.

Additional file 15: Scatterplots of number of AE cases by township against winter mean temperature for the period 0–4 years before diagnosis.

Additional file 16: Scatterplots of number of AE cases by township against annual mean temperature calculated for the period 11–15 years before diagnosis.

Additional file 17: Spatial distribution of annual raw relative risks for CE in NHAR for the period 1994 to 2013.

Additional file 18: Spatial distribution of annual relative risks for AE in NHAR for the period 1994 to 2013.

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Ethics approval and consent to participate

The protocol for this study was reviewed and approved by the Human Research Ethics Committees of Ningxia Medical University, QIMR Berghofer Medical Research Institute and The Australian National University.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AMCR and ACAC designed the study. AMCR and YRY collected, standardised and geo-referenced the clinical and environmental data. AMCR and ACAC developed the models with input from RJSM. ACAC, YRY, DPM, DJG, RJSM, TSB, GMW and NASH provided critical comments and helped in drafting the manuscript. AMCR and ACAC finalized the manuscript. All authors read and approved the final manuscript.

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CHAPTER 5

*Human exposure to *E. granulosus* and *E. multilocularis* in Xiji County, NHAR*

CHAPTER 5 HUMAN ECHINOCOCCOSES IN XIJI COUNTY, NHAR

5.1 Context

Evidence is accumulating that the geographical distribution of *Echinococcus* spp., particularly *E. multilocularis*, is associated with environmental factors that may be favouring the establishment of the life cycles of these parasites in certain areas of NHAR. Following the findings described previously in Chapter 3 and 4, the southern part of NHAR was identified as a hyper-endemic area for both CE and AE, and a region that has experienced substantial environmental transformation. Therefore, the study presented in this Chapter was conducted to characterise the spatiotemporal distribution of human exposure to *Echinococcus* spp. in Xiji County, which is a heavily echinococcosis-affected area in the south of NHAR, over a decade during which environmental transformation has been ongoing; and identify communities where targeted prevention and control efforts are required.

The study reported in this Chapter involved data that were collected prospectively using three cross-sectional surveys of school children aged 6–18 years. In this way, it was possible to ensure that the population sample provided data indicative of recent exposure to *E. granulosus* and *E. multilocularis*. Here, I developed Bayesian geostatistical models with environmental and demographic covariates to predict the evolving geographical distribution of the seroprevalence of each of these parasites at three different time points during the last decade.

Screening surveys for human echinococcoses use ultrasound as the method of choice for the diagnosis of human echinococcoses. However, this diagnostic technique has low sensitivity to detect small cysts. Serological-based screening surveys using specific antibody testing by enzyme linked immunosorbent assay have also a useful role

in the detection of cases in epidemiological settings. However, serological tests have specificity and may cross react with other helminthic infections and gastrointestinal malignancies. In this study, I used both, abdominal ultrasound to screen schoolchildren and detect and classify early CE and/or AE cyst using the World Health Organization classification scheme, and *E. granulosus* cyst fluid antigen B and *E. multilocularis* crude protoscolex extract to determine human seropositivity for the parasites. Due to the young age of the survey participants and the slow growth of the cysts, limited of number of ultrasounds showed undefined hepatic changes. The abdominal ultrasound reports are described in this Chapter; however, the findings were not included in the geostatistical models.

The conclusion indicates that CE risk expanded across Xiji during the study period, while AE risk became more confined in communities located in the south of the county. These changes were partially explained by selected climatic and land cover factors.

Supplementary material for this paper is provided in Appendix D.

5.2 Environmental risk factors and changing spatial patterns of human exposure to *Echinococcus* spp. in Xiji County, Ningxia Hui Autonomous Region, China

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Environmental risk factors and changing spatial patterns of human seropositivity for *Echinococcus* spp. in Xiji County, Ningxia Hui Autonomous Region, China

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Abstract

Background: Human echinococcoses are parasitic helminth infections that constitute a serious public health concern in several regions across the world. Cystic (CE) and alveolar echinococcosis (AE) in China represent a high proportion of the total global burden of these infections. This study was conducted to predict the spatial distribution of human seropositivity for *Echinococcus* species in Xiji County, Ningxia Hui Autonomous Region (NHAR), with the aim of identifying communities where targeted prevention and control efforts are required.

Methods: Bayesian geostatistical models with environmental and demographic covariates were developed to predict spatial variation in the risk of human seropositivity for *Echinococcus granulosus* (the cause of CE) and *E. multilocularis* (the cause of AE). Data were collected from three cross-sectional surveys of school children conducted in Xiji County in 2002–2003, 2006–2007 and 2012–2013. Environmental data were derived from high-resolution satellite images and meteorological data.

Results: The overall seroprevalence of *E. granulosus* and *E. multilocularis* was 33.4 and 12.2%, respectively, across the three surveys. Seropositivity for *E. granulosus* was significantly associated with summer and winter precipitation, landscape fragmentation variables and the extent of areas covered by forest, shrubland, water and bareland/artificial surfaces. Seropositivity for *E. multilocularis* was significantly associated with summer and winter precipitations, landscape fragmentation variables and the extent of shrubland and water bodies. Spatial correlation occurred over greater distances for *E. granulosus* than for *E. multilocularis*. The predictive maps showed that the risk of seropositivity for *E. granulosus* expanded across Xiji during the three surveys, while the risk of seropositivity for *E. multilocularis* became more confined in communities located in the south.

Conclusions: The identification of high-risk areas for seropositivity for these parasites, and a better understanding of the role of the environment in determining the transmission dynamics of *Echinococcus* spp. may help to guide and monitor improvements in human echinococcosis control strategies by allowing targeted allocation of resources.

Keywords: Human echinococcoses, *Echinococcus granulosus*, *E. multilocularis*, Environment, Geographical information systems, Remote sensing, Xiji County, Ningxia Hui Autonomous Region

Background

Cystic echinococcosis (CE), caused mainly by infection with *Echinococcus granulosus*, and alveolar echinococcosis (AE), caused by infection with *E. multilocularis*, are chronic and potentially fatal diseases that have a wide geographical distribution across the world.

According to global estimates, the number of new cases of CE is 188,000 every year, which represents a human health burden of 184,000 disability adjusted life years (DALYs) [1]. There are 18,235 new AE cases annually, which result in approximately 666,433 DALYs lost [2].

China is a country affected heavily by human echinococcoses [3]. In China, the nationally estimated numbers of CE and AE cases explain 40 and 95% of the total global burden of the infections, respectively [2, 4]. The second survey of parasitic diseases conducted in China in 2001–2004 found that approximately 380,000 people were affected by these two types of echinococcoses, and 50 million were at risk of infection nationwide [5]. Prevalence of CE and AE was particularly high in seven provinces/autonomous regions located in Western China: Qinghai, Gansu, Sichuan, Xinjiang Uighur Autonomous Region (AR), Tibet AR, Ningxia Hui AR and Inner Mongolia AR [6, 7]. However, regional and local variation in echinococcosis risk is high, with the diseases being particularly prevalent among poor pastoral minority groups [2, 8, 9].

The National Control Programme to prevent and cure echinococcoses in China was developed by the National Health and Family Planning Commission (formerly the Ministry of Health) in 2005 [6]. To date, applying and sustaining the programme has proven difficult in most endemic regions due to the lack of effective surveillance data, dispersed populations and movement of people and livestock to summer pastures [10]. Screening surveys to detect early cases are primarily conducted in the most-affected regions of China [6, 11]. Therefore, the national prevalence reports may be biased [10,

11]. Because human echinococcoses are characterised by long incubation periods that precede clinical diagnoses, current epidemiological estimates may be overlooking the relative contribution of asymptomatic or undiagnosed/untreated CE and AE cases [10]. Consequently, better surveillance and response tools are required to estimate and predict the real impact of these two diseases in China, and to strengthen the implementation of prevention and control interventions in targeted high-risk areas [12].

Echinococcus granulosus is primarily maintained in life-cycles that involve domestic animals, while *E. multilocularis* is typically a wildlife parasite [13]. Both species are transmitted in multi-host systems that are determined by factors that govern the presence/absence and infectivity of the parasites and also the population dynamics and interactions of the hosts [13]. Thus, special emphasis is currently being placed on identifying the role of environment factors in influencing the transmission patterns of *E. granulosus* and *E. multilocularis* and explaining the apparent emergence and re-emergence of human infections in several regions of the world [14–18]. The Chinese government is implementing a series of extensive landscape regeneration projects to restore the country's degraded ecological landscape [19, 20]. Studies conducted in various echinococcosis-endemic regions have documented that land cover transformations are related to higher population densities of key intermediate hosts for *E. multilocularis*, which has increased the risk of human AE infection [21–28]. Hence, research also needs to be conducted to better describe the ecological processes that may lead to variations in the transmission patterns of *E. granulosus* and *E. multilocularis* based on shifting environmental factors [29]. This information will be essential to monitor emergence or re-emergence of the transmission of both parasites [29].

Bayesian model-based geostatistical approaches have been increasingly used in research focused on characterising the geographical patterns of infectious diseases and

quantifying their associations with potential risk factors [1, 30–33]. Model-based geostatistics incorporates a model of the spatial correlation structure of the data with the effect of covariates to predict a variable of interest (e.g. seropositivity for *Echinococcus* spp.) in unsampled locations, and to quantify the associated uncertainty in the estimated parameter values [34]. These methods provide a valuable and flexible framework that can be used to support the process of decision-making during the implementation of a control programme [34].

Using Bayesian model-based geostatistics, we aimed to explain the spatiotemporal distribution of human seropositivity for *E. granulosus* and *E. multilocularis* in Xiji County, Ningxia Hui Autonomous Region (NHAR), China, based on selected environmental factors. In the study, the term human seropositivity was meant to signify that children harboured possibly the metacestode stage of *E. granulosus* and/or *E. multilocularis*, whether or not they had evidence of active cyst(s) in the abdominal ultrasound or any manifestation of disease (following the description of a possible echinococcosis case suggested elsewhere [35]). Also, we aimed to produce spatial prediction maps to show the evolving geographical distribution of seropositivity for these parasites species at three different time points during the last decade. These maps will be useful to inform decisions on where communities at high risk of echinococcoses are located in China, and to help prioritise and target resources for prevention and control.

Methods

Study area

Xiji is a County located in the south of NHAR, between latitudes 35°33' and 36°13'N, and between longitudes 105°20' and 106°4'E. Xiji covers an area of approximately 3985 km² and shares borders with Haiyuan County to the north, Guyuan County to the east,

Longde County to the south, and Huining and Jinning Counties that belong to Gansu Province, to the west. Administratively, Xiji is divided into 3 towns and 16 townships, which are then subdivided into 306 villages. In 2015, the total population was 344,045 inhabitants, of whom 58% were of the Hui Islamic ethnic minority and 42% were Han Chinese [36] (Fig. 1).

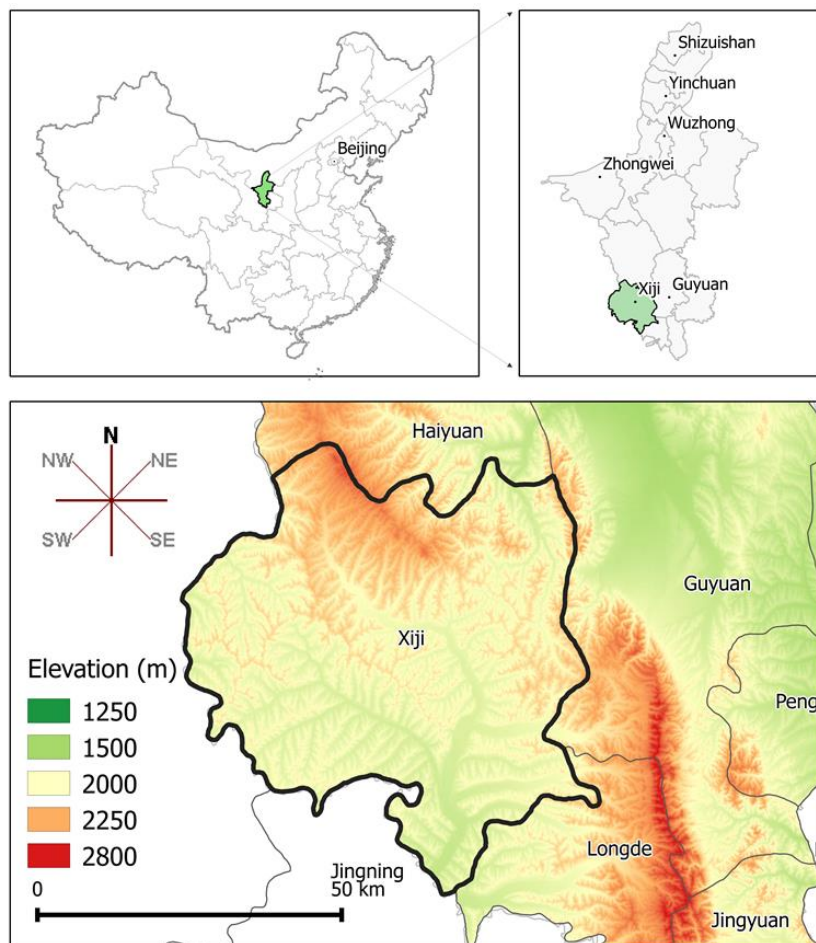


Fig. 1 Map and elevation of Xiji County and its location within NHAR, and the location of the Autonomous Region within China

Xiji lies in a temperate continental monsoon climate zone that is characterized by four distinct seasons. The annual average temperature is 5.37 °C and the average annual precipitation is 418.2 mm. Elevation ranges from 1688 to 2633 m.

Xiji County was selected as the study area because a previous retrospective survey of hospital records conducted in NHAR indicated that high prevalences of human echinococcoses, particularly AE, were concentrated mainly in the southern part of the Autonomous Region, where Xiji is located [37].

Data on human seropositivity for *E. granulosus* and *E. multilocularis*

Data were obtained from cross-sectional school-based surveys conducted across Xiji County during three distinct time periods: 2002–2003, 2006–2007 and 2012–2013. Surveys were carried out at 190, 219 and 25 locations for each time period, respectively, and included all children aged 6–18 years who lived in close proximity to the surveyed schools and agreed to participate (Fig. 2). This age-group was selected in order to ensure that the collected data were representative of recent cases of human exposure.

Exposure information and demographic data were collected with standardised questionnaires that were administered to the students by school teachers. Participants were also asked to provide a small blood sample from the ear lobe for specific antibody testing by enzyme linked immunosorbent assay (ELISA) using *E. granulosus* cyst fluid antigen B (EgB) and *E. multilocularis* crude protoscolex extract (EmP) [38]. Sensitivity of EgB and EmP ELISA is > 85% for CE and > 90% for AE, respectively [23, 38, 39]. Specificity ranges from 70 to 100% for CE [40] and 87% for AE [39]. Finally, abdominal ultrasound was used to screen schoolchildren and detect and classify early CE and/or AE cysts. The World Health Organization classification scheme of CE and AE was used to categorise the hepatic lesions [41–43]. Due to the young age of the study population and the slow rate of growth of the echinococcosis cysts, a very limited number of ultrasounds showed undefined hepatic changes. Therefore, the results were not included in the statistical models. Participants who were found to be positive for *E. granulosus*, *E.*

multilocularis or both were referred to the local health centre for adequate follow-up. Data collected previously from hospital records and landscape profiles were used for the selection of the schools for the first survey [44]. Details of the survey design from 2002 to 2003, data collection and acquisition of ethical approval are reported elsewhere [44]. The survey conducted in 2006–2007 followed the same protocol. A grid plus close pair design was used to select the schools for the survey in 2012–2013 [45]. A 15×15 km grid was created in a geographical information system, and overlaid on the county territory, noting that this survey also covered three other counties (data not presented here). The schools lying in closest proximity to the grid nodes were selected. A secondary set of schools located in near proximity to a random subset of those selected at the nodes of the grid (the close pairs) were also selected. This approach has been identified as the most efficient survey design for estimating spatial variability in environmental variables (Additional file 1) [45].

The geographical coordinates of each school were collected using a hand-held global positioning system. The locations of surveyed schools are shown in Fig. 2. Data collected from the three surveys were combined into a single database.

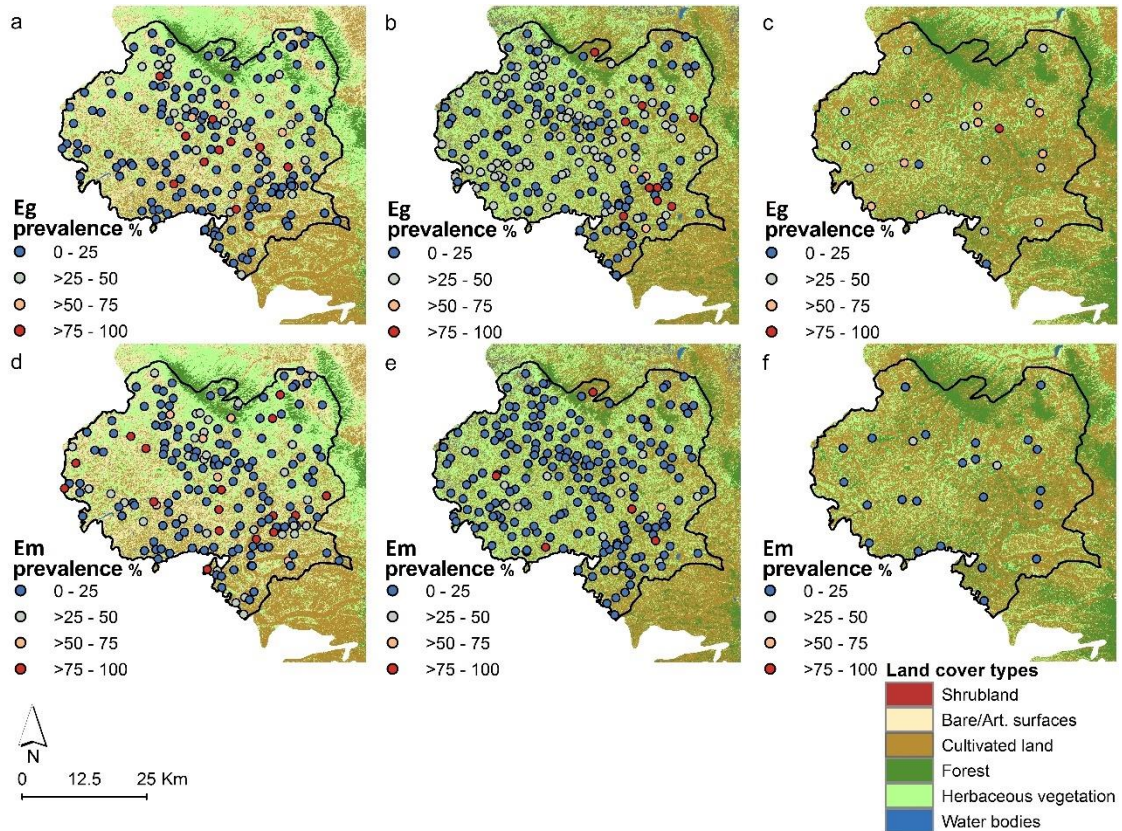


Fig. 2 Distribution of school surveys and observed seropositivity for *Echinococcus granulosus* and *E. multilocularis* in 2002–2003 (a, d), 2006–2007 (b, e) and 2012–2013 (c, f) in Xiji County, NHAR, China. A surface of the different land cover types in 2000, 2005 and 2010, respectively, is also presented

Environmental and remotely sensed data

The independent variables included in the analysis were derived from the following data sets: monthly mean temperature and precipitation, elevation, enhanced vegetation index (EVI) and land cover class.

Monthly mean temperature and precipitation data records for the period January 1 1998 to December 31 2013 were provided by the Chinese Academy of Sciences in a raster format at the spatial resolution of 1 km. Data were first collected from 16 local weather stations and interpolated using the Inverse Distance Weighting (IDW) method, but the original weather station data were not available.

Estimates of elevation were obtained from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM)

version 2 [46]. The ASTER GDEM is available in the USGS Earth Explorer website in GeoTIFF format at the resolution of 1 arcsecond (approximately 30 m).

Thirty metre resolution Landsat EVI data were obtained from the Earth Resources Observation and Science (EROS) Center Science Processing Architecture (ESPA) On Demand Interface [47]. Data were downloaded annually for the period 1998–2012. To the greatest extent possible, EVI data were acquired from a month between June and November each year for the period 1998–2012. These months correspond to the growing seasons in NHAR. However, acquisition dates varied depending on the availability of the data. When there were no data available for the specified months, the closest-in-time EVI estimates were downloaded for the analyses.

Land cover maps for the years 1996, 2000, 2005, 2010 and 2015 were produced using time-series images retrieved from the Landsat Surface Reflectance Climate Data Record available in Earth Explorer [48]. Six land cover classes were identified: water bodies, artificial surfaces, bare or sparsely vegetated areas, herbaceous vegetation, cultivated land, shrubland and forest (Table 1). Artificial surfaces and bare or sparsely vegetated areas were merged and represented as a single category in the maps and analyses due to significant spectral confusion between them. Details of the original images and the process of land cover classification are provided elsewhere [49].

An administrative boundary map of Xiji was downloaded from the DIVA-GIS website [50]. School survey locations were imported into ArcGIS software version 10.3.1 [51] and projected to the Universal Transverse Mercator (UTM) coordinate system zone 48N. Buffer zones of 1 km and 5 km centred on the survey site locations were created using ArcGIS software. All data sets were imported into ArcGIS and linked spatially to the surveyed schools to extract and summarise the environmental data by buffer area.

Table 1
Land cover classification scheme and definitions

| Land cover type | Description | Content |
|----------------------------------|--|--|
| Water bodies | All areas of water | Streams and canals, lakes, reservoirs, bays and estuaries |
| Artificial surfaces | Land modified by human activities | Residential areas, industrial and commercial complexes, transport infrastructure, communications and utilities, mixed urban or built-up land and other built-up land |
| Bare or sparsely vegetated areas | Areas with little or no “green” vegetation present | Dry salt flats, sandy areas, bared exposed rock and mixed barren land |
| Herbaceous vegetation | Areas characterized by natural or semi-natural vegetation | Grasses and forbs |
| Cultivated land | Areas where the natural vegetation has been removed/modified and replaced by other types of vegetative cover that have been planted for specific purposes such as food, feed and gardening | Cropland and pasture, orchards, groves, vineyards, nurseries and ornamental horticultural, other cultivated land |
| Shrubland | Natural or semi-natural woody vegetation with aerial stems less than 6 m tall | Evergreen and deciduous species of true shrubs and trees or shrubs that are small or stunted |
| Forest | Areas characterized by tree cover or semi-natural woody vegetation greater than 6 m tall | Deciduous forest, evergreen forest and mixed forest |

Data analysis

Summary statistics were calculated at each location at the time of the survey and at a 5-year lag. A moving 5-year average (MA) was also generated to smooth the estimates of the independent variables. The incorporation of a MA into the analyses allowed assessment of associations over an extended period of time rather than at a single point in time, accounting for the variable latency period of infection. For each location, the summary statistics computed were: (i) annual, summer (June, July and August) and winter (December, January and February) weighted mean series of temperature and precipitation, (ii) spatial mean values of elevation and EVI. The spatial extents (as a percentage of buffer areas) of each land cover category for the years 1996, 2000, 2005, 2010 and 2015 were extracted and used to calculate change rates by buffer area for the periods 1996–2000, 2000–2005, 2005–2010, and 2010–2015. In this way, it was possible to estimate the spatial extent of all land cover classes by buffer area for all years between 1998 and 2012.

The land reform policies and incentive programs to recover degraded land in China might have impacted on landscape fragmentation [52], which could impact on habitat availability for *Echinococcus* spp. intermediate hosts. The five landscape fragmentation metrics that were selected for the analyses were: number of patches (NumP), patch density (PD), mean patch size (MPS), mean shape index (MSI) and edge density (ED) (Table 2). These fragmentation metrics were selected because they provide information about landscape composition, shape, and configuration [53]. These metrics were computed using the Patch Analyst extension of ArcGIS [13].

Table 2

Description of the landscape fragmentation metrics that were included in the analyses of human seropositivity for *E. granulosus* and *E. multilocularis* in Xiji County

| Metric | Description | Units |
|--------------------------|---|---|
| Composition | | |
| Number of patches (NumP) | Total number of patches within a buffer | – |
| Patch density (PD) | Total number of patches per buffer area | /km ² |
| Mean patch size (MPS) | Average patch size within a buffer | km |
| Shape | | |
| Mean shape index (MSI) | Ratio of perimeter to area adjusted by a constant to account for a particular patch shape | – |
| Configuration | | |
| Edge density (ED) | Amount of edge relative to the buffer area | km/km ² (perimeter/area ratio) |

Variable selection

In order to examine separately the association of *E. granulosus* and *E. multilocularis* seropositivities with the environmental factors, univariate logistic regression models were implemented for each parasite exposure using R software version 3.2.2. [54]. Collinearity among all independent variables was assessed using Spearman correlation analyses. If a pair of covariates had a correlation coefficient > 0.9 , the variable with the highest value of Akaike Information Criterion (AIC) in the univariate regression models was discarded. Multivariate logistic regression models were developed using various subsets of available independent variables. The models with the lowest values of AIC

were used to select the variables for the final, spatial models. Nonlinear associations between all covariates and *E. granulosus* and *E. multilocularis* seropositivities were modelled using quadratic terms, and no interactions were considered.

Bayesian geostatistical models

Model-based geostatistics was implemented in a Bayesian framework [55] using the OpenBUGS software 3.2.3 rev 1012 [56].

Two distinct models for each of *E. granulosus* and *E. multilocularis* serological status, including parameters for the environmental variables were constructed. The first model (Model I) was developed including the selected explanatory variables for each seropositivity, but without considering the spatial dependence structure of the data; the second model (Model II) assumed that spatial autocorrelation is present in the relative risk of seropositivity. Hence, Model II included the explanatory variables as fixed-effects and a spatially structured random effect. Model fit was compared using the deviance information criterion (DIC), where low DIC values indicate a better model fit. In all analyses, statistical significance was determined with α -levels of 0.05 [as indicated by 95% credible intervals (95% CrI) for odds ratios (OR) that excluded 1].

The complete model, Model II, was a logistic regression model that assumed that Y_i ($Y_i = 1$ for seropositive schoolchildren and 0 for seronegative schoolchildren) followed a Bernoulli distribution where Y_{ij} was the serological status of the i th child ($i = 1 \dots 5,110$) in the j th location ($j = 1 \dots 434$), and p_{ij} was the probability an individual i being exposed in location j , that is,

$$Y_{ij} \sim \text{Bern}(p_{ij})$$

$$\text{logit}(p_{ij}) = \alpha_{\varepsilon} + \gamma \times \text{age}_i + \delta \times \text{female}_i + \sum_{z=1}^Z \beta_z \times \lambda_{zj} + s_j$$

where α_ϵ is the survey specific intercept, γ and δ are the coefficients for age and females respectively, β is a matrix of z coefficients, λ is a matrix of z environmental covariates, and s_j a geostatistical random effect. The spatial correlation structure of the geostatistical random effect was defined by an exponential function of the distance between points:

$$f(d_{ab}; \phi) = \exp[-\phi d_{ab}]$$

where d_{ab} are the distances between pairs of points a and b , and ϕ is the rate of decline of spatial correlation per unit of distance. A normal distribution was specified for the intercept and the coefficients (normal prior with mean = 0 and precision, the inverse of variance, = 1×10^{-3}). The priors distribution of ϕ was uniform with upper and lower bounds set at 0.09 and 100 (the lower bound set to ensure spatial correlation at the maximum separating distance between survey locations was < 0.5). The priors for the precision ($1/\sigma^2$) were specified using a non-informative gamma distribution (with shape and scale parameter values of 0.001 and 0.001, respectively).

A burn-in of 1000 iterations was run and discarded. Subsequent sets of 10,000 iterations were run and examined for convergence. Convergence was determined by visual inspection of history and density plots. The runs were also examined for autocorrelation by visual inspection of the autocorrelation plots. Because autocorrelation was observed for all variables, thinning of simulations was applied for subsequent sampling by storing every 10th iteration. Convergence was achieved successfully for all variables in each model at approximately 100,000 iterations. The last 10,000 values from the posterior distributions of each model parameters were stored for the analysis. The rate of decay of correlation between locations (ϕ) with distance and the variance of the spatial component (σ^2) were also recorded.

