

Allergies and suicidal behaviors: A systematic literature review

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ABSTRACT

Background: Allergies are among the most common chronic conditions. In addition to physical and social impacts, a number of studies have consistently linked allergies to poor psychological outcomes, including depression and anxiety.

Objectives: The aim of the present systematic literature review was to analyze the existing literature about the relationship between allergies and fatal and nonfatal suicidal behaviors.

Methods: Data sources include articles retrieved from Scopus, PubMed, ProQuest, and Web of Knowledge. Search terms: "suicid* and (allerg* or hay fever or atop* or eczema or aeroallergen*)" in English-language peer-reviewed journals between 1990 and 2014.

Eligibility Criteria: Original research articles that provide empiric evidence about the potential link between allergies and suicidal behaviors.

Results: The initial search identified a total of 769 articles with 17 original research articles that present empiric evidence. Nine articles analyzed the relationship between allergies and fatal suicidal behavior, and nine analyzed nonfatal suicidal behaviors (one article included both). There currently is little research into the relationship between allergies and suicidal behavior.

Limitations: The review was restricted to English-language articles published within the chosen time period; other limitations included the small number of articles that involve suicide mortality, and the fact that the majority of articles originated from the United States and Scandinavia.

Conclusions: Analysis of the results indicates a link between allergies and suicidality, particularly suicide mortality; however, results for nonfatal suicidal behaviors are mixed. It is important that further research by using more rigorous study designs be carried out to lend strength to these findings.

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The prevalence of allergies has increased significantly in Western countries since the 1960s.¹ Allergic rhinitis (AR), asthma, and atopic dermatitis (AD) are among the most common chronic conditions in Western countries,² have a severe impact on the use of health services, and contribute to major funding pressures on the health care system.³

Allergies are not only limited to physical effects, *e.g.*, red eyes, runny nose, sneezing, itchiness, breathing difficulties, hives, they are often coupled with other consequences, including reduced cognitive ability,⁴

work and/or school performance,⁵ increased daytime sleepiness due to disturbances in sleep patterns,⁶ and impoverished quality of life.⁷ In addition to these adverse physical and social impacts, a number of studies consistently linked atopy to poor psychological outcomes, including major depression^{8,9} and anxiety.¹⁰ A recent systematic review presented a link between asthma and suicidal behaviors¹¹; however, there are no current systematic reviews on the possible association between allergies and suicidal behaviors. Hence, the aim of the current article was to conduct a systematic literature review to explore the potential link between allergies and fatal and nonfatal suicidal behaviors.

METHODS

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Appendix).¹²

Search Strategy

A systematic search of (Elsevier B.V., Amsterdam, the Netherlands), PubMed, ProQuest (ProQuest LLC, Ann Arbor, MI), and Web of Knowledge (Thomson Reuters, Manhattan, NY) was conducted for English-language articles published between 1990 and 2014.

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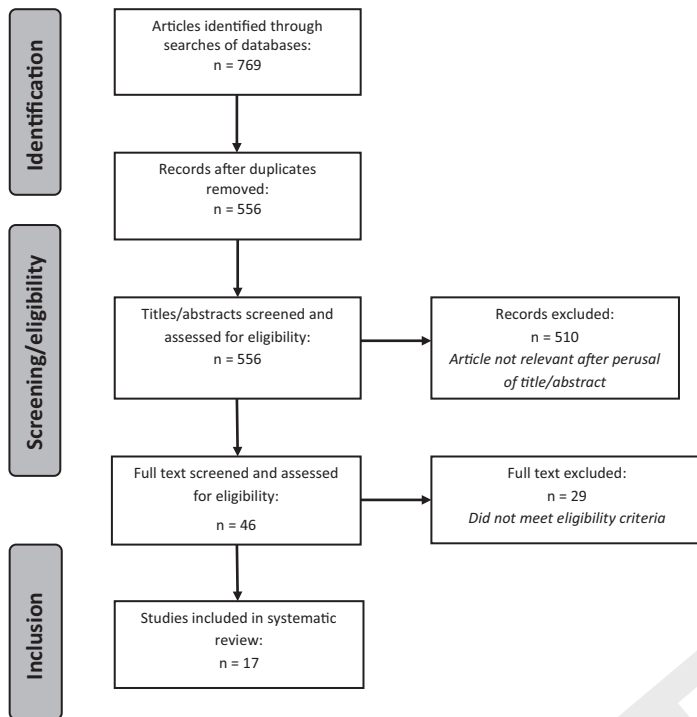


