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Climatic factors and long-term trends of influenza-like illness rates in The Netherlands, 1970-2016.

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ABBREVIATIONS

CI	confidence intervals
GP	general practitioner
ILI	influenza-like illness
IRR	incidence rate ratio

ABSTRACT

Background: Climatic factors affect the survival and transmissibility of respiratory viruses causing influenza-like illness (ILI), and we hypothesized that changes in absolute humidity and temperature may affect long-term trends of ILI incidence rate in temperate countries. We tested this hypothesis using ILI and meteorological time series in the Netherlands for the period 1970-2016. **Methods**: We described the long-term trends of ILI incidence, absolute humidity and temperature; modelled the association between climatic factors and ILI activity using negative binomial regression models; and assessed the strength of the association between the seasonal average absolute humidity (or temperature) and ILI incidence rate using the Spearman's rank correlation coefficient. **Results**: The ILI incidence rate declined from 1970 and reached a minimum in the season 2002-03, but started to increase again from the season 2003-04 onwards. In the negative binominal regression models, the weekly ILI count was inversely associated ($p<0.001$) with 0- and 1-week lagged absolute humidity and temperature. After three decades of rising absolute humidity and temperature (1970-2000), the early 2000s represented a trend-reversal point for the climatic time series. The seasonal average ILI incidence rate and absolute humidity (or temperature) were strongly (inversely) correlated. **Conclusions**: Our findings suggest that climate change may have played a role in the long-term trends of ILI incidence rates in the Netherlands, as we were able to show that lower humidity and temperature in a given week were associated with higher ILI incidence in the next week, there was a clear time point reversal in climatic parameters and ILI rates in the 2000s, and the average annual ILI incidence was inversely related to average annual temperatures and humidity.

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1. INTRODUCTION

Influenza-like illness (ILI) is an acute respiratory syndrome characterized by fever and other non-specific signs and symptoms including cough, sore throat, and malaise. In addition to influenza, common causes of ILI include rhinoviruses, respiratory syncytial virus, adenovirus, parainfluenza viruses, and some bacterial infections [1-2]. In temperate countries of the Northern hemisphere, seasonal ILI epidemics typically occur in the winter months, but ILI activity is documented year-round.

In the United Kingdom and the Netherlands, where influenza surveillance was started in 1968 and 1970, respectively, ILI incidence rate have declined markedly over time but the causes of these downward trends remain unclear [3-4]. One hypothesis is that rising influenza vaccination coverage rates have driven the decline but a recent ecological study linking ILI incidence rate and influenza vaccine coverage in fourteen European countries found a negative correlation in some countries and a positive correlations in others [5]. Considering there are many viral causes of ILI and only influenza can be prevented by vaccination, and influenza vaccine uptake is usually low in the younger age groups who usually experience the highest ILI incidence rate, it is likely that influenza vaccination programmes will only partially affect the ILI trends in the United Kingdom and the Netherlands. In addition, influenza vaccine uptake of around 70% or more is only achieved among the elderly in the general population [6-7], so protection is solely provided to a fraction of the whole population. Overall, the contribution of influenza vaccination to the declining trend in ILI incidence rate in the UK and the Netherlands still needs to be demonstrated and other factors should be considered.

Climatic parameters have been shown to be a major determinant of respiratory virus infections including influenza [8-9], respiratory syncytial virus [10] and rhinoviruses [11]. In temperate countries, ILI activity is inversely associated with humidity and temperature, which affect both the onset and size of ILI epidemics [12-15]. Although it remains unclear why transmission of respiratory viruses is most efficient under cold-dry conditions, increased host susceptibility and virus survival are among the most probable underlying mechanisms [14,16-17]. Given the epidemiological and biological evidence supporting the link between humidity/temperature and ILI activity, we hypothesized that changes in the average values of these climatic parameters (which have occurred in Europe in recent decades [18]) may help explain the declining trends in ILI incidence rate observed during the same period. In this paper, we tested this hypothesis by analyzing ILI and climatic time series data in the Netherlands for the period 1970-2016.

