Examining the Direct and Indirect Effects of Climatic Variables on Plague Dynamics

Ricci P.H. Yue * and Harry F. Lee *

Department of Geography and Resource Management, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

* Correspondence: ricciyue@cuhk.edu.hk (R.P.H.Y.); harrylee@cuhk.edu.hk (H.F.L.)

† These authors contributed equally to the work.

Received: 15 March 2020; Accepted: 10 April 2020; Published: 15 April 2020

Abstract: Climate change can influence infectious disease dynamics both directly, by affecting the disease ecology, and indirectly, through altering economic systems. However, despite that climate-driven human plague dynamics have been extensively studied in recent years, little is known about the relative importance of the direct and indirect effects of climate change on plague outbreak. By using Structural Equation Modeling, we estimated the direct influence of climate change on human plague dynamics and the impact of climate-driven economic change on human plague outbreak. After studying human plague outbreak in Europe during AD1347–1760, we detected no direct climatic effect on plague dynamics; instead, all of the climatic impacts on plague dynamics were indirect, and were operationalized via economic changes. Through a series of sensitivity checks, we further proved that temperature-induced economic changes drove plague dynamics during cold and wet periods, while precipitation-induced economic changes drove plague dynamics during the cold periods. Our results suggest that we should not dismiss the role of economic systems when examining how climate change altered plague dynamics in human history.

Keywords: climate change; plague; direct and indirect effects; Structural Equation Modelling

1. Introduction

Arguably, there is an increasing consensus in academia showing that climate change is a dominant driving force of plague outbreak in the intricate pattern of disease complexity. For example, climatic fluctuations have been found associated with the recurrent introduction of Yersinia pestis, the bacterium responsible for causing the plague, from Asia into Europe during the Black Death era [1,2]. Stenseth, et al. [3] pointed out that warmer springs and wetter summers favored the prevalence of plague dynamics at its natural reservoir in Kazakhstan. In China, the modeling results by Xu, et al. [4] demonstrated that historical plague intensities in Northern and Southern China were positively correlated to wetness and dryness, respectively. However, according to more updated findings from Xu, et al. [5], wetness accelerated the spread of the plague during the third plague pandemic in China. Apparently, some of these climate-plague nexuses are related to climatic phenomena at a larger scale. Plague outbreak is quantitatively known to be associated with El Nino Southern Oscillation [6–8], Indian Ocean Dipole [7], Pacific Decadal Oscillation [8], and Southern Oscillation Index [9].

Although the above studies help us understand the connection between climate change and plague outbreaks, they are all grounded on the same assumption: climatic variables have a direct and one-step impact on plague dynamics. In those studies, the investigated climatic variables and the plague-indicating variables are simply correlated for measuring their first-order relationship. However, is the association between climate and plague straightforward in nature? According to a series of studies by Zhang et al. [10–12], climatic variations might have worked through a specific set
of economic systems to cause the outbreak of epidemics. Hence, the climate-plague association is unlikely to be direct in nature, as there should be a medium in human societies translating climatic forcing to plague outbreaks.

If there is indeed a direct relationship between the climatic variables and plague dynamics, then the investigations of the climate-plague nexus would remain convincing that the nexus normally requires a lesser likelihood to include a third variable in explaining the correlation. If there is not such a relationship, although it cannot overturn the previous observations and computational results, it may somehow indicate that many scholars may have oversimplified the necessary pathways between climate change and plague outbreak. As Zhang et al. [12] indicated, climate change could generate chronic undernourishment in China through the shrinkage of agricultural production, which further weakened immunity to infectious diseases. Lee and Zhang [13] associated the causality of climate-induced famine on epidemics outbreak in historical China. Tian, et al. [14] worked further to reveal that cold and dry climate conditions, in large part, indirectly increased the frequency of epidemics outbreak through generating the prevalence of locusts and famines in China over the last two millennia. Dunca and Scott [15] also emphasized the crucial role of nutrition and immunity in the spread of infectious diseases in pre-industrial European societies. The study by Pei, et al. [16] outlined the dependence on climate of the macroeconomic structure in Europe, and further indicated that such dependence would be imperative in pulling human societies into the Malthusian trap, which includes epidemics outbreak, in pre-industrial Europe. Specifically, we also provided a hypothetical explanation of the climate-plague relationship and highlighted the possibility that climate change affected plague dynamics via economic systems. Hence, the influence of temperature/precipitation on plague dynamics appeared to have inconsistent time lags at the multi-decadal to centennial timescales [2]. However, despite efforts to demonstrate the climate-economic-epidemics relationship in the past decades, there exists little empirical understanding of how climatic variations and plague dynamics are integrated via economic systems.

In this study, we tried to fill in the research gap in the climate-economic-epidemic relationship by examining the direct and indirect effects of climatic fluctuations on the frequency of plague outbreak in pre-industrial Europe at the continental scale. In our study region over the course of AD1347–1760, there have been documented long-term counts of human plague outbreak; the economic trend has been described in fine resolution; and climatic variables have been reconstructed through widespread dendrochronology records. We used such long-term data on plague, climate, and economic attributes to answer the following questions: (1) whether the investigated climatic variable exhibited a direct and/or indirect influence (through economic systems) on human plague dynamics in Europe at the continental scale; (2) whether economic attributes deliver their influence to human plague activities in Europe at the continental scale; and (3) whether both climatic variables and economic factors maintain a long-term trend with human plague dynamics over the study period in Europe at the continental scale. To address the above issues, we applied structural equation modeling (SEM) to disentangle that direct and/or indirect importance of climatic fluctuations on historical plague activities in human societies. We showed all the hypothetical pathways being tested in our analysis in Figure 1. Our findings suggest that climate-driven economic fluctuations played a crucial role in translating climate change into plague outbreak.
Our study considered self-calibrated Palmer Drought Severity Index (scPDSI) as the projection of the natural hydroclimatic environment. As such, the PDSI reconstruction by Cook et al. [22] provides an ideal extended record of natural wetness/dryness variability for the pre-industrial era of Europe. The OWDA was developed from dendrochronological records over the European continent and calibrated with high-quality instrumental scPDSI gridded data from the Royal Netherlands Meteorological Institute. Our study retrieved available data points, specifically from Europe, for the reconstruction of past climatic variability of Europe at its continental scale in annual resolution. Particularly, the time series for temperature data is calibrated into temperature anomaly with respect to the period of AD1347–1760, there have been documented long-term counts of human plague outbreak; the outbreaks in pre-industrial Europe at the continental scale. In our study region over the course of centuries, we counted the number of cities identified with plague outbreak in each year and transformed the database into a time series. Only data from Europe was counted, as Europe was selected for our study region. Slightly different from the original dataset, which used the number of total plague outbreak count as its unit, the transformed dataset adopted in this study used the number of cities with plague outbreak count as our unit. Over the AD1347–1760 period, a total of 6764 plague outbreaks were recorded in Europe. The year with the most extensive plague outbreak is AD1630, with a record 119 cities affected by the plague. Out of 414 units of observation, plague quiet years are recorded 14 times. Zero-inflation of the dataset should not be considered as a problem.

