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Review article

A systematic review of environmental covariates and methods for spatial or temporal scrub typhus distribution prediction

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ABSTRACT

Background: Scrub typhus is underdiagnosed and underreported but emerging as a global public health problem. To inform future burden and prediction studies we examined through a systematic review the potential effect of environmental covariates on scrub typhus occurrence and the methods which have been used for its prediction.
Methods: In this systematic review, we searched PubMed, Scopus, Web of Science, China National Knowledge Infrastructure and other databases, with no language and publication time restrictions, for studies that investigated environmental covariates or utilized methods to predict the spatial or temporal human. Data were manually extracted following a set of queries and systematic analysis was conducted.
Results: We included 68 articles published in 1978–2024 with relevant data from 7 countries/regions. Significant environmental risk factors for scrub typhus include temperature (showing positive or inverted-U relationships), precipitation (with positive or inverted-U patterns), humidity (exhibiting complex positive, inverted-U, or W-shaped associations), sunshine duration (with positive, inverted-U associations), elevation, the normalized difference vegetation index (NDVI), and the proportion of cropland. Socioeconomic and biological factors were rarely explored. Autoregressive Integrated Moving Average (ARIMA) (n = 8) and ecological niche modelling (ENM) approach (n = 11) were the most popular methods for predicting temporal trends and spatial distribution of scrub typhus, respectively.
Conclusions: Our findings summarized the evidence on environmental covariates affecting scrub typhus occurrence and the methodologies used for predictive modelling. We review the existing knowledge gaps and outline recommendations for future studies modelling disease prediction and burden.
Trial registration: PROSPERO CRD42022315209.

1. Background

Scrub typhus is a vector-borne infectious disease caused by the bacteria *Orientia tsutsugamushi*, *Candidatus* Orientia chuto (Izzard et al., 2010) and *Candidatus* Orientia chiloensis (Abarca et al., 2020), and transmitted by the bite of larval stage of chigger mites. The common symptoms and signs are fever, myalgia, eschar, and regional lymphadenopathy. Multi-organ failure can develop, and the median case

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fatality rate in reported series of untreated cases is 6% (Taylor et al., 2015). This neglected tropical disease is often misdiagnosed (Koh et al., 2010; Kannan et al., 2020) but the impact is significant. Estimates published in 1997 suggested a large potential disease burden, with over a billion individuals susceptible to scrub typhus and a million clinical cases annually worldwide (Rosenberg, 1997). While it predominantly affects parts of South and Southeast Asia, northern Australia, the islands of the western Pacific, and Indian Ocean (Kelly et al., 2009), there is mounting evidence to suggest that the range of scrub typhus expands beyond these traditional boundaries to the Middle East, South America and Africa (Izzard et al., 2010; Weitzel et al., 2016). The true extent and distribution of scrub typhus remain unknown.

Climate and other environmental changes could be potential catalysts for unexpected occurrence and increasing trends in incidence, as they all affect the survival, development, reproduction, behavior, and population dynamics of vectors and hosts. The alterations in climate and habitat can facilitate migration and expansion of both (Walker, 2016; Ding et al., 2022), thereby amplifying the threat of vector-borne diseases globally (Jiang and Richards, 2018; Elliott et al., 2019). Changes in the proportion of the natural environment and the social environment, such as rapid urbanization and deforestation, are changing the scope of human activities, affecting the distribution of chiggers and the opportunities for human exposure to infected chiggers (Min et al., 2019). Chiggers act as both the reservoirs and primary vectors of scrub typhus and are hardy and present in a huge range of habitats (Pearson et al., 2019). This suggests that the natural cycles of the bacterium might have been well maintained over thousands of years across a large geographic distribution (Walker, 2016). However, our understanding of which environmental factors play an important role in this overall process and how they affect the occurrence of human cases is still lacking.

Prediction models play an important role in anticipating disease distribution, which is essential for guiding public health responses and policy decisions (DeFelice et al., 2017; Bhatt et al., 2013). Numerous studies have applied and adapted various prediction models for epidemic forecasting, resource allocation, identifying populations at risk and providing early public health warnings, especially during the COVID-19 period (Feng et al., 2020; Leung et al., 2021). However, the application of prediction models in the context of scrub typhus has been notably underexplored. To date, there has been no review systematically evaluating and comparing the different types of prediction models used in various study settings for scrub typhus, regardless of whether they focus on a specific area or span a broader geographical scope.

In this review, we critically appraise published studies using models to predict the spatial or temporal distribution of scrub typhus. First, we identified environmental covariates which have been found to have significant associations with scrub typhus. Second, we reviewed modelling frameworks that were used to predict the occurrence of scrub typhus. For each paper, we extracted information on the type of model, the data used, the metrics of model performance and the validation methodology. Finally, using this information, we point out knowledge gaps remaining in this field and suggest future research directions.

2. Methods

This systematic review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page et al., 2021) (Appendix Table S3). The protocol had been registered with the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42022315209.

2.1. Search strategy and selection criteria

To identify relevant publications, we did a systematic literature search without any language, publication date or geographical restrictions, to identify manuscripts that detailed associated environmental covariates and prediction models for scrub typhus. We searched six databases: PubMed, Scopus, Ovid Medline, Ovid Embase, Web of Science, and China National Knowledge Infrastructure. Additional searches to identify grey literature were conducted using MedNar, WHO Global Index Medicus, ProQuest Dissertations and Theses Global database, Preprints in Europe PMC, and the ProMED website. The first 200 results from Google Scholar were also examined (Haddaway et al., 2015).

We developed and refined an exhaustive search string assisted by an experienced university librarian, incorporating Medical Subject Headings (MeSH) terms, and customized for compatibility with each database. To ensure high sensitivity of the search, we used the combination of scrub typhus synonyms ("*Orientia tsutsugamushi*", etc.) and broad research outcomes of interest ("risk", etc.) as the search term. The full search syntax can be found in the Appendix (Table S1). The initial search results were pooled, and duplicates were removed using EndNote 20.

Studies were included if they contained human scrub typhus cases and examined the association between environmental covariates and scrub typhus or utilized modelling methods to predict spatial or temporal distribution. We excluded studies with unavailable full text, conference abstracts, and review studies without primary data.

The titles and abstracts of identified studies were independently screened by two reviewers (QW and TM), records in Korean and Japanese were reviewed by native speakers (AL and ST), and studies in other languages were translated and checked using Google Translate. Rayyan (Ouzzani et al., 2016), a web-based platform, was used to streamline this process. For any potential eligible articles, the full text was screened to make the final decision about inclusion. To ensure that no relevant studies were excluded erroneously, a third reviewer (KS) randomly selected and verified the screening results. Any disagreements were resolved by consensus or following discussions with RJM.