2. Materials and Methods

2.1 Influenza-like illness surveillance data

Weekly ILI surveillance data for the period 1970-2016 (week 20th) (referred to as "study period" henceforth) were obtained through the Sentinel Surveillance of the Netherlands Institute for Health Services Research (NIVEL) Primary Care Database. The sentinel surveillance system relies on a network of 60 sentinel general practitioners (GPs) in 40 practices which are distributed throughout the Netherlands (including urban and rural areas) and cover approximately 0.8% of the Dutch population [4,19-20]. The network of sentinel GPs was established in 1970 and has been active continuously (i.e. year-round) since this date. However, some of the weekly data were lost during the 1970s, and there are three data gaps between 1975 and 1978 (see Results). The number of GPs participating in the surveillance network has remained substantially stable over the years.

The case definition of ILI used since 1970 in the sentinel network is the following: an illness with acute onset, fever (≥38°C), and at least one of cough, rhinitis, sore throat, headache, retrosternal pain or myalgia. The GPs participating in the sentinel network report to NIVEL the weekly number of patients consulting with ILI, and take throat and nasal swabs from two ILI patients each week for the purpose of virological surveillance. The swabs are tested for the presence of respiratory viruses by the National Institute of Public Health and the Environment (RIVM).

2.2 Meteorological data

The Netherlands is located in North-Western Europe and has a temperate oceanic climate according to the Köpper classification. Average temperature ranges between 2°C-6°C in winter and 17°C-20°C in summer, and average absolute humidity between 5-7 gr/m^3 in winter and 11-13 gr/m^3 in summer, with limited precipitation difference between seasons. Daily data from 50 weather stations in the Netherlands are freely accessible from the Royal Netherlands Meteorological Institute webpage [21]. In the present analysis, we used data from the weather station of De Bilt, which is located in the middle of the country (so that all sentinel GPs' practices are located within a radius of ≈200 km around it [22]) and for which data completeness is above 99.9%. We retrieved data on daily average temperature and relative humidity for the period 1970-2016; the daily average absolute humidity (i.e. the water content of air, expressed in gr/m^3) was calculated from relative humidity and temperature. Previous research has shown that absolute humidity and temperature are the most important weather-related drivers of influenza activity in temperate climate countries such as the Netherlands [8-9]; therefore, we did not focus on other climatic parameters (like rainfall or wind velocity) in the present study.

2.3 Statistical methods

We defined a season as the period between week 27th of a year and week 26th of the following year. We calculated the average ILI incidence rate in each season by averaging the weekly incidence rate over all weeks in the season, and defined the height of the epidemic peak as the maximum value of weekly ILI incidence rate during the seasonal epidemic. We then used linear regression models to assess whether the season average ILI incidence rate and the height of the epidemic peak changed over time.

The relationship between climatic parameters and ILI activity in the Netherlands during 1970-2016 was modelled using negative binomial regression models with the weekly ILI count as dependent variable. The weekly ILI count was calculated by multiplying the weekly ILI rate by the Dutch population on January 1st (this information was retrieved from the Dutch Central Bureau of Statistics [23]). Negative binomial regression was chosen over Poisson regression in order to account for the overdispersion in the data [24]; the Dutch population was added to the model as an offset. Negative binomial regression yields incidence rate ratio (IRR), which should be interpreted as the change in incidence rate associated with a unit increase in the predictor. Absolute humidity and temperature could not be entered simultaneously in the models as they were very highly correlated in our time series (Pearson's r was 0.958); therefore, we fitted two separate regression models, using the weekly average of either absolute humidity or temperature as independent variable. Absolute humidity (or temperature) in the same week of the ILI count and up to 3 lagged weeks were entered together in the model; longer lags were considered biologically implausible as the incubation period of most infectious agents causing ILI is shorter than seven days [25]. Following the methodological recommendations made by Imai et al. for the study of short-term associations between weather and the morbidity of infectious diseases [24], all models were further adjusted by the logarithm of the 1-week lagged ILI count ("autocorrelation term") and by the cumulative sum of influenza-like illness cases occurred in the season ("immune term"). School holidays at the Christmas period were previously found not to affect influenza transmission in the Netherlands [22] and were not adjusted for in the present analysis. The season 2009-10 was not included in the regression model due to the AH1N1 influenza pandemic.
The results of the above investigations showed a statistically significant association between climatic variables (absolute humidity and temperature) and the weekly ILI count (see Results section), and we hypothesized that climatic changes could be a possible explanation of long-term trends in ILI incidence in the Netherlands over the study period. To test this hypothesis, we fitted linear regression models to explore whether the trend in daily average absolute humidity and temperature resembled that of ILI incidence rate, and used the Spearman rank correlation coefficient to assess the strength of the association between the seasonal average absolute humidity (or temperature) and ILI incidence rate.
Statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, TX). All statistical tests were two sided and considered as statistically significant when the p-value was lower than 0.05.