Figure 1. Path diagram showing all hypothesized direct and indirect links amongst climate change, economic fluctuations (including wheat price, CPI, and real wage), and plague outbreak. Climate change and economic fluctuations may directly cause the plague outbreak. Also, climate change may indirectly cause the plague outbreak by influencing the wheat price, and then the wheat price will affect CPI and the real wage.

2. Materials and Methods

2.1. Plague Data

To measure the historical plague outbreak in Europe, we adopted a detailed geo-referenced plague dataset digitalized by Büntgen, et al. [17]. The database records the starting year of each human plague outbreak in Europe at the city-scale. We counted the number of cities identified with plague outbreak in each year and transformed the database into a time series. Only data from Europe was counted, as Europe was selected for our study region. Slightly different from the original dataset, which used the number of total plague outbreak count as its unit, the transformed dataset adopted in this study used the number of cities with plague outbreak count as our unit. Over the AD1347–1760 period, a total of 6764 plague outbreaks were recorded in Europe. The year with the most extensive plague outbreak is AD1630, with a record 119 cities affected by the plague. Out of 414 units of observation, plague quiet years are recorded 14 times. Zero-inflation of the dataset should not be considered as a problem.

2.2. Climate Data

We considered three sets of climate data, namely temperature, precipitation, and scPDSI, for our analysis in this study. They were common parameters for historical study relating to climate-human relationships and were found strongly significant in influencing plague dynamics over time and space [18,19].

The temperature and precipitation dataset included for analysis are acquired from the climate reconstruction provided by Büntgen, et al. [20]. This climatic reconstruction was made possible through surveying 1547 sets of tree ring chronologies from Europe for the reconstruction of past climatic variability of Europe at its continental scale in annual resolution. Particularly, the time series for temperature data is calibrated into temperature anomaly with respect to the period of AD1901–2000. The vast coverage of raw data from this dataset ensured the reliability and validity of climate reconstruction. Thus, the dataset has been widely adopted in other historical studies of Europe [21].

Another set of climatic variables adopted in this study originated from the Old World Drought Atlas (OWDA) project of Cook et al. [22]. Our study considered self-calibrated Palmer Drought Severity Index (scPDSI) as the projection of the natural hydroclimatic environment. As such, the PDSI reconstruction by Cook et al. [22] provides an ideal extended record of natural wetness/dryness variability for the pre-industrial era of Europe. The OWDA was developed from dendrochronological records over the European continent and calibrated with high-quality instrumental scPDSI gridded data from the Royal Netherlands Meteorological Institute. Our study retrieved available data points,
which have a spatial resolution of half-degree longitude-by-latitude grid, from our study area and further aggregated relevant grids of the same year into a time series for our analysis.

2.3. Economic Data

For historical economic parameters, we selected wheat price, consumer price index (CPI), and real wages as variables for our estimations. The historical wheat price is extracted from the database created by Allen [23]. We extracted the data from each city and determined whether they fell onto our study region. The raw data is first standardized by \( \frac{x_i - \text{mean}}{\text{s.d.}} \), then we calculated the averaged standardized wheat price of Europe. The historical CPI data comes from Allen [23]. We calculated the averaged standardized CPI by the same method as suggested in wheat price. We here averaged the standardized real wages of laborers and standardized real wages of building craftsmen based on the database from Allen [23].

2.4. Structural Equation Modeling

We applied structural equation modeling (SEM) [24] to test for the relative importance of climatic variables and economic variables on plague dynamics, and whether climate change has a direct influence on plague dynamics. To do this, we first constructed all the hypothetical pathways that fully detailed the causality amongst variables within the system being studied [25]. Then, mathematically, the total pathway added up together as a series of linear regression. The technique hypothetically decomposed all the correlations of two variables into direct effects that pinpointed the causal influence of one factor on another and indirect effects that passed through other variables in the model and non-casual mediating predictors resulting from a common cause [26]. From the full casual model, the sum of direct effects and all indirect effects mediated by other variables between the predictor and response variable would yield total effect. In SEM, by assuming that all of the important variables and pathways were labeled, every effect listed in path analysis was considered linear, additive and unidirectional, and that residuals were presumably uncorrelated [27]. In this study, as also shown in Figure 1, the response variable is plague outbreak. We hypothesized that climate change and economic fluctuations (including wheat price, CPI, and real wage) may directly cause plague outbreak. Also, climate change may indirectly cause plague outbreak by influencing wheat price, which then will affect CPI and real wage.

2.5. Linear Regressions

To test whether different sets of data correlate directionally with each other over the long-run and in different climatic settings, we statistically compared the long-term trends between: (1) climate change and plague outbreak; (2) economic change and plague outbreak; (3) climate change and economic change; and (4) internal dynamics of economic change. For each set of correlation tested, we divided the study timespan into different climatic periods, namely: (1) warm periods (positive temperature anomaly); (2) cold periods (negative temperature anomaly); (3) dry periods (below-average precipitation with reference to AD1347–1760); and (4) wet periods (above-average precipitation with reference to AD1347–1760). To assess the afore-mentioned long-term relationship, we adopted simple linear regression models for each combination.

3. Results

3.1. Direct and Indirect Climatic Effect on Plague Outbreak

Over our study period in AD1347–1760, our SEM results showed that temperature and precipitation variations would have a substantial indirect impact on plague outbreak in Europe through climate-induced fluctuations in wheat prices (Figure 2). Yet, the climatic influence, as implied from the SEM results, is never directly linked to plague dynamics.
direct influence on plague dynamics. To do this, we first constructed all the hypothetical pathways climatic variables and economic variables on plague dynamics, and whether climate change has a implied from the SEM results, is never directly linked to plague dynamics.

we divided the study timespan into different climatic periods, namely: (1) warm periods (positive temperature anomaly); (2) cold periods (negative temperature anomaly); (3) dry periods (below-average precipitation with reference to AD1347); and (4) wet periods (above-average precipitation with reference to AD1347).

3.1. Direct and Indirect Climatic Effect on Plague Outbreak

we adopted simple linear regression models for each combination.

