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Suicide risk in relation to air pollen counts: a study based on data from Danish registers

Ping Qin,[1,2] Berit L Waltoft,[1] Preben B Mortensen,[1] Teodor T Postolache[3]

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[1]National Centre for Register-based Research, Aarhus University, Denmark
[2]National Centre for Suicide Research and Prevention, University of Oslo, Institute of Clinical Medicine, Oslo, Norway
[3]Department of Psychiatry, University of Maryland School of Medicine, Mood and Anxiety Program, Baltimore, Maryland, USA

Correspondence to
Professor Ping Qin;
ping.qin@medisin.uio.no

ABSTRACT

Objectives: Since the well-observed spring peak of suicide incidents coincides with the peak of seasonal aeroallergens as tree-pollen, we want to document an association between suicide and pollen exposure with empirical data from Denmark.

Design: Ecological time series study.

Setting: Data on suicide incidents, air pollen counts and meteorological status were retrieved from Danish registries.

Participants: 13 700 suicide incidents over 1304 consecutive weeks were obtained from two large areas covering 2.86 million residents.

Primary and secondary outcome measures: Risk of suicide associated with pollen concentration was assessed using a time series Poisson-generalised additive model.

Results: We noted a significant association between suicide risk and air pollen counts. A change of pollen counts levels from 0 to '10–<30' grains/m^3 air was associated with a relative risk of 1.064, that is, a 6.4% increase in weekly number of suicides in the population, and from 0 to '30–100' grains, a relative risk of 1.132. The observed association remained significant after controlling for effects of region, calendar time, temperature, cloud cover and humidity. Meanwhile, we observed a significant sex difference that suicide risk in men started to rise when there was a small increase of air pollen, while the risk in women started to rise until pollen grains reached a certain level. High levels of pollen had slightly stronger effect on risk of suicide in individuals with mood disorder than those without the disorder.

Conclusions: The observed association between suicide risk and air pollen counts supports the hypothesis that aeroallergens, acting as immune triggers, may precipitate suicide.

ARTICLE SUMMARY

Research focus

- Since the well-observed peaks of suicide incidents overlap with seasonal peaks of atmospheric pollen, the study aims to document an association between suicide and pollen exposure with individual level data from Danish registers.

Key messages

- This study demonstrates a significant association between suicide risk and air pollen counts.
- The observed association remained after controlling for effects of region, calendar time, temperature, cloud cover and humidity, but varies significantly by sex and slightly by personal history of mood disorders.
- The results are consistent with the overriding hypothesis that aeroallergens may precipitate suicide via mediators of allergic inflammation.

Strengths and limitations of this study

- The data span over 25 consecutive years and cover 2.86 million residents; the results are adjusted for important confounding factors.
- Data on pollen of individual species are not considered due to the limited availability.
- It is unclear if the results can apply to countries or regions with different climate and plants.

INTRODUCTION

A Spring peak of suicide incidents has been observed globally,[1–5] but its explanation remains unclear. A few studies have suggested a possible connection between seasonality of suicide rates and aeroallergens, via mediators of allergic inflammation affecting individuals susceptible to allergy, depression and suicide. For instance, a Finnish study found a Spring peak of suicide rates in victims with a hospital-treated allergy, but no such peak in non-atopic victims.[6] A study from the USA over 4 years reported an increased rate of suicide during peaks in tree-pollen intervals compared with low tree-pollen intervals in young women,[7] but another later study was not able to replicate this finding in a subsequent interval of 4 years.[8]

Considering these contradictory results from ecological studies, we have now aimed to test the hypothesis that aeroallergen (ie, pollen) may be a significant trigger for suicidal behaviour with data from Danish registries. We studied the effect of air pollen counts on risk for suicide with data covering

a population of 2.86 million over 1304 consecutive weeks, and adjusted for possible confounding effects of location, calendar time and weather conditions as temperature, cloud cover and humidity—factors previously implicated as potential environmental correlates of pollen counts and suicide rates.[9–12] We also explored the effect differences by sex and age and according to people's history of mood disorders.