3. Results

3.1 Influenza-like illness surveillance data

ILI surveillance data were available for all weeks in the study period, except from week 21/1975 to week 53/1976; weeks 27 to 52 in 1977; and weeks 25-26 and 50-52 in 1978. The height of the epidemic peak decreased gradually over time, although it stabilized in the last 15 years (Figure 1). The season average weekly ILI incidence rate decreased (p-value <0.001) each season from 1970-71 until 2002-03 (when it reached its lowest value: 17.3 cases per 100,000 populations). Subsequently, the trend reversed and the average ILI incidence rate increased (p-value <0.001) from the season 2003-04 onwards (Figure 2).

3.2 Climatic determinants of influenza-like illness activity

In univariate analyses, current (week 0) and 1- to 3-week lagged values of absolute humidity were all inversely associated with ILI count, with the IRR gradually approaching the null value while moving from week 0 to increasingly lagged weeks (Table 1). Namely, the incidence rate ratio was 0.881 (95%CI 0.857-0.905, p-value <0.001) for a change in absolute humidity of 1 gr/m^3 on week 0, and 0.965 (95%CI 0.939-0.991, p-value 0.009) for a similar change in the 3-week lagged value of absolute humidity. In multivariate analysis, statistical significance was maintained for absolute humidity on current and 1-week lagged absolute humidity: the IRR for a change by 1gr/m^3 were 0.965 (95%CI 0.951-0.979, p-value <0.001) and, respectively, 0.960 (95%CI 0.944-0.976, p-value <0.001). Instead, there was no association between 2- and 3-week lagged values of absolute humidity and ILI count in multivariate analysis (Table 1).
The ILI count was also inversely associated with temperature (Table 1). In univariate analysis, the IRR was 0.953 (95%CI 0.941-0.966, p-value <0.001) for a change in temperature by 1°C on the same week of the ILI count; and it was 0.964, 0.975 and 0.973 for temperature on 1, 2 and 3 weeks prior to the ILI count (p was ≤0.001 in all cases). Similar to absolute humidity, statistical significance was only maintained for current (week 0) and 1-week lagged temperature in multivariate analysis. Namely, the IRR was 0.985 (95%CI 0.979-0.992, p-value <0.001) for a change by 1°C in temperature on the same week of the ILI count, and 0.979 (95%CI 0.971-0.987, p-value<0.001) for its 1-week lagged value (Table 1).

3.3 Meteorological data and correlation with ILI incidence rate

The annual average values of both absolute humidity rose in the first three decades of the study period, to later show a trend reversal (absolute humidity, Figure 3) or a plateauing (temperature, Supplementary Figure 1) in subsequent years, with the exception of the 2006-07 season. The annual change in the daily average absolute humidity and temperature in each month of the year is reported in Supplementary Table 1. Since the ILI incidence rate showed a trend-reversal point around the 2003-2004 season, the annual changes were calculated for the whole study period (1970-2016) and separately for the two periods 1970-2003 and 2004-2016.

Both annual average absolute humidity and temperature rose significantly (p-value <0.001) in each month between 1970 and 2016, although with some variability by month. In sub-period analyses, the annual increase of absolute humidity and temperature was statistically significant in all months during 1970-2003, except for temperature in October (+0.012 °C per year, p-value 0.181). In the following period (2004-2016), the picture was more complex and there was substantial variability between months: both absolute humidity and temperature declined in April, June and September, and increased in November and December.
Finally, the annual average ILI incidence rate was inversely correlated with both annual average absolute humidity (Spearman's rho -0.687, 95%CI -0.821 to -0.482) and temperature (Spearman's rho -0.554, 95%CI -0.735 to -0.297). In the corresponding plots (Figure 4 for absolute humidity and Supplementary Figure 2 for

temperature), the earliest seasons in the study period (from 1970-71 to 1974-75) stood out as possible outliers as they had much higher ILI incidence rate compared to seasons with similar values of climatic parameters, while the season 2006-07 was a potential leverage point due to particularly high annual values of absolute humidity and temperature. The exclusion of those seasons attenuated the magnitude of the correlation coefficients, which remained however statistically significant (Spearman's rho was -0.581, 95% CI -0.766 to -0.308 for absolute humidity; and -0.399, 95% CI -0.646 to -0.076 for temperature).