2.5. Linear Regressions

cause plague outbreak. Also, climate change may indirectly cause plague outbreak by influencing economic change; and (4) internal dynamics of economic change. For each set of correlation tested, climate change and economic fluctuations (including wheat price, CPI, and real wage) may directly change and plague outbreak; (2) economic change and plague outbreak; (3) climate change and economic change; and plague outbreak. Also, climate change may indirectly cause plague outbreak by influencing economic change; and (4) internal dynamics of economic change. For each set of correlation tested, climate change and economic fluctuations (including wheat price, CPI, and real wage) may directly change and plague outbreak; (2) economic change and plague outbreak; (3) climate change and economic change; and (4) internal dynamics of economic change. For each set of correlation tested, climate change and economic fluctuations (including wheat price, CPI, and real wage) may directly

2.4. Structural Equation Modeling

Atmosphere 2020, 11, x FOR PEER REVIEW 4 of 17

Figure 2. Path diagrams for (a) Model 1: Temperature anomaly; (b) Model 2: Precipitation; (c) Model 3: PDSI, for the direct and indirect effects of climate change on plague outbreak. The residual variables (ε1, ε2, ε3, ε4) represent the unmeasured factors affecting the corresponding variable. Arrows represent the relationship of each pair of the variables, with the path coefficients stated next to the arrows. The path coefficients are standardized partial regression coefficients from linear regressions. We omit those statistically insignificant paths in the models, except for the path PDSI → Wheat Price. Red arrows represent statistically insignificant paths, while the black ones represent statistically significant ones.

Model 1 shows that temperature variation has a statistically-insignificant direct relationship with plague dynamics (Table 1).
Table 1. Correlation coefficients between each set of climatic/economic predictor and plague response. The correlation is decomposed into the direct and indirect effects, and the synergy of the direct and indirect effects gives the total effect.

|                     | Direct | Indirect  | Total    |
|---------------------|--------|-----------|----------|
| **Model 1**         |        |           |          |
| Temp → Plague       | −1.49  | −1.66 *** | −3.15 ***|
| Wheat price → Plague| 38.56 *** | −28.86 *** | 9.69 **  |
| CPI → Plague        | −31.68 *** | −0.32     | −31.99 ***|
| Real wage → Plague  | 3.02   |           | 3.02     |
| **Model 2**         |        |           |          |
| Precipitation → Plague| −0.03 | 0.02 ***  | −0.01    |
| Wheat price → Plague| 38.79 *** | −28.31 *** | 1048 *** |
| CPI → Plague        | −31.12 *** | −0.30     | 2.91 ***  |
| Real wage → Plague  | 2.91   |           | 2.91     |
| **Model 3**         |        |           |          |
| PDSI → Plague       | −0.51  | 0.09      | 0.47     |
| Wheat price → Plague| 38.91 *** | −28.70 *** | 10.21 ***|
| CPI → Plague        | −31.43 *** | −0.32     | −31.75 ***|
| Real wage → Plague  | 3.08   |           | 3.08     |

Significance level: *** \( p < 0.001 \), ** \( p < 0.05 \).

However, temperature would indirectly control the variations of plague frequency through wheat price fluctuations (intercept = −1.66, \( p < 0.001 \)). In Model 2, precipitation displayed a similar pattern as temperature. The command of precipitation on plague dynamics is undertaken indirectly through the manipulation of wheat prices (intercept = 0.02, \( p < 0.001 \)) during our study period. Likewise, the path model again denied the direct impact of precipitation on the plague outbreak. In Model 3, the estimation suggested that PDSI would have no directional effect on plague dynamics, both directly and indirectly. For each set of the path analysis, we also included selected economic factors to investigate the direct and indirect influence of climate change on plague dynamics. In all models, it is observed that, despite the climate-induced fluctuation, both wheat price and CPI have a direct effect on plague outbreak. The influence of wheat price and CPI was not mediated by other variables in the models when other factors were held constant. The models also universally demonstrated that the sensitivity of plague dynamics was indirectly correlated with the changes in wheat price via CPI. However, not all the economic variables tested were found relevant to plague outbreak. The historical real wage was not directly related to any variations of plague dynamics. By combining the direct effect and indirect effects of predictors, we were able to measure the total effect of both climatic variables and economic variables on plague outbreak. From the result, as indicated in Table 1, the total effect of temperature, precipitation, and CPI remained statistically negatively significant to any change of plague activity, while the effect of wheat price on plague was reported to be positive. In short, plague dynamics is favored by low temperature, dry environment, rising wheat price, and decreasing CPI.

3.2. Long-Term Trends of Climate, Economic Changes, and Plague Outbreak

In the process of creating SEM from climatic, economic, and plague data, we also looked for long-term trends between variables and checked for their consistency over our study period. In Figure 3, we laid out the general long-term sensitivity of plague dynamics and identified predictors deduced from SEM.
Plague dynamics, as estimated, had a negative trend with temperature (Coef. = −0.007, p < 0.001, F = 8.24) (Table A1), implying that cooling would effectively trigger plague outbreak. For precipitation, the long-term trend is statistically insignificant to the plague dynamics. For the two economic variables tested here, wheat price exhibited a consistent positive trend with the plague dynamics (Coef. = 0.0126, p < 0.001, F = 60.24); whilst CPI also showed a similar trend (Coef. = 0.0062, p < 0.001, F = 16.20).

Over the 414 years of observation, temperature and precipitation both have a persistent impact on wheat price. It was estimated that the price of wheat drops with increasing temperature (Coef. = −0.319, p < 0.001, F = 23.81) and decreasing rainfall (Coef. = 10.519, p < 0.001, F = 23.81). At the same time, wheat price, because it is closely related to the economy, was itself positively correlated with CPI (Coef. = 1.029, p < 0.001, F = 2597.16).

We also compared the long-term trend of temperature influence between warm and cold periods. It should be noted that climatic control on plague and economic parameters behaved differently in warm and cold periods. During cold periods, the long-term trend of all studied relationships performed the same as the overall long-term trend observed (Figure 4, Table A2). However, during warm periods, temperature no longer exerted its effect on plague dynamics and wheat price (Figure 5, Table A3). From the statistical results we obtained, the sensitivity of plague dynamics was primarily controlled by wheat price (Coef. = 0.0122, p < 0.001, F = 12.04) and CPI (Coef. = 0.0093, p < 0.001, F = 8.66) within the warm phases. Such control was also revealed in the SEM models presented in the previous section, in which growing CPI and rising wheat price occurred together during the warm periods (Coef. = 1.065, p < 0.001, F = 691.12).
Plague dynamics, as estimated, had a negative trend with temperature (Coef. = \(-0.007\), \(p < 0.001\), \(F = 8.24\)) (Table A1), implying that cooling would effectively trigger plague outbreak. For precipitation, the long-term trend is statistically insignificant to the plague dynamics. For the two economic variables tested here, wheat price exhibited a consistent positive trend with the plague dynamics (Coef. = \(0.0126\), \(p < 0.001\), \(F = 60.24\)); whilst CPI also showed a similar trend (Coef. = \(0.0062\), \(p < 0.001\), \(F = 16.20\)).