2.2. Data extraction and data analysis

A standardized data extraction form was developed using Microsoft Excel (version 2310). Relevant variables were extracted by two investigators independently (QW and TM), and for articles in Korean and Japanese, QW extracted information using Google Translate, and then AL and ST (native speakers) verified the extraction. The extracted data included: article and research information (authors, publication year, publication language, country of first author affiliation, geographical region of the study, study design and investigation date); characteristics of the study participants (sample size, diagnostic method and definition of disease); environmental covariates outcomes (definition, source, spatial and temporal resolution, association/relationship, statistical indicators and results); method/model outcome (volume and time-space scale of data used for modelling, mathematical or statistical methods or models developed and used, method/model performance (accuracy, discrimination) and validation methods).

For environmental covariates employed, we used descriptive statistics to summarize the number of studies, study sites, total number of cases. Additionally, we assessed the pattern of association between environmental covariates and scrub typhus occurrence, which was achieved by carefully reviewing and interpreting graphical representations and statistical findings presented in the studies. The analytical approaches used to evaluate those associations were also summarized. For the examination of prediction models, we sorted the identified models by their prediction objectives and number of studies and presented the data via Sankey chart to provide a structured overview.

2.3. Study quality assessment

Each epidemiological study that satisfied the inclusion criteria was subject to a quality assessment using the National Institute of Health (NIH) framework for Observational Cohort and Cross-sectional Studies (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). For prediction model studies, the EPIFORGE checklist (Pollett et al., 2021), a guideline for standardized reporting of epidemic forecasting and prediction research was used to assess the reporting quality of included prediction studies. We categorized the studies into four quality categories based on the calculated percentage of the overall score relative to the total possible score: poor (0–25%), fair (25%–50%), good (50%–75%), and excellent (75%–100%).

3. Results

3.1. Study selection

Our literature searches identified 13,674 records, with 6586 unique records after removal of duplicates. 4462 articles were not considered relevant after title and abstract screening, leaving 2124 articles. Following full text screening, 68 studies which investigated environmental factors or utilized models to predict spatial or temporal distribution were included in this review (Fig. 1). The results from every database are provided in the appendix (Table S2).

3.2. Quality assessment

All included studies received a 'good' quality rating or above, except for two studies which obtained a 'fair' quality rating, with the complete risk assessment result for each study provided in the appendix (Excel Table S1 and Excel Table S2).

3.3. Trend of included studies

From 68 studies reviewed, conducted between 1978 and 2024, the majority were in Mainland China (n = 42), followed by South Korea (n = 10), and Taiwan (n = 6). In Mainland China, research spanned across first (16 studies), second (16 studies), and third (two studies) administrative divisions, indicating a deep dive into local regions. South Korea's nine studies were mostly nationwide, with one detailed study at the first administrative division. Taiwan's three research covered the whole region, with two studies exploring the first administrative division and one exploring the second. Additional studies were noted in Japan (one study at the first and second administrative level each), Laos (one at the second level), Nepal (one countrywide), Thailand (one countrywide and two at the first level), and India (one at first level and 2 at s level). The full list of included publications can be found in appendix (Table S5 and Table S6).

3.4. Spatial focus of included studies

Since scrub typhus is an understudied disease and the data are not abundant, the overall number of studies is relatively low with only 1 study (Olson and Scheer, 1978) published before 2010 and an average of 4.47 studies published per year from 2010 to 2022. The year 2010 marked the beginning of an increase in publications, with Mainland China showing a notable rise (Fig. 2). The number of studies peaked in 2016, 2019, 2021 and 2022 at eight.

Most studies (n = 41, 60%) used case count data from routine passive surveillance (Fig. 3A). In several studies, incidence (n = 13, 19%) and presence/absence (n = 8, 12%) utilizing passive surveillance data were also investigated. Studies spanned a diverse spatial extent, from country/region down to the third administrative level and the spatial resolutions varied, ranging from point/pixel to country/region. (Fig. 3B). The majority of studies (n = 27, 40%) were conducted at the 3rd administrative level or below. Only six studies (9%) were performed on very fine spatial resolutions of points or pixels.

3.5. Environmental covariates

For environmental factors, 58 articles detailed 121 study sites across seven countries/regions which investigated 68 various environmental

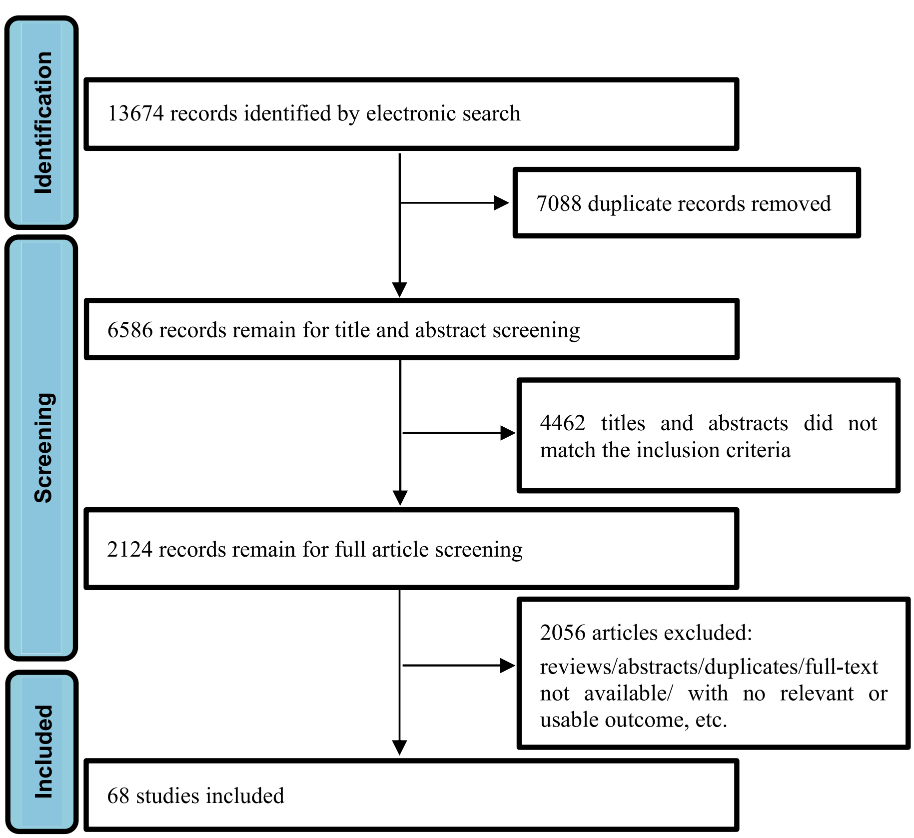


Fig. 1. PRISMA diagram of study selection.