The *spatial.unipred* function in OpenBUGS was used for spatial prediction at non-sample locations (defined using a regular 1 x 1 grid overlying the entire Xiji

territory). This function applies the model equation at each prediction location using the covariates values extracted for prediction locations and an interpolated value for the geostatistical random effects.

ArcGIS was used to generate maps that represent the posterior distributions of predicted seropositivity for *E. granulosus* and *E. multilocularis* in Xiji County.

Results

Sample description

The final data set consisted of 434 school locations and a total of 5110 schoolchildren aged 6–18 years who were screened for human echinococcoses. The surveys involved 845 students in 2002–2003, 2588 in 2006–2007 and 1677 in 2012–2013. The overall seroprevalences of *E. granulosus* and *E. multilocularis* were 33.4 and 12.2%, respectively, ranging from 0 to 100% by school for both parasites. In the first survey, the seroprevalence of *E. multilocularis* among schoolchildren was higher (18.1%) than the seroprevalence of *E. granulosus* (16.8%). However, seropositivity for *E. granulosus* became more common in the second and third survey with seroprevalences of 30.9 and 45.6% compared to seroprevalences of *E. multilocularis* of 12.8% and 8.4%, respectively (Table 3). An abnormal hepatic image compatible with a CE case (0.02% of the total number of schoolchildren in the study) and a query lesion (0.02%) were observed in two different participants in the first survey. Both cases were seropositive for *E. granulosus*. Calcified lesions were also observed in 8 (0.1%) participants in the first survey and 14 (0.3%) participants in the second survey. Among participants with calcifications, 4 (0.01%) were seropositive for *E. granulosus* and 2 (0.03%) were seropositive for *E. multilocularis*. Other asymptomatic liver abnormalities were reported in 4 (0.01%) participants, who were seronegative for both parasite species, in the second survey. The

mean age of participants with seropositivity for *E. granulosus* was 12.9 years [median: 13; standard deviation (SD): 2.9], and the mean age for those with seropositivity for *E. multilocularis* was 13.3 years (median: 14; SD: 2.9).

Figure 2 displays the observed spatial distributions of the seroprevalence of *E. granulosus* and *E. multilocularis* by schools for the three surveys. The maps confirm that seropositivity for *E. granulosus* became more widespread in Xiji County over time, while the distribution of *E. multilocularis* seropositivity became more confined.

Table 3

Human seroprevalence of *Echinococcus granulosus* and *E. multilocularis* infection stratified by gender from three school-based surveys conducted in Xiji County in 2002–2003 (survey 1), 2006–2007 (survey 2) and 2012–2013 (survey 3)

| | <i>E. granulosus</i> | | <i>E. multilocularis</i> | | Total <i>n</i> (%) |
|----------|--------------------------|--------------------------|--------------------------|--------------------------|-----------------------|
| | Positive <i>n</i> (%) | Negative <i>n</i> (%) | Positive <i>n</i> (%) | Negative <i>n</i> (%) | |
| Survey 1 | 142 (16.8) | 703 (83.2) | 153 (18.1) | 692 (81.9) | 845 (100) |
| Survey 2 | 799 (30.9) | 1789 (69.1) | 331 (12.8) | 2257 (87.2) | 2588 (100) |
| Survey 3 | 765 (45.6) | 912 (54.4) | 141 (8.4) | 1536 (91.5) | 1677 (100) |
| Total | 1706 (33.4) | 3404 (66.6) | 625 (12.2) | 4485 (87.8) | 5110 (100) |

Bayesian geostatistical models

Based on DIC estimates, the Bayesian spatial models (Models II) of seropositivities for *E. granulosus* and *E. multilocularis* were the best-fitting models (Tables 4 and 5). In Model II of *E. granulosus*, girls had a 15.0% (95% CrI: 1.7–29.8%) higher risk of exposure than boys. Also, within the 1 km buffers, there was a 0.7% increase in the odds of seropositivity (95% CrI: 0.4–0.9%) for an increase of 1 mm in summer mean

precipitation at the time of the survey, and 6.5% increase (95% CrI: 2.0–10.9%) with 1% increase in water extent at the five-year lag. Forest, shrubland and water coverage in the 5 km buffers were also positively associated with the risk of *E. granulosus*. There were estimated increases of 2.2% (95% CrI: 0.5–3.9%), 194.3% (95% CrI: 44.7–523.1%) and 18.8% (95% CrI: 1.4–38.5%) in the odds of seropositivity for *E. granulosus* for a 1% increase in the extent of forest at the time of the survey, and the extent of shrubland and water at five-year lags. There was a decrease of 2.8% (95% CrI: 0.4–4.8%) in the odds of seropositivity for every year of age. The odds of seropositivity for *E. granulosus* decreased 1.6% (95% CrI: 0.8–2.6%) with a unit increase in NumP, 64.7% (95% CrI: 26.1–82.8%), with 1 km increase in MPS, 6.8% (95% CrI: 4.3–9.3%) with a 1 mm increase in winter mean precipitation and 1.7% (95% CrI: 0.2–3.2%) with a 1% increase in the coverage of bareland/artificial surfaces. In Model II, the variance of the spatially structured random effect increased from 8.4×10^4 (1.6×10^4 to 4.1×10^3) in the first survey to 1.2×10^3 (2.4×10^4 to 4.4×10^3) in the second survey. From this value, the variance decreased to 7.2×10^4 (1.7×10^4 to 2.8×10^3) in the final survey. These findings imply that the amount of spatial variability in the data changed over time with the distribution of seropositive cases becoming more homogeneous at the end of the study period (Table 4).

Table 4

Regression coefficients, ORs and 95% CrI from the Bayesian spatial model (Model II) for human seropositivity for *Echinococcus granulosus* in three school-based surveys conducted in Xiji County in 2002–2003, 2006–2007 and 2012–2013

| Model | Coefficient, posterior mean (95% CrI) | OR, posterior mean (95% CrI) |
|--|--|------------------------------------|
| α_1 (Intercept study 1) | -0.23 (-1.79–1.27) | – |
| α_2 (Intercept study2) | 0.94 (-0.74–2.56) | – |
| α_3 (Intercept study 3) | 0.38 (-1.10–1.76) | – |
| Female ^a | 0.14 (0.02–0.26) | 1.15 (1.01–1.29) |
| Age | -0.03 (-0.05– -0.01) | 0.97 (0.95–0.99) |
| Summer precipitation same year (1 km) | 0.01 (0.00–0.01) | 1.01 (1.01–1.02) |
| EVI same year (1 km) | -5.12×10^4 (-5.10×10^4 – 4.91×10^4) | 0.99 (0.99–1.00) |
| Cultivated land same year (1 km) | 3.24×10^3 (-3.22×10^3 – 9.94×10^3) | 1.00 (0.99–1.01) |
| Water bodies 5 years prior (1 km) | 0.06 (0.02–0.10) | 1.06 (1.02–1.10) |
| Forest same year (1 km) | 0.01 (-6.95×10^4 –0.02) | 1.00 (0.99–1.01) |
| NumP 5-year average (1 km) | -0.01 (-0.02– -0.01) | 0.98 (0.97–0.99) |
| PD 5-year average (1 km) | 1.08 (-0.23–2.83) | 2.95 (0.79– 16.89) |
| MPS 5-year average (1 km) | -1.04 (-1.76– -0.30) | 0.35 (0.17–0.73) |
| Winter precipitation same year (5 km) | -0.07 (-0.09– -0.04) | 0.93 (0.91–0.95) |
| Bareland/art surfaces same year (5 km) | -0.02 (-0.03– -0.01) | 0.98 (0.96–0.99) |
| Forest same year (5 km) | 0.02 (0.01–0.03) | 1.02 (1.01–1.03) |
| Water bodies 5 years prior (5 km) | 0.17 (0.01–0.32) | 1.18 (1.01–1.38) |
| Herbaceous vegetation 5 years prior (1 km) | 0.01 (-0.01–0.02) | 1.01 (0.99–1.02) |
| Shrubland 5 years prior (5 km) | 1.08 (0.36–1.82) | 2.94 (1.44–6.23) |
| Cultivated land 5 years prior (5 km) | -0.01 (-0.02–0.01) | 0.98 (0.97–1.10) |
| MPS 5 years prior (5 km) | -0.14 (-0.54–0.17) | 0.86 (0.58–1.19) |
| Heterogeneity structured (survey 1) | 8.40×10^4 (1.63×10^4 – 4.12×10^3) | – |
| Heterogeneity structured (survey 2) | 1.18×10^3 (2.42×10^4 – 4.42×10^3) | – |
| Heterogeneity structured (survey 3) | 7.18×10^4 (1.75×10^4 – 2.79×10^3) | – |
| ϕ_1 (Decay of spatial correlation survey 1) | 0.61 (0.04–1.31) | – |
| ϕ_2 (Decay of spatial correlation survey 2) | 0.19 (0.03–0.56) | – |
| ϕ_3 (Decay of spatial correlation survey 3) | 0.17 (0.02–0.50) | – |

^aReference category: gender (male)

Abbreviations: ORs, Odds ratios; 95% CrI, 95% credible interval; DIC, deviance information criterion

Model II of *E. multilocularis* seropositivity showed that, within the 1 km buffers, there was an increase of 0.6% (95% CrI: 0.3–0.9%) in the odds of seropositivity for a 1 mm increase in summer mean precipitation. Also, 82.6% (95% CrI: 27.4–150.5%) and 0.5% (95% CrI: 0.02–1.00%) increases in the odds of seropositivity for increases of 1% in the 5-year average of water coverage and 1 km/km² of ED, respectively. The odds of seropositivity for *E. multilocularis* decreased 1.5% (95% CrI: 0.7–2.2%) with a unit increase in NumP, and by 10.6% (95% CrI: 4.6–16.1%) with a 1 mm increase in winter mean precipitation. The odds of seropositivity also decreased 79.4% (95% CrI: 25.8–94.8%) with a 1% increase in the coverage of shrubland. The variance of the spatial random effects decreased from 3.1×10^3 (5.3×10^4 to 9.2×10^3) in survey 1 to 2.3×10^3 (3.1×10^4 to 5.3×10^3) in survey 2 and to 2.3×10^3 (3.1×10^4 to 5.3×10^3) in survey 3.

The values of the decay parameter for spatial correlation (ϕ) in the model of *E. granulosus* seropositivity were 0.6 in the first survey, 0.2 in the second survey and 0.2 in the third survey. These estimates indicate that after accounting for the effect of covariates, the radii of the clusters were approximately 555, 1752 and 1959 km, respectively (ϕ is measured in decimal degrees, therefore, the cluster size is calculated dividing 3 by ϕ ; at the equator, one decimal degree is approximately 111 km). The same values in the model of seropositivity for *E. multilocularis* were 0.07, 0.10 and 0.26, for surveys 1, 2 and 3, with cluster sizes of 4757, 3330 and 1280 km, respectively. These results imply that spatial correlation in the risk of seropositivities for *E. granulosus* and *E. multilocularis* was evident between schools with relatively large distances separating them.

Table 5 Regression coefficients, ORs and 95% CrI from Bayesian spatial model (Model II) for human seropositivity for *Echinococcus multilocularis* in three school-based surveys conducted in Xiji County in 2002–2003, 2006–2007 and 2012–2013

| Model/Variable | Coefficient, posterior mean (95% CrI) | ORs, posterior mean (95% CrI) |
|--|--|-------------------------------|
| α_1 (Intercept study 1) | -2.25 (-3.38– -1.39) | – |
| α_2 (Intercept study2) | -1.75 (-2.47– -0.94) | – |
| α_3 (Intercept study 3) | -2.88 (-3.90– -2.13) | – |
| Female ^a | 0.09 (-0.11–0.24) | 1.09 (0.89–1.28) |
| Age | -0.01 (-0.03–0.02) | 0.99 (0.96–1.02) |
| Summer precipitation same year (1 km) | 6.53×10^3 (3.40×10^3 – 9.31×10^3) | 1.01 (1.01–1.02) |
| EVI same year (1 km) | 4.97×10^6 (7.10×10^4 – 6.21×10^4) | 1.00 (0.99–1.00) |
| Bareland/Art surfaces same year (1 km) | -0.02 (-0.05–0.01) | 0.99 (0.99–1.00) |
| Cultivated land 5 years prior (1 km) | 0.01 (-0.01–0.02) | 1.01 (0.99–1.02) |
| Cultivated land same year (1 km) | -0.01 (-0.01–0.01) | 0.99 (0.98–1.01) |
| Herbaceous vegetation 5-year average (1 km) | -0.01 (-0.01–0.01) | 0.99 (0.98–1.00) |
| Water bodies average (1 km) | 0.60 (0.24–0.91) | 1.82 (1.27–2.50) |
| Forest same year (1 km) | -0.01 (-0.01–0.01) | 1.00 (0.99–1.01) |
| NumP 5-year average (1 km) | -0.01 (-0.02– -0.01) | 0.98 (0.97–0.99) |
| MPS 5-year average (1 km) | -0.19 (-0.68–0.13) | 0.82 (0.50–1.14) |
| ED 5-year average (1 km) | 5.11×10^3 (2.10×10^4 – 9.97×10^3) | 1.01 (1.01–1.02) |
| Elevation (5 km) | 3.99×10^4 (1.64×10^3 – 1.00×10^3) | 0.99 (0.99–1.01) |
| Winter precipitation 5-year average (5 km) | -0.11 (-0.17– -0.04) | 0.89 (0.83–0.95) |
| Summer temperature 5 years prior (5 km) | -0.01 (-0.38–0.35) | 0.99 (0.67–1.42) |
| Forest 5-year average (5 km) | 0.01 (-0.01–0.01) | 1.00 (0.99–1.01) |
| Water bodies 5 years prior (5 km) | 0.02 (-0.16–0.20) | 1.02 (0.84–1.23) |
| Water bodies 5-year average (5 km) | -0.02 (-0.07–0.01) | 0.97 (0.92–1.01) |
| Shrubland 5 years prior (5 km) | -1.58 (-2.95– -0.29) | 0.20 (0.05–0.74) |
| Shrubland same year (5 km) | 0.95 (-0.45–2.10) | 2.59 (0.63–8.23) |
| Cultivated land same year (5 km) | -0.01 (-0.02–0.01) | 0.99 (0.97–1.01) |
| NumP same year (5 km) | 1.66×10^4 (1.25×10^4 – 4.71×10^4) | 1.01 (0.99–1.01) |
| Heterogeneity structured (survey 1) | 3.09×10^3 (5.33×10^4 – 9.19×10^3) | – |
| Heterogeneity structured (survey 2) | 2.29×10^3 (3.11×10^4 – 5.28×10^3) | – |
| Heterogeneity structured (survey 3) | 2.29×10^3 (3.11×10^4 – 5.28×10^3) | – |
| ϕ_1 (Decay of spatial correlation survey 1) | 0.07 (0.01–0.23) | – |
| ϕ_2 (Decay of spatial correlation survey 2) | 0.10 (0.02–0.40) | – |
| ϕ_3 (Decay of spatial correlation survey 3) | 0.26 (0.09–0.52) | – |
| DIC | 3697 | – |

^aReference category: gender (male)

Abbreviations: OR, odds ratio; 95% CrI, 95% credible interval; DIC, deviance information criterion

Spatial predictions

Maps of the mean and SD of the posterior distributions of predicted seroprevalence of *E. granulosus* for the years 2002–2003, 2006–2007 and 2012–2013 are shown in Fig. 3. The north-central part of the county was an area with persistent high predicted seroprevalence during the surveys, with the range of high seroprevalence areas expanding to cover the entire county by the time of the third survey. Prediction uncertainty was generally higher in the central and eastern parts of the county.

Maps of the mean and SD of the posterior distributions of predicted seroprevalence of *E. multilocularis* are presented in Fig. 4. Areas of high predicted seroprevalence in the north, northeast and centre of the county gradually decreased from survey 1 to survey 3, leaving some residual foci of high seroprevalence in the central north and southwest parts of the county. Maps of the posterior SDs demonstrate that the level of uncertainty increased over time.

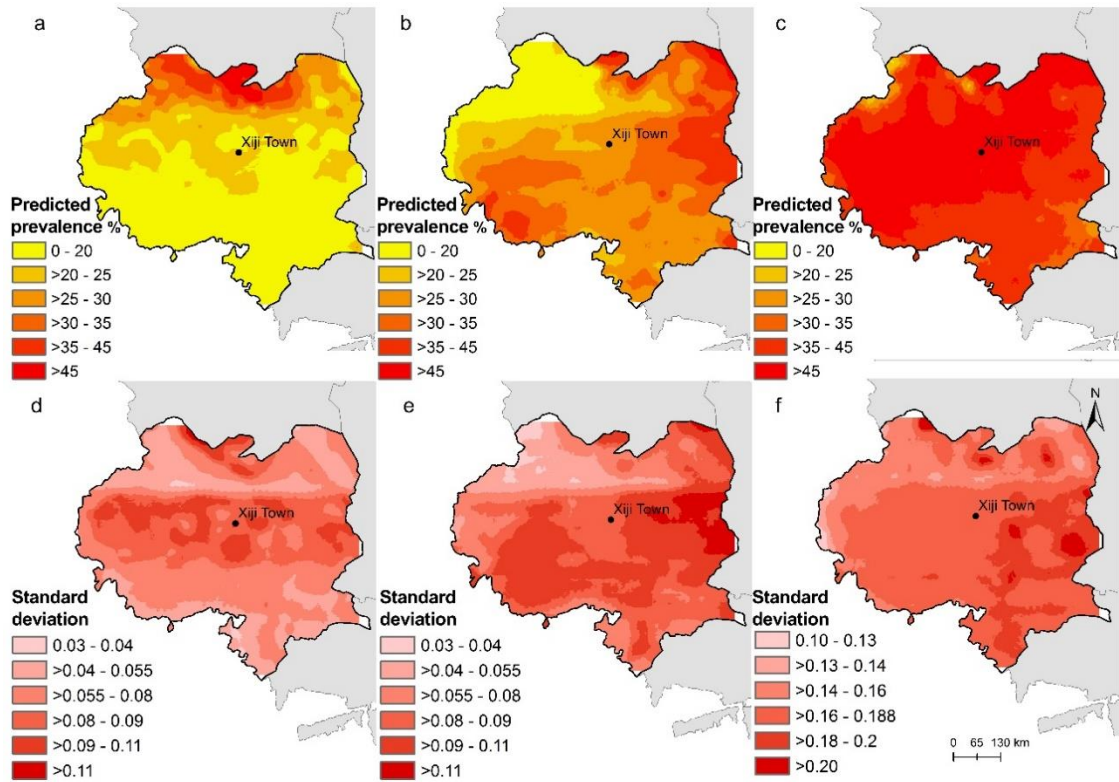


Fig. 3 Spatial distribution of predicted seropositivity for *Echinococcus granulosus* in schoolchildren aged 6–18 years and standard deviations in 2002–2003 (a, d), 2006–2007 (b, e) and 2012–2013 (c, f) in Xiji County, NHAR, China

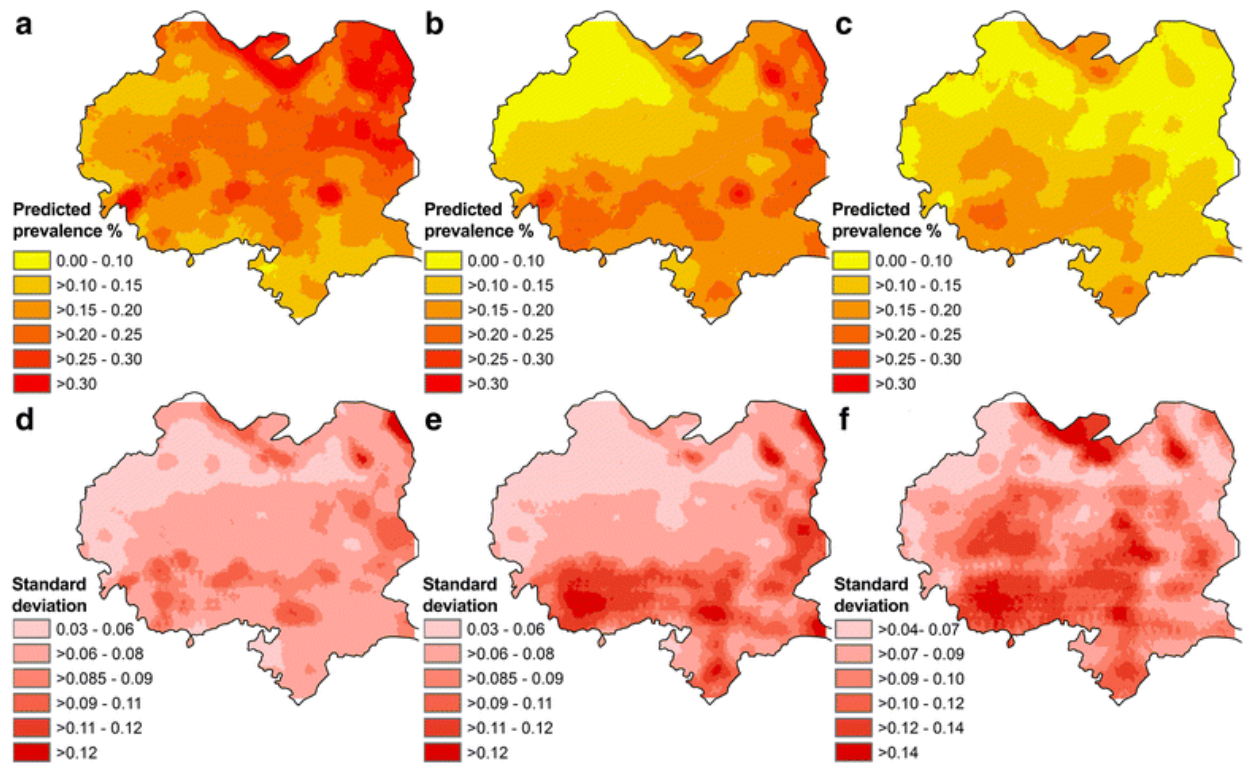


Fig. 4 Spatial distribution of predicted seropositivity for *Echinococcus multilocularis* in schoolchildren aged 6–18 years and standard deviations in 2002–2003 (a, d), 2006–2007 (b, e) and 2012–2013 (c, f) in Xiji County, NHAR, China

Discussion

In this study, we present model-based predictive risk maps of human seropositivities for *E. granulosus* and *E. multilocularis* for Xiji County, for the years 2002–2003, 2006–2007 and 2012–2013. Previous epidemiological reports on CE and AE infections in NHAR were mostly descriptive, reporting prevalence estimates at specific locations [44, 57, 58]. Spatially explicit statistical models were constructed previously to predict the spatial distribution of infection with *E. multilocularis* among the non-student population in Xiji County in 2002–2003 [27]. That model showed that the landscape features associated with an increased AE risk in Xiji County differed from previous observations in Zhang County in the neighbouring Gansu Province [21, 23]. Unlike the findings in Zhang

County, where grassland/shrubland favoured the creation of optimal peri-domestic habitats for *E. multilocularis* intermediate host species, and the development of a peri-domestic cycles involving dogs [21, 23], in Xiji County, abundance of reforested lowland pastures was correlated with higher prevalence of human AE risk. This finding supports the hypothesis that the transmission of *E. multilocularis* may occur through a diversity of host communities in China [27]. Therefore, extended monitoring of the seroprevalence of both, CE and AE, in the context of landscape transformation was suggested for Xiji County to assess the potential impact of local environmental factors on the transmission dynamics of *E. granulosus* and *E. multilocularis* [27]. Also, predictive estimates of the prevalence of infections in humans over time are currently required to inform and support the ongoing implementation process for prevention and control [10, 29].

In general, the risk of seropositivity for *E. granulosus* expanded in Xiji County over the study period. In 2002–2003, *E. granulosus* risk was clustered mainly in the north-central part of Xiji, an area that corresponds largely to the Yueliang mountain range (2626 m), and where predominant vegetation consist of forest, grassland and cultivated land [49]. *Echinococcus granulosus* risk expanded towards the east in 2006–2007 and decreased in the north-west. Finally, the risk of seropositivity was between 35 and 45% in almost the entire county territory in 2012–2013. These findings concur with reports of the apparently expanding geographical range of *Echinococcus* spp. [16, 59–64]. In Xiji County, livestock and arable agriculture are common practices among most local communities and represent higher risk of *Echinococcus* spp. exposure. Therefore, intensification in livestock production to supply the growing demand for resources may have pushed the local human settlements into close proximity with their livestock and the habitats of other potential *Echinococcus* spp. hosts [65]. According to data from the Gridded Livestock of the World v.2.0, in 2006, sheep and cattle populations were

distributed in the entire territory of Xiji County with higher densities, 20–50 and 10–50 heads per square kilometre, respectively, in the north-west [65]. The prevalence of CE in sheep was estimated to be 52% in NHAR in 2008, and between 0–9% according to more recent studies conducted in local areas no larger than counties [66–68]. These prevalence estimates may have varied due to local or individual conditions that facilitated high transmission within patches of CE endemicity. Also, studies conducted at the provincial level have found that 81% of cattle, 3% of goats, 19% of camels and 24% of pigs were infected with *E. granulosus* in 2008 [69].

The land cover in NHAR has been modified considerably in recent decades [49, 70]. Because landscape characteristics may determine directly or indirectly the feeding behaviour, growth rates, reproductive efficiency and immunological mechanisms of domestic animals [71], it was not surprising to find that the extent of various vegetation types were associated with the risk of seropositivity for *E. granulosus*. A reduction of bareland and the increases of woody vegetation types such as forest and shrubland may have sustained the *E. granulosus* life-cycle by facilitating the geographical expansion and interactions of competent hosts that move in response to available food sources [8, 72]. The movement of domestic animals and changes in their feeding practices can also be explained by land cover changes that contributed to loss or fragmentation of natural habitats indicated by metrics such as, NumP and MPS, that were significantly associated with the risk of seropositivity for *E. granulosus* [73–75]. The positive association between the seroprevalence of *E. granulosus* and the extent of area covered by water was unexpected and deserves further investigation. However, this relationship may be explained partially by the same mechanism that associates positively and negatively *E. granulosus* risk with summer and winter precipitation, respectively, at the time of the survey. Sufficient ground moisture is an important determinant of the survival and

infectivity of *Echinococcus* spp. eggs in the external environment [76, 77]. Also, due to the lack of piped water in some areas in the south of NHAR in past decades, the inhabitants had to rely mainly on natural drinking water supplies such as seasonal rivulets and temporary wells dug in dry-river beds [78]. Domestic dogs had also free access to these water supplies, which may have led to water contamination with the parasite eggs and increased risk of *Echinococcus* spp. transmission to the human population [78].

Increased annual rainfall has been shown to be associated with high infection rates of *E. granulosus* in livestock from hyperendemic regions for CE in Ethiopia and north-central Chile [79, 80]. Also, studies conducted in Iran and Saudi Arabia reported seasonal variations in the prevalence of *E. granulosus* infection during abattoir meat inspections [81, 82].

The observed differences of *E. granulosus* risk among females and males and the negative association with age may be exposure-related [44, 83, 84]. However, it has also been suggested that immunological and hormonal gender differences may account for higher infection rates in females than males [44].

In contrast to the high seroprevalence and geographical expansion of the seropositivity for *E. granulosus*, the seropositivity for *E. multilocularis* was lower and decreased during the three surveys. In 2002–2003, most areas in the county had estimated seroprevalences of *E. multilocularis* between 10 and 30%, with higher risk in those communities located in the north-east and central part. An important reduction was observed in the north-western area of Xiji in 2006–2007, and in north-eastern Xiji in 2012–2013. Seroprevalences of *E. multilocularis* remained highest in the south-west throughout the surveys. Overall, the findings of this study do not support the evidence from Europe and other regions in Asia that indicates the spreading of *E. multilocularis* [2, 85, 86]. This discrepancy could be due to different local transmission dynamics of the

parasite in Xiji County and to novel interactions between the recently transformed local landscape, the parasite and its hosts [27]. However, issues related to the inherent limitations of sampling variation and different methodological approaches should also be considered.