4. Discussion

We looked at long-term trends in the incidence rate of ILI in the Netherlands during 1970-2015, and found that the annual average ILI incidence rate decreased sharply after 1970 and reached a minimum in the season 2002-03, but started to increase from the season 2003-04 onwards. We then modelled the link between weekly absolute humidity and weekly temperature using negative binomial regression, and found that lower values of those climatic parameters in a given week were statistically associated with higher weekly ILI incidence rate in the same and the next week. Although these two variables are very strongly correlated in temperate-climate countries, so that their impact on ILI rate is difficult to examine separately, the hypothesis most corroborated by data is that the main driver of ILI epidemics in temperate countries is absolute humidity [12], while the association with temperature is observed mainly because of its strong correlation with absolute humidity. In fact, temperature may have a mediating effect on the relationship between absolute humidity and ILI rate, but this is unlikely to be substantial when temperature is below 20°C, i.e. when ILI epidemics take place in The Netherlands [9]. We chose not to focus on meteorological parameters other that absolute humidity and temperature (e.g. precipitations) because their role in survival and transmission of most respiratory viruses appears to be negligible in temperate climate countries, unlike tropical-climate countries [8-9].

We then examined the time-series of absolute humidity and temperature and verified that the early 2000s represented a trend-reversal point for these factors as well. Finally, we found that the annual average ILI incidence rate were inversely correlated with the annual average values of both absolute humidity and temperature, with influential points represented by the earliest seasons in the study period (1970-71 to 1974-75) and the season 2006-07 (of note, the two-year period 2006-2007 was the hottest ever measured in the Netherlands [26]).

Cold-dry weather conditions, which are typical of winter months in temperate climate countries, increase host susceptibility and enhance virus survival in the environment [14,16-17], which provides biological support to the epidemiological evidence linking weather conditions and ILI incidence. Other hypotheses have also been advanced to explain the declining trend observed in The Netherlands and the UK in recent decades (e.g. vaccination [5]). As already mentioned in the introduction, we find the influenza vaccine hypothesis implausible based on a number of *a priori* considerations. Influenza is only one of many causes of the ILI syndrome, and accounted for 15% to over 60% of all ILI cases in a season in the Netherlands in recent years (29% on average during 2003-14) [4,27]; vaccination protects only against the viruses contained in the vaccine and antigenically similar strains [28]; most ILI cases occur among younger age groups [29], but vaccine coverage was above 75% in the Netherlands only among the elderly [30], which is not sufficient to establish herd immunity [31].

Our findings suggest that changes in climatic parameters may have played a role in shaping the trends of ILI incidence rate in the Netherlands during 1970-2016; however, part of the results presented here are based on ecological analyses and cautious conclusions should be drawn. Moreover, the drivers behind the long-term shifting pattern of ILI rates are likely to be multiple and need to be examined in detail, particularly considering their importance can vary between countries and over time. For instance, while Spruijt et al. did not find convincing evidence of a negative correlation between influenza vaccination coverage and ILI incidence in Europe [5], the role of influenza vaccination in generating a moderate, yet important reduction in the total ILI incidence rate cannot be ruled out when the target population (e.g. elderly people and high-risk groups) account for a substantial proportion of the general population (as in the Netherlands [32]) and the uptake of the vaccine is high. Changes in the ILI sentinel system (which gradually switched from pen-and-paper to electronic data collection from 2005) or in the Dutch health system may also have affected the observed ILI incidence rate over the study period: for instance, Dutch Health Insurance companies decided to stop reimbursing patients for antitussants and analgesics in the late nineties of the 20th century, thus discouraging GP consultations for this reason. Changes in the healthcare seeking behaviour of patients with respiratory symptoms or in recording of symptoms and syndromes by general practitioners may also have contributed to the observed trends [33-34].