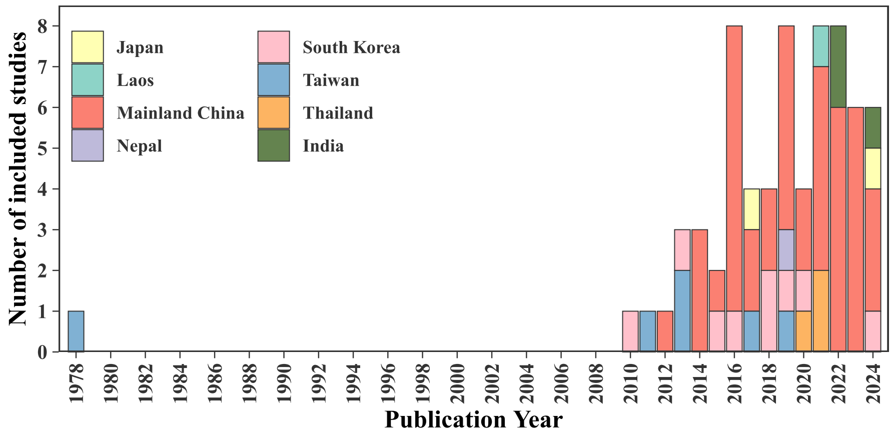


Fig. 2. Number of included studies per year by study country/region.

Fig. 3. A. Data source and response variables used in included studies; and B. Geographical scale and spatial resolution of included studies.

covariates (Fig. S1) and we grouped them into five categories: meteorological, geographic, socioeconomic, biological, and spatial-temporal covariates (Table 1). Detailed statistical results of the top ten environmental covariates with the highest frequency investigated in the included studies were visualized in Fig. S2 and non-linear effects between various covariates and scrub typhus extracted from included studies can be found in appendix Table S7.

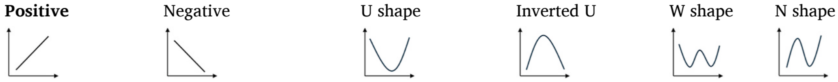
Meteorological factors are commonly recognized as important covariates related to scrub typhus (Roberts et al., 2021; Mungmungpuntipantip and Wiwanitkit, 2021; Lu et al., 2021; Lin et al., 2021; Bhopdhornangkul et al., 2021; Li et al., 2021), with temperature, precipitation and humidity dominating. Among the studies reviewed, 83% (n = 48) included temperature as a covariate, while 74% (n = 43) included precipitation. Over half of the studies (n = 33, 56.9%) included humidity. Temperature analysis frequently utilized mean temperature whereas relative humidity was the primary metric for humidity. The lagged effects of meteorological factors, ranging from one week to one year, were explored in multiple studies conducted in mainland China (Ding et al., 2022; Lu et al., 2021; Yang et al., 2014; 陈胤忠 徐慧 et al., 2016; 吴义城 and 李申龙, 2016; Luo et al., 2024; K et al., 2024; Huang et al., 2023; Han et al., 2023; Wei et al., 2023; Li et al., 2023; Luo et al., 2022; H et al., 2022; He et al., 2022a), South Korea (Kwak et al., 2015a; Kim et al., 2020; Chang et al., 2024), Japan (Seto et al., 2017) and India (Narang et al., 2022; D'Cruz et al., 2024). The relationships between temperature and precipitation and scrub typhus were found to be either positive (Min et al., 2019; Olson and Scheer, 1978; Lu et al., 2021; Lin et al., 2021; Li et al., 2021; Yang et al., 2014; 吴义城 and 李申龙, 2016; Kim et al., 2020; Seto et al., 2017; Kim and Jang, 2010; Tsai and Yeh, 2013; Li et al., 2014; 陈纯 et al., 2016; Wu et al., 2016; Sun et al., 2018; Chang et al., 2017; Wei et al., 2017a; Chang et al., 2019; Yao et al., 2019; Zheng et al., 2019; Luo et al., 2020; Wangrangsimakul et al., 2020; 李文 and 刘小波, 2021)or to follow an inverted-U pattern (吴义城 and 李申龙, 2016; Kim et al., 2020; 孙烨, 2016; 孙烨 and 曹务春, 2016), in which the response variable increases up to a certain point, after which it begins to decrease. The humidity displayed more complex associations, including positive, inverted-U, and W-shaped patterns where response variable increases, decreases, and then increases again across different humidity levels. This W-shaped pattern of association with humidity was specifically observed in one study conducted in Thailand (Bhopdhornangkul et al., 2021). Other meteorological variables such as sunshine hours (Min et al., 2019; Lu et al., 2021; 陈胤忠 徐慧 et al., 2016; Tsai and Yeh, 2013; Li et al., 2014; 陈纯 et al., 2016; Yao et al., 2019; Luo et al., 2020; 孙烨, 2016; 孙烨 and 曹务春, 2016; Xin et al., 2020a)(n = 17, 29.3%), atmospheric pressure (Lu et al., 2021; Tsai and Yeh, 2013; Li et al., 2014; 孙烨 and 曹务春, 2016) (n = 8, 13.8%), and wind speed (Lu et al., 2021; Kim et al., 2020; Kwak et al., 2015b) (n = 9, 15.5%) have been identified as important indicators in a number of studies, exhibiting positive, negative, and negative correlations, respectively. Four studies from

Table 1
The environmental covariates found to have significant associations with scrub typhus in 2 or more studies.