Landscape change and fragmentation have been identified as important determinants of the population dynamics of several species of wild mammals that are common intermediate host of *E. multilocularis* [87–90]. In eastern France, population outbreaks of *Microtus arvalis* and *Arvicola terrestris* were reported in areas where ploughed fields were converted into permanent grassland [21, 22]. Significant positive associations of *E. multilocularis* infection in humans and foxes with the extent of grassland were also reported in the same region [21, 91, 92]. The distribution of small mammals also varied in response to the transient augmentation of grassland/shrubland that followed a period of deforestation in Gansu Province [21, 23], and to overgrazing and fencing practices in the north-western part of Sichuan Province on the Tibetan Plateau [24, 25, 26]. Recently, it was demonstrated that low-biomass degraded grassland habitats influence the presence of *Ochotona* spp. in Serxu County, Sichuan Province [28]. In NHAR, the diversity of small mammal assemblages was related to afforestation and was lower than that of assemblages in areas where deforestation occurred [93]. Lowland pastures that were described as heavily grazed grassland interspersed with forest or shrub cover were associated with higher prevalence of human AE [27]. The results of this study showed significant associations with fragmentation metrics and seropositivity for *E. multilocularis*. It was also found that shrubland did not provide an optimal habitat for the transmission of *E. multilocularis*. Because different classification methods and definitions were used in relation to the previous study in Xiji County, the results need to be interpreted with caution. However, the results support the hypothesis that the land

cover characteristics facilitating *E. multilocularis* transmission in Xiji County are different from those favouring the transmission of the parasite in the south of Gansu Province [27]. Despite many epidemiological differences between *E. granulosus* and *E. multilocularis*, the significant positive associations between *E. granulosus* risk and the extent of water and summer precipitation, and the negative association with winter precipitation, were also found for *E. multilocularis* risk in Xiji County. Examination of the viability of *E. multilocularis* eggs particularly, has revealed that the eggs are sensitive to microclimatic conditions such as moisture levels or humidity [76]. Laboratory studies indicated that *E. multilocularis* eggs are more resistant to heat if suspended in water [94].

Interventions to reduce the risk of human infection in NHAR are in line with the guidelines of the National Control Programme [6]. Mass-community screening surveys, health education campaigns, regular dog treatment with praziquantel, patient treatment and animal offal inspection and control in slaughterhouses have been taking place across the NHAR since 2005 [6, 7]. Due to the lack of surveillance data and an incomplete understanding of the factors influencing parasite transmission, it has been difficult to forecast the impacts of the control measures [10]. The results of the current study are important for estimating the burden of CE and AE in Xiji County. In addition, considerable small-scale spatial variation in seropositivities for *E. granulosus* and *E. multilocularis* was observed which indicates that there is scope for predictive risk maps to help inform spatially targeted control measures in Xiji County. Areas of priority for AE control include the north and south-western part of the county, whereas CE control is required throughout.

Important limitations of the study were the different survey designs used between periods, affecting comparability of the data, and the use of schools to geolocate children, which might not reflect where exposure occurred. Also, children seropositivity for *E.*

granulosus and/or *E. multilocularis* was defined using specific antibody testing by ELISA using EgB and EmP. The poor diagnostic performance of these current serological tests and cross-reaction with other helminthic infections, including other types of human echinococcoses [95], and gastrointestinal malignancies remain a critical issue for the diagnosis of CE and AE and represent a source of misinterpretation in areas where both infections co-exist [35, 90]. Nevertheless, the analyses revealed that *E. granulosus* risk has increased and become more widespread across Xiji County during the study period. The patterns of *E. multilocularis* risk did not concur with the reported expansion of *E. multilocularis* in other regions. Clearly, control of CE is a public health priority in Xiji County, whereas further research is required to explore in more detail the potential factors that may be influencing the changing burden of AE.

Conclusions

This work provides detailed geographical information regarding the changes in the predicted prevalence of human seropositivities for *E. granulosus* and *E. multilocularis* in Xiji County, a highly endemic area for human echinococcoses. The study period was from 2002 to 2013, during which extensive landscape restoration projects were implemented in NHAR and other parts of China. The different models developed in this study indicate that the human seropositivity for *E. granulosus* expanded across Xiji during the study period, while seropositivity for *E. multilocularis* became more confined in communities located in the south of the county. These results help to identify priority areas where targeted prevention and control efforts are most required.

Additional files (Appendix D)

Additional file 1 Stylised diagram of the grid plus close-pairs geostatistical sampling design

Abbreviations

95% CrI: 95% credible intervals; AE: Alveolar echinococcosis; AIC: Akaike information criterion; ASTER: Advanced Spaceborne Thermal Emission and Reflection Radiometer; CE: Cystic echinococcosis; DALYs: Disability-adjusted life years; DIC: Deviance information criterion; ED: Edge density; EgB: Cyst fluid antigen B; EmP: *E. multilocularis* crude protoscolex extract; ELISA: Enzyme-linked immunosorbent assay; EROS: Earth Resources Observation and Science; ESPA: Center Science Processing Architecture; EVI: Enhanced vegetation index; GDEM: Global digital elevation model; IDW: Inverse distance weighting; MA: Moving average; MPI: Mean shape index; MPS: Mean patch size; NHAR: Ningxia Hui Autonomous Region; NUMP: Number of patches; OR: Odds ratio; PD: Patch density; SD: Standard deviation; USGS: United States Geological Survey; UTM: Universal Transverse Mercator

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Declarations

Ethics approval and consent to participate

The protocol for this study was reviewed and approved by the Human Research Ethics Committees of Ningxia Medical University, QIMR Berghofer Medical Research Institute and The Australian National University.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AMCR and ACAC designed the study. AMCR and YRY collected, standardised and geo-referenced the clinical and environmental data. AMCR and ACAC developed the models with input from RJSM. ACAC, YRY, DPM, DJG, RJSM, TSB and GMW provided critical comments and helped in drafting the manuscript. AMCR and ACAC finalised the manuscript. All authors read and approved the final manuscript.

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CHAPTER 6

Human and dog exposure to Echinococcus spp. in southern NHAR

CHAPTER 6 HUMAN AND DOG EXPOSURE TO *ECHINOCOCCUS* SPP. IN SOUTHERN NHAR

6.1 Context

E. granulosus and *E. multilocularis* are transmitted in domestic and sylvatic life cycles, respectively. These life cycles are maintained by a wide range of intermediate and definitive hosts (140). Domestic dogs are susceptible to infection with both parasites, and are currently regarded as important sources of human CE and AE in China (117, 181). Therefore, major goals of the national prevention and control initiative against echinococcoses in China are to decrease the seropositivity rate in children aged <12 years and reduce infestation rates in dogs. However, strategies to control echinococcosis infections implemented at the county level in NHAR are being guided primarily by provincial estimates of the prevalence of these infections. Consequently, to date, it is difficult to provide evidence on the local impact and effectiveness of the National Control Programme to prevent and cure echinococcoses.

The study presented here extends the work reported in Chapter 5 by incorporating into the analysis data not only collected in Xiji County between 2012 and 2013, but also data collected in the same years in Haiyuan, Guyuan and Tongxin Counties, which are counties located in the southern mountainous area of NHAR. In addition, this study includes data on *E. granulosus* and *E. multilocularis* infection status in domestic dogs which are the presumed local definitive host for both parasites in Western China. Therefore, this study is the first of its kind to predict and compare the spatial distribution of human exposure to *E. granulosus* and *E. multilocularis* and infections with these parasites in dogs.

Supplementary material for this paper is provided in Appendix E

6.2 Spatial prediction of the risk of exposure to *Echinococcus* spp. among schoolchildren and dogs in Ningxia Hui Autonomous Region, China

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Spatial prediction of the risk of exposure to *Echinococcus* spp. among schoolchildren and dogs in Ningxia Hui Autonomous Region, China

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Abstract

The geographical distribution of *Echinococcus* spp. infections in Ningxia Hui Autonomous Region (NHAR) has been reported to be expanding in response to environmental change. The aim of the present study was to predict and compare the spatial distribution of human seropositivity for *E. granulosus* and *E. multilocularis* and infections with these parasites in dogs in four counties in the south of NHAR, to identify communities where targeted prevention and control efforts are required. Predicted seroprevalence of *E. granulosus* in schoolchildren and *E. granulosus* infections in dogs concurred spatially, whereas predicted seroprevalence of *E. multilocularis* in schoolchildren and *E. multilocularis* infections in dogs differed spatially. Enhanced vegetation index was significantly associated with *E. multilocularis* seropositivity among schoolchildren, and infections with *E. granulosus* and *E. multilocularis* in dogs. A positive association was also found between dog infection with *E. granulosus* and cultivated land, and a negative association between human seropositivity for *E. granulosus* and bareland/artificial surfaces. The findings of this study support the importance of land cover and climatic variables in determining habitat suitability for *Echinococcus* spp. infections, and suggest that definitive hosts other than dogs (e.g. foxes) are important in defining the geographical risk of human seropositivity for *E. multilocularis* in NHAR.

Key words: *Echinococcus granulosus*; *Echinococcus multilocularis*; environment; geographic information systems; Ningxia Hui Autonomous region

Introduction

Cystic echinococcosis (CE), caused predominantly by infection with *Echinococcus granulosus*, and alveolar echinococcosis (AE), due to infection with *E. multilocularis*, have long incubation periods (5–15 years) that delay diagnosis and treatment (Ammann and Eckert 1996), and require long-term monitoring and medical care for most patients (Brunetti et al. 2011; Kern et al. 2017). It is estimated that 188,000 people are infected with *E. granulosus* globally every year which represents a human health burden of 184,000 disability-adjusted life years (DALYs) lost (Torgerson et al. 2015). An estimate of 18,235 cases of AE occur annually resulting in a loss of approximately 666,433 DALYs (Torgerson et al. 2010). From these figures, 91% of the total number of cases and 95% of the disease burden of AE are estimated to be in the People's Republic (P.R.) of China (Torgerson et al. 2010).

The transmission of *E. granulosus* and *E. multilocularis* in domestic and sylvatic life cycles, respectively, is maintained by a wide range of intermediate and definitive hosts (Romig et al. 2017). The transmission of *E. granulosus* involves domestic dogs and other canids as typical definitive hosts, and sheep and other ungulates as intermediate hosts (Eckert and Deplazes 2004). *E. multilocularis* is transmitted within predator-prey cycles that involve different species of foxes as main definitive hosts and small mammals as intermediate hosts (Eckert and Deplazes 2004; Kapel et al. 2006). Domestic dogs are susceptible to infection with both parasites, and are currently regarded as significant hosts for *E. granulosus* and *E. multilocularis* (Moss et al. 2013; Rausch 1995). In Gansu Province and the eastern Tibetan plateau, P.R. China, particularly, domestic dogs have been identified as the main transmission source of both parasites to the local human population (Craig et al. 2000; Wang et al. 2010). Comprehensive reviews of the life cycles of *E. granulosus* and *E. multilocularis*, clinical manifestations of human

echinococcoses, diagnosis, treatment, prevention and control are available (Craig et al. 2017; Kern et al. 2017; Romig et al. 2017).

CE and AE are characterised by great variation in their geographical distributions, with important differences at regional and local spatial scales (Cringoli et al. 2007; Eckert 2001; Giraudoux et al. 2006; Giraudoux et al. 2013a; Mastin et al. 2011). CE has a widespread global distribution with the highest disease burden in poor pastoralist communities, whilst AE occurs within defined areas of temperate and subarctic regions of the northern hemisphere (Deplazes et al. 2017). Various socio-demographic, economic and environmental factors that act at different spatial scales have been found to be associated with the distributions of CE and AE risk (Atkinson et al. 2013; Cadavid Restrepo et al. 2015; Danson et al. 2003; Giraudoux et al. 2007). These factors determine the population dynamics and behaviour of the hosts, predator-prey interactions and the survival and development of the parasites.

Land cover change factors have been found to be linked to the distribution and dynamics of *E. multilocularis* intermediate hosts (Raoul et al. 2008; Silva et al. 2005). Deforestation (Giraudoux et al. 1998; Giraudoux et al. 2003), afforestation (Raoul et al. 2008), and specific farming and fencing practices (Raoul et al. 2006; Wang et al. 2004) have been shown to modify the distribution of various species of small mammals. Overgrazing and low grass height were also linked positively to the presence and abundance of intermediate hosts for *E. multilocularis* in highly endemic areas on the Tibetan Plateau (Raoul et al. 2006; Wang et al. 2010), while enhanced vegetation index (EVI) had a negative association with the presence of *Ochotona curzoniae* (plateau pika) and *Ochotona cansus* (Gansu pika), key intermediate hosts for the parasite in Serxu County, Sichuan Province (Marston et al. 2016). To date, surprisingly few studies have

been conducted to investigate the host-environment interactions that regulate the domestic life cycle of *E. granulosus* (Eckert and Deplazes 2004).

Spatial epidemiological approaches that integrate the use of geographical information systems (GIS), remote sensing and model-based geostatistics serve as valuable analytical tools to quantify and predict the spatial heterogeneities in the risk of echinococcoses across different spatial scales (Cadavid Restrepo et al. 2015). Because control interventions against CE and AE require a long period of implementation in order to be successful, the outcome of spatial epidemiological approaches may help define national and regional policies to reduce the burden of these diseases, and also to prioritise areas where interventions are required (Cadavid Restrepo et al. 2015; Craig et al. 2017).

Nine valid species are currently recognised within the genus *Echinococcus*: *E. granulosus*, *E. multilocularis*, *E. ortleppi*, *E. canadensis*, *E. oligarthrus*, *E. vogeli*, *E. shiquicus*, *E. felidis*, *E. equinus*. *E. granulosus* and *E. multilocularis* are the species found in Ningxia Hui Autonomous Region (NHAR) (McManus et al. 1994; Yang et al. 2005). A spatial prediction study of *E. multilocularis* in Xiji county, south of NHAR found that *E. multilocularis* transmission was determined by landscape factors, such as presence of lowland pasture (Pleydell et al. 2008). It was also suggested that the infection did not occur primarily through arvicoline species which are key intermediate hosts for this parasite in other areas (Pleydell et al. 2008). In this study, we extend the previous work that was undertaken in Xiji County to encompass three additional neighbouring counties, Haiyuan, Guyuan and Tongxin, located in the south of NHAR. Using Bayesian model-based geostatistics, we aimed to create spatial predictions of the risk of human seropositivity for *E. granulosus* and *E. multilocularis*, and the risk of dog infections with these parasites. In the present study, the term human exposure was meant to signify that children harboured possibly the metacestode stage of *E. granulosus* and/or *E.*

multilocularis, whether or not, they had clinical, serological or ultrasound evidence of active cysts (based on the description of a possible echinococcosis case suggested elsewhere (Brunetti et al. 2010). These maps can guide decision-makers to spatially target echinococcosis control interventions.

Material and methods

The protocol for this study was reviewed and approved by the Human and Animal Research Ethics Committees of the Ningxia Medical University, QIMR Berghofer Medical Research Institute, and the Human Ethics Committee of The Australian National University. After explaining the purpose and procedures of the surveys, parents or adult representatives of the students and dog owners who agreed to participate were asked to sign an informed written consent form.

Study area

The surveys were conducted in four contiguous counties of NHAR, Xiji, Haiyuan, Guyuan and Tongxin Counties, which are located in the south of the Autonomous Region between latitudes 35°33'–36°98' N, and between longitudes 105°64'–106°24' E. The four counties together cover an area of approximately 21,557 km². Based on the estimates of the national census in 2015, the total populations were, 344,045 in Xiji, 396,938 in Haiyuan, 1,211,789 Guyuan and 325,441 in Tongxin, of whom 58.0%, 70.8%, 46.1% and 86.1% were of the Hui Islamic ethnic minority, respectively, while almost all others were Han Chinese (National Bureau of Statistics of China 2015) (Figure 1).

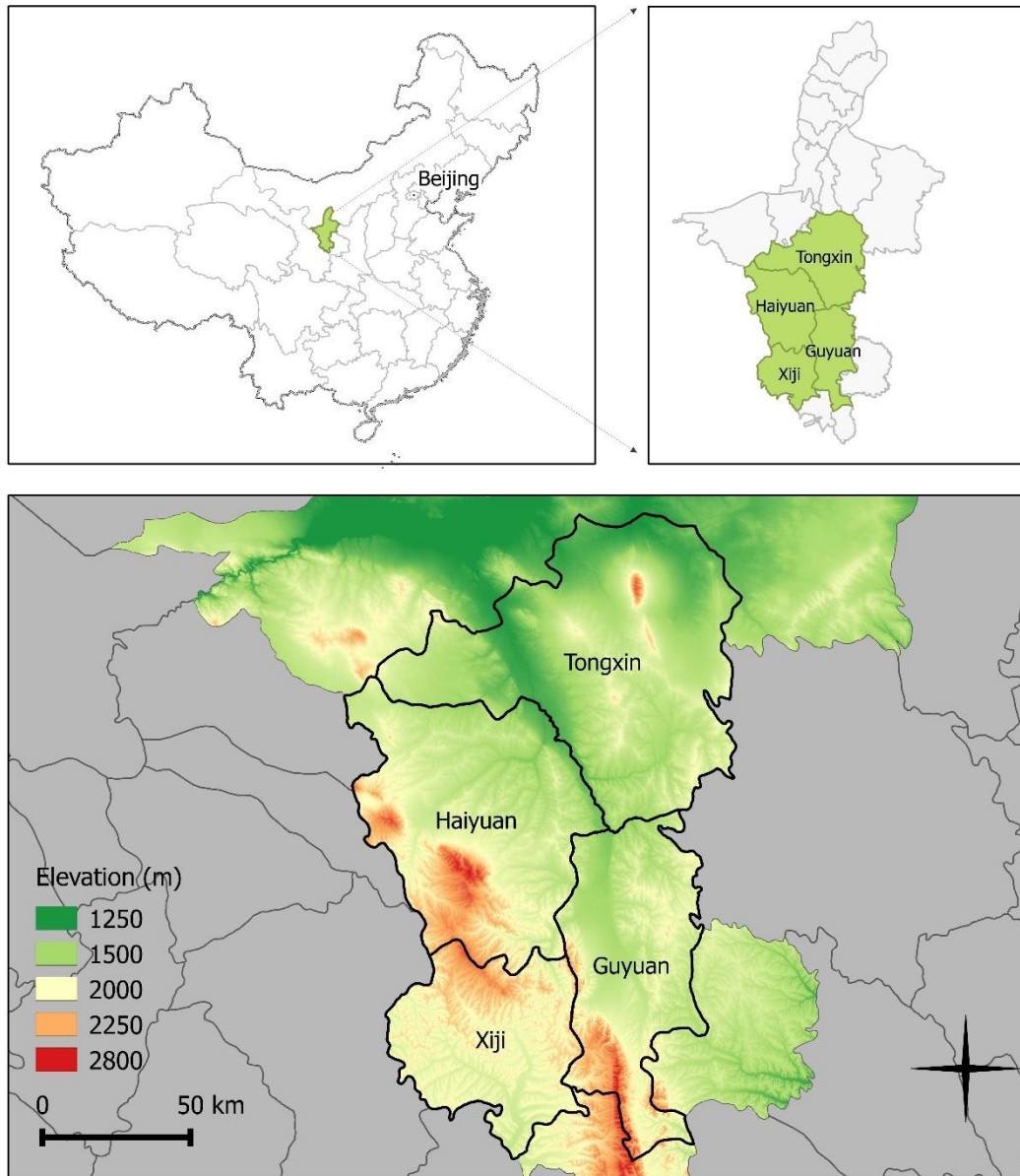


Figure 1. Map and elevation of Xiji, Haiyuan, Guyuan and Tongxin counties and location of NHAR within China.

The counties lie in a temperate continental monsoon climate zone that is characterized by four distinct seasons. The annual average temperature is 5.37 °C and the average annual precipitation is 418.2 mm. Approximately 60% of the precipitation is in the form of rainstorms that take place during the rainy season, from June to September. Elevation ranges from 1,500 to 2,800 meters above sea level. The geography of this part of NHAR include mountainous areas around Mt. Liupan, and the Loess hills. Vegetation varies

from forest mainly in the southeast to slope farmland that accounts for most of the cultivated land, and to desert in the northeast and northwest.

Data on seroprevalence of E. granulosus and E. multilocularis

Data on the seroprevalence of *E. granulosus* and *E. multilocularis* were obtained from a cross-sectional school-based survey conducted across the four counties in 2012–2013. Children aged 6–18 years were selected to ensure that the collected data were representative of recent exposure risk (as adults might have been exposed over a long duration in the past). A geostatistical design (grid plus close pairs) was used to select the schools for the survey (Diggle and Ribeiro 2007). A 15×15 km grid was created and overlaid on the entire study area using ArcGIS software version 10.3.1 (ESRI 2015). The primary set of schools selected for the survey consisted of those schools located in closest proximity to the grid nodes. A second set of schools was also selected comprising schools located in near proximity to those selected at the nodes of the grid (the close pairs). The origin of the grid, the distance and direction of the close pairs from the primary set, and the primary subset for which close pairs were selected, were generated using a random number generator. This approach was used because it has been identified as the most efficient survey design for estimating spatial variability in environmental variables (Diggle and Ribeiro 2007).

All children who agreed to participate in the survey were first assembled and asked to provide demographic and exposure information using standardised questionnaires that were administered by the school teachers. Then, a blood sample from the ear lobe was collected from participants for specific antibody testing by enzyme linked immunosorbent assay (ELISA) using *E. granulosus* cyst fluid antigen B and *E. multilocularis* crude protoscolex extract (Craig et al. 1992; Yang et al. 2008). EgB and

EmP ELISA sensitivity is >85% for CE and >90% for AE, respectively (Bartholomot et al. 2002; Craig et al. 1992; Craig et al. 2000). Specificity is from 70% to 100% for CE (Carmena et al. 2006) and 87% for AE (Bartholomot et al. 2002). Finally, abdominal ultrasound was used to screen schoolchildren and detect and classify early CE and/or AE cysts. The classification scheme of CE and AE proposed by the World Health Organization was used to categorise the hepatic lesions (Kern et al. 2006; WHO Informal Working Group 2003; WHO Informal Working Group on Echinococcosis 2001). Although ultrasound is the method of choice to confirm human echinococcoses, it has low sensitivity to detect small cysts (McManus et al. 2012). Therefore, due to the young age of participants and the slow rate of growth of the cysts, the results of the ultrasound are not reported here. Schoolchildren, who were screen-positive for one of the infections or both, were referred to the local medical centre for free treatment.

Data on dog infection

Faecal samples were collected from domestic dogs presenting to the veterinary centre nearest to the selected schools, including rural and urban locations, between 2012 and 2013. The faecal samples were initially stored separately for at least 7 days at -80°C to inactivate the parasite eggs, and then transferred to a -20°C freezer. The processing and copro-analysis were conducted at the Zoonoses Laboratory of the Ministry of Agriculture in the Lanzhou Veterinary Research Institute, Gansu Province, P.R. China. A Multiplex polymerase chain reaction (PCR) assay was used for simultaneous detection of *E. granulosus* and *E. multilocularis* DNA (Liu et al. 2015). The geographic coordinates of each school and veterinary centre were collected using a hand-held global positioning system. Maps of the surveyed locations is available (Figure 2).

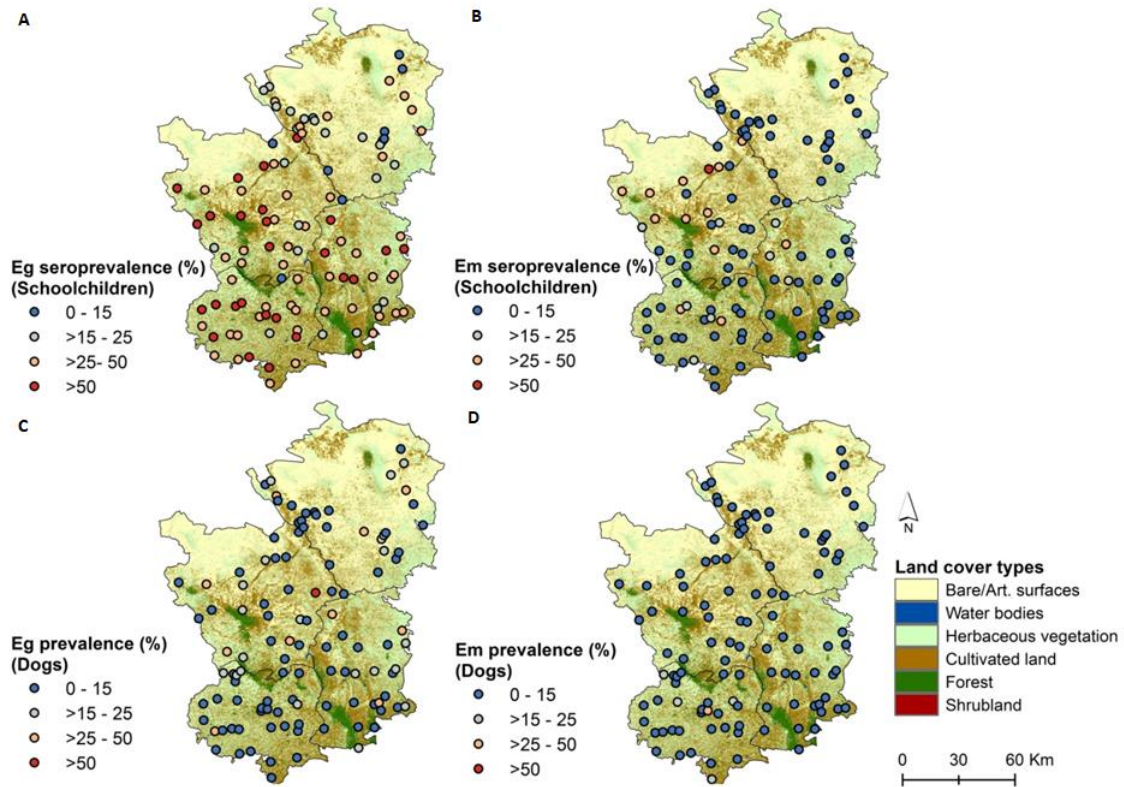


Figure 2. Distribution of surveys of *E. granulosus* and *E. multilocularis* exposure in schoolchildren and dogs and observed seroprevalence of (A) *E. granulosus*, (B) *E. multilocularis*, (C) infection with *E. granulosus* in dogs and (D) infection with *E. multilocularis* in dogs in 2012–2013 in Xi Ji, Haiyuan, Guyuan and Tongxin counties, NHAR, P.R. China. Locations of the different land cover types are also indicated.

Environmental and remotely sensed data

Land cover maps at a 30-meter spatial resolution for the years 2005, 2010 and 2015 were obtained from a previous study that assessed and quantified land cover change in NHAR between 1991 and 2015 (Cadavid Restrepo et al. 2017). The maps were created using time series images retrieved from the Landsat Surface Reflectance Climate Data Record available in Earth Explorer (The United States Geological Survey (USGS)). Seven land cover categories were initially identified: water bodies, artificial surfaces, bare or sparsely vegetated areas, herbaceous vegetation, cultivated land, shrubland and forest (Table 1). However, due to significant spectral confusion between artificial surfaces and bare or sparsely vegetated areas, these land cover classes were merged and represented as a single

category in the maps and further analyses. Details of the process of land cover classification and accuracy assessment are provided elsewhere (Cadavid Restrepo et al. 2017).

Landsat 30-meter enhanced vegetation index (EVI) data were extracted from the Earth Resources Observation and Science (EROS) Center Science Processing Architecture (ESPA) On Demand Interface (The United States Geological Survey (USGS)). Data were downloaded from a month during the growing season in NHAR (June–November) for the years 2008 and 2012. However, when there were no data available for the specified time period, the closest-in-time EVI estimates were retrieved for the analyses.

Elevation estimates were obtained in a GeoTIFF format at the spatial resolution of 1 arc-second (approximately 30 m) from the Advanced Spaceborne Thermal Emission and Reflection Radiometer (ASTER) Global Digital Elevation Model (GDEM) version 2 (The National Aeronautics and Space Administration (NASA) and Ministry of Economy Trade and Industry (METI)). The ASTER GDEM was downloaded from the Earth Explorer website (The United States Geological Survey (USGS)).