The ILI surveillance was established in 1970 in the Netherlands, shortly after the A(H3N2) virus subtype emerged in 1968 [35]. The introduction of a novel virus strain into an entirely susceptible population may explain why the ILI incidence rate in the earliest seasons in our time-series (from 1970-71 to 1974-75) were considerably higher than one would expect based on climatic characteristics. In accordance with Elliot et al. [3], it may indeed be speculated that the decreasing size of annual ILI epidemics during the 1970s and the 1980s may be caused (in addition to the effect of climate) by the increasing level of immunity in the host population, which is only partially balanced by the continuous immune escape via antigenic drift [36-40]. More research is needed in order to confirm this hypothesis or propose an alternate explanation.

The main strength of our paper is the availability of reliable epidemiological and meteorological time series that extend over a long period of time. With regard to the ILI time series, the case definition has been consistent throughout the years so that no major bias is expected to have occurred [4]. The analysis of the association between climatic parameters and ILI activity was conducted using statistical techniques developed specifically for this purpose [24]. Reassuringly, our findings are consistent with what is known about the incubation period of most ILI-causing infectious agents: since this is estimated to last between 1 and 5 days [25], it is biologically plausible to see an association with climatic parameters on both the same and the previous week of the ILI count, while longer lags (≥2 weeks) were not associated once shorter lags are adjusted for. Despite the meteorological parameters being correlated on consecutive weeks, collinearity did not appear to be an issue as shown by the rather stable risk estimates in multivariable analysis (possibly because of the very large study size). Our study also has some limitations, the most important of which is the ecological nature of the some of the analyses that were conducted: we therefore recommend caution in drawing conclusions from the results that were presented. We focused on climatic parameters in our attempt to explain the long-term trend in ILI incidence rate; however, other factors may have played a role by affecting virus transmission, like changes in household sizes [41-42], improvements in levels of hygiene [43-44], and demographic factors and social contact patterns [45]. However, it is unclear how these factors could account for the rise in ILI incidence rate observed over the last fifteen years in the Netherlands. The availability of respiratory virus-specific time-series would have made it possible to assess whether the long-term trends in ILI incidence and their link with climatic factors were common to all respiratory viruses or limited to only some of them. A further limitation is the lack of adjustment for air pollution. The concentration of several common pollutants in the air is linked to meteorological parameters, and air pollution could therefore be seen as a potential mediator in the relationship between climate and ILI incidence. Previous reports have shown that air pollution can affect both the risk and severity of respiratory infections [46-47]. Incorporating air pollution time series (where available) into studies similar to ours could help disentangle the role of climatic variables and air pollution in shaping long-term trends of ILI incidence.

4.1 Conclusions

Human populations live in ecosystems that are the result of multiple and complex interactions between ecological and social processes. Because of this, the consequences of climate change on human health are probably all-pervasive and, although very challenging to predict and quantify in detail, unlikely to be overestimated. Our findings add to the existing evidence suggesting that climate change may be affecting the interaction between infectious agents (in particular, respiratory viruses) and their human hosts in temperate countries, which may represent a serious threat for human health. Although global warming may cause an overall decline in the burden of disease of influenza and other respiratory viruses in temperate climate countries, our data show that this effect can be reversed (as in 2000-2016 compared to 1970-2000 in the Netherlands). It is also crucial to emphasize that these findings may be different at other latitudes and in different climates, where virus survival and transmission may be affected by other climatic parameters (e.g. rainfall) in addition to temperature and humidity [8]. Moreover, climate change may cause an increase in the overall incidence and geographical spread of infectious diseases with different modes of transmission, for instance vector-borne disease like malaria and dengue [48-49], or water-and food-borne diarrhoeal diseases like cholera [50]. In particular, strong evidence exists that less developed countries (especially those in the tropics) are and will be more affected by climate change than industrialized countries, thus expanding health inequalities globally [51]. Therefore, we support the recommendation that more resources should be allocated to expand existing knowledge on how climate change affects the interaction between infectious agents and human populations; to monitor climate-related changes in the epidemiology of infectious diseases at various levels; and to put in place effective, proactive measures aimed to mitigate the impact of climate change on human health [52-53].

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FIGURES AND TABLES.