METHODS

Data on pollen counts and weather conditions

The Danish Meteorological Institute has systematically collected data on weather and pollen exposures at several stations over the country since 1980s.[13] Daily pollen amount is registered by a standard pollen trap which sucks in 10 litre of air/min—the amount approximately corresponds to the human breathing. The pollen is then captured on a sticky tape, and later identified and counted using a light microscope. The reported pollen count of a day refers to the average pollen grains per cubic metre air during the day.[13] In Denmark, the most prominent allergenic pollen source according to the time of the year is represented by alder, hazel, elm and birch (in spring), grass (in spring and summer) and ragweed (in late summer and early fall).[13] With small year-to-year variation, a period for monitoring air pollen normally starts in the middle of February and ends at the beginning of October.

For this study, we obtained data from two stations which had recorded pollen data over a long period, ranging back to the year 1982. One station is located in the city of Viborg—the headquarter of the Middle Jutland Region with 1.227 million residents, while another is located in Copenhagen—the headquarter of the Capital Region with 1.636 million residents. The 2.863 million residents in these two regions account for 52.56% of the national population of Denmark.

Daily data on meteorological conditions were also gathered from these two locations, including average temperature (°C), cloud cover (%, defined as percentage of the sky covered by cloud at a given point of the day) and humidity (%). We considered data of grand pollen counts and meteorological conditions collected at these two stations from 1982 through 2006 in the analyses.

Data on suicide deaths and psychiatric history

Denmark has a well-functioning health registration system that records medical contacts and vital status for all residents and comprises a number of subregistries including the Cause-of-Death register and the Psychiatric Central Register. The Cause-of-Death register records the cause and date of each death in Denmark with computerised data since 1970.[14] The Psychiatric Central Register contains individual information on contacts to psychiatric hospitals or wards with computerised data for inpatient contacts since 1969 and outpatient contacts since 1995.[15] Diagnosis of an illness or cause of a death in the Danish health registration system was coded according to the International Classification of Diseases, the 8th revision (ICD-8) until the year 1993, and thereafter according to the 10th revision (ICD-10). ICD-9 was never used in Denmark.

The Civil Registration System,[16] established in the year 1968, is the most important and fundamental registration in Denmark. It contains a personal identifier of all residents in Denmark, their demographic information as well as historical addresses of residences among other information.[16] The unique personal identifier, assigned to each new-born or new resident of Denmark, is used in all public registries, allowing for the accurate linkage of an individual's data across registries.

We obtained data on all suicide deaths in Denmark during the year 1982 through 2006 from the Cause-of-Death Register (E950–959 in ICD-8 and X60-84 in ICD-10),[14] and restricted study cases to victims who were, at the time of suicide, residents in either the Middle Jutland Region or the Capital Region. In Denmark, all citizens are obliged to inform the authorities about the changes of permanent living address within 5 days, and failure to report this information will result in the inability to receive supplementary benefits. This ensures prompt updating of personal place of residence with rare exceptions of delay, and also means that people generally die at the same places where they are registered as residents.

For each suicide case in the study, we also retrieved personal information from the Danish Psychiatric Central Register[15] on whether or not the person had ever visited a psychiatric hospital or ward, as either an inpatient or an outpatient, with a diagnosis of mood disorders (codes: 296, 298.09, 298.19, 300.49, 301.19 in ICD-8, or F30-F34, F38, F39 in ICD-10). The presence of such a diagnosis, either as the primary or secondary diagnosis during an inpatient or outpatient contact, was regarded as a positive history.