Category	Covariates	Number of studies (%)	Number of study sites	Case count	Associations (number of study sites)
Biological	Rodent density	4 (6.9)	4	19241	Positive (4)
Geographic	NDVI	12 (20.7)	21	171775	Positive (12), negative (3), inverted U (3), suitable range: 0.18–0.39 (1); 0.6–0.8 (1)
	Elevation	10 (17.2)	11	79942	Positive (3), negative (4), N-shape (1), 1 U shape (1), 1 inverted U (1)
	Proportion of cropland	9 (15.5)	9	221304	Positive (2), inverted U (2), negative (2), U shape (1)
	Proportion of forest	9 (15.5)	9	199359	Negative (4), positive (3)
	Proportion of grassland	5 (8.6)	5	191985	Negative (4), 1 U shape (1)
	Proportion of shrub	4 (6.9)	4	70225	Positive (3), 1 inverted U (1)
	Proportion of water body	4 (6.9)	4	80871	Positive (1), negative (3)
	Farmland	3 (5.2)	3	9210	Positive (2)
	Landcover	2 (3.4)	2	57304	Paddy field and artificial land positive (1), built-up land high risk (1)
	Proportion of built-up land	2 (3.4)	3	92948	Positive (2), negative (1)
	Proportion of Mosaic habitat	2 (3.4)	2	105541	Positive (1), negative (1)
	Slop	2 (3.4)	3	16657	Negative (3)
Meteorological	Temperature	48 (82.8)	93	1077077	Positive (50), inverted U (10), negative (6), U (1), suitable range: 8.9–11.1 of monthly average temperature (1)
	Precipitation	43 (74.1)	59	1016434	Positive (31), inverted U (3), negative (9), N shape (4), suitable range:196.0–275.0 for precipitation of wettest month (1)
	Humidity	33 (56.9)	50	839083	Positive (22), inverted U (7), negative (6), W-shape (3), U-shape (1)
	Sunshine hour	17 (29.3)	21	269342	Positive (11), inverted U (4), negative (4)
	Wind speed	9 (15.5)	12	212359	Negative (6), inverted U (1), inverted N (1)
	Atmospheric pressure	8 (13.8)	11	39674	Negative (7), positive (3)
	ENSO	2 (3.4)	3	4795	Positive
Socioeconomic	Population density	10 (17.2)	10	210016	Positive (7), negative (2), inverted U (1)
	Farmer population	4 (6.9)	6	2854	Positive (4), negative (1), inverted U (1)
	GDP	3 (5.2)	3	7327	Positive (1), negative (1)
	Elderly population	2 (3.4)	2	1296	Positive
	Income	2 (3.4)	2	2196	Negative (2)
	Urban accessibility	2 (3.4)	2	989	Inverted U (2)
	Urbanization	2 (3.4)	2	5810	Positive (2)
Spatial temporal	Location	3 (5.2)	3	121683	Complex
	Time	2 (3.4)	3	52473	Complex

Associations graphic schema

Positive	Negative	U shape	Inverted U	W shape	N shape



China, demonstrated that the El Niño/Southern Oscillation (ENSO), as well as the Multivariate ENSO Index (MEI) (Lu et al., 2021; 吴义城 and 李申龙, 2016; He et al., 2022a; Wei et al., 2017a), also played an important role in affecting the occurrence of scrub typhus. Notably, the interaction of temperature, precipitation and sunshine were explored in a recent study (K et al., 2024).

Geographic factors such as elevation, the Normalized Difference Vegetation Index (NDVI), and various land cover types including cropland, forest, and grassland are frequently examined for their associations with scrub typhus, displaying positive, negative, and inverted-U patterns. Elevation was a important predictor in 17% of the studies (n = 10), NDVI in 21% (n = 12), cropland in 16% (n = 9), forest in 16% (n = 9), and grassland in 9% (n = 5). A higher NDVI usually led to an increased risk of scrub typhus (吴义城 and 李申龙, 2016; Zheng et al., 2019; 李文 and 刘小波, 2021; Kuo et al., 2011; Kim and Kim, 2018a) due to the crucial role of vegetation in maintaining vectors (such as chiggers) and hosts (like rodents). The proportion of forest (Wu et al., 2016; Wangrangsimakul et al., 2020; 李文 and 刘小波, 2021) area was found to be negatively associated with scrub typhus, whereas recreational forest area (Tsai and Yeh, 2013) and deforestation (Min et al., 2019) exhibited positive associations. Two studies also found terrain slope had a negative impact on scrub typhus (Wei et al., 2023; Acharya et al., 2019) and one study in Thailand included habitat complexity and fragmentation as predictors (Wangrangsimakul et al., 2020).

Socioeconomic variables such as population density (n = 10, 17.2%), farming and elderly population (n = 4, 6.9%, n = 2, 3.4%), income (n = 2, 5%), gross domestic product (GDP) (n = 2, 5%), urban accessibility and urbanization were also considered to be relevant. The higher numbers of farmer (Min et al., 2019; Kim et al., 2020; Tsai and Yeh, 2013; Kuo et al., 2011) and elder populations (Kim et al., 2020; Kang and Choi, 2018) were generally associated with an increased risk of scrub typhus. The relationship with population density was inconsistent across studies: some studies indicating a positive association (吴义城 and 李申龙, 2016; Seto et al., 2017; Wangrangsimakul et al., 2020) and others suggesting a negative one (Min et al., 2019; 李文 and 刘小波, 2021). GDP was studied in three articles with varying effect directions: one article from southern China indicated a negative effect (Zheng et al., 2019), and the other article from Qingdao City in northern China showing a positive effect (Xin et al., 2020b).

Biological variables, such as rodent density and information on mites, were infrequently reported in the literature. Rodent density was explored in four studies (Huang et al., 2023; Wei et al., 2017a; 刘晓宁, 2019; 余向华, 2019) and demonstrated a positive association with scrub typhus. Similarly, the Orientia infection rate in mites/rodents was only examined in one study (刘晓宁, 2019), which found positive associations of both with scrub typhus. The full list and frequency of the environmental covariates can be found in appendix (Fig. S1).

Five methodological classes for analyzing associations were identified: correlation testing, multivariate regression, linear/nonlinear modelling, machine learning, and spatial-temporal modelling

(Table S4). Among these, multivariable regression was the most frequently employed modelling approach, utilized in 36% of studies (n = 21), with negative binomial multivariable regression being the most common variant (n = 9), followed by Poisson regression (n = 4). Machine learning approaches were preferred for analyses involving point/pixel data, whereas multivariable regression was the method of choice for areal-type data aggregated over administrative regions (Fig. 4). The majority of studies (n = 44, 75.9%) utilized monthly aggregated data as their input, with yearly data being the next most common (n = 12, 20.7%). Additionally, 13 studies (22.4%) employed more than one analytical method to investigate association.

3.6. Prediction models

Beyond solely investigating associations between covariates and scrub typhus, between 2012 and 2024, 25 studies were dedicated to modelling and predicting the occurrence of scrub typhus over time and/or space. These were primarily conducted in mainland China (n = 20), with additional studies in South Korea (n = 4) and Nepal (n = 1). These studies mainly utilized data from the national disease surveillance systems, although some also drew on hospital records and surveys for their analyses. On average, the duration covered by these studies was 8.46 years, with sample sizes varying widely from specific case numbers (ranging from N = 225 to N = 166,839) to broad geographical scopes encompassing multiple administrative regions such as cities, counties, or provinces. Detailed information on the publications included in this section can be found in the Appendix (Table S6).