Table 1. Land cover classification scheme and definitions

| Code | Land cover type | Description | Content |
|------|----------------------------------|--|--|
| 1 | Water bodies | All areas of water | Streams and canals, lakes, reservoirs, bays and estuaries |
| 2 | Artificial surfaces | Land modified by human activities | Residential areas, industrial and commercial complexes, transport infrastructure, communications and utilities, mixed urban or built-up land and other built-up land |
| 3 | Bare or sparsely vegetated areas | Areas with little or no "green" vegetation present | Dry salt flats, sandy areas, bared exposed rock and mixed barren land |
| 4 | Herbaceous vegetation | Areas characterized by natural or semi-natural vegetation | Grasses and forbs |
| 5 | Cultivated land | Areas where the natural vegetation has been removed/modified and replaced by other types of vegetative cover that have been planted for specific purposes such as food, feed and gardening | Cropland and pasture, orchards, groves, vineyards, nurseries and ornamental horticultural, other cultivated land |
| 6 | Shrubland | Natural or semi-natural woody vegetation with aerial stems less than 6 meters tall | Evergreen and deciduous species of true shrubs and trees or shrubs that are small or stunted |
| 7 | Forest | Areas characterized by tree cover or semi-natural woody vegetation greater than 6 meters tall | Deciduous forest, evergreen forest and mixed forest |

Average monthly values of temperature and precipitation for the period January 1 2008 to December 31 2013 were provided by the Chinese Academy of Sciences in a raster format at the spatial resolution of 1 km. The monthly climate values had first been collected from 16 local weather stations and then interpolated using the Inverse Distance Weighting (IDW) method.

A boundary map of the four counties was downloaded from the DIVA-GIS website (DIVA GIS). The geo-referenced data sets that included the locations of the surveyed schools and veterinary centres were imported into ArcGIS and projected to the Universal Transverse Mercator (UTM) coordinate system zone 48N. ArcGIS was used to delineate 1 km and 5 km radii buffer zones around the centres of the survey site locations and all covariates were summary estimates extracted from these buffer zones. The buffer sizes were selected in order to examine areas of environmental conditions that provide suitable habitat for the parasite hosts. Land cover variables were summarized as percentages of each land cover type within the buffer zones for the years 2005, 2010 and 2015. The extracted estimates were then used to calculate change rates for the periods 2005–2010, and 2010–2015. In this way, it was possible to estimate the spatial extent of all land cover classes by buffer area for the years 2008 and 2012. For climate, elevation and EVI variables, a moving 5-year average (MA) of the values of the independent variables was generated for the period 2008–2012 to examine the host/environment interplay over an extended period of time rather than at a single point. For each surveyed location, the data extracted included: annual, summer (June, July and August) and winter (December, January and February) weighted average temperature and precipitation, and spatial mean values of EVI and elevation within the buffer zone.

Variable selection

Using R software version 3.2.2. (R Core Team 2015), non-spatial univariate binomial logistic regression models were developed to examine the association between the environmental variables with *E. granulosus* and *E. multilocularis* infections in humans and dogs. Spearman correlation analyses were conducted to assess collinearity among all independent variables. If the correlation coefficient between a pair of covariates was >

0.9, the covariate with the highest value of Akaike Information Criterion (AIC) in the univariate regression models was excluded. Various non-spatial binomial multivariate logistic regression models were also created to compare differences in model fit. Multivariate logistic regression models were also developed for human and dog infections and for each species. The models with the lowest AIC were selected for subsequent geostatistical analyses. Nonlinear associations between the environmental covariates and the infections were modelled using quadratic terms.

Model-based geostatistics

Separate multivariable geostatistical logistic regression models were created in a Bayesian framework for human serological status and dog infections with each parasite species using the OpenBUGS software 3.2.3 rev 1012 (Members of OpenBUGS Project Management Group 2014). First, Bayesian geostatistical models were developed with the explanatory variables as fixed-effects but without considering the spatial dependence structure of the data. Then, Bayesian geostatistical models for each infection were created including the explanatory variables and a spatially structured random effect.

The fit of the models was compared using the deviance information criterion (DIC), where low DIC values indicate a better fit. Statistical significance of the covariates in the models was deemed to be achieved if the 95% credible intervals (95% CrI) of the estimated odds ratios (OR) excluded 1.

For all infections, the best-fit model was a logistic regression model the one that included the spatial random effect. Assuming a Bernoulli-distributed dependent variable, Y_{ij} , corresponding to the serological/infection status (0=seronegative/noninfected, 1=seropositive/infected) of an individual i in location j , the model structures for schoolchildren (formula 1) and dogs, (formula 2), were as follows:

$$[1] \quad Y_{ij} \sim \text{Bern}(p_{ij})$$

$$\text{logit}(p_{ij}) = \alpha + \gamma \times \text{age}_i + \sum_{z=1}^z \beta_z \times \lambda_{zj} + s_j$$

$$[2] \quad Y_{ij} \sim \text{Bern}(p_{ij})$$

$$\text{logit}(p_{ij}) = \alpha + \sum_{z=1}^z \beta_z \times \lambda_{zj} + s_j$$

where α is the intercept, γ is the coefficient for age, β is a matrix of z coefficients, λ is a matrix of z environmental variables, and s_j a geostatistical random effect. The correlation structure of the geostatistical random effect was assumed to be an exponential function of the distance between points:

$$f(d_{kl}; \phi) = \exp[-\phi d_{kl}]$$

where d_{kl} are the distances between pairs of points k and l , and ϕ is the rate of decline of spatial correlation per unit of distance. A normal distribution was used for the priors for the intercept and the coefficients (mean = 0 and precision, the inverse of variance, = 1×10^{-3}), whereas a uniform distribution was specified for ϕ (with upper and lower bounds $s = 0.01$ and 100 ; the lower bound set to ensure spatial correlation at the maximum separating distance between survey locations was <0.5). A non-informative gamma distribution was used to specify the priors for the precision (shape and scale parameters = $0.001, 0.001$).

A burn-in of 1,000 iterations was run first and discarded. Sets of 20,000 iterations were then run and examined for convergence. Convergence was assessed by visual inspection of history and density plots and by examining autocorrelation of the model parameters. Because autocorrelation was observed for most variables, thinning was applied by storing every 10th iteration. In each model, convergence was achieved for all variables at approximately 80,000 iterations. The last 10,000 values from the posterior distributions of each model parameter were recorded. The rate of decay of spatial correlation between locations (ϕ) with distance and the variance of the spatial structured random effect (σ^2) were also stored.

To define the prediction locations, a regular 5 km \times 5 km grid was overlaid over the entire study territory. The risk of human seropositivity and dog infection at the prediction locations was estimated using the *spatial.unipred* function in OpenBUGS. The function applies the model equation at each non-sampled location using the covariates values extracted for them and the separating distance between those locations and the surveyed locations.

Maps that represent the posterior distributions of predicted seroprevalence of these parasite species in humans and predicted prevalence of both infections in dogs were created in ArcGIS for the four counties.

Results

Sample description

The final data set of the surveyed schools consisted of 106 locations and a total of 7,547 schoolchildren who were screened for *Echinococcus* spp. seropositivity. Haiyuan (64.5%) and Xiji (54.0%) were the two counties with the highest observed overall seroprevalence of both infections, followed by Guyuan (43.3%) and then by Tongxin

(24.6%). The seroprevalence of *E. granulosus* among schoolchildren by county was higher (45.6%) in Xiji, while a higher seroprevalence of *E. multilocularis* was observed in Haiyuan (21.1%) (Table 2 and Additional file 1). Co-infection with *E. granulosus* and *E. multilocularis* was observed in 7.9% of the children being higher in Haiyuan (5.0%) and followed by Xiji (1.6%), Guyuan (1.1%) and Tongxin (0.2%). The mean age of participants who were seropositive for *E. granulosus* was 11.4 years (standard deviation (SD): 2.6), and the mean age for those who were seropositive for *E. multilocularis* was 11.3 years (SD: 2.5).

The final data set of the survey conducted in the veterinary centres included 111 locations and a total of 3,324 dogs. The county with the highest overall prevalence of dogs infected with each of the parasite species, *E. granulosus* and *E. multilocularis*, was Xiji County (16.5% and 14.2%, respectively). The prevalences of dog infection with *E. granulosus* in the other three counties were 12.0%, 11.8% and 9.5% in Tongxin, Haiyuan and Guyuan, respectively. The prevalence of dog infection with *E. multilocularis* were notably lower in Haiyuan (3.4%), Tongxin (1.6%) and Guyuan (1.5%) compared with Xiji (Table 2 and Additional file 1). Co-infections with both parasite spp. were higher in Xiji (0.4%) and Tongxin (0.2%) followed by Guyuan (0.06%) and Haiyuan (0.03%).

Figure 2 shows the observed spatial distributions of the prevalence of the infections in humans and dogs by parasite species and locations. From the maps, it is difficult to identify a clear geographical pattern. However, the maps confirm that seropositivity for *E. granulosus* was more widespread than the seropositivity for *E. multilocularis* in the study areas.

Table 2. Seroprevalence of human seropositivity for *E. granulosus* and *E. multilocularis* and dog infections with these parasites in dogs by county in the cross-sectional surveys conducted in schools and veterinary centres in 2012–2013

| <i>E. granulosus</i> | | | <i>E. multilocularis</i> | | |
|----------------------|-------------|---------------|--------------------------|---------------|--------------|
| a. Humans | | | | | |
| | Positive | Negative | Positive | Negative | Total |
| Xiji | 765 (45.6%) | 912 (54.4%) | 141(8.4%) | 1,536 (91.6%) | 1,677 (100%) |
| Guyuan | 601 (36.4%) | 1,051 (63.6%) | 114 (6.9%) | 1,538 (93.1%) | 1,652 (100%) |
| Haiyuan | 842 (43.4%) | 1,099 (56.6%) | 409 (21.1%) | 1,532 (78.9%) | 1,941 (100%) |
| Tongxin | 523 (22.9%) | 1,754 (77.1%) | 39 (1.7%) | 2,238 (98.3%) | 2,277 (100%) |
| b. Dogs | | | | | |
| Xiji | 124 (16.5%) | 626 (83.5%) | 106 (14.1%) | 644 (85.9%) | 750 (100%) |
| Guyuan | 63 (9.5%) | 597 (90.5%) | 10 (1.5%) | 650 (98.5%) | 660 (100%) |
| Haiyuan | 91 (11.8%) | 680 (88.2%) | 26 (3.4%) | 745 (96.6%) | 771 (100%) |
| Tongxin | 137 (12.0%) | 1,006 (88%) | 18 (1.6%) | 1,125 (98.4%) | 1,143 (100%) |

Models of *E. granulosus* and *E. multilocularis* seropositivities in schoolchildren

The DICs of the models of seropositivity for *E. granulosus* with and without accounting for spatial correlation were 8,699 and 8,903, respectively. In the spatial model, bareland/artificial surface land cover class, was the only variable that had a statistically significant association with seropositivity. The estimated decrease in seropositivity was 0.9% (95% CrI: 0.04%–1.8%) for an increase of 1% in the extent of bareland/artificial surfaces (Table 3). The *E. multilocularis* model with the spatial component had a DIC of 3,575, while the model without the spatial component had a DIC of 3,667. In the spatial model, EVI had a significant positive association with seropositivity for *E. multilocularis*. There was an estimated increase of 0.2% (95% CrI: 0.1%–0.3%) in seropositivity for *E.*

multilocularis for 1-unit increase in EVI within the 5-km buffer area at a 5-year lag. Additionally, the quadratic terms for winter and summer temperature in the 5-km buffers were statistically significant in the 5 years prior to the survey, indicating a significant nonlinear association (Table 4).

The variance of the spatially structured random effect was 0.6 (0.4 to 1.0) in the model of seropositivity for *E. granulosus* and 1.2 (0.7 to 1.9) in the model of seropositivity for *E. multilocularis*. These estimates imply that, after accounting for the effect of the statistically significant variables, the residual spatial variation was higher for human seropositivity for *E. multilocularis*. Phi (ϕ), that is the rate of decay of spatial correlation (with bigger ϕ indicating smaller clusters), was 20.9 in the *E. granulosus* model and 45.2 in the *E. multilocularis* model. This means that, after accounting for the effect of covariates, the radii of the clusters were larger for human seropositivity for *E. multilocularis* than for human seropositivity for *E. granulosus*.

Table 3. Regression coefficients, ORs and 95% CrI from Bayesian spatial model for seroprevalence of *E. granulosus* in schoolchildren in Xiji, Haiyuan, Tongxin and Guyuan counties in 2012–2013

| Model | Coefficient, posterior mean (95% CrI*) | Odds ratios, posterior mean (95% CrI) |
|--|---|---|
| Intercept | -0.68 (-1.07 to -0.31) | - |
| Age | -4.2×10^{-3} (-0.03 to 0.02) | 0.99 (0.97 to 1.02) |
| Summer precipitation same year (5 km) | -1.83×10^{-3} (-7.98×10^{-3} to 4.20×10^{-3}) | 0.99 (0.99 to 1.01) |
| Winter temperature 5 years prior (1km) | -0.07 (-1.32 to 1.23) | 0.93 (0.26 to 3.43) |
| Winter temperature 5 years prior (1km) squared | 0.22 (-0.17 to 0.59) | 1.24 (0.84 to 1.80) |
| Winter temperature same year (5km) | -0.71 (-2.00 to 0.68) | 0.49 (0.13 to 1.99) |
| Winter temperature same year (5km) squared | -0.07 (-0.27 to 0.13) | 0.92 (0.76 to 1.14) |
| Bareland/Art. surfaces same year (1 km) | -0.01 (-0.01 to -4.02×10^{-4}) | 0.99 (0.98 to 0.99) |
| Cultivated land 5 years prior (1 km) | -0.01 (-0.01 to 3.63×10^{-3}) | 0.99 (0.98 to 1.00) |
| Forest 5 years prior (1 km) | -0.01 (-0.04 to 0.02) | 0.99 (0.95 to 1.02) |
| Herbaceous vegetation same year (1 km) | 3.24×10^{-4} (-0.01 to 0.01) | 0.99 (0.98 to 1.01) |
| Shrubland same year (1 km) | -7.36 (-16.43 to 1.73) | 6.32×10^{-4} (7.26×10^{-8} to 5.68) |
| Heterogeneity structured | 0.58 (0.36 to 0.99) | - |
| ϕ (Decay of spatial correlation) | 20.89 (5.86 to 71.23) | - |
| Deviance information criterion | 8,669 | - |

* 95% CrI, 95% credible interval

Table 4. Regression coefficients, ORs and 95% CrI from Bayesian spatial model for seroprevalence of *E. multilocularis* in schoolchildren in Xiji, Haiyuan, Tongxin and Guyuan counties in 2012–2013

| Model | Coefficient, posterior mean (95% CrI*) | Odds ratios, posterior mean (95% CrI) |
|--|--|---|
| Intercept | -2.69 (-3.58 to -1.88) | - |
| Age | 0.03 (-0.01 to 0.07) | 1.03 (0.99 to 1.07) |
| Summer precipitation 5 years prior (5 km) | 0.01 (-0.01 to 0.02) | 1.01 (0.99 to 1.02) |
| Summer temperature 5 years prior (5 km) | -3.32 (-6.38 to -0.28) | 0.03 (0.01 to 0.75) |
| Summer temperature 5 years prior (5 km) squared | -1.96 (-3.07 to -0.81) | 0.14 (0.04 to 0.44) |
| Winter temperature 5 years prior (5 km) | -2.09 (-5.20 to 1.23) | 0.12 (0.01 to 3.44) |
| Winter temperature 5 years prior (5 km) squared | 0.97 (0.26 to 1.68) | 2.64 (1.30 to 5.38) |
| Bareland/Art. surfaces 5 years prior (5 km) | 0.01 (-0.02 to 0.03) | 1.00 (0.98 to 1.03) |
| Bareland/Art. surfaces same year (5 km) | -0.01 (-0.03 to 0.02) | 0.99 (0.96 to 1.02) |
| Cultivated land 5 years prior (5 km) | 0.01 (-0.02 to 0.02) | 1.00 (0.98 to 1.02) |
| Forest 5 years prior (5 km) | -0.01 (-0.05 to 0.04) | 0.99 (0.94 to 1.04) |
| Shrubland 5 years prior (5 km) | -3.70 (-8.05 to 0.47) | 0.02 (3.00 x 10 ⁻⁴ to 1.60) |
| Shrubland 5 same year (5 km) | -4.28 (-10.81 to 2.16) | 0.01 (0.02 x 10 ⁻⁵ to 8.72) |
| Water bodies 5 years prior (5 km) | 0.89 (-0.40 to 2.25) | 2.44 (0.66 to 9.52) |
| EVI 5 years prior (1 km) | -3.39 x 10 ⁻⁴ (-1.01 x 10 ⁻³ to 4.00 x 10 ⁻⁴) | 0.99 (0.99 to 1.00) |
| EVI 5 years prior (5 km) | 1.80 x 10 ⁻³ (5.00 x 10 ⁻⁴ to 3.00 x 10 ⁻³) | 1.00 (1.00 to 1.01) |
| Heterogeneity structured | 1.18 (0.71 to 1.91) | - |
| ϕ (Decay of spatial correlation survey 1) | 45.17 (11.74 to 95.22) | - |
| Deviance information criterion | 3,575 | - |

* 95% CrI, 95% credible interval

The models of dog infection with *E. granulosus* with the spatial component had a lower DIC, 2.121, compared with the one without the spatial component, 2,250. There was an increase of 2.0% (95% CrI: 0.8–3.3%) in the prevalence of dog infection with *E. granulosus* for a 1% increase in the coverage of cultivated land, and 0.05% (95% CrI: 0.001–0.1%) for an increase of 1 unit of EVI (Table 5). The spatial model for *E. multilocularis* infection in dogs also had a lower DIC (805.2) compared with the non-spatial model (963.2) (Table 6). The prevalence of *E. multilocularis* infection was found to increase by 0.1% (95% CrI: 0.04–1.2%) with a 1-unit increase in EVI.

In the model of dog infection with *E. granulosus*, the variance of the spatially structured random effect was 0.6 (0.3 to 1.0) and in the model of dog infection with *E. multilocularis* this parameter was 1.6 (0.4 to 5.7), meaning residual spatial variation was higher for the model of infection with *E. multilocularis*. The values of the decay parameter for spatial correlation (ϕ) in the models of dog infection with *E. granulosus* and *E. multilocularis* were 69.4 and 41.2, respectively, indicating that the radii of the clusters were larger for dog infection with *E. granulosus* than infection with *E. multilocularis*.

Table 5. Regression coefficients, ORs and 95% CrI from Bayesian spatial model for dog infection with *E. granulosus* in Xiji, Haiyuan, Tongxin and Guyuan counties in 2012–2013

| Model | Coefficient, posterior mean (95% CrI*) | Odds ratios, posterior mean (95% CrI) |
|---|--|---|
| Intercept | -2.38 (-2.61 to -2.18) | - |
| Winter precipitation 5 years prior (5 km) | -0.04 (-0.11 to 0.01) | 0.95 (0.89 to 1.01) |
| Winter temperature 5 years prior (1 km) | 0.91 (-4.40 x 10 ⁻³ to 1.86) | 2.51 (0.99 to 6.47) |
| Bareland/Art. surfaces 5 years prior (5 km) | 0.01 (-4.40 x 10 ⁻⁴ to 0.02) | 1.01 (0.99 to 1.02) |
| Cultivated land 5 years prior (1 km) | 0.02 (0.01 to 0.03) | 1.02 (1.01 to 1.03) |
| Herbaceous vegetation 5 years prior (5 km) | 0.01 (-3.10 x 10 ⁻⁴ to 0.02) | 1.01 (0.99 to 1.02) |
| Shrubland 5 years prior (5 km) | -1.42 (-3.68 to 0.87) | 0.24 (0.02 to 2.41) |
| Water bodies same year (5 km) | -0.16 (-0.57 to 0.23) | 0.84 (0.56 to 1.25) |
| EVI 5 years prior (1 km) | -5.51 x 10 ⁻⁴ (-1.20 x 10 ⁻³ to 1.00 x 10 ⁻⁴) | 0.99 (0.99 to 1.00) |
| EVI 5 years prior (5 km) | 5.77 x 10 ⁻⁴ (1.74 x 10 ⁻⁵ to 1.15 x 10 ⁻³) | 1.00 (1.00 to 1.01) |
| Heterogeneity structured | 0.59 (0.29 to 1.00) | - |
| ϕ (Decay of spatial correlation) | 69.37 (25.85 to 98.64) | - |
| Deviance information criterion | 2,121 | - |

* 95% CrI, 95% credible interval

Table 6. Regression coefficients, ORs and 95% CrI from Bayesian spatial model for dog infection with *E. multilocularis* in Xiji, Haiyuan, Tongxin and Guyuan counties in 2012–2013

| Model | Coefficient, posterior mean (95% CrI) | Odds ratios, posterior mean (95% CrI) |
|---|--|---|
| Intercept | -4.09 (-4.99 to -2.41) | - |
| Annual temperature 5 years prior (1 km) | -1.57 (-17.50 to 9.6) | 0.20 (2.50×10^{-8} to 1.50×10^4) |
| Annual temperature same year (1 km) | -4.53 (-19.58 to 10.08) | 0.01 (3.10×10^{-9} to 2.24×10^4) |
| Summer temperature 5 years prior (5 km) | 0.92 (-9.78 to 14.50) | 2.52 (5.61×10^{-5} to 1.99×10^6) |
| Summer temperature same year (5 km) | 2.82 (-8.75 to 13.49) | 16.89 (1.57×10^{-4} to 7.26×10^5) |
| Winter temperature 5 years prior (1 km) | 3.62 (-12.59 to 21.39) | 37.65 (3.38×10^{-6} to 1.95×10^9) |
| Winter temperature 5 years prior (1 km) squared | 0.85 (-0.66 to 2.14) | 2.34 (0.51 to 8.56) |
| Winter temperature same year (1 km) | 28.74 (-4.27 to 56.02) | 3.02×10^{12} (0.01 to 2.13×10^{24}) |
| Winter temperature same year (1 km) squared | 4.42 (-3.54 to 13.70) | 83.49 (0.02 to 8.95×10^5) |
| Winter temperature 5 years prior (5 km) | -0.28 (-18.58 to 19.62) | 0.75 (8.44×10^{-9} to 3.33×10^8) |
| Winter temperature same year (5 km) | -28.97 (-56.69 to 0.06) | 2.61×10^{-13} (2.37×10^{-25} to 1.06) |
| Winter temperature same year (5 km) squared | -6.12 (-16.11 to 2.11) | 2.22×10^{-3} (1.00×10^{-7} to 8.26) |
| Bareland/Art surfaces 5 years prior (5 km) | 0.01 (-0.01 to 0.03) | 1.01 (0.98 to 1.03) |
| Cultivated land 5 years prior (5 km) | -6.01×10^{-3} (-0.03 to 0.02) | 0.99 (0.95 to 1.02) |
| Forest same year (5 km) | -7.61×10^{-3} (-0.04 to 0.02) | 0.99 (0.95 to 1.02) |
| Herbaceous vegetation 5 years prior (5 km) | -8.82×10^{-3} (-0.01 to 0.03) | 1.01 (0.98 to 1.03) |
| Shrubland 5 years prior (5 km) | -4.60 (-9.88 to 0.17) | 0.01 (5.10×10^{-5} to 1.19) |
| Shrubland same year (5 km) | -8.73 (-26.85 to 3.63) | 1.61×10^{-4} (2.17×10^{-12} to 37.79) |
| Water bodies 5 years prior (5 km) | -0.39 (-2.06 to 1.08) | 0.67 (0.12 to 2.95) |
| Elevation (1km) | 1.90×10^{-3} (-8.37×10^{-4} to 4.80×10^{-3}) | 1.00 (0.99 to 1.00) |
| EVI 5 years prior (1 km) | 6.84×10^{-4} (1.90×10^{-3} to 5.00×10^{-4}) | 0.99 (0.99 to 1.00) |
| EVI 5 years prior (5 km) | 1.00×10^{-3} (4.90×10^{-5} to 1.97×10^{-3}) | 1.00 (1.00 to 1.00) |

| | | |
|---------------------------------------|--------------------------|---|
| Heterogeneity structured | 1.62 (0.36 to 5.74) | - |
| ϕ (Decay of spatial correlation) | 41.23 (1.14 to 96.61) | - |
| Deviance information criterion | 805.2 | - |

* 95% CrI, 95% credible interval

Spatial predictions of human seroprevalence of *E. granulosus* and *E. multilocularis*

The predictive risk maps of seroprevalences of *E. granulosus* and *E. multilocularis* in Xiji, Haiyuan, Guyuan and Tongxin Counties in 2012–2013 were created (Figures 3A and B). The highest seroprevalence of *E. granulosus*, >60%, was predicted for west-central Xiji and Haiyuan. However, *E. granulosus* seroprevalences between 40% and 60% were predicted in large areas throughout these two counties and in the central part of Guyuan. For most of the northern part of the study area, which corresponds to Tongxin county, low seroprevalences were predicted (<40%) (Additional file 2). The highest seroprevalence of *E. multilocularis*, >20%, was found in a large area of the central part of Haiyuan county (Additional file 3). In northern Xiji and north-western Guyuan seroprevalences were between 8% and 16%, while low seroprevalences of *E. multilocularis*, 0-6%, were predicted for most of Tongxin and the southern part of Xiji County. Maps of the SDs of the posterior distributions of predicted seroprevalences of *E. granulosus* and *E. multilocularis* were also created (Figures 3C and D). The spatial distribution of high prediction uncertainty concurs with that of the areas with high seroprevalences of *E. granulosus* and *E. multilocularis*.

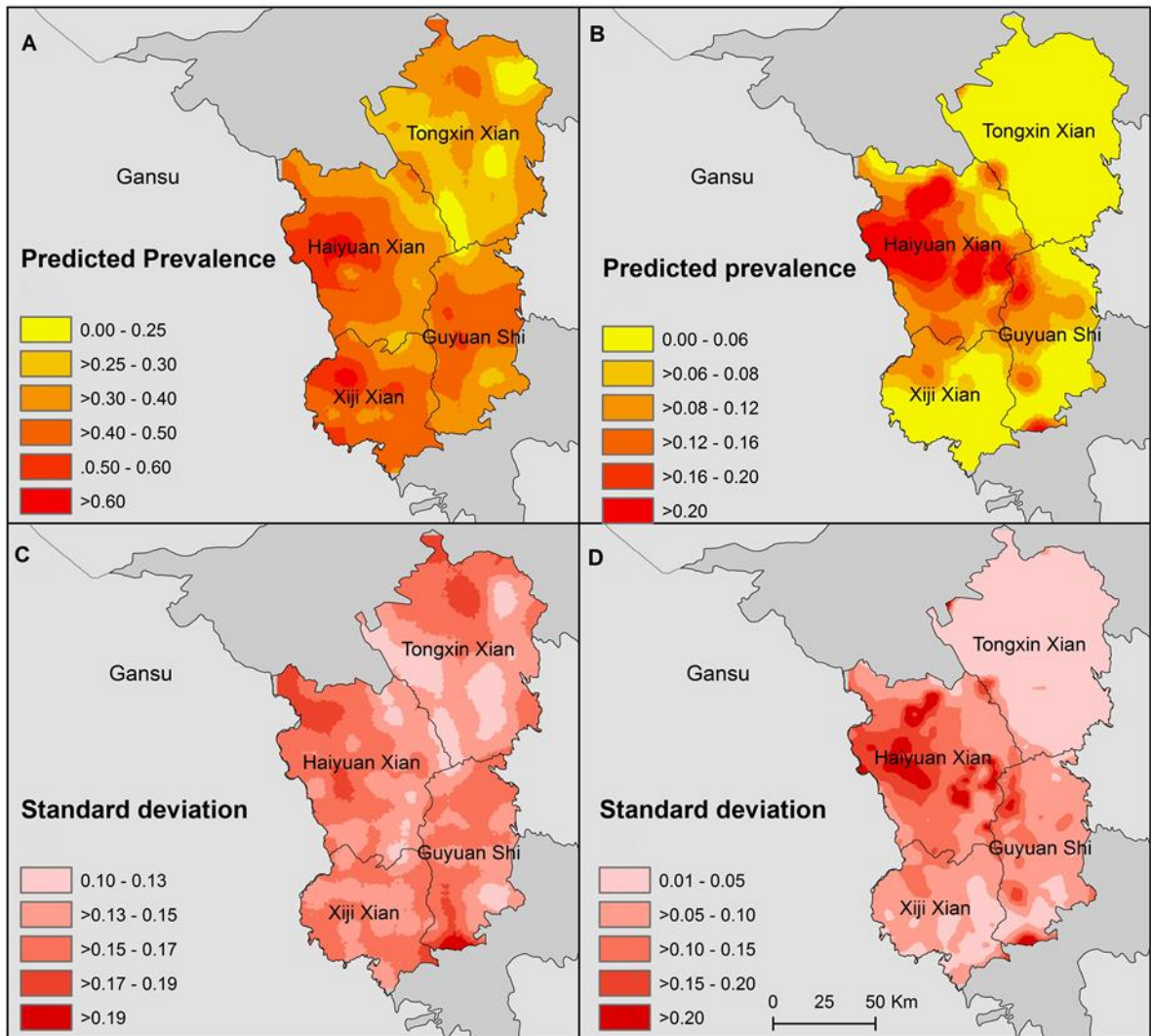


Figure 3. Spatial distribution of predicted seroprevalences of (A) *E. granulosus* and (B) *E. multilocularis* in schoolchildren aged 6–18 years and (C and D) standard deviations, respectively, in Xiji, Haiyuan, Guyuan and Tongxin counties, NHAR, P.R. China in 2012–2013

*Spatial predictions of prevalence of dog infection with *E. granulosus* and *E. multilocularis**

The highest predicted prevalence of dog infection with *E. granulosus* (>20%) was apparent in northern and eastern Haiyuan (Figure 4A). Almost all counties were predicted to be affected by this form of the infection except for Tongxin, where most of the territorial area had a predicted risk of 0-6%. A large high-risk area of dog infection with

E. multilocularis, >0.20%, was found in a region covering most of the south of the study area, which corresponds to the eastern part of Xiji and the south of Guyuan. More circumscribed areas of high risk of this infection in dogs were observed in the central part of Haiyuan. There was a large area of low risk, 0-6%, in northeast Haiyuan and almost the entire territory of Tongxin (Figure 4B). The maps of predicted SDs also showed high prediction uncertainty in areas with high mean predicted risk (Figures 4C and D).