Statistical methods

We applied a generalised-additive Poisson model (GAM)[17] to fit the effect of average pollen counts per week on relative risk of suicide (changes on the weekly number of suicide deaths) in the population. The GAM model estimates the rate of a Poisson model by an additive function. The function consists not only of parametric confounders as in a multiplicative Poisson model but also of non-parametric (time series) confounders estimated by the local regression method (LOESS).[18] We estimated both the non-parametric effect of the average pollen counts (in pollen grains per cubic metre air) per week and the parametric effect of the average pollen counts per week, categorised according to internationally wide-accepted cut-points[13] into five levels: no pollen (0), very low level (<10), low level (10 to <30), middle level (30–100) and high level (>100). A week was defined as the interval from Monday to Sunday, and we

considered only full weeks into the analysis by including the data from 4 January 1982 (which was a Monday) to 31 December 2006 (which was a Sunday). This resulted in 1304 consecutive full weeks included in the study. The average pollen counts of a week were calculated upon the available data of the week days, meaning that if a week only held data on pollen count for 5 days, then the average pollen count of this week would be the average pollen of these 5 days. If there were no information on pollen counts for all 7 weekdays of a week, then the pollen count of that week was set at 0. In our data, days with missing value on pollen counts are about 4.8% in April, 3.4% in May, 2.7% in June, 5.9% in August, 83.7% in October and almost 100% in November, December and January. Instances of having missing data on pollen counts on all 7 days of a week only occurred in the off season for pollen collection, usually from the middle of October to the middle of February.

To assess the effect of change on pollen level on suicide, we first estimated the relative risk of suicide associated with level of pollen concentration by the LOESS method on the continuous average pollen counts per week, and then estimated the effect of pollen level with the categorised data using the weeks with 0 pollen count as the reference group. We should note that, our term of 'an increase of air pollen counts' means a change of pollen counts from the reference level (0 pollen) to a higher level (eg, 1–10 pollen grains), which does not indicate any temporal change as which pollen level comes first. We obtained the estimates from both crude and adjusted analyses. In the adjusted model, we controlled for region (ie, location) as a parametric effect and used the local regression smoother to fit non-parametric effect of adjustments for calendar weeks (defined as the date of the Monday of the week) and weekly average of temperature, cloud cover and humidity. More details about the model can be found in the appendix. We also performed the stratified analyses by sex, age group and history of mood disorder of the participants. The results of all analyses were produced by the GAM procedure in SAS V.9.1.[19] p Values were two sided.

RESULTS

General description

The study period was from 4 January 1982 to 31 December 2006, covering 1304 consecutive weeks for each region and 2608 weeks in total. During this period, we observed 13 700 suicides from the study population, accounting for 53.5% of the total suicides during the period in Denmark. In total, 8544 of these victims were residents of the Capital Region, while 5156 residents of the Middle Jutland Region. The number of weekly suicides varied from 0 to 20 in the Capital Region and 0 to 13 in the Middle Jutland Region. Detailed distributions, by sex, age group, history of mood disorder and level of air pollen at the time of suicide, are shown in table 1.

Table 1 Distribution of suicide deaths and air pollen counts

	Region of the capital	Region of middle Jutland	Total
Number of suicide deaths	8544	5156	13700
By sex			
Females	3289	1658	4947
Males	5255	3498	8753
By age group (years)			
≤35	1616	1141	2757
36–60	4005	2460	6465
>60	2923	1555	4478
By history of mood disorder			
With such a history	1260	867	2127
Without such a history	7284	4289	11573
By level of pollen counts* at the time of suicide			
0	2690	2326	5016
<10	1424	698	2122
10–<30	799	789	1588
30–100	2277	959	3236
>100	1354	384	1738
Number of total weeks	1304	1304	2608
By level of pollen counts*			
0	397	605	1002
<10	247	165	412
10–<30	115	183	298
30–100	321	250	571
>100	224	101	325

*In average pollen grains per cubic metre air.