The predicted response variables across these studies encompassed a diverse range, including six focusing on presence/absence, ten on case count, two on incidence, and one on Disability-Adjusted Life Years (DALYs). Reflecting their primary objectives, as depicted in Fig. 5, these investigations were categorized into two groups: twelve studies concentrated on temporal prediction (extrapolations into future time), while nine focused on spatial prediction (interpolation within the same region as data points or extrapolation to regions outside of the spatial extent of data points). Two studies uniquely combined both temporal and spatial predictions to enhance understanding of scrub typhus dynamics (吴义城 and 李申龙, 2016; Kim et al., 2020).

For projections into the future, Autoregressive Integrated Moving Average (ARIMA) and its variations, including Seasonal Autoregressive Integrated Moving Average (SARIMA) and Seasonal Autoregressive Integrated Moving-Average with Exogenous Regressors (SARIMAX), were frequently used with nine papers focusing on case number and one on DALYs (Yang et al., 2015). These temporal extrapolation studies primarily analyzed time series data, concentrating on identifying trends, seasonality, and random fluctuations. Notably, one study demonstrated that a SARIMA model incorporating eight exogenous environmental variables significantly outperformed a standard SARIMA model in forecasting scrub typhus case number (He et al., 2022b).

In terms of spatial prediction, Boosted Regression Trees (BRT) (Yao et al., 2019; Zheng et al., 2019; 孙烨 and 曹务春, 2016; Xin et al., 2020b; Y et al., 2023) and other ecological niche modelling (ENM) approach, specifically with Maxent (吴义城 and 李申龙, 2016; Li et al., 2023; Kim et al., 2020; Acharya et al., 2019; Yu et al., 2018; L et al., 2023) and random forest (Huang et al., 2023; Acharya et al., 2019), were commonly employed for mapping the presence/absence of the disease across different areas. One study conducted in South Korea used a spatially structured random effect within a Bayesian spatial-temporal model to analyze scrub typhus risk (Kim and Kim, 2018b) and one study conducted in China used a GAM to predict the case number under the future scenario (Ding et al., 2022). A study conducted in Nepal utilized both ENM with Maxent and ENM with Random Forest, finding that both methods effectively mapped the environmental suitability for scrub typhus (Acharya et al., 2019). For predictions that required both temporal and spatial analysis, the ENM approach with Maxent was widely adopted (吴义城 and 李申龙, 2016; Kim et al., 2020).

No mechanistic models have yet been applied in the field of scrub typhus research. Out-of-sample validation is a common practice in prediction studies, employed in 84% of them (n = 21). For studies extrapolating spatial distributions, 75% and 70% of data were typically used for training leaving 25% and 30% for validation; 10-fold cross validation was adapted in three studies (Zheng et al., 2019; Acharya et al., 2019; Xin et al., 2020b). The number of simulations run for a single model varied, ranging from 10[32,76] to 300 (Zheng et al., 2019; Xin et al., 2020a). The threshold values defining high environmental suitability for scrub typhus showed variation among the studies, with a range from 0.065[76] to 0.5[58]. Six studies utilized these specific thresholds to conduct further analyses, including the estimation of populations at risk (吴义城 and 李申龙, 2016; Yao et al., 2019; Zheng et al., 2019; Xin et al., 2020a; Acharya et al., 2019; Yu et al., 2018). All presence/absence predictions were modelled based on data at the third administrative level or below or on point/pixel data. The primary evaluation metric was Area Under the Curve (AUC).

For temporal extrapolations, data from initial periods-such as early years, months or weeks in the whole dataset - were frequently used for training and modelling, and data of subsequent periods, whether they be later years, months, or weeks, was reserved for prediction validation (Kim et al., 2020; Kwak et al., 2015b; Yang et al., 2015; He et al., 2022b; 丁磊 and 赵仲堂, 2012; Wang et al., 2014; 颜玉炳 et al., 2016; 阮春来 et al., 2017; 李文 赵嘉欣 et al., 2021; Wang et al., 2022) (N = 10). In this time-based cross-validation, the 'folds' are not random but rather sequential segments that respect the temporal order of observations. Evaluation metrics for training fit include the Akaike Information Criterion (AIC) in three studies, Bayesian Information Criterion (BIC) in five studies, R^2 in six studies, and Root Mean Square Deviation (RMSE) in three studies. Validation metrics include R^2 and RMSE (each in three

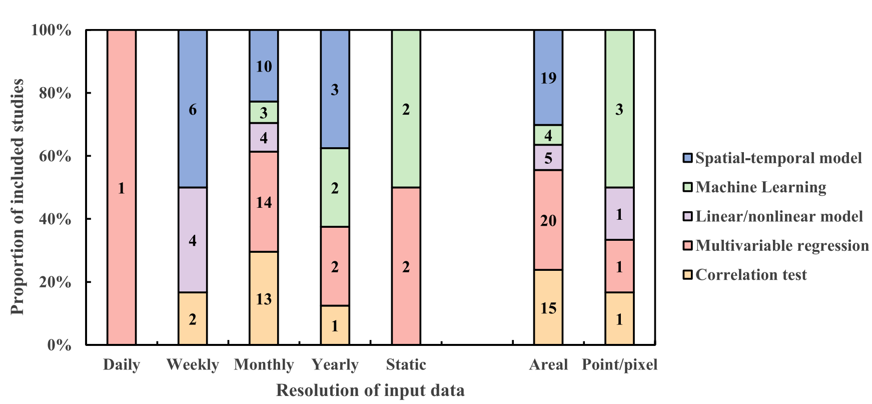


Fig. 4. Analytical approaches for association evaluation by input data resolution, temporally from daily to yearly and spatially using areal or point/pixel.