Fig. 1. Incidence rate of influenza like-illness (cases per 100,000 population) in the Netherlands, from week 2/1970 to week 26/1993 (top panel), and from week 27/ 1993 to week 20/2016 (bottom panel). Data are missing from week 21/1975 to week 53/1976; on weeks 27–52 in 1977; and on weeks 25–26 and 50–52 in 1978.

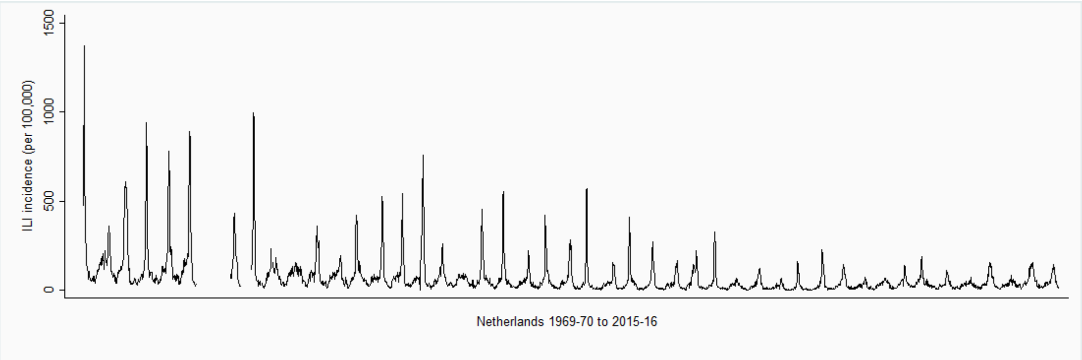

Fig. 2. Season average influenza-like illness incidence rate (cases per 100,000 population, connected line) and population (million, bars) in the Netherlands from 1970- 71 until 2015–16 (seasons from 1975-76 to 1978-79 and season 2015–16 were not included because of missing data in some or all weeks; season 2009–10 was not included because of the A(H1N1) influenza pandemic).