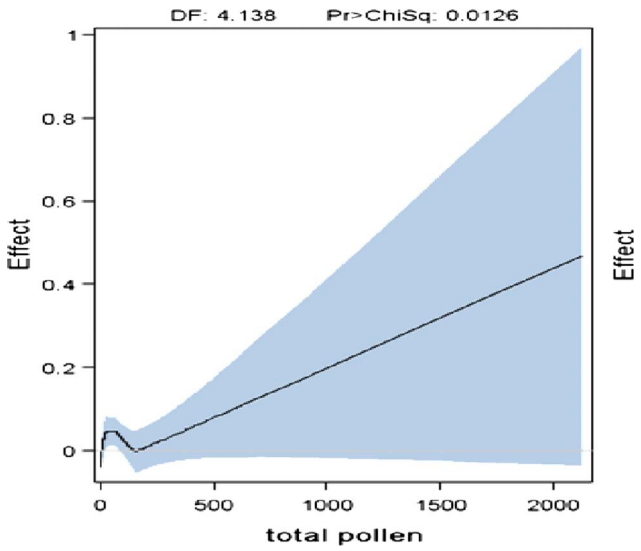

Figure 1 Non-parametric effect of air pollen counts on weekly number of suicides in the population, adjusted for region and seasonality. Effect is the untransformed effect of the smoothing function of study variables on the weekly number of suicide incidents. Total pollen refers to weekly average number of pollen grains per cubic metre air. The specific model used is $\log(\lambda)=\mu+\beta x+s_1(v_1,DF_1)+s_2(v_2,DF_2)$, where β is the untransformed parametric effect of region (Copenhagen or Viborg); and $s_i(v_i,DF_i)$ the untransformed non-linear non-parametric effect of pollen counts, adjusted for calendar weeks and estimated using the local regression method (LOESS).

During the study period, the weekly average counts of air pollen varied from 0 to 2126 pollen grains/m^3 air in Copenhagen and from 0 to 1590 in Viborg. There were 1002, 412, 298, 571 and 325 weeks, respectively, with pollen counts of '0', '<10', '10–<30', '30–100' and '>100' grains, respectively, in either Copenhagen or Viborg. Detailed distributions of pollen counts at the two regions are also shown in table 1.

Association between weekly number of suicides and air pollen counts

When modelling the data with the GAM procedure, we noted a significant increase of relative risk for suicide associated with increasing pollen counts in the air. In the first model using the LOESS method and adjusting for effects of region and calendar time, we noted a significant effect of pollen counts on the relative risk of suicide in the population (p=0.0126), meaning that the effect of weekly average pollen counts on the weekly number of suicides is not constantly at 0. The effect seems to have variations for smaller pollen counts and seems to increase linearly for a large number of pollen counts (figure 1). Such effect remained similar when further adjusting for weather conditions as cloud cover, temperature and humidity.

In order to precisely capture the effect variation, we conducted analyses using data on pollen counts as a categorised variable. Again, we detected an increase of the relative risk for suicide associated with the increased levels of pollen counts. For instance, a change of pollen counts level from 0 to '10 to <30' pollen grains/m^3 air was associated with a relative risk of 1.064—a 6.4% increase in weekly number of suicides in the population. A change of pollen counts from 0 to a middle level of '30–100 counts' was associated with a 13.2% increase of suicide incidents in the population. The observed association remained almost unchanged when we adjusted for the effects of region, calendar time and weather conditions (table 2). A sensitive analysis restricting the data to the period from March to June showed the same trend of the association, although the estimates did not reach statistical significance, probably due to insufficient statistical power (data not shown).

Moreover, we noted that the influence of pollen counts on suicide differed significantly by sex (p=0.0021; table 3). For women, the relative risk of suicide tended to increase gradually with the increase of air pollen counts until the concentration reached to a middle level of 30–100 counts (adjusted relative risk 1.195, 95%CI 1.111 to 1.285). For men, the relative risk of suicide increased significantly even when the pollen counts level changed from 0 to a very low level (adjusted relative risk 1.080, 95%CI 1.014 to 1.150). Further examination by age group supports these observations—that is, the relative risk of suicide in men, especially young men, started to rise when there was a small increase of air pollen count while the relative risk of suicide in women increased slowly with increasing level of pollen counts with the strongest effect of pollen at a middle level—