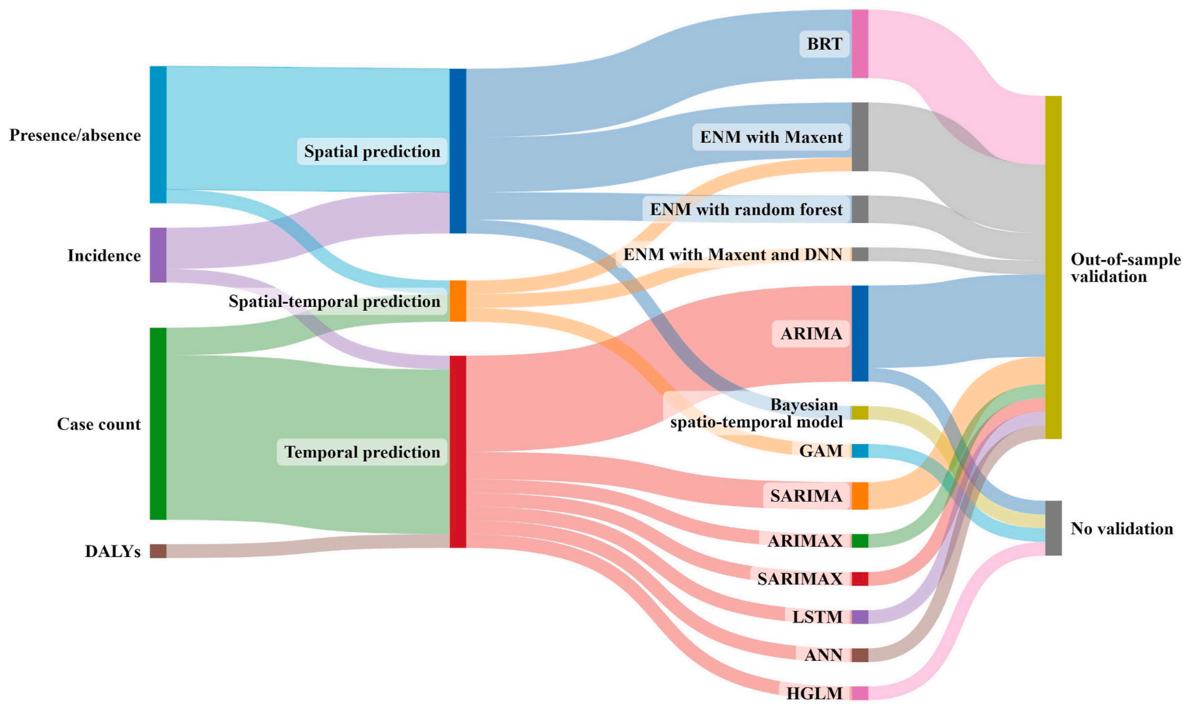


Fig. 5. Prediction models by response variables, objectives and validation status.

studies), Mean Absolute Error (MAE) in one study, Intraclass Correlation Coefficient (ICC) in one study, and descriptive descriptions in three studies.

4. Discussion

Our review provides a comprehensive examination of published research conducted on environmental risk factors significantly associated with occurrence of scrub typhus, and the models utilized for predicting its occurrence, drawing evidence from 68 studies. Remarkably, only one study published before 2010 (in 1978) linked temperature to scrub typhus, with the remaining 57 studies published after 2010. This underscores the historical neglect of scrub typhus, and its significant potential for future research and exploration. In the face of escalating climate change, the insights gleaned from this review become even more pivotal. The shifting climate not only influences existing ecological balances but also dictates the spread and emergence of diseases like scrub typhus, like our previous work done in China suggesting that the case number would increase with global warming (Ding et al., 2022). This review help lay the groundwork for a framework to identify regions where transmission may intensify, new areas where scrub typhus may emerge, and locations that could become unsuitable for transmission due to climatic shifts. We believe these evaluations is instrumental in steering global health policies and offering a strategic compass to navigate the shifting landscape of scrub typhus transmission in an era of climatic uncertainty.

Given that humans are typically incidental hosts, and the bacterium of scrub typhus is mainly reservoired in, and transmitted by, chigger mites in the natural cycle, the activities and distribution of vectors and hosts, such as mites, alongside human behaviors, and activities, are undoubtedly closely linked to the disease occurrence. These elements are significantly influenced by climatic and environmental conditions. Our analysis of 58 articles highlighted meteorological and geographic factors as principal risk factors. Crucial climate parameters such as temperature, precipitation, humidity, sunshine hour, atmospheric pressure, and wind speed are deeply intertwined with disease occurrence. Most studies found positive associations with temperature, precipitation, and humidity, indicating that warm and humid environments provide favorable conditions for the occurrence of scrub typhus (Pearson et al., 2019; Kong et al., 2007; Traub and Wisseman, 1974). The observation of inconsistent patterns, such as inverted U, N shape (李文 and 刘小波, 2021), and W shape (Bhopdhornangkul et al., 2021), reflect differences in measurement methods and regional characteristics. Linear analyses may not capture the complexity evident in more flexible, non-linear approaches like generalized additive model (GAM). Additionally, environmental heterogeneity and different dominant species of mite, such as the warmth-preferring *Leptotrombidium deliense* (Kuo et al., 2015; Ma et al., 2022; Traub and Wisseman, 1968) in southern regions and the cooler-climate *Leptotrombidium scutellare* (Kuo et al., 2015; Xiang and Guo, 2021) in northern areas, further contribute to these diverse patterns. These factors underscore the need for tailored approaches that consider local ecological and methodological contexts when studying climate influences on scrub typhus. The few studies on atmospheric pressure (Lu et al., 2021; Tsai and Yeh, 2013; Li et al., 2014; 孙烨 and 曹务春, 2016) and wind speed (Lu et al., 2021; Kim et al., 2020; Kwak et al., 2015b) reported negative relationships, which could be explained by lower atmospheric pressure and higher wind speeds being less conducive to the survival of chiggers or reducing the frequency of outdoor human activities.

Geographic variables such as elevation exhibit variable effects on the occurrence of scrub typhus, reflecting the complex interplay of local ecologies across different regions and suggesting that there may be an optimal elevation range for the disease's vectors and hosts. The Normalized Difference Vegetation Index (NDVI), a measure of vegetation health and density, is often associated positively with scrub typhus, which is attributed to better vegetation conditions providing suitable habitats for both chiggers and hosts (Traub and Wisseman, 1974; Santibáñez et al., 2015). The positive and inverted U-shaped relationships with cropland, and the negative associations with forested areas, suggest that croplands offer conducive environments for human-chigger interactions (Chaisiri et al., 2017), while denser forest regions might be less favorable for the survival and reproduction of these vectors and their hosts or offer less opportunities for chigger-human interactions.

The impact of socioeconomic factors on the occurrence of scrub typhus is multifaceted and complex, indicating that population structure, economic conditions and urbanization all contribute to the disease's risk profile. The observed positive correlations between the proportion of farmers in the population and scrub typhus cases underscore the link between agricultural activities and the disease's occurrence (Min et al., 2019; Kim et al., 2020; Tsai and Yeh, 2013; Kuo et al., 2011), aligning with the previously mentioned positive association with cropland. Similarly, the positive relationship with the elderly population might indicate a higher susceptibility among older adults to scrub typhus, potentially due to diminished immunity and the presence of chronic health conditions (Kim et al., 2020; Kang and Choi, 2018). The observed inverted U-shaped relationship with urban accessibility suggests that the risk of scrub typhus initially increases and then decreases through the urbanization process, likely due to changes in population density, sanitary conditions, and public health infrastructure over time (Zheng et al., 2019; Xin et al., 2020a). This pattern, alongside the positive correlation with the level of urbanization, supports the notion that early stages of urban development may heighten disease risk, which subsequently declines as living conditions improve (孙烨 and 曹务春, 2016; Xin et al., 2020a). Given the limited number of studies contributing to these insights, further research is necessary to confirm these preliminary findings and fully understand the dynamics involved.