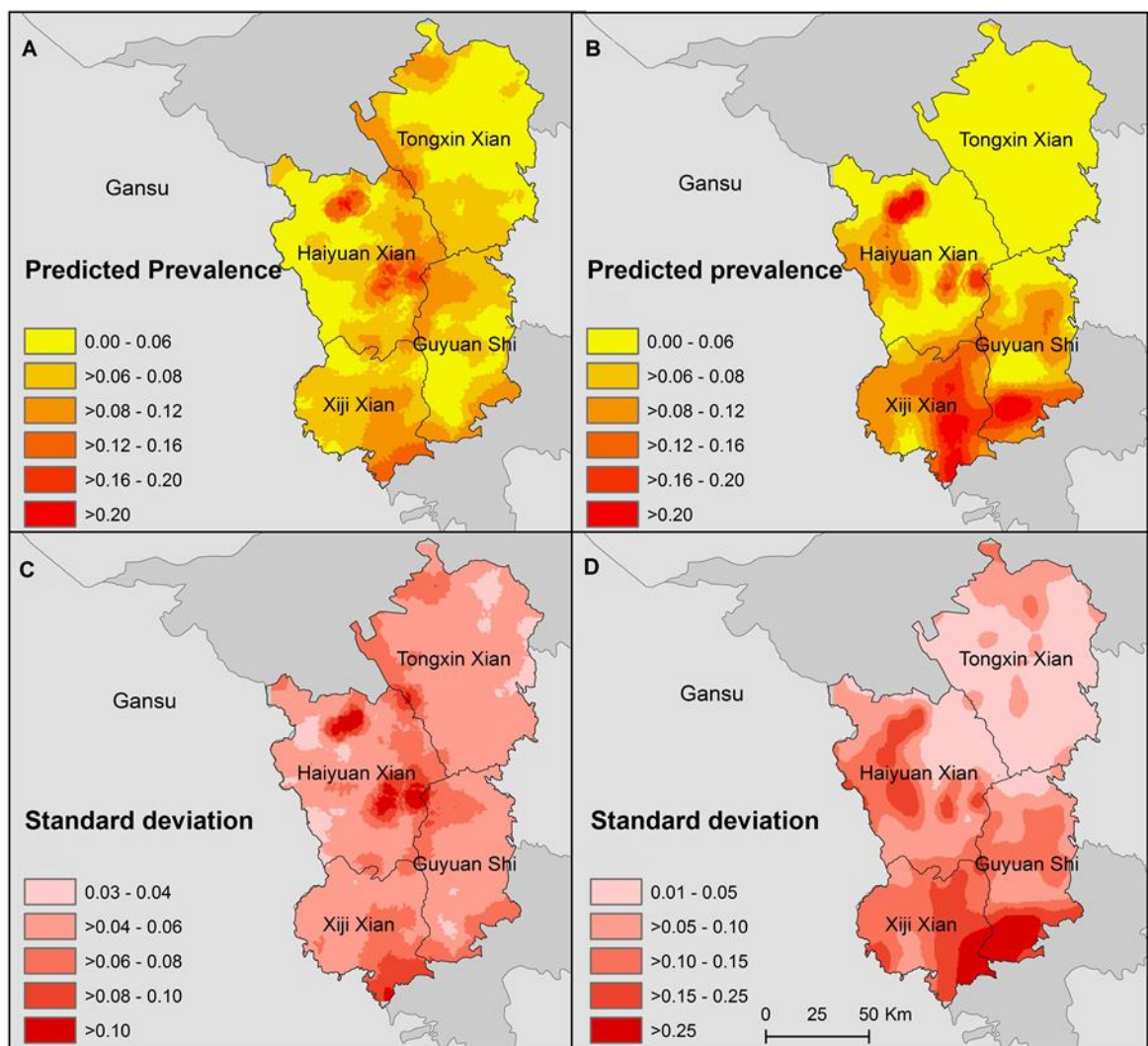


Figure 4. Spatial distribution of predicted prevalences of infection with (A) *E. granulosus* and (B) *E. multilocularis* in dogs, and (C and D) standard deviations, respectively, in Xiji, Haiyuan, Guyuan and Tongxin counties, NHAR, P.R. China in 2012–2013

Discussion

This study presents detailed information on the predicted geographical distribution of the risk of seropositivity for *E. granulosus* and *E. multilocularis* among schoolchildren aged 6–18 years, and infection with these parasites in dogs, in an important endemic area of P.R. China. To our knowledge, these are the first species-specific risk maps created for the region that concurrently reveal the spatial variation in echinococcosis risk for humans and dogs at a local spatial scale. Important climatic and land cover factors associated with the observed geographical heterogeneity in the risk of seropositivity were also identified. The findings are of current relevance in NHAR due to the ongoing process of landscape restoration in the Autonomous Region (Cadavid Restrepo et al. 2017; Li et al. 2013). Since 2002, the Grain for Green Project (GGP), a large national initiative to recover the degraded landscape, has been implemented in NHAR (Liu et al. 2008; Wang et al. 2007; Zhang et al. 2008). With the aim of reducing cropland on steep slopes, the GGP promotes three different types of land conversions: cropland to grassland, cropland to forest, and wasteland to forest (The University of Nottingham 2010; Zhou et al. 2012). The project also advocates for desertification control and prohibition of enclosures for grazing practices (Wang et al. 2007). Studies conducted in other echinococcosis-endemic regions, where landscape transformation processes have taken place, indicate that some types of land cover change may have had an impact on the transmission patterns of *E. multilocularis* and, consequently, the risk of infection has increased for animals and humans (Craig et al. 2000; Giraudoux et al. 1998; Giraudoux et al. 2003).

This study demonstrated visual similarities in the spatial distribution of the predicted seroprevalence of *E. granulosus* among schoolchildren and infection in domestic dogs in the four counties in 2012-2013. Human seropositivity for *E. granulosus* was predicted for most of the study area, and dog infections with *E. granulosus* was

predicted for almost all of Xiji County and in large areas of Haiyuan, Guyuan and Tongxin Counties. The north-eastern and central parts of Tongxin were shown to have the lowest predicted prevalence of this parasite in humans and dogs. This geographical area of Tongxin is covered primarily by dry steppe vegetation and desert grassland (Li et al. 2008). These characteristics of the local environment may be providing unfavourable ecological conditions for the transmission of *E. granulosus*, most probably due to the effects on the parasite eggs. Soil moisture/humidity and temperature particularly have been identified as important determinants of the survival and longevity of the *Echinococcus* spp. eggs in the external environment (Thevenet et al. 2005; Veit et al. 1995). Notably, the highest predicted prevalence of human seropositivity, unlike the highest predicted prevalence of dog infection, was found in areas from Xiji and Haiyuan Counties that share borders with the south of Gansu Province. In Gansu, human seropositivity and animal infections are also highly prevalent, with current estimates indicating that the annual incidence of human CE is between 2 and 10 cases per 10⁵ inhabitants (Deplazes et al. 2017). Therefore, the high predicted prevalence of human seropositivity for *E. granulosus* in these areas may be partially explained by the pastoral nomadic culture practices and the movement of people and domestic dogs across the provincial borders (Miller 2006; Shen 2012) .

The geographical distribution of the predicted prevalence of *E. multilocularis* among the students did not concur with the distribution of the predicted prevalence of *E. multilocularis* infection in dogs. While high prevalence of human seropositivity for *E. multilocularis* was predicted for almost all Haiyuan County, high prevalence of dog infection with this species was predicted for the eastern Xiji and southern Guyuan Counties. Although this study involved a different population group, the finding in Xiji confirms the prediction of the distribution of human seropositivity for *E. multilocularis*

conducted in the county in 2008, showing a similar geographical pattern (Pleydell et al. 2008). However, the findings do not support the current hypothesis that domestic dogs serve as the primary host of *E. multilocularis* in south NHAR (Budke et al. 2005a; Budke et al. 2005b; Romig et al. 2017). Dog ownership and high levels of interaction between domestic dogs and humans are risk factors identified commonly in AE endemic-regions in north-western P.R. China (Craig et al. 2000; Craig 2006; Schantz et al. 2003; Tiaoying et al. 2005), including NHAR (Yang et al. 2006c). High prevalences of dog infections with *E. multilocularis* have also been reported in highly endemic areas for AE (Budke et al. 2005a; Xiao et al. 2006; Ziadinov et al. 2010). Therefore, there is evidence that suggests dogs are an important reservoir of infections in humans (Romig et al. 2017). However, the observed differences in the geographical distribution of the predicted prevalence of the infection in both hosts may suggest greater importance of other definitive host species in transmitting the parasite in the south of NHAR. The transmission of *E. multilocularis* through life cycles that involve both Tibetan sand foxes (*Vulpes ferrilata*) and domestic dogs has been reported in Sichuan Province (Vaniscotte et al. 2011). Similar transmission patterns have been described in areas of the Altai, Tien Shan and Pamir mountains in the south of Kyrgyzstan and Kazakhstan (Ziadinov et al. 2008; Ziadinov et al. 2010). There, red foxes (*Vulpes vulpes*) were identified as principal definitive hosts, while domestic dogs were identified secondary definitive hosts of *E. multilocularis* (Ziadinov et al. 2008; Ziadinov et al. 2010). Reports of infection with *E. multilocularis* in red foxes in NHAR are only available for the mid-1980's (Li W et al. 1985). At that time, 15% of trapped red foxes were infected with *E. multilocularis* in Xiji and Guyuan Counties (Li W et al. 1985). Although infection with *E. multilocularis* has also been described in wolves (*Canis lupus*) and corsac foxes (*Vulpes corsac*) in other parts of P.R. China (Craig et al. 2000), corsac and red foxes are presumed absent in areas

of high risk of human AE in Xiji County (Giraudoux et al. 2013a). Hence, there is still a need for a more holistic approach that can help identify other important predator-prey communities in the area and other potential key definitive host for this parasite species in the region.

The results indicate that differences in vegetation, as indicated by EVI values, played a key role in explaining the observed spatial variation in the seropositivity for *E. multilocularis* among children aged 6–18 years, and infections with *E. granulosus* and *E. multilocularis* in dogs in the four counties. In addition, a positive association was found between dog infection with *E. granulosus* and cultivated land and a negative association between human seropositivity for *E. granulosus* and bareland/artificial surfaces. Associations between land cover and the spatial distribution of *E. multilocularis* seropositivity in humans and intermediate hosts are well documented in Eastern France, South Gansu, western Sichuan and Qinghai Provinces and in the South of NHAR (Giraudoux et al. 2003; Giraudoux et al. 2006; Giraudoux et al. 2013b; Pleydell et al. 2008; Wang et al. 2004; Wang et al. 2006). The previous study conducted in Xiji County indicated that the abundance of degraded lowland pasture was associated with a higher prevalence of AE in humans (Pleydell et al. 2008). The presence of 16 species of small mammals communities was also revealed in a survey of small-mammal conducted in relation to different land cover types in the same area (Raoul et al. 2008). That survey also showed that in areas that experienced afforestation, species diversity was lower than that in deforested areas (Raoul et al. 2008). However, the richness of the species was not affected by land conversion processes (Raoul et al. 2008). In abandoned grasslands and recently afforested set-aside fields, there was higher trapping success of potential intermediate hosts for *E. multilocularis* such as *Cricetulus longicaudatus* and *Ochotona daurica*, while in young plantations the species *Spermophilus alashanicus/dauricus* were

observed (Raoul et al. 2008). Reports of the link between foxes and the landscape in France are available (Pleydell et al. 2004). The evidence indicates that these associations are based on the influence of specific ecology characteristics on intermediate host population dynamics (Giraudoux et al. 2013a).

With regard to climatic covariates, the observed non-linear relationship between human AE prevalence and the values of winter and summer temperatures at the 5 years prior to the survey are consistent and interpretable with animal population dynamics, predator-prey interactions and the biology of the parasites. Temperature has been identified as a contributing factor that affects the geographical range and composition of foxes and small mammal communities (Hersteinsson and Macdonald 1992; Moritz et al. 2008; Zhenghuan et al. 2008). Experimental studies indicate that the *Echinococcus* spp. eggs develop at temperature-dependent rates in the external environment (Veit et al. 1995). The optimal temperature range for their survival has been established to be between 0°C and 10°C (Veit et al. 1995). However, differences have been found between species and strains (Thevenet et al. 2005; Veit et al. 1995). Temperatures of 4°C and of -18°C particularly, are well tolerated by *E. multilocularis* eggs with survival times of 478 and 240 days, respectively (Veit et al. 1995). Also, the evidence show that these eggs, if suspended in water, can remained infectious for a longer time than when exposed to heat (Federer et al. 2015).

Current estimates of the burden of human echinococcoses in NHAR rely primarily on data collected from hospital records (Yang et al. 2006b; Yang et al. 2006c). These data include primarily symptomatic patients who seek medical care (Yang et al. 2006a; Yang et al. 2006b). Therefore, it is assumed that the extent and distribution of human CE and AE cases occurring in remote areas and asymptomatic infections may be underestimated in current epidemiological reports (Yang et al. 2006b). In 2005, the National Control

Programme against echinococcoses was developed by the National Health and Family Planning Commission (formerly the Ministry of Health) in P.R. China. The measures that are currently being implemented in endemic areas include: community-based epidemiological surveys for early detection, treatment and surveillance of the disease, education campaigns to increase awareness among local people and health officials, and regular antihelminthic treatment for deworming of dogs (World Health Organization and World Organisation for Animal Health 2011; Yang et al. 2006c). Prevalence data on these infections are essential for enhancing these control activities and monitoring their cost-effectiveness and sustainability over time. Therefore, the findings of this study indicate that there is scope for the predictive maps created here to inform and guide spatially targeted interventions in those areas where they are most necessary. An additional benefit of this type of approach is that the maps allow monitoring of the transmission patterns of *E. granulosus* and *E. multilocularis* based on local environmental factors. In this way, it is possible to provide detailed information on the potential health effects of anthropogenic environmental change factors, including those that are associated with the implementation of national policies to recover the degraded landscape.

An important limitation of the study was the use of specific antibody testing by enzyme linked immunosorbent assay using *E. granulosus* cyst fluid antigen B and *E. multilocularis* crude protoscolex extract to define seropositivity of schoolchildren to *E. granulosus* and/or *E. multilocularis*. These tests have poor diagnostic performance with limited specificity and cross-reactivity with other helminthic infections and gastrointestinal malignancies (Brunetti et al. 2010; Torgerson et al. 2009). However, serology, although not ideal, is the only diagnostic method available for small echinococcosis lesions that are probably asymptomatic. Therefore, follow-up examination is recommended to confirm the infections.

Conclusions

This work provides detailed information regarding the geographical distribution of echinococcoses in humans and dogs in NHAR. The different models developed in this study indicate that human seropositivity for *E. granulosus* and dog infection with *E. granulosus* are widespread across the southern part of the Autonomous Region. Discrepancies in the geographical distribution of human seropositivity for *E. multilocularis* and dog infection with *E. multilocularis* suggest that further research is required to better understand the transmission dynamics of this parasite species. The results presented help to identify priority areas for echinococcosis control and may be used to target interventions where they have the greatest impact on the transmission of the infections.

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CHAPTER 7

Discussion

CHAPTER 7 DISCUSSION

7.1 Introduction

Previous studies undertaken in China reported and described the heterogeneous geographical distribution of human echinococcoses in the country, and highlighted the importance of various environmental, demographic and socio-economic factors influencing the variation in disease risk across endemic regions (1-8). However, the complexities of the life cycles of *Echinococcus* spp., in which a variety of risk factors combine to determine spatial patterns of echinococcosis transmission, require further investigation (9). In this research, a combination of multi-spatial landscape epidemiological approaches with GIS, EO data and modern spatial analytical techniques, provided a unique opportunity for a better assessment of the epidemiology of human echinococcoses in NHAR, a highly endemic area for CE and AE in western China.

The research has important practical implications for the understanding and control of these infections in the following ways: firstly, it provides a better insight into the local epidemiology of echinococcoses in NHAR, in which the local process of landscape transformation and climatic change may have contributed substantially to increasing the risk of infection to human populations; secondly, it provides maps of the distribution of CE and AE (or exposure to the parasites causing these diseases) at different geographical scales, which could be used as operational tools to guide and implement the interventions proposed by the National Action Plan for Echinococcosis Control in China; and thirdly, it provides comparative mapping approaches that help visualise human exposure to *E. granulosus* and *E. multilocularis* and dog infections with these parasites, showing that definitive hosts other than domestic dogs may be playing an important role in defining the geographical risk of *E. multilocularis* exposure to humans in NHAR.

7.2 Key research findings

The study detailed in Chapter 3 revealed that the process of land conversion in NHAR between 1991 and 2015 concurred with the large-scale impact of the GGP in increasing forest and herbaceous vegetation coverage and in regenerating bareland areas. The findings extended the existing evidence on the process of land conversion in NHAR and confirms previous provincial reports of short-term (ten years or less) land cover assessments conducted in the autonomous regions (10-13). Additionally, land cover change in NHAR from 1991 to 2015 was consistent with environmental assessments conducted in other regions in western China, where ecological restoration policies have also been adopted (14-16). The observed land cover changes have been reported by researchers as positive or negative effects based on the environmental needs of each region (17, 18). One of the major concerns of the process of landscape transformation was its potential to compromise human health by inducing variations in infectious disease patterns, including human echinococcoses (19-23).

Land cover change in NHAR was not exclusively the result of policies implemented to improve ecological conditions in China (12, 24). In addition to the effects of the GGP, there are other potential socio-economic, demographic and environmental causes of land cover change such as meteorological disasters, economic growth and rural-urban migration that still need to be considered and explored (24-27). The results of this Chapter provide evidence that may help facilitate future landscape planning, management and decision making in NHAR. Providing food, energy, housing and other ecosystem services while preserving biodiversity and ecosystem functions that maintain their sustainable supply, is currently a great challenge (28). The land cover maps created as part of this research and the land cover change detection analysis may help the local government in NHAR identify optimal locations in which is appropriate to modify the

ecological network without affecting local ecosystem processes that determine the human and animal well-being. Also, monitoring land cover change may help to develop effective responses to local emerging environmental risks, such as rapid budget preparation processes, prioritization and allocation of required resources including mobilization of personnel to support the implementation of control interventions in areas in risk (29).

The study presented in Chapter 4 provided a spatio-temporal analysis of land cover and climatic factors associated with the number of CE and AE cases by township in NHAR between 1994 and 2013. The approach followed a framework that is similar to the ones adopted in previous research that explained patterns in human echinococcosis prevalence or incidence data in China using spatial statistics, EO data and GIS (4, 5, 30). However, a novel component of the study presented in Chapter 4 is the spatial and temporal extent of the data being analysed. The study found a negative trend in annual CE, a positive association with winter mean temperature at a 10-year lag and a significant nonlinear relationship with annual mean temperature at a 13-year lag. The study also revealed a negative association between AE incidence and moving averages of bareland/artificial surface coverage and annual mean temperature for the period 11-15 years before diagnosis and winter mean temperature for the period 0-4 years. Unlike CE risk, the selected environmental covariates incorporated in the analysis explained most of the spatial variation in the risk of AE. The association found between some of the selected environmental variables and the risk of human echinococcoses, particularly AE, suggests that land cover change and climate variability in past decades may have contributed substantially to shape the current spatial patterns of these infections in NHAR by influencing the population dynamics of potential *Echinococcus* spp. hosts and facilitating human exposure to the parasite eggs (31, 32).

The study in Chapter 4 also provided the first echinococcosis incidence maps for NHAR. These maps are in line with previous data on human echinococcoses in endemic regions which showed that *E. granulosus* and *E. multilocularis* are heterogeneously distributed across endemic regions (5, 22, 30). Based on these maps, it was possible to identify the southern part of the autonomous region as a highly endemic area for both CE and AE. NHAR lacks reliable historical incidence estimates, and the mapped outputs presented in this study will help support targeted control interventions that include education and screening surveys in the southern counties for improving awareness among the population and the early detection and treatment of echinococcosis cases.

The results of Chapter 5 indicate that the risk of exposure to *E. granulosus* expanded across Xiji during the study period (2002-2013), while the risk of exposure to *E. multilocularis* became highly focal in the south-west part. This finding contrasts with evidence from Europe and other regions in Asia that indicate *E. multilocularis* has been spreading in those areas (33-35). This difference may be partially explained by different local transmission patterns of the parasite in this highly endemic area and to novel interactions between the recently transformed local landscape, the parasite and its hosts (36). This study found that the observed risk of human exposure to these parasites had significant associations with vegetated areas and landscape fragmentation variables. Therefore, the study presented in Chapter 5 provides further evidence that supports the potential role of the GGP and other ecological policies implemented to recover the landscape in increasing the risk of human exposure to *Echinococcus* eggs.

From a public health perspective, the predictive risk maps of human exposure to *E. granulosus* and *E. multilocularis* created for Xiji County in this study are an important resource that will help to guide and monitor improvements in human echinococcosis control measures. In general, by mapping and analysing the distribution of the risk of

human exposure to *E. granulosus* in Xiji County, it was clear that the implementation of control strategies in order to be successful will need to be applied broadly across the whole of Xiji County.

Domestic dogs have been identified as the main transmission source of *E. granulosus* and *E. multilocularis* to the local human population in Gansu Province and the eastern Tibetan plateau, P.R. China (6, 37). In NHAR, dog ownership and high levels of interaction between domestic dogs and humans were identified as risk factors for AE infections (38, 39). However, there are no data available on the prevalence of dog infections with *E. multilocularis* in the Autonomous Region. Therefore, the study presented in Chapter 6 offers a unique public health insight for the south of NHAR because it provides the first species-specific predictive risk maps that allow to compare spatial variation in human exposure to *Echinococcus* spp. and infection with these parasites in domestic dogs. The study found that the risks of human exposure and dog infection with *E. granulosus* were widely distributed across the four counties. Human exposure to this parasite species was predicted for most of the study area, and dog infection with *E. granulosus* was predicted for almost all Xiji County and in large areas of Haiyuan, Guyuan and Tongxin Counties. The risk of human exposure to *E. multilocularis* was higher in Haiyuan County, while the risk of dog infection with this parasite species was higher in Xiji County. The findings in Xiji County were consistent with a spatial risk prediction study of the distribution of human exposure to *E. multilocularis* conducted in this area in 2008 (4). However, the findings do not support the current hypothesis that domestic dogs serve as the primary host of *E. multilocularis* in south NHAR (40-42). The observed differences in the geographical distribution of predicted risk of infection in both hosts suggests that data on the infection status of other species of definitive hosts should be included in future echinococcosis research. In this

way, it will be possible to identify other important predator-prey communities in the area, and other potential key definitive host for *E. multilocularis* in the region. It also suggests that interventions targeted at dogs will have limited impact on the burden of AE.

EVI was identified as a common risk factor explaining the observed spatial variation in the exposure to *E. multilocularis* among children aged 6–18 years, and infections with *E. granulosus* and *E. multilocularis* in dogs in the four counties. A positive association was also found between dog infection with *E. granulosus* and cultivated land and a negative association between human exposure to *E. granulosus* and bareland/artificial surfaces. These findings support evidence that indicates that, unlike other echinococcosis endemic areas in China where EVI was negatively associated with *Ochotona* spp. Communities (43, 44), high densities of other potential host species for *E. multilocularis* are present in reforested lowland pasture in NHAR (4, 45). The findings presented in this chapter are of current relevance in the Autonomous Region due to the ongoing process of landscape restoration that may have favoured the establishment of the life cycles of these parasites in areas where land cover was converted to vegetated areas.

By mapping the distribution of the risk of human exposure to *E. granulosus* and *E. multilocularis* in the south of NHAR, incorporating environmental factors, I provided a means to identify priority areas for echinococcosis control. The risk maps may be used to target interventions where they have the greatest impact on the transmission of infections.

7.3 Limitations

There were some limitations in the analyses encompassed in this thesis. These limitations have been outlined in each of the research chapters (Chapters 3 to 6). Some of the limitations that need to be highlighted include: in the study presented in part one of

Chapter 3, the selection of high-resolution (30 m) imagery from Landsat 4/5-TM and 8-OLI for the entire region was affected by the limited availability of the data. Comparing land cover in different vegetation seasons may have had an impact on the accuracy of the results. To address this limitation, a primary criterion for image selection was acquisition date whereby, to the extent possible, images were collected from the summer and autumn growing seasons in NHAR. When there were no scenes available for the defined period, the closest-in-time and most cloud-free scenes available were used for the analyses. An inescapable difficulty with classifying Landsat data from rural NHAR was the lack of archived data sets suitable for training and validation purposes. Multiple data sources were required to produce reference data sets for land cover classification and validation. In the study presented in Appendix A, interpolated temperature and precipitation surfaces for the estimation of the climate trends were used for the trend detection analysis. The lack of a sufficiently dense station network may have affected the accuracy of interpolated spatial variability in temperature and precipitation trends across the autonomous region. To address this limitation and also to validate the results of the study, geo-referenced data on the location of the 16 stations were requested from the Chinese Academy of Sciences for the analysis. However, this information was not available due to privacy and confidentiality concerns.

The study presented in Chapter 4 relied mainly on data collected from selected county hospitals. Clinical records are the only available source of data on historical patterns of these infections in NHAR, but the use of this type of data poses multiple challenges. First, these data exclude CE and AE cases that were not referred to health care institutions for confirmation of diagnosis, treatment and follow-up. Second, the long latency period of echinococcosis results in slow epidemiological shifts in response to environmental change that could be difficult to quantify. Third, the township in which

patients resided at the time of diagnosis was assumed as the place where acquisition of infection occurred. Population movement could obscure or introduce bias in analyses of spatiotemporal disease patterns. Fourth, immunosuppression can be a source of bias for the interpretation of the results due to induction of rapid cyst development and earlier diagnosis, but co-morbidities, such as tuberculosis and infection with the human immunodeficiency virus, and medication exposures that are known to affect the immune response to the infections were not accounted for in the multivariate regression analysis, because data on these factors were not available. Therefore, it is recommended that future studies conducted to identify risk factors for echinococcosis transmission also involve individual biologic conditions that may be associated with progression and time of diagnosis of the disease. Finally, some level of uncertainty may have been incorporated into this study by using interpolated surfaces for the estimation of climatic and land cover variables. The precision of the interpolated values at point locations may vary considerably over time and over the entire study area. However, the interpolated land cover and climate surfaces were the most consistent long-term records available to conduct a meaningful assessment of the associations between human echinococcosis risk and the environment.