Table 2 Relative risk of suicide associated with the level of air pollen counts, total participants

	Crude model†		Adjusted model†	
Pollen counts	**RR**	**95% CI**	**RR**	**95% CI**
0	1		1	
<10	1.029	0.978 to 1.082	1.034	0.982 to 1.088
10–<30	1.064*	1.006 to 1.126	1.069*	1.010 to 1.131
30–100	1.132**	1.083 to 1.183	1.128**	1.079 to 1.180
>100	1.068**	1.012 to 1.128	1.066*	1.009 to 1.127

*p < 0.05; **p<0.01.
†Crude model was without any adjustment; adjusted model was adjusted for region, calendar time and weather conditions as temperature, cloud cover and humidity.
RR, relative risk.

Table 3 Relative risk of suicide associated with the level of air pollen counts, stratified by sex

	Males		Females	
Pollen counts	**RR†**	**95% CI**	**RR†**	**95% CI**
0	1		1	
<10	1.080*	1.014 to 1.150	0.953	0.873 to 1.040
10–<30	1.057	0.985 to 1.135	1.074	0.978 to1.180
30–100	1.086**	1.027 to 1.149	1.195**	1.111 to 1.285
>100	1.074*	1.003 to 1.151	1.047	0.955 to 1.148
Differences by sex‡	χ^2=14.9048, df=3.1089 p=0.0021			

*p<0.05; **p<0.01.
†Estimates were adjusted for region, calendar time, temperature, cloud cover and humidity.
‡The p value represents the reduction down to a model estimating the effect of levels of pollen counts adjusted for region, sex, seasonality, temperature, cloud cover and humidity.
RR, relative risk.

albeit the effect seems to vary marginally by age in the women (table 4).

At the same time, we observed a slightly stronger influence of air pollen on the relative risk of suicide in persons with, than those without, a history of mood disorder (p=0.1816; table 5). Such tendency was somewhat more dominant in male than female participants. The increased risk of suicide associated with high level of pollen concentration is most notable among men with mood disorders.

DISCUSSION

Findings and interpretations

This study, to our knowledge, is the first to quantify the association between air pollen counts and risk for suicide with empirical data that covered 13 700 suicide incidents in a population of 2.86 million over 1304 consecutive weeks. We observed a significant increase of suicide risk associated with increasing pollen counts in the air. The observed association remained almost unchanged after controlling for effects of region, calendar time and weather conditions such as temperature, cloud cover and humidity. At the same time, we detected a significant sex difference that suicide risk of men, especially young men, started to rise when there was a small increase of air pollen while the risk of women increased slowly with increasing pollen counts with the strongest effect of pollen at a middle level. We also noted a tendency, though not statistically significant, that increased level of air pollen counts had a slightly stronger effect on suicide risk in persons, especially men,

Table 4 Relative risk of suicide associated with the level of air pollen counts, stratified by age group

	≤35 years old		36–60 years old		>60 years old		
Pollen counts	**RR‡**	**95% CI**	**RR‡**	**95% CI**	**RR‡**	**95% CI**	**Difference by age†**
Total							
0	1		1		1		χ^2=6.6092
<10	1.028	0.917 to 1.152	1.037	0.963 to 1.117	1.039	0.949 to 1.136	df=8.0246
10–<30	1.143*	1.011 to 1.292	1.057	0.973 to 1.148	1.059	0.958 to 1.170	p=0.5819
30–100	1.106*	1.001 to 1.222	1.103**	1.033 to 1.177	1.200**	1.112 to 1.296	
>100	1.026	0.907 to 1.162	1.091*	1.007 to 1.181	1.082	0.983 to 1.192	
Males							
0	1		1		1		χ^2=7.3468
<10	1.133	0.996 to 1.288	1.068	0.974 to 1.171	1.076	0.958 to 1.208	df=8.0017
10–<30	1.168*	1.013 to 1.346	1.076	0.971 to 1.192	0.983	0.859 to 1.125	p=0.4999
30–100	1.057	0.940 to 1.189	1.105*	1.019 to 1.199	1.149**	1.037 to 1.273	
>100	1.099	0.953 to 1.267	1.142**	1.035 to 1.260	1.066	0.938 to 1.212	
Females							
0	1		1		1		χ^2=13.3307
<10	0.738	0.575 to 0.946	0.976	0.861 to 1.106	0.979	0.850 to 1.128	df=8.4450
10–<30	1.062	0.832 to 1.355	1.012	0.881 to 1.163	1.150	0.990 to 1.335	p=0.1207
30–100	1.239**	1.029 to 1.491	1.088	0.977 to 1.212	1.254**	1.116 to 1.409	
>100	0.860	0.667 to 1.109	1.005	0.879 to 1.150	1.094	0.945 to 1.267	