Over the 414 years of observation, temperature and precipitation both have a persistent impact on wheat price. It was estimated that the price of wheat drops with increasing temperature (Coef. = \(-0.319\), \(p < 0.001\), \(F = 23.81\)) and decreasing rainfall (Coef. = \(10.519\), \(p < 0.001\), \(F = 23.81\)). At the same time, wheat price, because it is closely related to the economy, was itself positively correlated with CPI (Coef. = \(1.029\), \(p < 0.001\), \(F = 2597.16\)).

We also compared the long-term trend of temperature influence between warm and cold periods. It should be noted that climatic control on plague and economic parameters behaved differently in warm and cold periods. During cold periods, the long-term trend of all studied relationships performed the same as the overall long-term trend observed (Figure 4, Table A2). However, during warm periods, temperature no longer exerted its effect on plague dynamics and wheat price (Figure 5, Table A3). From the statistical results we obtained, the sensitivity of plague dynamics was primarily controlled by wheat price (Coef. = \(0.0122\), \(p < 0.001\), \(F = 12.04\)) and CPI (Coef. = \(0.0093\), \(p < 0.001\), \(F = 8.66\)) within the warm phases. Such control was also revealed in the SEM models presented in the previous section, in which growing CPI and rising wheat price occurred together during the warm periods (Coef. = \(1.065\), \(p < 0.001\), \(F = 691.12\)).

**Figure 4.** Long-term trend of plague outbreak with (top left) temperature anomaly; (top right) precipitation; (bottom left) wheat price; and (bottom right) CPI during the cold periods. The cold periods refer to the time with negative temperature anomaly. Red lines represent the trends, and the green envelopes provide the 95% confidence interval areas.

**Figure 5.** Long-term trend of plague outbreak with (top left) temperature anomaly; (top right) precipitation; (bottom left) wheat price; and (bottom right) CPI during the warm periods. The warm periods refer to the time with positive temperature anomaly. Red lines represent the trends, and green envelopes provide the 95% confidence interval areas.
In addition, the performance of the climatic variable differed in the dry and wet periods. Further analyses showed that temperature could not change the trend of plague outbreak during dry periods (Figure 6, Table A4). The pressure from the temperature on wheat price and plague outbreak did not exist at all during dry periods. However, in wet periods, the dynamics of plague activity increased with temperature cooling (Coef. = −0.0119, \( p < 0.001, F = 12.90 \)), whilst increasing wheat price was also associated with decreasing temperature (Coef. = −0.524, \( p < 0.001, F = 32.18 \)) (Figure 7, Table A5).

\[ \text{Figure 6. Long-term trend of plague outbreak with (top left) temperature anomaly; (top right) precipitation; (bottom left) wheat price; and (bottom right) CPI during the wet periods. The wet periods refer to the time with above-average precipitation over our study period. Red lines represent the trends, and the green envelopes provide the 95\% confidence interval areas.} \]

\[ \text{Figure 7. Cont.} \]
were all indirect. Indeed, previous studies suggested that high summer temperature could inactivate human plague occurrence in the case of the United States [32,33] and may cause the reduction of flea survival, early-stage development, reproduction rate, and the ability to transmit the disease [34,35]. The influence of precipitation was previously well documented but defined in a complicated manner. The trend of precipitation was depicted as a positive and linear indicator of plague outbreak in the United States [29,30]. However, the recognition of such an indirect climatic effect as a direct indicator to plague activities without testing the potential existence of an indirect effect has not received significant attention in academia. Most often, previous studies considered climatic influence as a direct indicator to plague activities without testing the potential existence of an indirect pathway. Our results challenged the previous perspective and demonstrated that the economic system is an important element of the indirect effect of climate on plague outbreak. In fact, our SEM approach could not detect any direct climatic effect on plague activity; instead, only temperature displayed total effect on plague dynamics, and the pathways of temperature influence on plague dynamics is indirect but considerably insignificant as a whole.

Although many disease outbreaks are characteristically associated with climate directly [29,30], the indirect pathway is not uncommon [31]. However, the recognition of such an indirect climatic effect has not received significant attention in academia. Most often, previous studies considered climatic influence as a direct indicator to plague activities without testing the potential existence of an indirect pathway. Our results challenged the previous perspective and demonstrated that the economic system is an important element of the indirect effect of climate on plague outbreak. In fact, our SEM approach could not detect any direct climatic effect on plague activity; instead, only temperature displayed total effect on plague dynamics, and the pathways of temperature influence and precipitation influence were all indirect. Indeed, previous studies suggested that high summer temperature could inactivate human plague occurrence in the case of the United States [32,33] and may cause the reduction of flea survival, early-stage development, reproduction rate, and the ability to transmit the disease [34,35]. The influence of precipitation was previously well documented but defined in a complicated manner. The trend of precipitation was depicted as a positive and linear indicator of plague outbreak in the U.S. [36]. Nonetheless, the correlation is negative in Vietnam and Uganda, where dry seasons favored the risk of plague outbreak to a greater extent than wet seasons [37,38]. However, regardless of the disparity in the study area, the variation in climate (both temperature and precipitation) did not post any direct effect on plague dynamics in our study when we held the economic parameters constant.

4. Discussion

Given that climate change and the risk of plague outbreak are closely coupled [28], actions need to focus on the pathways and patterns of climate-plague nexus. In particular, the mechanism of those climatic effects—whether they are direct and/or indirect, remain largely unclear and understudied so far. In this study, we found that the effect of climatic forcing on the temporal distribution of plague outbreak was solely indirect in nature. Furthermore, the long-term trend of climate-plague nexus was only significant in the cold and wet periods.

4.1. Direct and Indirect Paths Embedded in the Climate-Plague Nexus

The statistical results from SEM led us to similar conclusions: (1) that climate has an indirect influence on plague dynamics; (2) that economic factors have a direct influence on plague dynamics; (3) that climate has a direct influence on economic factors, also meaning that the influence of climate on plague dynamics is mediated by economic systems. More specifically, the effect of temperature on plague dynamics is indirect but as a whole significant, whilst the effect of precipitation on plague dynamics is indirect but considerably insignificant as a whole.