Although only a limited number of studies have focused on biological variables such as rodent density or the distribution of mites (刘晓宁, 2019; 余向华, 2019; Wei et al., 2017b), their critical role in the transmission dynamics of scrub typhus is undeniable. The high incidence of scrub typhus in human is directly influenced by density and distribution of chiggers and rodents. Their sparse mention might predominantly stem from the challenges in obtaining data for rodent and chigger densities, which can be labor-intensive and require specialized expertise.

Scrub typhus transmission can be influenced by environmental factors through three main pathways: vector development, host dynamics and human exposure (Fig. 6). The lifecycle of mites is a critical component in the transmission of scrub typhus, and it is heavily influenced by a range of environmental factors. The larvae are parasitic and responsible for transmitting the pathogen to vertebrate hosts, including humans (Rapmund et al., 1969; Frances et al., 1999; Roberts et al., 1975). Temperature and precipitation are pivotal in regulating the development, survival, and reproduction of these mites. Warmer and more humid climates tend to favor mite population growth by providing optimal conditions for egg-laying and larvae survival (Audy, 1961; Wharton and Fuller, 1952; Kawamura and Ikeda, 1936). Additionally, vegetation types, such as grasslands, shrublands, and croplands, offer suitable habitats for the larvae to cluster and wait for hosts, while rodent density plays a crucial role as rodents are the primary hosts. Climate factors like temperature and rainfall influence rodent breeding cycles and survival rates, thereby affecting the availability of hosts for the mites. Favorable climate conditions, coupled with abundant vegetation, provide more food resources, potentially boosting rodent populations and, consequently, increasing the number of infected mites. Agricultural practices, especially in rural areas, increase human exposure to mite-infested environments (Elliott et al., 2019). Changes in land use, including the abandonment of farmland or the creation of ecotones (areas where different habitats meet), can influence the distribution of mites and their hosts (Audy et al., 1947; Audy and Harrison, 1951). Farmland, built-up land, and mosaic habitats (areas with a mix of vegetation types) affect where mites are most likely to encounter hosts and subsequently transmit the disease. In rural, agricultural, or fringe habitats, people are more likely to encounter infected mites. Climatic variables—such as temperature, precipitation, humidity, wind speed, and atmospheric pressure—further influence mite behavior and transmission. ENSO events, for instance, can lead to shifts in precipitation patterns, indirectly affecting mite populations and the timing of human cases (Wei et al., 2017a). Higher population density and urbanization, particularly during the early stages of urban growth, increase human exposure to mite habitats, while economic factors such as GDP and income levels may modulate access to healthcare and preventive

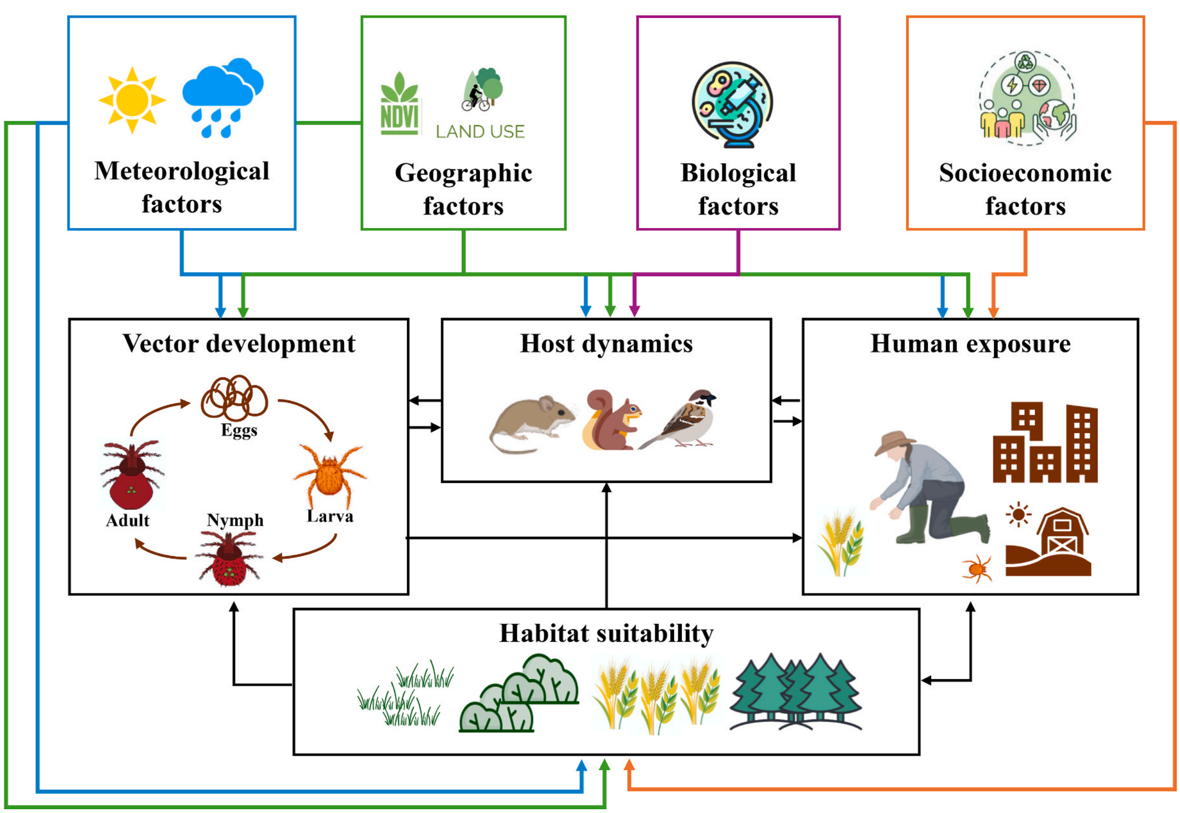


Fig. 6. Potential mechanisms of environmental covariates influencing scrub typhus.

measures. Overall, the transmission of scrub typhus depends on a multifaceted interaction between biological, environmental, and socioeconomic factors, making it essential to consider local ecological and societal contexts when studying the occurrence of the disease.

The diversity of relationships observed across various climate, geographic, and socioeconomic factors with respect to the incidence of scrub typhus underscores the complexity of its epidemiology. While the existing data provide valuable insights into potential risk factors and their associations with the disease, the current evidence base is relatively narrow, pointing to the necessity for a more expansive research effort. Understanding both environmental and biological determinants is essential for establishing accurate predictive models and tailoring effective public health measures.