*p<0.05; **p<0.01.
†The p value represents the reduction down to a model estimating the effect of levels of pollen counts adjusted for region, age groups, calendar time, temperature, cloud cover and humidity in the total participants, the men and the women, respectively.
‡Estimates of relative risk were derived from the model adjusted for region, calendar time, temperature, cloud cover and humidity.
RR, relative risk.

Table 5 Relative risk of suicide associated with the level of air pollen counts, stratified by history of mood disorder

	Without mood disorder		With mood disorder		
Pollen counts	**RR‡**	**95% CI**	**RR‡**	**95% CI**	**Difference by mood disorder†**
Total					
0	1		1		χ^2=6.3897
<10	1.001	0.947 to 1.059	1.125	0.989 to 1.279	df=4.1074
10–<30	1.056	0.993 to 1.123	1.164*	1.009 to 1.343	p=0.1816
30–100	1.100**	1.048 to 1.155	1.186**	1.059 to 1.329	
>100	1.015	0.956 to 1.079	1.148*	1.001 to 1.318	
Males					
0	1		1		χ^2=9.6604
<10	1.042	0.974 to 1.115	1.248**	1.039 to 1.499	df=4.1001
10–<30	1.034	0.958 to 1.115	1.334**	1.092 to 1.631	p=0.0498
30–100	1.072*	1.009 to 1.138	1.169	0.988 to 1.384	
>100	1.043	0.969 to 1.122	1.229*	1.007 to 1.501	
Females					
0	1		1		χ^2=3.6531
<10	0.911	0.824 to 1.007	1.015	0.847 to 1.216	df=4.1342
10–<30	1.091	0.982 to 1.213	1.010	0.824 to 1.239	p=0.4754
30–100	1.146**	1.055 to 1.245	1.179*	1.011 to 1.374	
>100	0.966	0.869 to 1.074	1.065	0.880 to 1.288	

*p<0.05; **p<0.01.
†The p value represents the reduction down to a model estimating the effect of levels of pollen counts adjusted for region, history of mood disorder, calendar time, temperature, cloud cover and humidity in the total participants, the men and the women, respectively.
‡Estimates of relative risk were derived from the model adjusted for region, calendar time, temperature, cloud cover and humidity.
RR, relative risk.

with a history of mood disorder than those without such a history.

A massive release of tree-pollen in the spring, via mediators of inflammation, can result in a sharp increase in the production of certain cytokines[20] that have depressogenic and prosuicidal effects and thus affect individuals susceptible to allergy, depression and suicide. A recent Danish study demonstrated that the seasonality among suicides with psychiatric illness apparently existed, but its effect could vary across different periods of time and among genders.[21] Recently, we identified a more obvious spring peak of suicide in victims with, rather than those without, a history of mood disorders,[22] and also detected a significantly increased risk of suicide for people with allergic illnesses.[23] We are now reporting a significant relationship between air pollen, the most seasonal of aeroallergens, and suicide risk in the population.