Figure 7. Long-term trend of plague outbreaks with (top left) temperature anomaly; (top right) precipitation; (bottom left) wheat price; and (bottom right) CPI during the dry periods. The dry periods refer to the time with below-average precipitation over our study period. Red lines represent the trends, and the green envelopes provide the 95% confidence interval areas.
Academically, much more is known about how climate affects economic systems, or how economic attributes led to epidemics—partly because climate-epidemics study is a comparatively new subject for researchers. A series of work by Pei et al. \cite{16,39–41} is most prominent in justifying the casual pathway from cooling to the shrinkage of crop productivity, and thus, shock in the agricultural market and the stability of agrarian society. In fact, before the time of the Industrial Revolution, when most people were farmers, it is understandable that an agrarian society relies heavily on "good climate". The study by Zhang et al. \cite{12} extended further the idea of climate-induced food shortage to malnutrition and hypothesized a declined cohort immunity through examining the time series of human height in Europe. Moreover, because of malnutrition, the undernourished population would easily be more susceptible to infectious diseases through dysfunctional immunological responses \cite{42}. Thus, it is possible, with the support of past literatures, to demonstrate that climatic variables could be hypothetically correlated to increasing plague activities through their commands on the agro-economy. However, from our SEM result, only temperature and precipitation variations were deemed significant in such a pathway, with PDSI coming up short in showing a statistically significant relationship with plague dynamics both directly and indirectly. As a result, since not all the climatic variables we tested in this analysis were found to be correlated, additional climatic variables, or the term "climatic influence" should be considered carefully when we describe their impact on plague outbreak.

Our study also delineated the indirect effect of precipitation on plague outbreak in time series. In fact, previous results once questioned the role of precipitation in producing any significant change in plague dynamics \cite{2}. Yet, those studies might have only considered the total effect of precipitation but not the indirect effect of it. Our study also highlighted the indirect positive effect of wetness on plague dynamics. However, our SEM results indicate that this association could be weak, yet significant, in magnitude. The reason behind this might lie in the contextual variations in the agricultural markets or major crop types. In this study, we used wheat price as a representation of crop market and Europe as the study area, and it could be that wheat is more sensitive to wetness than dryness and historical Europe was capable of absorbing shocks in mild climatic variations, and thus, generating the result we saw from our analysis. In an alternative study adopting the same methodology of ours but working on a region with a completely different market and key crop types, the role of precipitation in influencing plague dynamics might also appear different.

Furthermore, our results, suggest that the sustainability and resilience of societies to climate change matters for their survival against the plague. Some researchers identify climate as the direct driver of plague activities in European history, with such climate-plague tropes supported by robust palaeoclimatic and reconstructed disease data. Yet, those hypotheses might have simplified social responses and failed to account for the complexity of disease dynamics in human society. To a certain extent, the lack of synchronous climate-driven plague outbreak mechanisms in China in the work of Xu et al. \cite{4} should have already implied profound regional variations in plague resilience and buffers to climatic variability. Such recognition of regional variation in plague resilience had been stifled by treating the disease dynamics of plague to climatic variation as a homogenous and universal entity. Statistical analyses that assumed a single, homogenous and direct response of plague dynamics to climate forcing were therefore at odds with empirical data relevant only to a certain spatial level so that the results might appear dichotomous, inconsistent, mild, or insignificant. Consequently, there is a dissonance between method and hypothesis.

Five important caveats should be noted in interpreting our study results. First, our study results did not refute the role of climatic variation in any previous studies, although our study showed that climatic variation was not directly related to plague dynamics. Our intent was to demonstrate that the effects of climate on the economic system exert a stronger influence on temporal plague outbreak patterns, and to call for addressing the role of social responses to plague outbreak. Second, the disease dynamics of plague remained extremely complex. Our study is pilot in nature to outline the plausible indirect effect of climate on the plague outbreak dynamics at our study scale. Yet, the interpretation of such results should not be overgeneralized to plague dynamics in other contexts such as virus-host relationship,
rodent plague outbreak dynamics, host-to-human transmission, and so on. Third, the indirect effect of climate change on plague dynamics might not only bypass social response. For example, Yue, et al. [43] explored the influence of trade routes on plague spreading patterns. Despite the fact that they assumed the transportation route as static over their study period, one can easily forecast the evolution of transportation could also contribute to plague dynamics in time. Forth, in a similar sense, the effect of other climatic variables on the plague dynamics should await further analysis. Plague dynamics might not only be influenced by temperature and precipitation. Instead, recent progress in climate-plague nexus had frequently suggested the role of large-scale climatic phenomenon [44,45]. Finally, this paper focused mainly on the climate-plague nexus at the macro-scale. However, we should not overlook the importance of studying micro-regions in Europe during this outbreak. A series of recent work [46–50] has called for attention between the balanced view of macro-scale study of plague dynamics and micro-perspective of it in medieval Europe.

4.2. Long-Term Trends of the Climate-Plague Nexus

Long-term trends between different variables suggested that human plague dynamics is sensitive to particular climatic situations, and economic attributes are potentially more consistent in influencing plague dynamics. To be more specific, the long-term trend of human plague activities with different predictors suggested that only temperature remained significant in correlating with plague outbreak patterns in cold and wet climate, whilst the effect of precipitation showed no significant relationship with plague directly in any sensitivity tests. Furthermore, the effect of temperature displayed no total or indirect relationship with plague outbreak when the climate is warm and dry. Similarly, the increasing temperature only promoted the drop of wheat price during cold and wet periods but made no significant impact on the wheat market when the climate was already warm and dry. In comparison, decreasing precipitation also contributed to the lowering of wheat price in cold and wet periods. On the one hand, the above long-term dynamics are consistent with and supportive of our SEM results. On the other hand, the pattern might also indicate that the direct/indirect/total effects of climate variation were spatio-temporally selective and variable-dependent. Thus, such reshaping of the idea of direct/indirect climate-plague nexus at the temporal domain might also be applicable in similar fashion at the spatial domain, or in a multi-scalar study [51]. Second, the results suggested that cooling during cold times and growing wetness in wet times could stimulate plague outbreak. In a similar vein, extreme coldness and flooding were the contributors to plague outbreak in Europe [2]. Third, to expand on the previous point, our result might have explained the insignificant climate-plague association in some other studies. To a large extent, the meticulous picture of the climate-plague association we obtained from this study was attributable to the centennial-scale historical panel data applied. Other studies that utilize shorter time frames or contemporary plague outbreak might unavoidably fall onto the “warm period”, which provided a null result, rejecting the legitimacy of climate-plague relationship.

In addition, both wheat price and CPI exhibited a positive relationship with human plague outbreak regardless of any climatic situations. The consistent relationship between economic parameters and plague might seem persuasive in confirming their dominant role in governing plague dynamics. Yet, one should also consider that plague dynamics, or any other pandemics, would certainly shock agricultural markets and living standards [52]. Therefore, a cyclic correlation between epidemics and economic systems might reinforce each other, making their correlation become consistent and stable. Besides, factors such as wars, social turmoils, urbanizations, and famine could have a fundamental impact on both agricultural markets and infectious disease outbreak [10]. Based simply on the analysis performed in this study, it remained unknown whether socio-economic variables were more important than climatic variables in driving plague dynamics, and that whether factors like wars and urbanization might play a part in climate-plague nexus. Yet, given that our analytic results could address the consistent significant correlation between economic changes and plague dynamics, further research for the aforementioned questions should be warranted. As our analysis focused on the long-term relationship of climate-plague nexus over a continental spatial unit, future study could be arranged at
case studies in the modern context with a smaller spatial study unit to capture the potential variation of climate-plague nexus with a moving scalar window.