Ultrasound is the method of choice for the confirmation of echinococcosis diagnoses (46). However, due to the low sensitivity to detect small cysts, this diagnostic technique was not used to identify recent cases of human infection with *Echinococcus* spp. In the studies presented in Chapters 5 and 6, human exposure to *E. granulosus* and *E. multilocularis* was defined using specific antibody testing by enzyme linked immunosorbent assay using *E. granulosus* cyst fluid antigen B and *E. multilocularis* crude protoscolex extract. However, these tests also have poor diagnostic performance, limited specificity and cross reactions with other helminthic infections and

gastrointestinal malignancies (47, 48). Therefore, follow-up examination is recommended to determine development of the infections.

7.4 Future research

The research presented in this thesis addressed some of the gaps in the knowledge of the local epidemiology of human echinococcoses in NHAR and described the process of landscape transformation in the autonomous region in the last thirty years. However, there are several potential areas for further research that would assist in improving the evidence for the impact of national ecological rehabilitation projects in China, and to support surveillance and sustainable preventive and control measures against *Echinococcus* spp., and these include:

- The impact of the Grain for Green Project was not formally tested in this study. This was not possible due to the lack of adequate and specific data on the design and coverage of the programme at the provincial level. Also, the programme is a large-scale government-initiated project that was implemented in the entire NHAR territory. Therefore, future holistic and rational approaches that examine the contributions of ecological restoration projects and other economic and social factors in the process of landscape restoration in NHAR, and elsewhere, are required.
- Long-term sentinel sites in the south of NHAR should be established for surveillance of human and animal exposure to *E. granulosus* and *E. multilocularis*, and for the accumulation of local environmental data. This information will provide considerable opportunities to explore in more detail the

mechanisms by which land cover and climate change affect *Echinococcus* spp. transmission. This research created predictive modelling tools capable of providing early warning for high risk areas or emergence in transmission patterns. Model-based geostatistics as a prediction method has been used successfully in early warning systems for infectious diseases such as malaria (49), dengue (50, 51) and West Nile virus (52). In the context of human echinococcoses, early warning predictions, although challenging due to the complex transmission systems of *Echinococcus* spp. (36), also offer a great potential in the efforts against the infections. Active early warnings, under the framework of an echinococcosis surveillance system, will allow timely decision-making processes that can lead to the rapid implementation of interventions tailored to specific local settings. Targeted education and screening campaigns within emerging high-transmission areas, are cost-effective alternatives to mass screening surveys (31).

- Predicted seroprevalence of human exposure to *E. multilocularis* and dog infection with this parasite differed spatially. Further research is required to help identify other important predator-prey communities in the area and other potential key definitive host for this parasite species in the region.
- *Echinococcus* spp. transmission models developed to date have focused primarily in the life cycles of these parasites in the animal definitive and intermediate hosts, and do not include the human transmission pathway (32). The integration of the echinococcosis risk maps with mathematical models of *Echinococcus* spp. transmission may lead to the development of spatially explicit disease transmission models.

- The inclusion of human echinococcosis risk maps in future mathematical models would be an advance that would help with the design of optimal public health interventions against echinococcosis infections.
- The echinococcosis risk maps may be used as inputs in future economic analyses to determine and compare spatial variation in cost-effectiveness of different competing control interventions, alone and as part of an integrated approach.

7.5 Conclusions

The research included in this thesis explores contemporary landscape epidemiological approaches to characterise the spatiotemporal patterns of environmental change in NHAR, define the geographical distribution of human echinococcosis risk over time, and quantify the role of the physical environment in influencing local patterns of *Echinococcus* spp. exposure and disease in the autonomous region at different spatial scales. Based on the findings, it was possible to define communities at higher risk of exposure to *E. granulosus* and *E. multilocularis* in this highly endemic area for CE and AE infections in China. Echinococcosis control strategies could be more efficiently targeted to these high-risk communities to yield the greatest public health benefits.

I used GIS, remotely sensed data and in situ environmental data to quantify land cover and climate change in the autonomous region, and in doing so, I provided six land cover and climate trend maps that allowed visualisation and quantification of changes in the environment that occurred in NHAR during a period of extensive landscape regeneration. Although the impact of ecological restoration projects was not formally tested in this research, the results serve as evidence for the potential effects of these projects on local ecosystems services and may facilitate future ecosystem management and protection. Additionally, quantification of environmental change in NHAR is

essential for implementing an effective response to emerging local environmental risks such as environmentally-influenced infectious diseases including human echinococcoses. The comparisons of the spatio-temporal patterns of clinically diagnosed human echinococcoses and recent exposure to *E. granulosus* and *E. multilocularis* demonstrated that human echinococcosis risk has geographically changed in NHAR over the past three decades. The risk of exposure to *E. granulosus* expanded and became more widespread across the southern part of NHAR at the end of the research period, while the risk of exposure to *E. multilocularis* became more confined. Vegetation growth and the relatively temperate climate in the higher altitudes of the south of NHAR were identified as potential factors favouring habitat suitability for *Echinococcus* spp., and the presence and spatial overlap of large populations of potential hosts species. Discrepancies in the geographical distribution of human exposure to *E. multilocularis* and dog infection with *E. multilocularis* suggest that definitive hosts other than dogs are important in defining the geographical risk of *E. multilocularis* exposure to humans in NHAR.

The epidemiological situation of echinococcosis in villages of southern NHAR has been unmonitored. Estimates of the burden of human echinococcoses in NHAR have relied primarily on data collected from hospital records. Therefore, the findings of this thesis will be essential to track future requirements for scaling up and targeting of control strategies proposed by the National Action Plan for Echinococcosis Control in China. Additionally, the predictive models developed as part of this research can be used as a platform for future monitoring of the prevalence of echinococcosis infections and the emergence in *Echinococcus* spp. transmission in the most affected areas.

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Appendix A

Appendix A

Temperature and precipitation trends in NHAR for the period 1 January 1980 to 31 December 2013

2.2.1 Introduction

The spatial distribution of recent mean temperature trends over NHAR during the period 1980–2013 at annual and seasonal time scales was estimated in this study by applying geostatistical modelling techniques to data collected and interpolated from 16 weather stations by the Chinese Academy Sciences. The analysis showed statistically significant positive trends in annual, summer and winter temperatures in most of NHAR. Also, statistically significant upward trends in annual and summer precipitation in northern and central NHAR, whereas significant negative precipitation trends were found in the south.

Appendix A provides a connection between the processes of land cover and climate change by presenting box plots that compare the effect of climate on the most relevant land cover changes identified in Chapter 3.

2.2.2 Climate data

Monthly mean temperature and precipitation data records for the period January 1 1980 to December 31 2013 were analysed. Data were first collected from 16 local weather stations and interpolated by the Chinese Academy of Sciences using the Inverse Distance Weighting (IDW) method. The original data were not available for the current study.

The Chinese Academy of Sciences provided the monthly averages of the climate data in a raster format at the spatial resolution of 1 km. An administrative boundary map of the province was downloaded from the DIVA-GIS website (59). The climate data sets were imported into ArcGIS and linked spatially to the boundary map (60). Monthly records were summed in the GIS to provide annual, summer (June, July and August) and

winter (December, January and February) weighted mean series. The weights were the number of days in a month. Temperature and precipitation anomalies were calculated for each pixel and year to define parameters in subsequent statistical models. An anomaly is defined as the deviation of a variable of interest at a given location and a particular time from the long-term average for that location. The reference period used in the study to calculate temperature and precipitation anomalies was January 1 1980 to December 31 2013. A positive anomaly indicated that the parameter under study was higher than the baseline, while a negative value indicated that the parameter was lower than the baseline. This anomaly-based approach was used to improve the consistency of the climate data for subsequent analyses (61).

A selection of a random sample of 700 locations from each data set (53,157 pixels) was used because computationally, it was not possible to use all pixels.

2.2.3 Climate trend analysis

Precipitation and temperature trend analyses at annual and seasonal (summer/winter) temporal resolution were carried out by applying a linear model in a Bayesian geostatistical framework. Six separate geostatistical models (annual, summer and winter, for temperature and precipitation) were developed using the OpenBUGS software, version 3.2.3 (62).

Each model assumed that the annual and seasonal averages of temperature/precipitation measurements, Y , for the i th location, ($i = 1. . .700$) in the j th year (1980-2013) followed a normal distribution with mean (μ_{ij}) and variance σ_i^2 , that is,

$$Y_{ij} \sim \text{Normal}(\mu_{ij}, \sigma_i^2)$$

$$\mu_{ij} = \alpha + \beta_i \times T_j + \lambda \times T_j$$

where α is the intercept, β_i (the main parameters of interest), modelled as a spatially-smoothed random effect, are the magnitudes of the trends for each location, T is the number of years from the baseline year (1980), and λ is the mean trend for the province. The spatial correlation in β_i was assumed to be an exponential function of the distance between points, i.e. $\sigma_2^2 \exp(-\rho d_{kl})$, where d_{kl} is the straight-line distance between pixels k and l , σ_2^2 is the geographical variability known as the sill and ρ is a smoothing parameter that controls the rate of correlation decay with distance.

A normal prior distribution was specified for α and λ (with a mean=0 and a precision=0.001). Precision refers to the inverse of variance (i.e. $1/\sigma_i^2$), and the priors for this parameter were specified using non-informative gamma distributions with shape and scale parameters equal to 1. The prior distribution of ρ (rate of decay) was uniform with upper and lower bounds set at 0.01 and 100.

A burn-in of 1000 iterations was run and discarded. Subsequent blocks of 10,000 iterations were run and examined for convergence. Visual inspection of the posterior density and history plots was used to assess convergence, which occurred at approximately 20,000 iterations for each model. After convergence, ten thousand iterations were run and the values from the posterior distributions of each model parameter were stored for analysis. The posterior mean and 95% credible intervals of the posterior distributions were used to summarise the parameters.

ArcGIS software was used to interpolate and generate maps that represent the spatial distribution of the relative trend in annual, summer and winter temperature and precipitation anomalies in NHAR for the period January 1980–December 2013. These maps were created by calculating the posterior means of the trend from the provincial average calculated at the 700 randomly selected points and interpolating the values using

the inverse distance interpolation technique. Thus, maps produced showed smoothed areas where the trend was higher or lower than the overall average.

Box plots were created using a random sample of 35,000 locations (pixels) to depict differences in annual temperature and precipitation trends in NHAR between 1980 and 2013 among the land cover change types observed in bareland/artificial surfaces and cultivated land from 1991 to 2015. In addition, the mean trends for each group were tested by using two-way analysis of variance (ANOVA) using the R language and environment for statistical computing (63).

2.2.4. Results

Maps of the spatial distribution of annual, summer and winter temperature and precipitation anomaly trends are presented in Figure 1. The overall results found statistically significant positive trends in annual, summer and winter temperatures in most of Northern, Central and Western NHAR and negative trends in the southern mountainous area during the period January 1980–December 2013. The average magnitude change in annual temperature was 0.2 °C/decade for the whole period in the province. The range of annual temperature location-specific trends varied between -0.8 °C and 0.2 °C per decade from the provincial average trend. Summer temperature for the whole province increased by 0.7°C/decade, with the range of location-specific trends differing between -1°C and 0.3°C per decade from the provincial average trend. The spatial pattern of annual warming was similar for summer temperature trends but with higher magnitude. The greatest trend magnitude in temperature anomalies appeared in winter, with an increase of 0.9 °C/decade. The winter temperature location-specific trends differed between -0.3°C and 0.08 °C per decade from the provincial average trend. The spatial distribution of the winter trend varied slightly from the spatial pattern described

for annual and summer temperatures. In winter, temperature rose more rapidly in areas located throughout the central part of the province. Similar to annual and summer temperatures, a significantly lower trend was found in winter in the southern mountainous area.

The analysis of the time series of annual precipitation anomalies revealed that there was a slight positive trend in annual precipitation for NHAR for the period January 1980–December 2013 (Figure 1d). In general, there was a small magnitude change in annual precipitation, 0.11 mm/decade for the whole period, with distinctive spatial and seasonal patterns. A statistically significant positive trend was observed in the northern and central part of the province, whereas significant negative trends were found in the south. The annual precipitation location-specific trend differed between -7 mm and 7 mm per decade from the provincial average trend.

Summer precipitation anomaly for the whole province showed a statistically significant decreasing trend. The spatial pattern of the trend was similar to that of annual precipitation (Figure 1e). Significant positive trends were mostly found in the north and centre of NHAR and significantly negative trends were observed in the south. The range of location-specific trends in summer precipitation differed between -25 mm and 30 mm per decade from the provincial average trend.

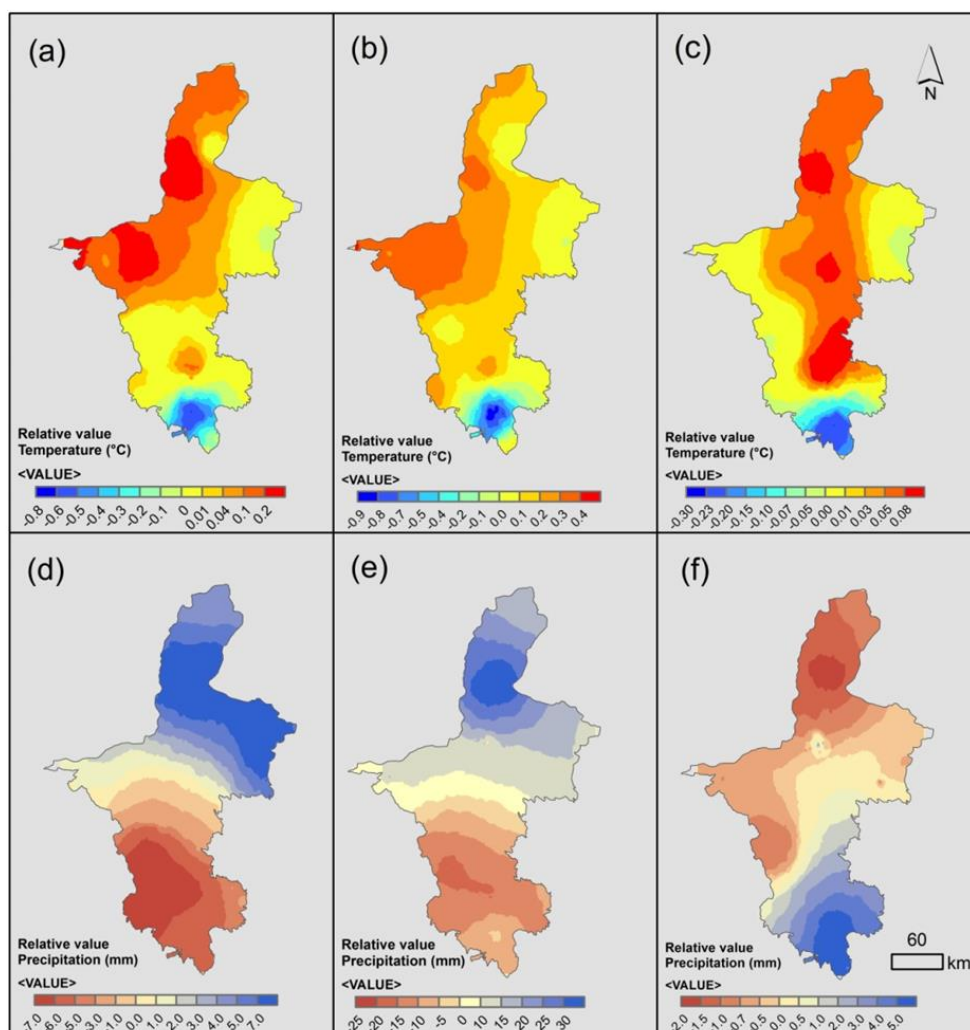


Figure 1 Maps of the spatial distribution of (a) annual, (b) summer and (c) winter temperature trends, and (d) annual, (e) summer and (f) winter precipitation trends in NHAR for the period 1 January 1980 to 31 December 2013. Note, the values presented in the figure are relative to the provincial average per decade

The highest increasing precipitation trend for the entire province was observed in the winter season, with an increase of 2.4 mm over the study period. However, winter precipitation anomaly trends exhibited an opposite spatial distribution when compared to that of annual and summer precipitation. Winter precipitation showed negative trends in the northern and central part of NHAR and positive trends in the southern mountainous and loess hilly district (Figure 1f). The magnitude of this trend differed from -2 mm and 5 mm per decade from the provincial average trend in specific locations.

The mean trends for annual temperature were significantly different among the land cover changes experienced in bareland/artificial surfaces (two-way ANOVA, $F = 3,543$; $P < 0.05$) and cultivated land (two-way ANOVA, $F = 2,600.9$; $P < 0.05$). Also, the mean trends for annual precipitation were significantly different among the land cover changes in bareland/artificial surfaces (two-way ANOVA, $F = 4,768$; $P < 0.05$) and cultivated land (two-way ANOVA, $F = 1,392.7$; $P < 0.05$). Based on the box plots, higher variability in temperature trends is observed in areas that converted from bareland/artificial surfaces to herbaceous vegetation and areas that converted from cultivated land to forest. The highest temperature trends were found in those areas where bareland/artificial surfaces converted to forest and in areas that remained unchanged (Figure 2a). Also, the largest magnitudes of estimated temperature trends were observed in cultivated land that remained unchanged, and in areas that experienced a different type of land cover change, not classified as bareland/artificial surfaces, forest or herbaceous vegetation (Figure 2c). Areas that converted from bareland/artificial surfaces to herbaceous vegetation and from cultivated land to forest are characterized mainly by negative temperature trends whereas the majority of the regions that experienced other type of land cover changes showed positive temperature trends.

The lowest precipitation trend occurred in bareland/artificial surface areas converted to cultivated land and herbaceous vegetation (Figure 2c). The highest precipitation trend occurred in bareland/artificial surface areas and cultivated land that remained unchanged, and bareland/artificial surface areas converted to forest (Figures 2c and d).

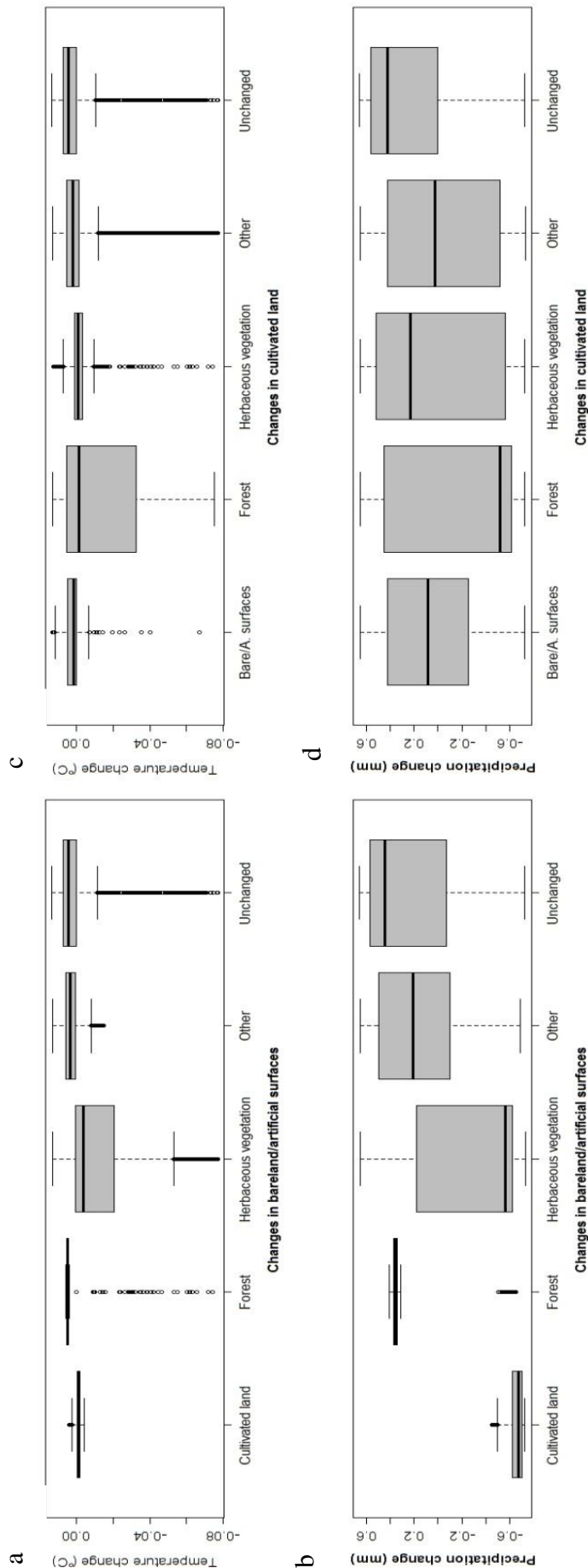


Figure 2 Box plots showing the distribution of annual temperature and precipitation trends in NHAR from 1980 to 2013 in the main land cover changes observed in bareland/artificial surfaces (a and b) and cultivated land (c and d) from 1991 to 2015. The middle bar of each box shows the 50% percentile, while the top and bottom of the box bars show the 75% and 25% percentiles (first and third quartiles, respectively). Whiskers extend to the 5% and 95% percentiles. Temperature (°C) and precipitation (mm) trends are presented as values relative to the provincial average per annum.

2.2.5 Discussion

Climate in NHAR follows the same long-term warming and drying trend described for China (64). From January 1980 – December 2013 the trend in annual, summer and winter temperatures showed a significant increase. More rapid warming was observed during the winter season. More rapid increases in temperature were observed in areas located in the north and central part of the province and a slower warming trend was observed in areas near the Liupan Mountains in the south. Similar, statistically significant positive temperature trends for NHAR have been reported by other authors (65, 66). Contrasting with previous studies that reported a downward trend in annual precipitation, we noted a slight increase in the average annual precipitation trends for NHAR. Winter precipitation increased and summer precipitation decreased following the same trends as other local reports (65).

Correlations were found between climate trends and LULC change, as represented in the box plots. Areas that changed from cultivated land to forest and bareland to herbaceous vegetation were the ones that experienced the lowest trends in annual temperature. This is the type of land conversion that was promoted by the GGP in the Southern Mountainous region of the province (67). Previous evidence suggested that responses in forest growth and productivity are inversely associated with the magnitude of temperature increase (68, 69), although this correlation might have been coincidental, given that high altitude areas experience lower rates of warming, and these were the areas that were also forested. In general, it is difficult to attribute the observed changes in land cover in NHAR during the study period to the estimated temperature and precipitation trends, or vice versa, due to the relatively short period of time, so the correlations presented in the box plots need to be interpreted with caution.

The use of interpolated surfaces for the estimation of the climate trends represented a challenge for the interpretation of the results. The interpolated surfaces were based on only 16 meteorological stations and the precision of the interpolated values at individual point locations may vary considerably over the entire study area. This is a particularly important point for the interpretation of the trends in those areas where the distribution of meteorological stations was sparse. We believe that a meaningful analysis on climate change can only be achieved with the utilization of consistent and long-term climate records, and networks that are sufficiently dense to capture significant spatial variability.

The findings from the analysis presented in this section of Chapter 3 are used as inputs into the models presented in Chapters 4–6.

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Appendix B

APPENDIX B

SUPPLEMENTARY MATERIAL FOR CHAPTER 3

Cadavid Restrepo, A.M.; Yang, Y.R.; Hamm, N.A.S.; Gray, D.J.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; McManus, D.P.; Guo, D.; Clements, A.C.A. Land cover change during a period of extensive landscape restoration in Ningxia Hui Autonomous Region, China. *Science of The Total Environment*. 2017; 598:669-79.

Table A.1 Maximum likelihood parameters to conduct supervised classification in ENVI software and create land cover maps for the years 1991, 1996, 2000, 2005, 2010 and 2015

| Classification parameters | 1991 | 1996 | 2000 | 2005 | 2010 | 2015 |
|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Spectral subset (band combinations) | 2,3,4,5,6 | 2,3,4,5,6 | 2,3,4,5,6 | 1,4,5,6 | 2,3,4,5,6 | 2,3,4,5,6 |
| Number of Regions of interest (ROIs) | 425 | 474 | 486 | 478 | 500 | 456 |
| - Class 1: Bareland/artificial surfaces | 196 | 200 | 200 | 171 | 270 | 266 |
| - Class 2: Cultivated land | 9 | 20 | 25 | 30 | 30 | 30 |
| - Class 3: Forest | 9 | 12 | 18 | 60 | 68 | 33 |
| - Class 4: Shrubland | 4 | 4 | 5 | 5 | 5 | 5 |
| - Class 5: Herbaceous vegetation | 195 | 221 | 221 | 182 | 112 | 110 |
| - Class 6: Water bodies | 12 | 17 | 17 | 30 | 15 | 12 |
| Select classes for region | 6 | 6 | 6 | 6 | 6 | 6 |
| Probability threshold | Single value | Single value | Single value | Single value | Single value | Single value |
| Probability threshold value | - | - | - | - | - | - |
| Data scale factor | 1 | 1 | 1 | 1 | 1 | 1 |

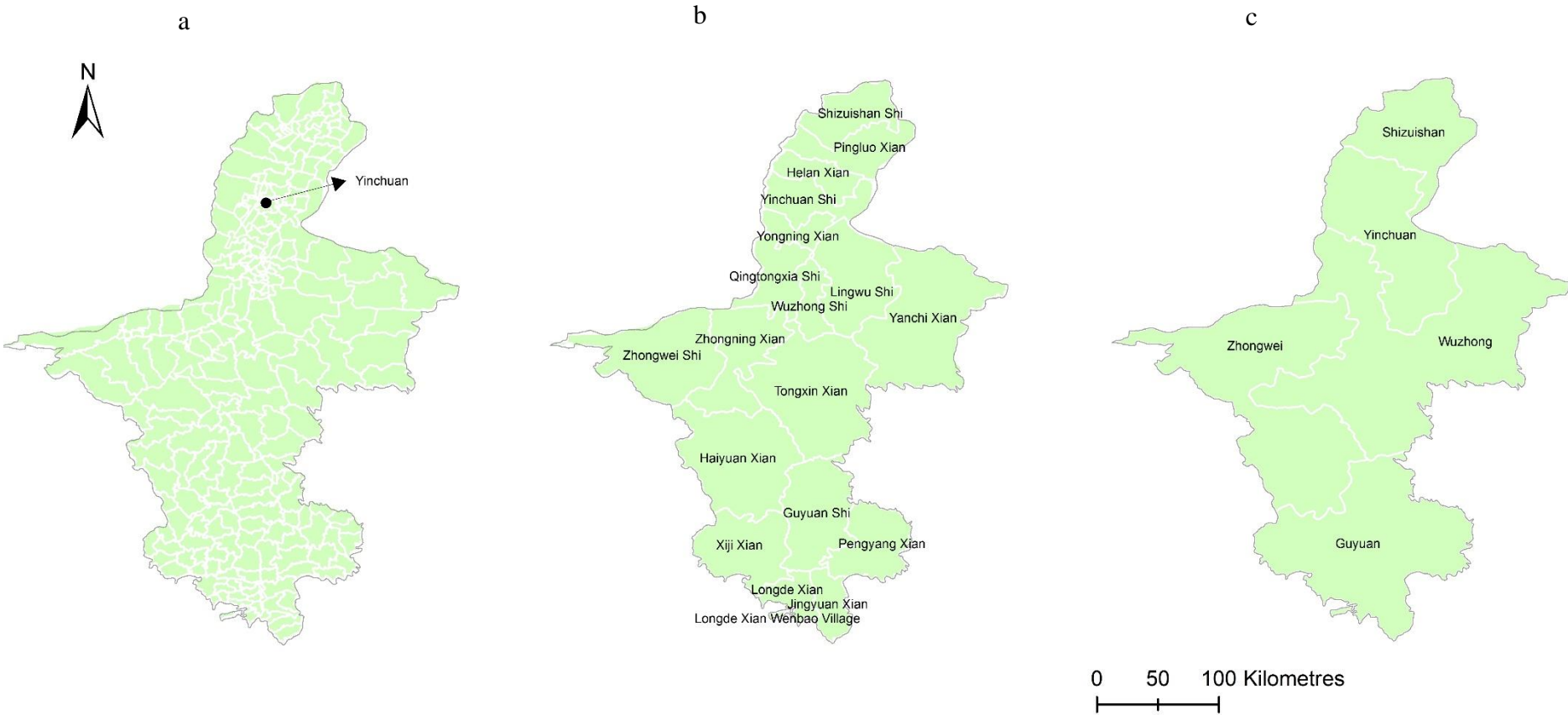
Appendix C

APPENDIX C

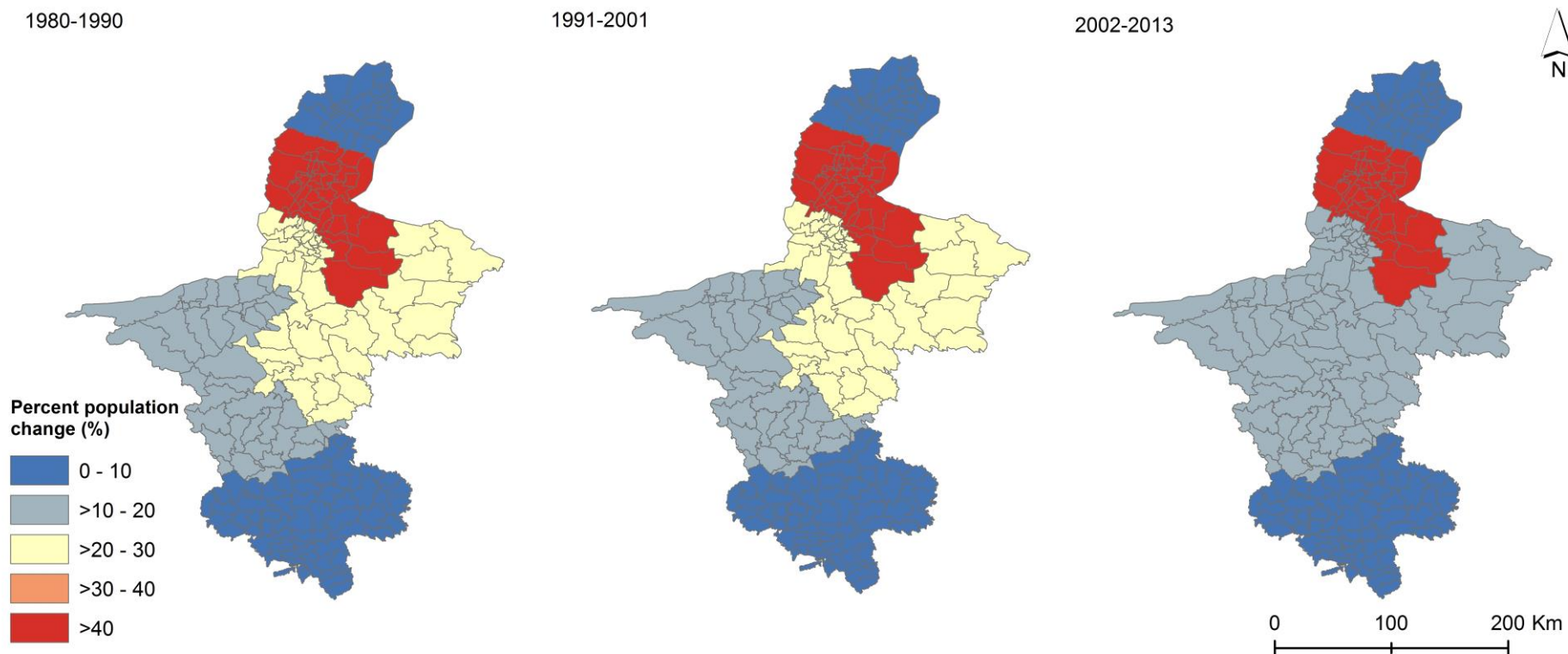
SUPPLEMENTARY MATERIAL FOR CHAPTER 4

Cadavid Restrepo, A.M.; Yang, Y.R.; McManus, D.P.; Gray, D.J.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Hamm, N.A.S; Clements, A.C.A. Spatiotemporal patterns and environmental drivers of human echinococcoses over a twenty-year period in Ningxia Hui Autonomous Region, China. *Parasites & Vectors*. 2018; 11:108.