This finding is consistent with early observations linking suicide seasonality with pollen exposure,[6 7] but different from a recent US ecological study reporting a non-significant relationship between pollen counts and suicide.[8] It is unclear to us to what extent the result discrepancy between the present Danish study and the US study[8] was induced by methodological differences adopted in the two studies, for example, analytic approach, precision of outcome measurement (changes of weekly suicide rate in the present study but of quarterly suicide rate in the US study) or some confounders included for adjustment (personal history of mood disorders and local weather conditions in the present study, but local median income and number of psychiatrists in the US study). It may also be possible that species producing allergenic pollen available at study areas in Denmark vary somewhat from those in the USA because of geographic location.[13 24] Nevertheless, this study indicates a modest, but significant, effect of pollen on suicide risk, which is supported by further analyses stratified by sex, age group and personal history of mood disorder.

There are several possible mechanisms underlying the link between pollen and suicide. One possibility is that air pollen triggers episodes of seasonal allergic rhinitis, a relatively common condition affecting more than 20% of adults[25] with deterioration in their quality of life.[26] In seasonal allergic rhinitis, pollen induces allergy-related cytokine (ie, Th2 cytokine) production in the nose of individuals who are sensitive to tree pollen.[20] The cytokines in nasal cavity may be transported via preferential pathways to the brain, where they may induce an amplified production of Th2 cytokine that can result in the impairment or inhibition of the limbic structures involved in impulsivity, aggression, anxiety and especially depression.[20 27] A recent study of suicide victims found an increased expression of Th2 cytokines[28] in a region of the prefrontal cortex previously implicated in suicide.[29] At the same time, pollen could also induce an increased expression of Th1 cytokines in the later phases of allergic inflammation,[20] which, according to an experiment study of rodents, could occur alongside expression of depressive-like behaviours.[30]

There is a congruent evidence supporting a relationship between allergy and depression,[31 32] the most

common psychiatric condition associated with suicide.[33] Clinical studies have shown that changes of depression scores is positively associated with changes of allergy scores when atopic individuals are exposed to different levels of airborne pollen, and that worsening in depression score is greater during exposure to high pollen counts in bipolar patients who are sensitised to pollen.[34] Thus, one may conclude that triggering of allergic rhinitis (such as by pollen) may be in fact associated with worsening of mood disorders. This is supported by our early reports of a greater spring peak of suicides with mood disorders,[22] and a significantly increased suicide risk associated with allergy[23] as well as a reduced suicide rate associated with the prescription of medication intranasal corticosteroids.[35] Although we observed only a slightly rather than significantly stronger effect of pollen on suicide in individuals with mood disorders, one should not dismiss the hypothesis that an exacerbation of mood disorders mediates the relationship between allergens and suicide. Meanwhile, the side effect of some antiallergic medications (systemic decongestants, antihistamines, leukotriene inhibitors and corticosteroids) may worsen prosuicidal factors such as night-insomnia, day-somnolence, agitation, anxiety, depression and cognitive disturbance.[36 37]

Certainly, a psychological rather than biological explanation is possible. Consistent evidence has shown that medical illness, and as such anything that could worsen the functioning or quality of life of patients, would increase the suicide risk of the patients.[38 39] Allergen-induced asthma, with its connotation of suffocation and marked restriction imposed on physical activity,[20] may also contribute to the observed connection.

This study indicates that men appear more sensitive to lower concentrations of pollen, while women tend to show a stronger effect, but only when the pollen counts reach to a certain level. This is consistent with earlier studies suggesting a stronger association between tree pollen peaks and suicide in women than in men,[7] and a stronger spring peak of suicide in women with atopic illness as compared with that in men with this illness.[6] Men could be more sensitive to small concentrations as they are more reactive in regard to the patency of the small airways, while for women, the effect might be stronger because of greater inflammation in the smaller airways.[40] Another explanation could be the sex-differentials in the comorbidity of asthma with allergic rhinitis, as women who were IgE positive had more asthma control problems, lower asthma-related quality of life and were more susceptible to asthma triggering than men.[41] In addition, a genome-wide analysis showed major sex differences in gene expression in allergen-challenged $CD4^+$ cells, and an underexpression of chemotaxis-related genes in women,[42] suggesting that it might take a stronger stimulus in women to induce a cellular infiltrate that could perpetuate and augment allergic inflammation. This is supported by the observation of a lower concentration of allergen-specific IgE in the nasal fluid in women than in men with seasonal allergic rhinitis.[42] Alternatively, the significant sex-difference may be relevant to non-specific psychological mechanisms related to sex-differentials in their reactions to medical illness and activity limitations.[38 39] At the level of exposure, men are known to spend more time outdoors, either professionally or recreationally, which may potentially exploit their response to lower levels of pollen.