The application of various methods to explore spatial trends and predict the spread of scrub typhus epidemics has laid a foundation for forecasting occurrences of the disease over time and space. Our findings demonstrated the ARIMA and ecological niche modelling approach were particularly favored for temporal extrapolation and spatial prediction, respectively. The diversity in the chosen models and methodologies mirrors the complex nature of scrub typhus and highlights the necessity for ongoing innovation in predictive modelling techniques.

Temporal models like ARIMA are effective for capturing time series patterns, especially when trends and seasonality are present, making them suitable for short-term forecasting. However, ARIMA struggles with irregular data and requires stable, long time-series data for accuracy, thus it cannot handle sudden changes. SARIMA improves on this by handling seasonal fluctuations, which is useful for diseases like scrub typhus that are influenced by climatic cycles, though it still faces challenges with short-term irregularities. Exponential smoothing models, while computationally efficient and adaptive to recent trends, are limited in capturing long-term trends or seasonal patterns. The effectiveness of the SARIMA model with additional exogenous environmental variables underscores the importance of integrating external factors into temporal prediction models (He et al., 2022b). However, it is important to acknowledge the limitations inherent in time series analyses, particularly when applied to scrub typhus. Many climate variables, such as temperature, exhibit gradual changes with annual cycles, along with scrub typhus incidence. The co-variation reflects underlying environmental dependencies, which could help prediction. While short-term changes may be less pronounced, the consistent patterns in climate data can be leveraged to predict disease outbreaks over time, if models are appropriately designed to account for the cyclical nature of these variables. However, the slow, cyclical nature of climate factors can introduce confounding effects, as other variables with similar patterns might distort the relationship between the climate and disease incidence. This confounding, especially when not accounted for, should be recognized as a significant limitation in time series models, particularly in studies with limited data. On the spatial side, ENMs are powerful tools for predicting the spatial distribution of scrub typhus, using environmental factors such as temperature and precipitation to map risk areas. These models are effective for identifying potential outbreaks in regions with sparse data but are less useful for temporal forecasting. Geostatistical models, like spatial regression, offer a more statistically robust approach by accounting for spatial autocorrelation and incorporating socio-economic factors, though they require extensive spatial data and are computationally intensive. In regions with rich time-series data and spatial information, combining spatial and temporal models can provide comprehensive insights into scrub typhus outbreaks, accounting for both time and place.

The adaptation of multiple models within a single study, as demonstrated in Nepal (Acharya et al., 2019), and the comparative analysis of their performance, provide valuable information for selecting and combining appropriate models based on the specific objectives and available data of future studies. Our analysis also indicated that out-of-sample validation is a common approach in prediction studies, although the metrics used to assess model performance vary depending on the type of response variable and desired output. Employing multiple evaluation metrics is recommended for a more comprehensive understanding of model accuracy and reliability. Even though challenges in predicting the spatial distribution of scrub typhus due to its specific environmental and biological constraints exist, these models remain valuable tools for identifying potential risk areas and guiding targeted public health interventions.

However, unlike other vector-borne diseases such as dengue and malaria, mechanistic models have not yet been applied for scrub typhus. Future research directions should include the integration of mechanistic models, the incorporation of a broader range of environmental and socio-economic data, and the development of adaptable models capable of responding to shifts in disease transmission dynamics. It is also important to tailor different approaches to various types and levels of scrub typhus data, ensuring that they can be effectively applied across different scales of analysis, and the comparison and combination of different modeling approaches to identify the most suitable model for specific situations are recommended. Collaboration across disciplines and regions will be essential to enhance our predictive capabilities and, ultimately, to mitigate the impact of scrub typhus through informed public health interventions.

Our search strategy was implemented in an inclusive manner through relevant and grey literature databases without language or publication time restriction. However, reliance on one Chinese and one international database means that some studies published in national or local journals may have been overlooked during our search process. Additionally, reviews were excluded as we focused on original analytical research. It is also important to note that our synthesis is limited to quantitative research studies; consequently, several studies employing qualitative analysis were not considered. Another limitation of this study is the high degree of heterogeneity among the included studies. The variation in study designs, sample sizes, statistical methods, and measurement standards led to differences in the reported effects. This heterogeneity complicates the aggregation of results and ultimately led us to refrain from conducting a meta-analysis, as combining such diverse data could produce misleading conclusions due to the differences in underlying assumptions and methodologies.

5. Conclusions

Our review bridges key gaps in the understanding of scrub typhus regarding the relevant environmental factors and prediction models and proposes a framework for guiding future research directions. With the expanding impact of scrub typhus, it is imperative that the covariates identified in this review be systematically taken into consideration for the development of association models. Further exploration into the complex dynamic relationships between socioeconomic and biological factors is highly recommended. Cross-national and long-term studies are essential to generate more generalizable insights into the varied patterns and dynamics of scrub typhus, thereby enhancing our understanding and management of the disease.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its additional information files.

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CRediT authorship contribution statement

Qian Wang: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Tian Ma:** Writing – review & editing, Methodology, Investigation, Data curation. **Fang-Yu Ding:** Writing – review & editing, Funding acquisition, Data curation. **Ahyoung Lim:** Writing – review & editing, Data curation. **Saho Takaya:** Writing – review & editing, Data curation. **Kartika Saraswati:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Meng-Meng Hao:** Writing – review & editing. **Dong Jiang:** Writing – review & editing. **Li-Qun Fang:** Writing – review & editing. **Benn Sartorius:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Nicholas P.J. Day:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Richard J. Maude:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Qian Wang reports financial support was provided by Wellcome Trust. Fangyu Ding reports financial support was provided by National Natural Science Foundation of China. Fangyu Ding reports financial support was provided by Chinese Academy of Sciences Youth Innovation Promotion Association. Kartika Saraswati reports financial support was provided by NRF International Partnership Funding Initiative. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data generated or analyzed during this study are included in this published article and its additional information files.

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Abbreviations

NDVI	normalized difference vegetation index
ARIMA	Autoregressive Integrated Moving Average
BRT	Boosted Regression Trees
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
MeSH	Medical Subject Headings
ENSO	El Niño/Southern Oscillation
MEI	Multivariate ENSO Index
GDP	gross domestic product
DALYs	Disability-Adjusted Life Years
SARIMA	Seasonal Autoregressive Integrated Moving Average
SARIMAX	Seasonal Autoregressive Integrated Moving-Average with Exogenous Regressors
ENM	ecological niche modelling
AUC	Area Under the Curve
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
RMSE	Root Mean Square Deviation
MAE	Mean Absolute Error
ICC	Intraclass Correlation Coefficient
GAM	generalized additive model

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.120067.

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