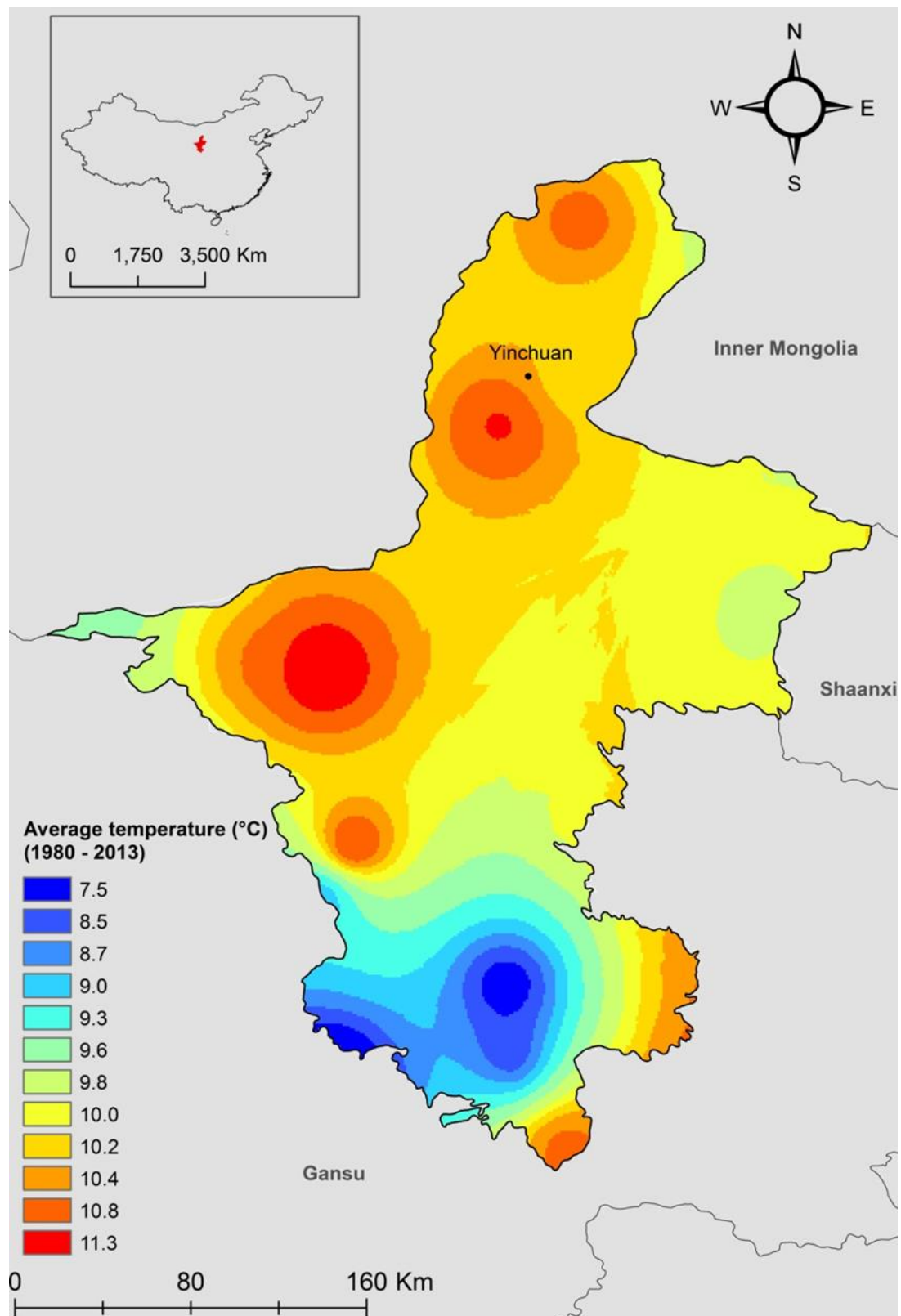
Additional file 1: Administrative map of NHAR at the (a) township, (b) county and (c) prefectural level.



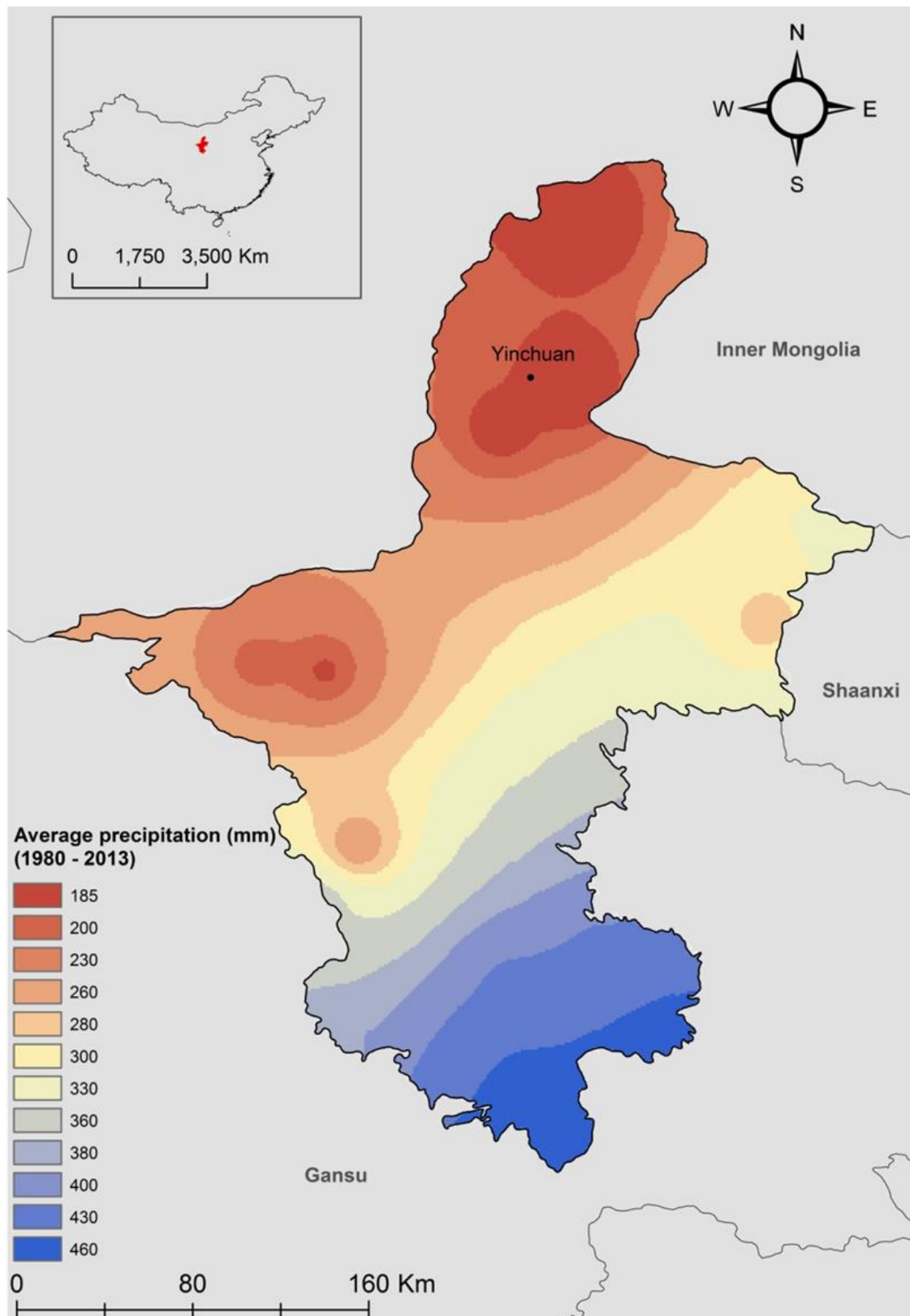
Additional file 2 Percent population change in NHAR for the periods 1980–1990, 1991–2001 and 2002–2013



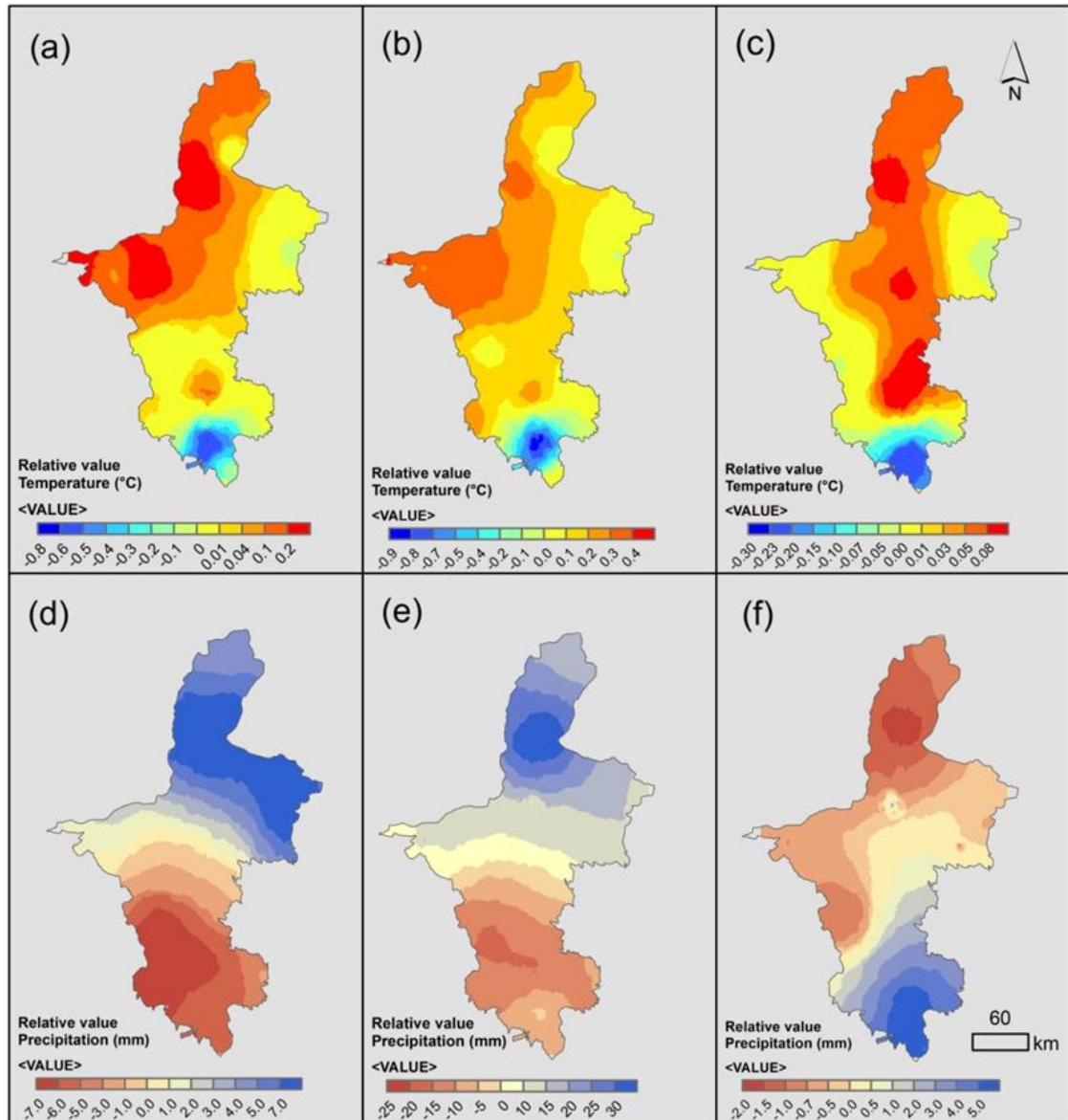
Additional file 3 Spatial distribution of the average annual mean temperature in °C in NHAR for the period 1980–2013



Additional file 4 Spatial distribution of the average annual mean precipitation in mm in NHAR for the period 1980–2013



Additional file 5 Maps of the spatial distribution of (a) annual, (b) summer and (c) winter temperature trends, and (d) annual, (e) summer and (f) winter precipitation trends in NHAR for the period 1 January 1980 to 31 December 2013. Note, the values presented in the figure are relative to the provincial average per decade



Additional file 6 OpenBUGS code used to develop the Bayesian spatial model (Model II) for cystic echinococcosis in NHAR from 1 January 1994 to 31 December 2013

```

model{

s[1:227] ~ car.normal(adj[], weights[], num[], tau.s);
for (k in 1:sumNumNeigh){
weights[k] <- 1
}

for(i in 1:4540){
Cases[i]~dpois(mu[i])
log(mu[i])<-log.RR[i] + log(Exp[i])
log.RR[i]<-alpha +s[Township[i]] + beta[1]*Tmean[i] + beta[2]*T_winmean[i] +
beta[3]*herb[i] + beta[4]*MA5bare[i] + beta[5]*MA5Cult[i] +beta[6]*MA5Forest[i] +
beta[7]*MA5Shrub[i] + beta[8]*MA6Water[i] + beta[9]*MA2Tmean[i] +
beta[10]*MA4Pmin[i] +beta[11]* pow(Tmean[i],2) + beta[12]*Time[i]

RR[i]<-exp(log.RR[i])

}

for(i in 1:227){

#u[i]~dnorm(0,tau.u)
}
alpha~dflat()
for(i in 1:12){
beta[i]~dnorm(0,0.001)
}

tau.s~dgamma(0.5,0.0005)
}

list(alpha=0,beta=c(0,0,0,0,0,0,0,0,-0.1,-0.1,-0.1), tau.s=0.5)

```

Additional file 7 OpenBUGS code used to develop the Bayesian spatial model (Model II) for alveolar echinococcosis in NHAR from 1 January 1994 to 31 December 2013

```
model{

s[1:227] ~ car.normal(adj[], weights[], num[], tau.s);
for (k in 1:sumNumNeigh){
weights[k] <- 1
}

for(i in 1:4540){
Cases[i]~dpois(mu[i])
log(mu[i])<-log.RR[i] + log(Exp[i])
log.RR[i]<-alpha +s[Township[i]] + beta[1]*MA6bare[i] + beta[2]*MA4forest[i] +
beta[3]*MA1pwin[i] + beta[4]*MA2tmean[i] + beta[5]*MA6tmean[i]
+beta[6]*MA2trange[i] + beta[7]*MA1twin[i] + beta[8]*MA6twin[i] + beta[9]*
pow(MA6twin[i],2) + beta[10]*Time[i]

RR[i]<-exp(log.RR[i])

}

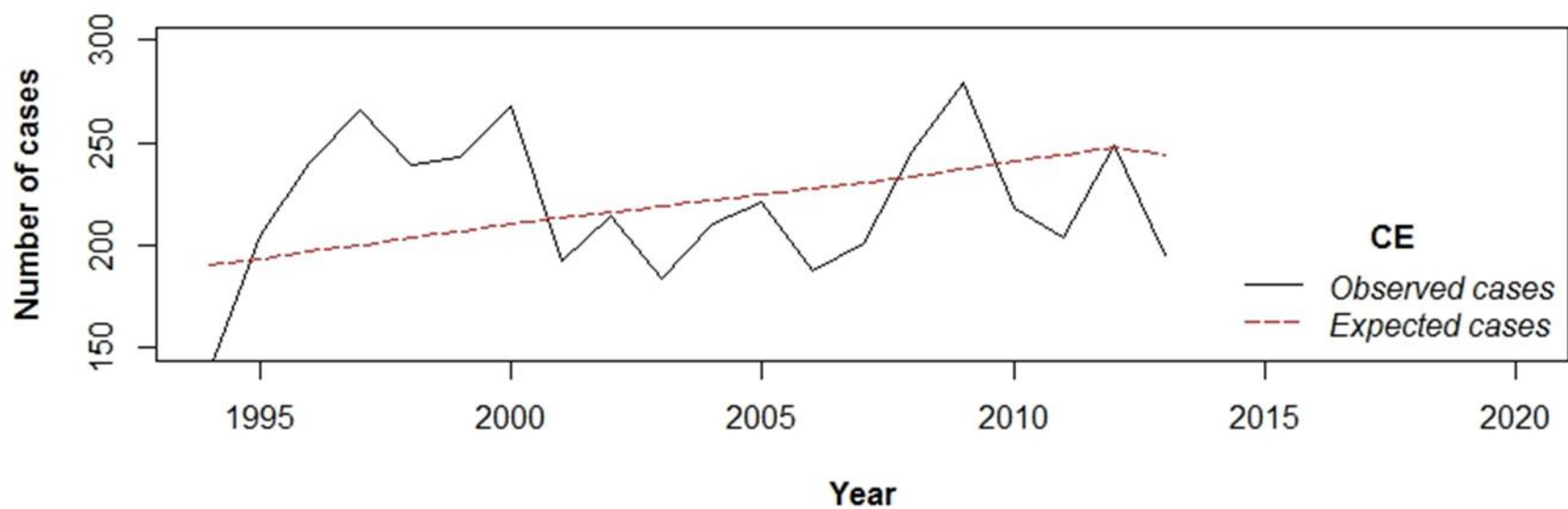
for(i in 1:227){

#u[i]~dnorm(0,tau.u)
}
alpha~dflat()
for(i in 1:10){
beta[i]~dnorm(0,0.001)
}

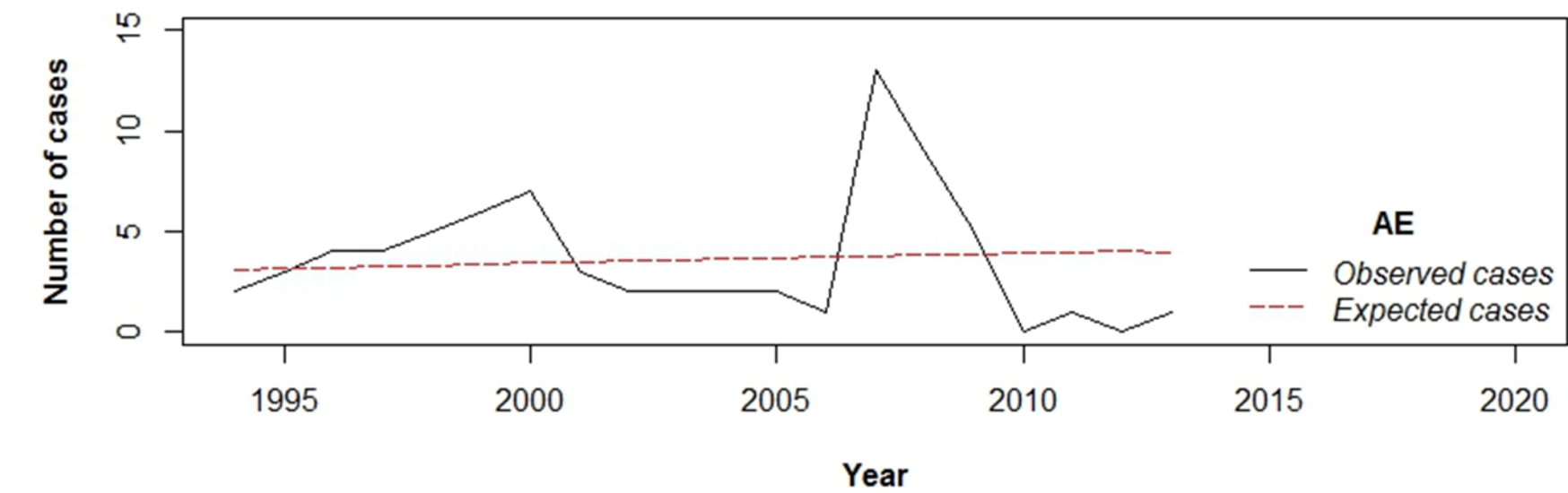
tau.s~dgamma(0.5,0.0005)
}

list(alpha=0,beta=c(0,0,0,0,0,0,0,0,0,-0.1), tau.s=0.5
```

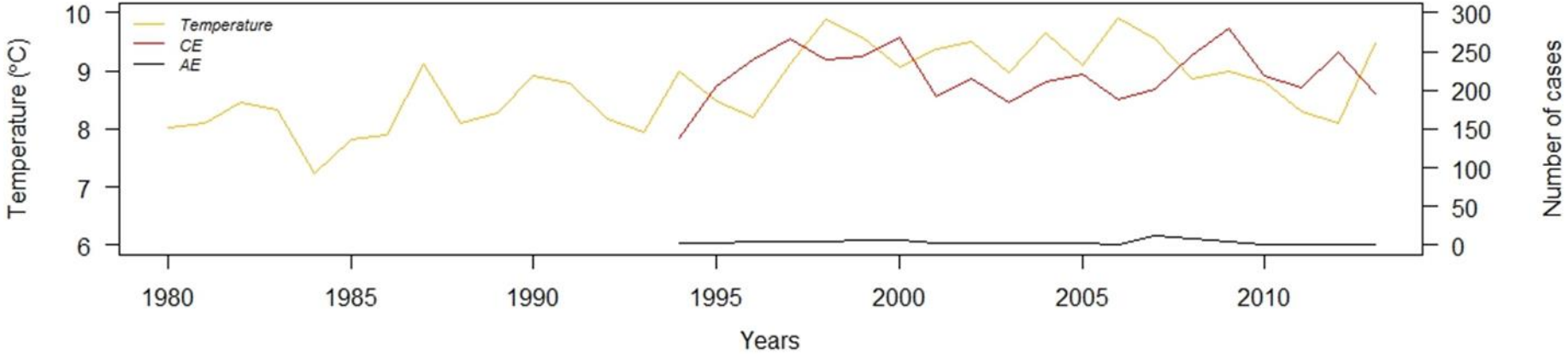

Additional file 8 Number of observed and expected number of CE cases by year (1994–2013) in NHAR for the period 1 January 1994 to 31 December 2013



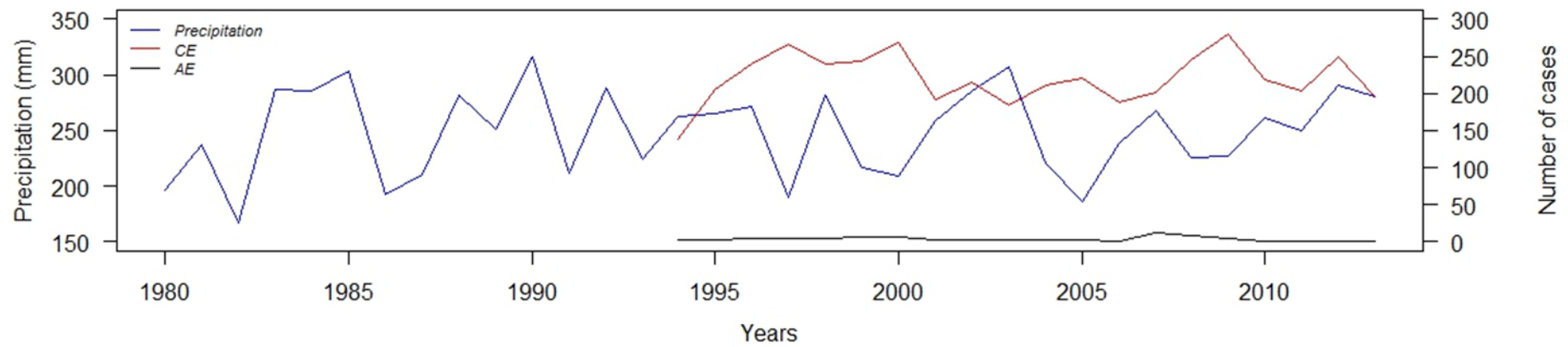
Additional file 9 Number of observed and expected number of AE cases by year (1994–2013) in NHAR for the period 1 January 1994 to 31 December 2013