It is intriguing that we did not noted an additional effect of a very high level of air pollen, that is, more than 100 pollen grains/m^3 air, on suicide rate in the population, regardless of sex, age and history of mood disorders. This is probably because most allergy sufferers begin to experience symptoms when the pollen count reaches the moderate level,[43 44] although the threshold, the level of pollen exposure at which allergy symptoms occur, may vary from one person to another. The results may also suggest that aeroallergens may trigger and precipitate suicide mostly in individuals who carry a high sensitivity to aeroallergens, or that there may be a selection that susceptible individuals had already committed suicide before the even higher increase of pollen, as in reality there is a temporal relationship and pollen levels succeed temporally each other. On the other hand, when pollen concentrations reach to a very high level, a large proportion of allergy sufferers may be receiving intranasal corticosteroids rather than only antihistamines or decongestants and intranasal corticosteroids are known to reduce cytokine production in nasal airways, which may consequently attenuate the risk for suicide.[35] It is also intriguing that our data indicated a lowered, rather than increased, risk of suicide in women ≤35 years old when pollen level changed from 0 counts to a very low level (<5), for which we do not know how to explain. While age differences in sex-specific hormones, mood regulation and allergic sensitivity, etc, may contribute to the observation, it may also be a chance finding, or due to unmeasured environmental factors. More studies are needed to gain a firm conclusion and further insights.

Limitation, strength and implications

The present study has several limitations. One specific issue is that we were only able to analyse the grand total pollen count, rather than pollen of individual species due to the limited availability. It is known that incidents of asthma and suicide are associated with increased levels of air pollutants and environmental smoke[45–47]—factors not measured in this study. Some meteorological factors previously reported to be associated with suicide, such as direct measurement of sunlight,[3 48] were not considered in the analyses either. Other limitations include not having the individual data on sensitisation to tree pollen (skin prick or allergen specific IgE) and medication use as well as socioeconomic status. Meanwhile, this study is based on an extensive sample size which, on one hand, ensures a strong statistical power in the analysis; on the other hand, may find significant connections that are not dominantly present in the real world. Also, the measure of weekly average pollen counts should be seen as rough

approximations of the actual exposure on an individual level. Additionally, the results from this study may not apply to countries or regions where the climate and therefore plants producing allergenic pollen are very different from that in Denmark.

On the other hand, this study has a number of strengths and advantages. It is, to our knowledge, the first to test the association between atmospheric pollen and suicide risk using empirical data from longitudinal registers. Second, the data span over 25 consecutive years and cover 13 700 suicides in the areas with 2.86 million residents, which make it probably the longest and largest population study addressing the temporal association between the two incidents, and therefore ensure the reliability of the observed results. Third, this study generates an estimate of relative risk of suicide corresponding to the levels of pollen counts, a more precise and visualised measurement than the estimate of coefficiencies often used in existing correlation studies. Moreover, the results are adjusted for calendar time as well as temperature, cloud cover and humidity —factors that have been suggested to be possible bioclimatic mediators of seasonal peaks of suicide through changes in neurotransmitters and hormones.[9–11]

Overall, the interesting findings from this study should lead to novel research directions at multiple levels of inquiry, ultimately to confirm or negate a direct causal link between allergen and suicidality. If the relationship is confirmed, identifying the underlying molecular, cellular, physiopathological or pharmacological mechanisms will be important for defining new targets in suicide prevention.

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