5. Conclusions

The identification of the direct and indirect relationship between climate change and human plague dynamics is a topic of high interest in the context of surging researches over the potential elevating risk of plague outbreak under climate change. Although many studies have revealed the possible linkages in the climate-plague nexus and have highlighted the concern of scale-dependent variability in climate-driven plague dynamics in the spatio-temporal dimension [45], they seldom explicitly consider the possibility that the relationship is an indirect one. In this study, we applied SEM to quantitatively justify that the casual pathway from climate change to plague dynamics in historical Europe was not a direct one but was mediated by climate-driven economic changes. In a nutshell, the influence of temperature was only significant in the cool and wet periods, corresponding to the total effect and indirect effect of temperature in SEM; whilst the influence of precipitation on human plague dynamics seemed to be indirect in nature and was significant only in cold climate. The study evidenced that climate-driven economic changes, rather than climate change alone, were the direct cause of human plague outbreak. The investigation on such indirect influence of climate change on human plague dynamics should receive more attention in the future.

Author Contributions: R.P.H.Y. and H.F.L. designed research; R.P.H.Y. and H.F.L. performed research; R.P.H.Y. and H.F.L. analyzed data; and R.P.H.Y. and H.F.L. wrote the paper. Both authors read and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This study is supported by the Improvement on Competitiveness in Hiring New Faculties Funding Scheme (4930900) and Direct Grant for Research 2018/19 (4052199) of the Chinese University of Hong Kong.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix

Table A1. Linear regression results of the long-term relationship between different sets of variable employed in the path analysis, AD1347–1760 (n = 414).

| Variable A         | Variable B            | Coef  | F     | R²   |
|--------------------|-----------------------|-------|-------|------|
| Temperature anomaly| Plague outbreak       | −0.007*** | 8.24  | 0.0196|
| Precipitation      | Plague outbreak       | −0.090  | 0.60  | 0.0014|
| Wheat price        | Plague outbreak       | 0.0126*** | 60.57 | 0.1282|
| CPI                | Plague outbreak       | 0.0062*** | 16.20 | 0.0378|
| Temperature anomaly| Wheat price           | −0.319*** | 23.81 | 0.0546|
| Precipitation      | Wheat price           | 10.519*** | 10.29 | 0.0244|
| Wheat price        | CPI                   | 1.029***  | 2597.16| 0.8631|

Significance level: *** p < 0.001.

Table A2. Linear regression results of the long-term relationship between different sets of variable used in path analysis during the cool periods of AD1347–1760 (n = 319).

| Variable A         | Variable B            | Coef  | F     | R²   |
|--------------------|-----------------------|-------|-------|------|
| Temperature anomaly| Plague outbreak       | −0.007*** | 11.73 | 0.0357|
| Precipitation      | Plague outbreak       | −0.090  | 0.08  | 0.0002|
| Wheat price        | Plague outbreak       | 0.0125*** | 48.11 | 0.1318|
| CPI                | Plague outbreak       | 0.0054*** | 9.70  | 0.0297|
| Temperature anomaly| Wheat price           | −0.229*** | 14.90 | 0.0449|
| Precipitation      | Wheat price           | 13.655*** | 13.84 | 0.0418|
| Wheat              | CPI                   | 1.025***  | 1875.74| 0.8554|

Significance level: *** p < 0.001.
Table A3. Linear regression results of the long-term relationship between different sets of variable used in path analysis during the warm periods of AD1347–1760 (n = 95).

| Variable A  | Variable B         | Coef     | F       | R²  |
|-------------|---------------------|----------|---------|-----|
| Temperature anomaly | Plague outbreak     | −0.0007  | 0.08    | 0.0009 |
| Precipitation | Plague outbreak     | 2.503    | 0.11    | 0.0012 |
| Wheat price  | Plague outbreak     | 0.0122 *** | 12.04   | 0.1146 |
| CPI          | Plague outbreak     | 0.0093 *** | 8.66    | 0.0852 |
| Temperature anomaly | Wheat price     | 0.020    | 0.09    | 0.0010 |
| Precipitation | Wheat price        | 2.503    | 0.11    | 0.0012 |
| Wheat price  | CPI                 | 1.065 *** | 691.12  | 0.8814 |

Significance level: *** p < 0.001.

Table A4. Linear regression results of the long-term relationship between different sets of variable used in path analysis during the wet periods of AD1347–1760 (n = 217).

| Variable A  | Variable B         | Coef     | F       | R²  |
|-------------|---------------------|----------|---------|-----|
| Temperature anomaly | Plague outbreak     | −0.0119 *** | 12.9    | 0.0566 |
| Precipitation | Plague outbreak     | 0.088    | 0.00    | 0.0000 |
| Wheat price  | Plague outbreak     | 0.0147 *** | 47.82   | 0.1819 |
| CPI          | Plague outbreak     | 0.0064 *** | 8.66    | 0.0852 |
| Temperature anomaly | Wheat price     | −0.524 *** | 32.18   | 0.1302 |
| Precipitation | Wheat price        | 0.879    | 0.00    | 0.0000 |
| Wheat price  | CPI                 | 1.020 *** | 1166.35 | 0.8444 |

Significance level: *** p < 0.001.

Table A5. Linear regression results of the long-term relationship between different sets of variable used in path analysis during the dry periods of AD1347–1760 (n = 197).

| Variable A  | Variable B         | Coef     | F       | R²  |
|-------------|---------------------|----------|---------|-----|
| Temperature anomaly | Plague outbreak     | −0.001   | 0.06    | 0.0566 |
| Precipitation | Plague outbreak     | 3.679    | 1.73    | 0.0088 |
| Wheat price  | Plague outbreak     | 0.0104 *** | 18.86   | 0.0882 |
| CPI          | Plague outbreak     | 0.0061 ** | 7.46    | 0.0369 |
| Temperature anomaly | Wheat price     | −0.142   | 2.38    | 0.0120 |
| Precipitation | Wheat price        | 3.68     | 1.73    | 0.0088 |
| Wheat price  | CPI                 | 1.038 *** | 1377.92 | 0.8760 |

Significance level: *** p < 0.001; ** p < 0.01.