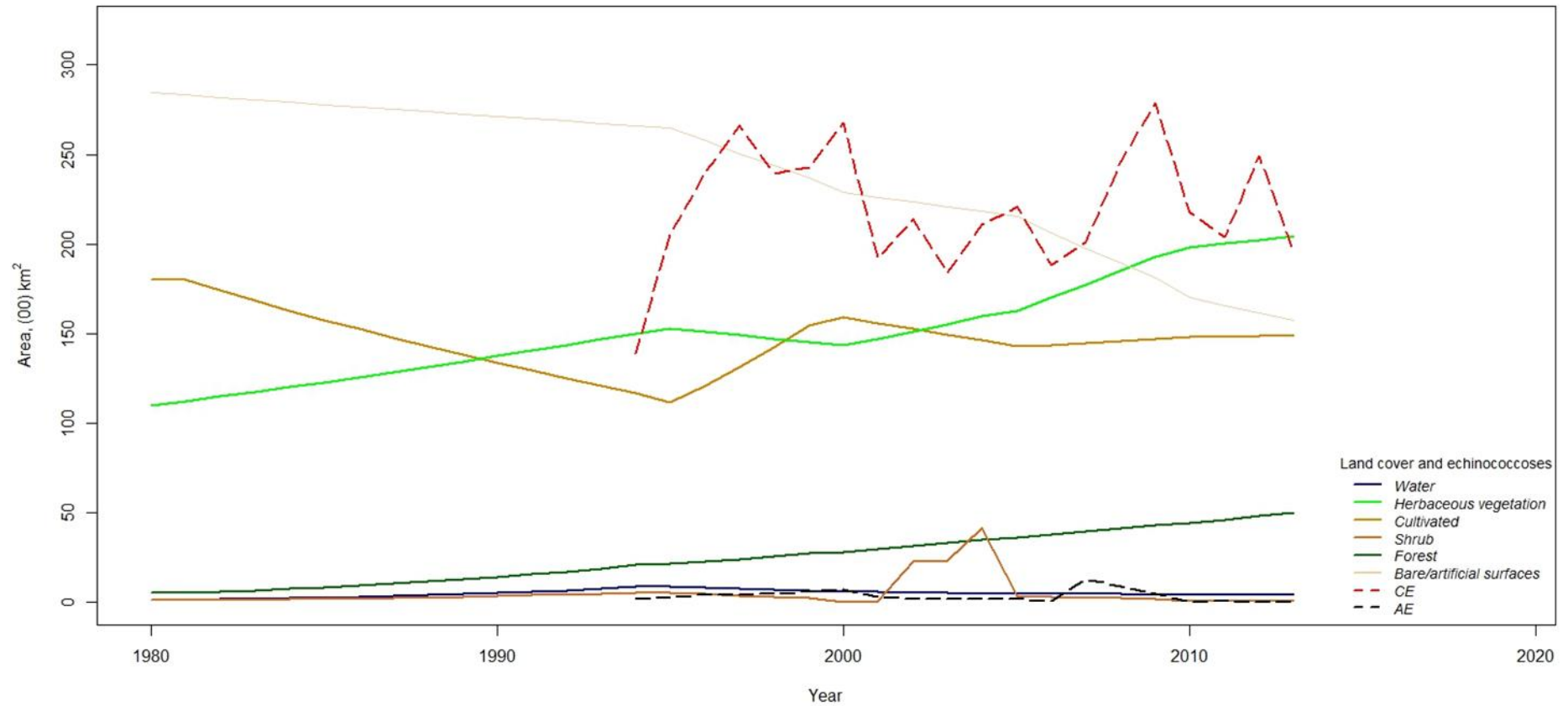
Additional file 10 Annual temperature in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013



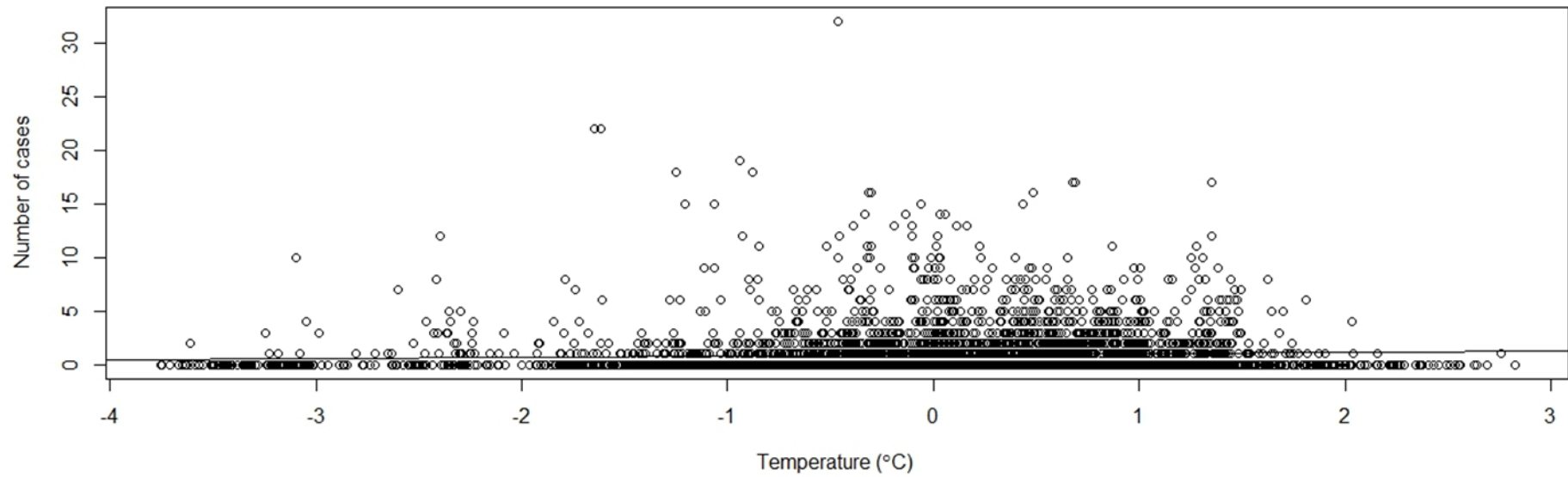
Additional file 11 Annual precipitation in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013



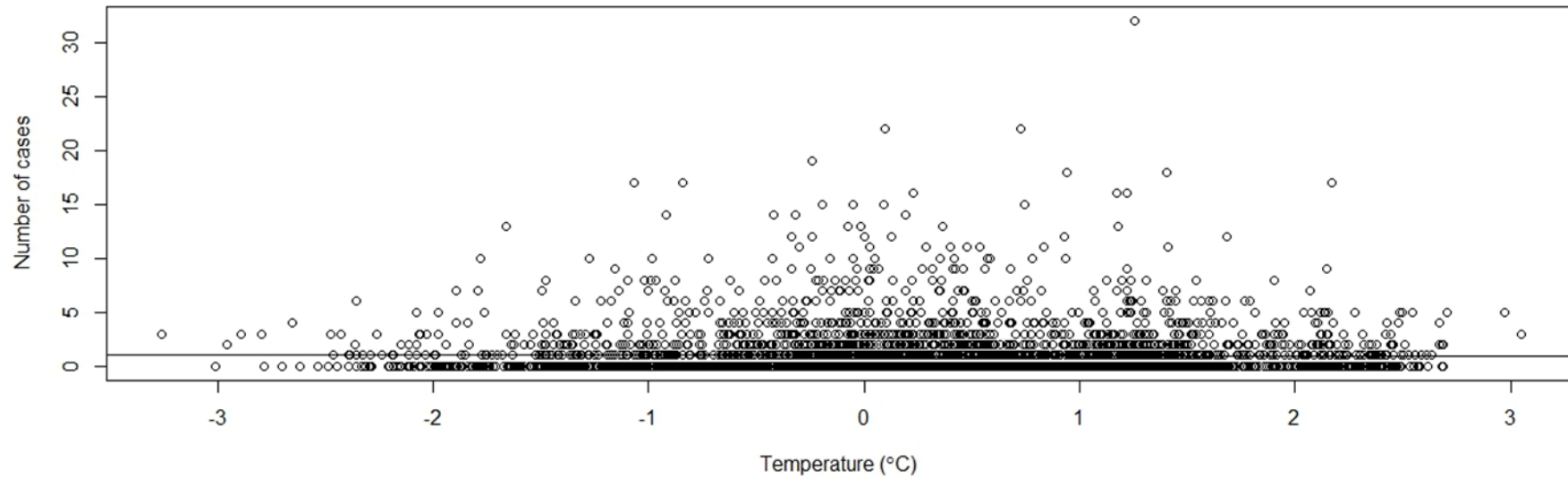
Additional file 12 Township area covered by each land cover class in NHAR for the period 1 January 1980 to 31 December 2013 and number of cases of CE and AE for the period 1 January 1994 to 31 December 2013



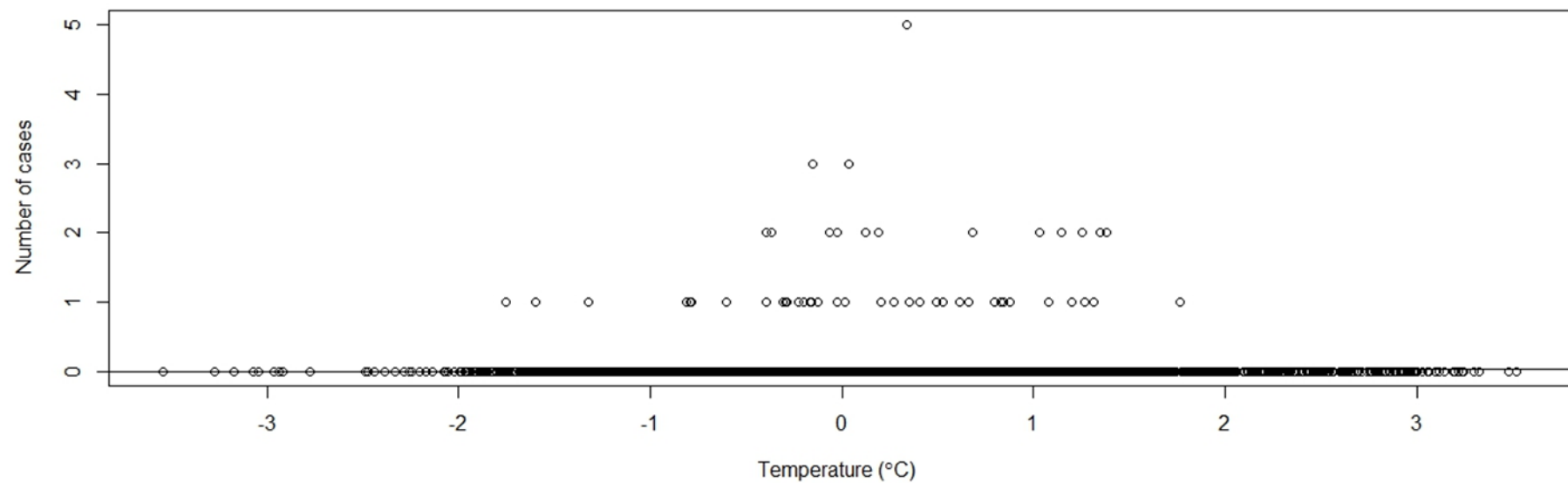
Additional file 13 Scatterplots of number of CE cases by township against winter mean temperature at a 10-year lag



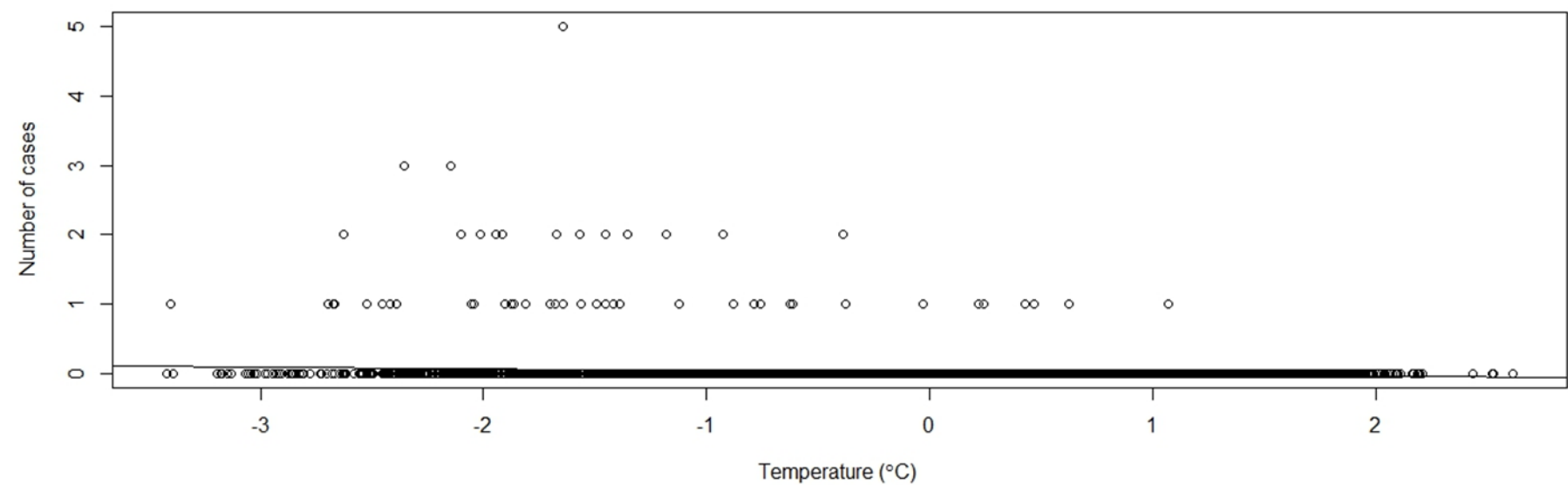
Additional file 14 Scatterplots of number of CE cases by township against annual mean temperature at 13-year lag



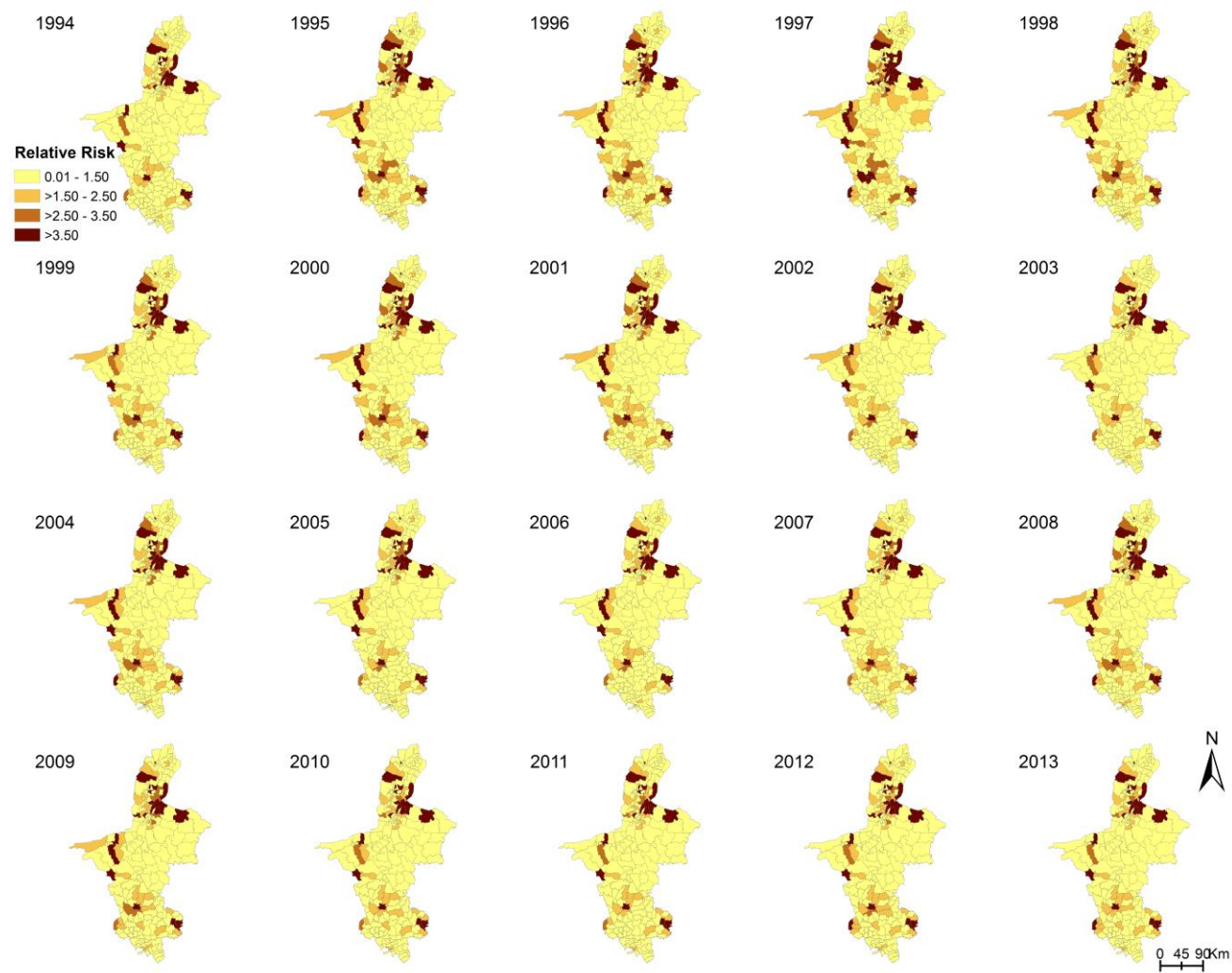
Additional file 15 Scatterplots of number of AE cases by township against winter mean temperature for the period 0–4 years before diagnosis



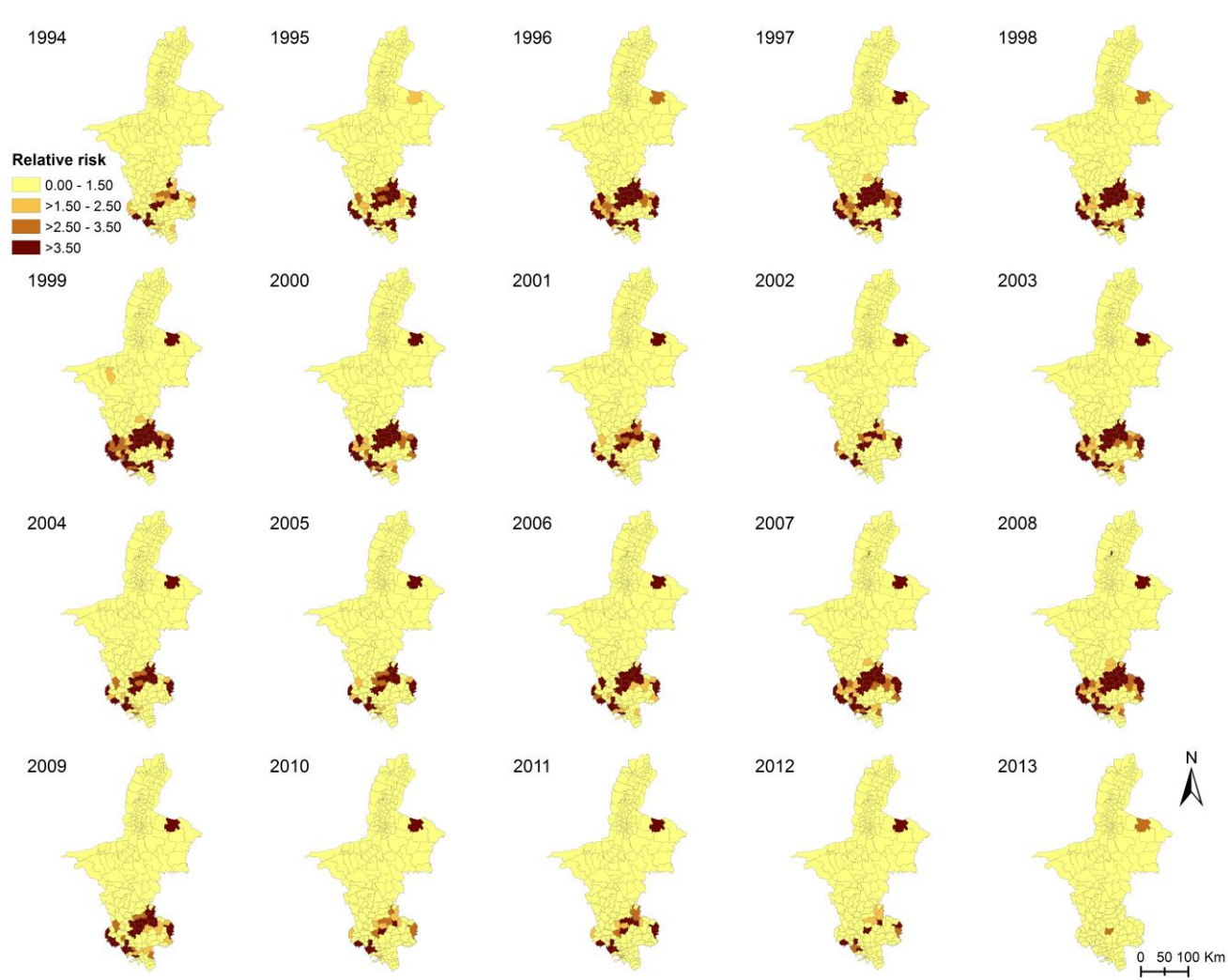
Additional file 16 Scatterplots of number of AE cases by township against annual mean temperature calculated for the period 11–15 years before diagnosis



Additional file 17 Spatial distribution of annual raw relative risks for CE in NHAR for the period 1994 to 2013



Additional file 18 Spatial distribution of annual relative risks for AE in NHAR for the period 1994 to 2013



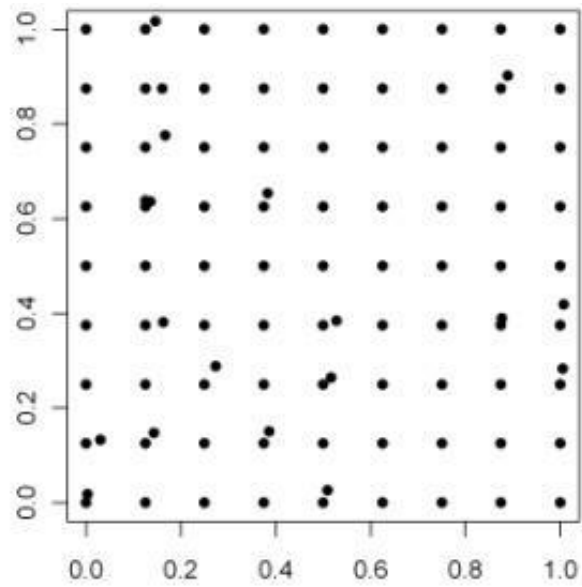
Appendix D

APPENDIX D

SUPPLEMENTARY MATERIAL FOR CHAPTER 5

Cadavid Restrepo, A.M.; Yang, Y.R.; McManus, D.P.; Gray, D.J.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Clements, A.C.A. Environmental risk factors and changing spatial patterns of human seropositivity for *Echinococcus* spp. in Xiji County, Ningxia Hui Autonomous Region, China. *Parasites & Vectors*. 2018; 11:159

Additional file 1 Stylised diagram of the grid plus close-pairs geostatistical sampling design



Appendix E

APPENDIX E

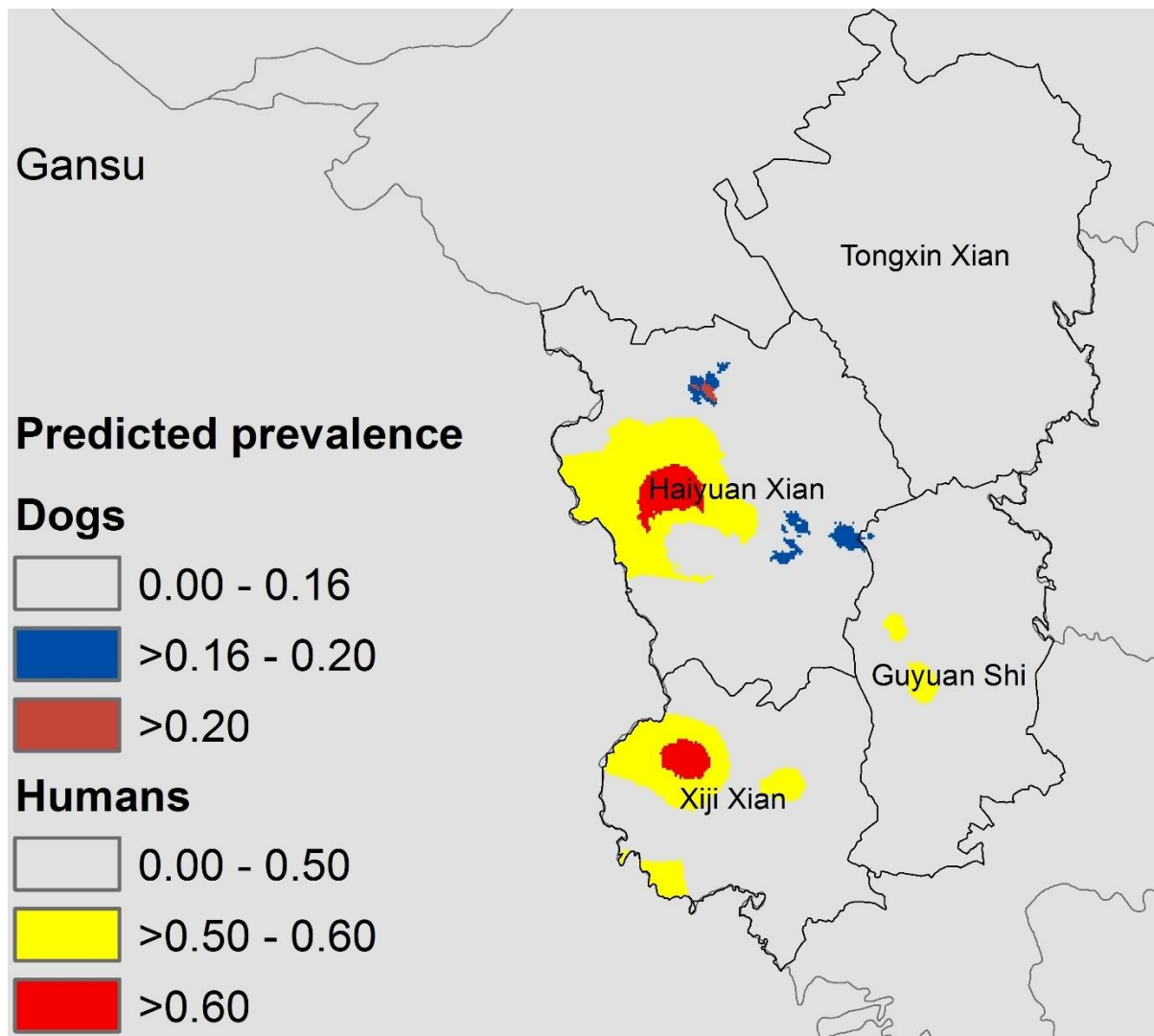
SUPPLEMENTARY MATERIAL FOR CHAPTER 5

Cadavid Restrepo, A. M., Yang, Y.R.; McManus, D.P.; Gray, D.J.; Barnes, T.S.; Williams, G.M.; Magalhães, R.J.S.; Clements, A.C.A. Spatial prediction of the risk of exposure to *Echinococcus* spp. among schoolchildren and dogs in Ningxia Hui Autonomous Region, China. *Geospatial Health*. 2017. In press.

Additional file 1. 95% confidence intervals of the prevalence of human seropositivity for *E. granulosus* and *E. multilocularis* and dog infections with these parasites in dogs by county in the cross-sectional surveys conducted in schools and veterinary centres in 2012–2013

| | <i>E. granulosus</i> | | <i>E. multilocularis</i> | |
|------------------|----------------------|-------------|--------------------------|-------------|
| | % | | % | |
| | Positive | Negative | Positive | Negative |
| a. Humans | | | | |
| Xiji | 43.2 – 48.0 | 51.9 – 56.7 | 7.1 – 9.7 | 90.2 – 92.9 |
| Guyuan | 34.1 – 38.7 | 62.1 – 65.9 | 5.6 – 8.1 | 91.8 – 94.3 |
| Haiyuan | 41.1 – 45.5 | 54.5 – 58.8 | 19.2 – 22.8 | 77.1 – 80.7 |
| Tongxin | 21.2 – 24.6 | 75.3 – 78.7 | 1.1 – 2.2 | 97.7 – 98.8 |
| b. Dogs | | | | |
| Xiji | 13.8 – 19.1 | 80.8 – 86.1 | 11.6 – 16.6 | 83.3 – 88.3 |
| Guyuan | 7.3 – 11.7 | 88.2 – 92.6 | 0.5 – 2.4 | 97.5 – 99.4 |
| Haiyuan | 9.5 – 14.0 | 85.9 – 90.4 | 2.1 – 4.6 | 95.3 – 97.9 |
| Tongxin | 10.1 – 13.8 | 86.1 – 89.8 | 0.8 – 2.2 | 97.7 – 99.1 |

Additional file 2. Areas of high predicted prevalence of human exposure to *E. granulosus* and dog infection with this parasite species in Guyuan, Haiyuan, Tongxin and Xiji counties.



Additional file 3. Areas of high predicted prevalence of human exposure to *E. multilocularis* and dog infection with this parasite species in Guyuan, Haiyuan, Tongxin and Xiji counties.