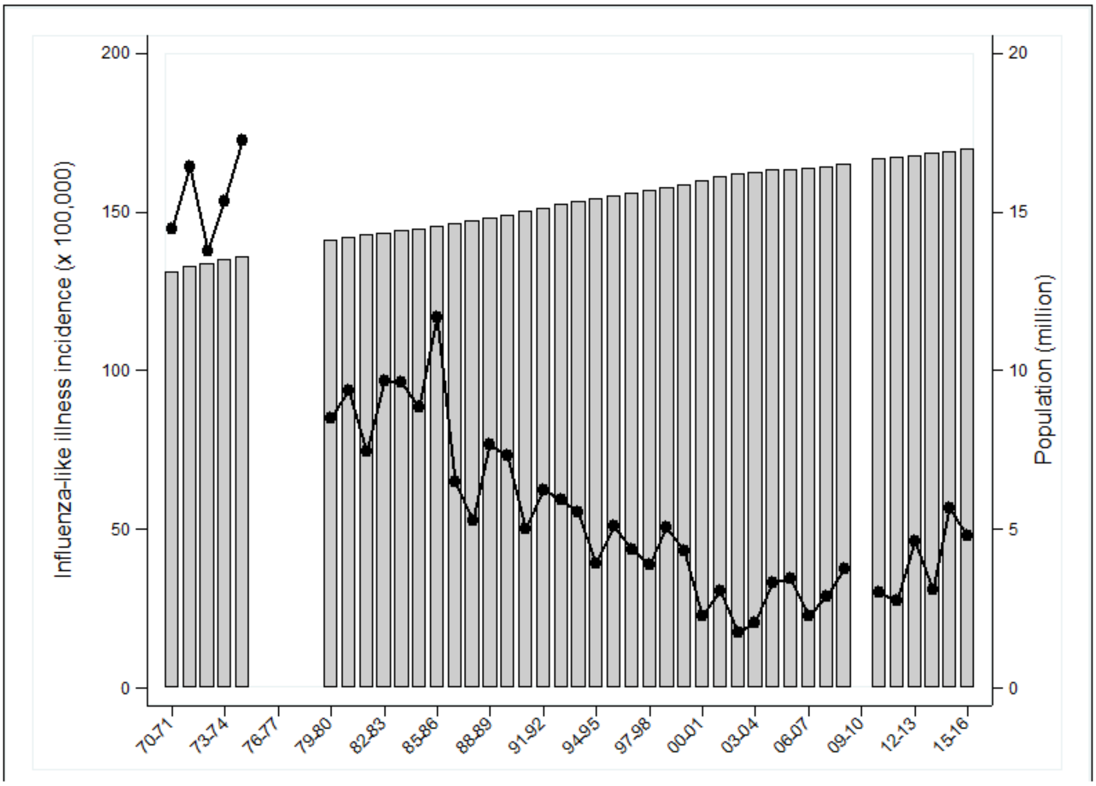

Fig. 3. Season average influenza-like illness incidence rate (cases per 100,000 population, black line) and seasonal average absolute humidity (gr/m3, red line) in the Netherlands from 1970 to 71 until 2015–16 (seasons from 1975-76 to 1978-79 were not included because of missing data in some or all weeks; season 2009–10 was not included because of the AH1N1 influenza pandemic).

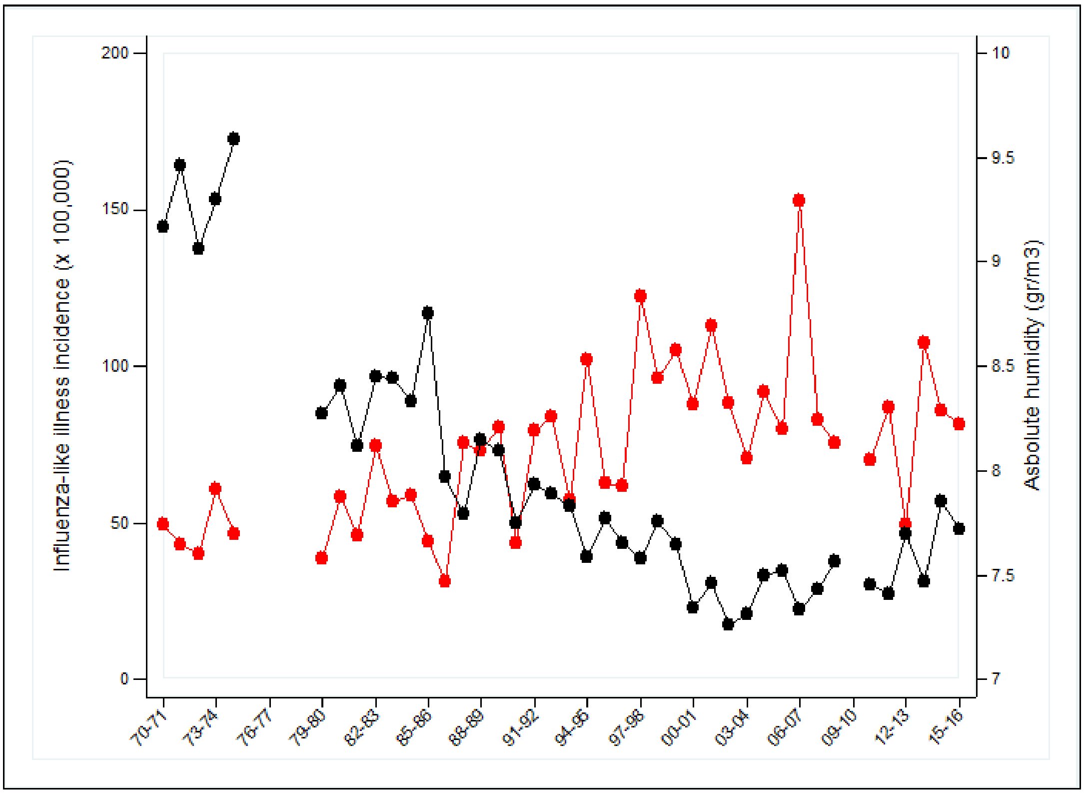

Fig. 4. Season average influenza-like illness incidence rate (cases per 100,000 population) and seasonal average absolute humidity (gr/m3) in the Netherlands from 1970- 71 until 2015-16 (seasons from 1975-76 to 1978-79 were not included because of missing data in some or all weeks; season 2009–10 was not included because of the AH1N1 influenza pandemic).