References

1. Schmid, B.V.; Büntgen, U.; Easterday, W.R.; Ginzler, C.; Wallæe, L.; Bramanti, B.; Stenseth, N.C. Climate-driven introduction of the Black Death and successive plague reintroductions into Europe. Proc. Natl. Acad. Sci. USA 2015, 112, 3020–3025. [CrossRef] [PubMed]

2. Yue, R.P.; Lee, H.F. Pre-industrial plague transmission is mediated by the synergistic effect of temperature and aridity index. BMC Infect. Dis. 2018, 18, 134. [CrossRef] [PubMed]

3. Stenseth, N.C.; Samia, N.I.; Viljugrein, H.; Kausrud, K.L.; Begon, M.; Davis, S.; Leirs, H.; Dubyanskiy, V.; Esper, J.; Ageyev, V.S. Plague dynamics are driven by climate variation. Proc. Natl. Acad. Sci. USA 2006, 103, 13110–13115. [CrossRef] [PubMed]

4. Xu, L.; Liu, Q.; Stige, L.C.; Ari, T.B.; Fang, X.; Chan, K.S.; Wang, S.; Stenseth, N.C.; Zhang, Z. Nonlinear effect of climate on plague during the third pandemic in China. Proc. Natl. Acad. Sci. USA 2011, 108, 10214–10219. [CrossRef]

5. Xu, L.; Stige, L.C.; Kausrud, K.L.; Ben Ari, T.; Wang, S.; Fang, X.; Schmid, B.V.; Liu, Q.; Stenseth, N.C.; Zhang, Z. Wet climate and transportation routes accelerate spread of human plague. Proc. R. Soc. B Biol. Sci. 2014, 281, 20133159. [CrossRef]
6. Stapp, P.; Antolin, M.F.; Ball, M. Patterns of extinction in prairie dog metapopulations: Plague outbreaks follow El Ninò events. *Front. Ecol. Environ.* 2004, 2, 235–240.

7. Kreppel, K.S.; Caminade, C.; Telfer, S.; Rajerison, M.; Rahalison, L.; Morse, A.; Baylis, M. A non-stationary relationship between global climate phenomena and human plague incidence in Madagascar. *PLoS Negl. Trop. Dis.* 2014, 8, e3155. [CrossRef]

8. Ben Ari, T.; Gershunov, A.; Gage, K.L.; Snäll, T.; Ettestad, P.; Kausrud, K.L.; Stenseth, N.C. Human plague in the USA: The importance of regional and local climate. *Biol. Lett.* 2008, 4, 737–740. [CrossRef]

9. Zhang, Z.; Li, Z.; Tao, Y.; Chen, M.; Wen, X.; Xu, L.; Tian, H.; Stenseth, N.C. Relationship between increase rate of human plague in China and global climate index as revealed by cross-spectral and cross-wavelet analyses. *Integr. Zool.* 2007, 2, 144–153. [CrossRef]

10. Zhang, D.D.; Brecke, P.; Lee, H.F.; He, Y.Q.; Zhang, J. Global climate change, war, and population decline in recent human history. *Proc. Natl. Acad. Sci. USA* 2007, 104, 19214–19219. [CrossRef]

11. Zhang, D.D.; Lee, H.F.; Wang, C.; Li, B.; Zhang, J.; Pei, Q.; Chen, J. Climate change and large-scale human population collapses in the pre-industrial era. *Glob. Ecol. Biogeogr.* 2011, 20, 520–531. [CrossRef]

12. Zhang, D.D.; Lee, H.F.; Wang, C.; Li, B.; Pei, Q.; Zhang, J.; An, Y. The causality analysis of climate change and large-scale human crisis. *Proc. Natl. Acad. Sci. USA* 2011, 108, 17296–17301. [CrossRef] [PubMed]

13. Lee, H.F.; Zhang, D.D. A tale of two population crises in recent Chinese history. *Clim. Chang.* 2013, 116, 285–308. [CrossRef]

14. Tian, H.; Yan, C.; Xu, L.; Büntgen, U.; Stenseth, N.C.; Zhang, Z. Scale-dependent climatic drivers of human epidemics in ancient China. *Proc. Natl. Acad. Sci. USA* 2017, 114, 12970–12975. [CrossRef] [PubMed]

15. Duncan, C.; Scott, S. The key role of nutrition in controlling human population dynamics. *Nutr. Res. Rev.* 2004, 17, 163–175. [CrossRef]

16. Pei, Q.; Zhang, D.D.; Li, G.; Lee, H.F. Climate change and the macroeconomic structure in pre-industrial Europe: New evidence from wavelet analysis. *PLoS ONE* 2015, 10, e0126480. [CrossRef]

17. Büntgen, U.; Ginzler, C.; Esper, J.; Tegel, W.; McMichael, A.J. Digitizing historical plague. *Clin. Infect. Dis.* 2012, 55, 1586–1588. [CrossRef]

18. Lee, H.F.; Zhang, D.D.; Pei, Q.; Jia, X.; Yue, R.P.H. Demographic impact of climate change on northwestern China in the late imperial era. *Quat. Int.* 2016, 425, 237–247. [CrossRef]

19. Lee, H.F. Internal wars in history: Triggered by natural disasters or socio-ecological catastrophes? *Holocene* 2018, 28, 1071–1081. [CrossRef]

20. Büntgen, U.; Tegel, W.; Nicolussi, K.; McCormick, M.; Frank, D.; Trouet, V.; Kaplan, J.O.; Herzig, F.; Heussner, K.-U.; Wanner, H. 2500 years of European climate variability and human susceptibility. *Science* 2011, 331, 578–582. [CrossRef]

21. Yue, R.P.H.; Lee, H.F. Climate change and plague in European history. *Sci. China Earth Sci.* 2018, 61, 163–177. [CrossRef]

22. Cook, E.R.; Seager, R.; Kushnir, Y.; Briolla, K.R.; Büntgen, U.; Frank, D.; Krusic, P.J.; Tegel, W.; van der Schrier, G.; Andreu-Hayles, L. Old World megadroughts and pluvials during the Common Era. *Sci. Adv.* 2015, 1, e1500561. [CrossRef] [PubMed]

23. Allen, R. Allen-Unger Database: European Commodity Prices 1260–1914. 2007. Available online: http://www2.history.ubc.ca/unger/htmlfiles/newgrain.htm (accessed on 20 February 2020).

24. Shipley, B. *Cause and Correlation in Biology: A User’s Guide to Path Analysis, Structural Equations and Causal Inference with R*; Cambridge University Press: Cambridge, UK, 2016.

25. Grace, J.B.; Schoolmaster, D.R., Jr.; Guntenspergen, G.R.; Little, A.M.; Mitchell, B.R.; Miller, K.M.; Schweiger, E.W. Guidelines for a graph-theoretic implementation of structural equation modeling. *Ecosphere* 2012, 3, 1–44. [CrossRef]

26. Jansson, R. Global patterns in endemism explained by past climatic change. *Proc. R. Soc. Lond. Ser. B Biol. Sci.* 2003, 270, 583–590. [CrossRef]

27. Rohlf, F.J.; Sokal, R.R. *Biometry: The Principles and Practice of Statistics in Biological Research*; Freeman: New York, NY, USA, 1981.

28. Stenseth, N.C.; Atshabar, B.B.; Begon, M.; Belmain, S.R.; Bertherat, E.; Carniel, E.; Gage, K.L.; Leirs, H.; Rahalison, L. Plague: Past, present, and future. *PLoS Med.* 2008, 5, e3. [CrossRef]
29. Colwell, R.R.; Patz, J.A. Climate, Infectious Disease, and Health. In *An Interdisciplinary Perspective*; American Academy of Microbiology: Washington, DC, USA, 1998.

30. Gubler, D.J.; Reiter, P.; Ebi, K.L.; Yap, W.; Nasci, R.; Patz, J.A. Climate variability and change in the United States: Potential impacts on vector-and rodent-borne diseases. *Environ. Health Perspect.* 2001, 109, 223–233.

31. WHO. *Using Climate to Predict Infectious Disease Epidemics*; World Health Organization: Geneva, Switzerland, 2005.

32. Enscore, R.E.; Biggerstaff, B.J.; Brown, T.L.; Fulgham, R.E.; Reynolds, P.J.; Engelthaler, D.M.; Levy, C.E.; Parmenter, R.R.; Montenieri, J.A.; Cheek, J.E. Modeling relationships between climate and the frequency of human plague cases in the southwestern United States, 1960–1997. *Am. J. Trop. Med. Hyg.* 2002, 66, 186–196. [CrossRef]

33. Ari, T.B.; Gershunov, A.; Tristan, R.; Cazelles, B.; Gage, K.; Stenseth, N.C. Interannual variability of human plague occurrence in the Western United States explained by tropical and North Pacific Ocean climate variability. *Am. J. Trop. Med. Hyg.* 2010, 83, 624–632. [CrossRef]

34. Cavanaugh, D.C. Specific effect of temperature upon transmission of the plague bacillus by the oriental rat flea, *Xenopsylla cheopis*. *Am. J. Trop. Med. Hyg.* 1971, 20, 264–273. [CrossRef]

35. Krasnov, B.; Khokhlova, I.; Fielden, L.; Burdelova, N. Development rates of two *Xenopsylla* flea species in relation to air temperature and humidity. *Med. Vet. Entomol.* 2001, 15, 249–258. [CrossRef]

36. Parmenter, R.R.; Yadav, E.P.; Parmenter, C.A.; Ettestad, P.; Gage, K.L. Incidence of plague associated with increased winter-spring precipitation in New Mexico. *Am. J. Trop. Med. Hyg.* 1999, 61, 814–821. [CrossRef] [PubMed]

37. Moore, S.M.; Monaghan, A.; Griffith, K.S.; Apangu, T.; Mead, P.S.; Eisen, R.J. Improvement of disease prediction and modeling through the use of meteorological ensembles: Human plague in Uganda. *PLoS ONE* 2012, 7, e44431. [CrossRef] [PubMed]

38. Pham, H.V.; Dang, D.T.; Tran Minh, N.N.; Nguyen, N.D.; Nguyen, T.V. Correlates of environmental factors and human plague: An ecological study in Vietnam. *Int. J. Epidemiol.* 2009, 38, 1634–1641. [CrossRef] [PubMed]

39. Pei, Q.; Zhang, D.D.; Lee, H.F.; Li, G. Climate change and macro-economic cycles in pre-industrial Europe. *PLoS ONE* 2014, 9, e88155. [CrossRef]

40. Pei, Q.; Zhang, D.D.; Li, G.; Winterhalder, B.; Lee, H.F. Epidemics in Ming and Qing China: Impacts of changes of climate and economic well-being. *Soc. Sci. Med.* 2015, 136, 73–80. [CrossRef]

41. Pei, Q.; Zhang, D.D.; Forêt, P.; Lee, H.F. Temperature and precipitation effects on agrarian economy in late imperial China. *Environ. Res. Lett.* 2016, 11, 064008. [CrossRef]

42. Keusch, G.T. The history of nutrition: Malnutrition, infection and immunity. *J. Nutr.* 2003, 133, 336S–340S. [CrossRef]

43. Yue, R.P.; Lee, H.F.; Wu, C.Y. Trade routes and plague transmission in pre-industrial Europe. *Sci. Rep.* 2017, 7, 1–10. [CrossRef]

44. Yue, R.P.; Lee, H.F. Drought-induced spatio-temporal synchrony of plague outbreak in Europe. *Sci. Total Environ.* 2020, 698, 134138. [CrossRef]

45. Ben-Ari, T.; Neerinckx, S.; Gage, K.L.; Kreppel, K.; Laudisoit, A.; Leins, H.; Stenseth, N.C. Plague and climate: Scales matter. *PLoS Pathog.* 2011, 7, e1002160. [CrossRef]

46. Roosen, J.; Curtis, D.R. Dangers of noncritical use of historical plague data. *Emerg. Infect. Dis.* 2018, 24, 103. [CrossRef] [PubMed]

47. Roosen, J.; Curtis, D.R. The ‘light touch’ of the Black Death in the Southern Netherlands: An urban trick? *Econ. Hist. Rev.* 2019, 72, 32–56. [CrossRef] [PubMed]

48. Van Bavel, B.J.; Curtis, D.R.; Hannaford, M.J.; Moatsos, M.; Roosen, J.; Soens, T. Climate and society in long-term perspective: Opportunities and pitfalls in the use of historical datasets. *Wiley Interdiscip. Rev. Clim. Chang.* 2019, 10, e611.

49. Curtis, D.R. *Coping with Crisis: The Resilience and Vulnerability of Pre-Industrial Settlements*; Ashgate Publishing, Ltd.: Farnham, UK, 2014.

50. Van Bavel, B.; Curtis, D. Better Understanding Disasters by Better Using History: Systematically Using the Historical Record as One Way to Advance Research into Disasters. *Int. J. Mass Emergencies Disasters* 2016, 34, 143–169.
51. Lee, H.F.; Fei, J.; Chan, C.Y.; Pei, Q.; Jia, X.; Yue, R.P. Climate change and epidemics in Chinese history: A multi-scalar analysis. *Soc. Sci. Med.* **2017**, *174*, 53–63. [CrossRef] [PubMed]

52. Voigtländer, N.; Voth, H.J. The three horsemen of riches: Plague, war, and urbanization in early modern Europe. *Rev. Econ. Stud.* **2013**, *80*, 774–811. [CrossRef]