Figure 1. Selection process followed when deciding which studies to exclude and include.

The search terms used were suicid* and (allerg* or hay fever or atop* or eczema or aeroallergen*).

Inclusion Criteria

The initial search retrieved 769 articles, which were further limited to 46 potentially relevant articles after removing duplicates and perusal of the titles and abstracts. After reading the full text, 17 asthma on suicidal behavior were selected (Fig. 1).

Data Extraction

The following information was extracted:

- Author(s) and year
- Sample, country, and time of the study
- Study design
- Measures of allergy and suicidal behavior
- Main findings

Risk ratios (RR), odds ratios (OR), and differences in prevalence were examined and presented when possible.

Quality Scores

Each article was given a quality score, adapted from Pompili *et al.*,¹³ by two of us (K.K., E.B.). Further information regarding the determination of these scores can be found in the footnote of Supplemental Tables 1 and 2. Quality scores were not applied for studies that used an ecological study design due to the aggregate nature compared with other study types.

In this article, suicidal behavior refers to a range of phenomena that include suicide ideation, planning for suicide, self-harming, attempting suicide, and suicide. The latter is also defined interchangeably as “fatal suicidal behavior,” whereas all other phenomena are considered to be “nonfatal suicidal behavior.”¹⁴

RESULTS

Fatal Suicidal Behavior

Nine of the 17 articles focus on the relationship between allergies and fatal suicidal behavior; one of them also included self-harm and is also presented under nonfatal suicidal behavior (details in Supplemental Table 1). Four studies used an ecological study design; four used a cohort study design, whereas the remaining article used a nested case-control design. Studies originated from a range of countries, with multiple studies from the United States or the United States and Canada ($n = 3$), Denmark ($n = 2$), the United Kingdom ($n = 2$), one article from Finland, and one from Taiwan.

Ecological studies used seasonal tree and ragweed pollen counts^{15–17} and prescription rates of intranasal corticosteroid and nonsedating antihistamines for AR¹⁸ to measure allergies. Other studies used International Classification of Diseases, Revision (ICD) 8 to ICD-10 diagnoses of AD and/or AR^{19–21} and parental reports of AR²² and self-reports of atopy conditions.²³ All the studies used suicide numbers or rates. The majority of the studies analyzed AR or AR-related proxies, one

study analyzed only AD (eczema),²¹ and two studies also included AD.^{19,20}

Postolache *et al.*¹⁵ and Woo *et al.*¹⁶ both used ecological designs to test the association between suicide rates and seasonal pollen counts in the United States and Canada and in the United States. Postolache *et al.*¹⁵ originally found an increase in nonviolent suicide cases in young females during the peak-pollen period and older females during the postpollen period. However, this analysis did not account for other biologic and psychosocial factors that may occur during allergy season. Woo *et al.*¹⁶ attempted to replicate this result and found a significant between-county effect for grass and ragweed pollen but not for tree pollen in the United States. When controlling for other potential confounding factors (urban or rural location, number of psychiatrists, mean income), the results did not remain statistically significant and previous findings were not replicated. More recently, Qin *et al.*¹⁷ completed a similar study in Denmark by using an ecological design and found an increase in the relative risk of suicide when allergic pollen counts increased. In this particular study, the association remained significant, even when other factors were considered. There was a significant sex difference, with males experiencing immediate increases in suicide risk after small changes in pollen counts, whereas the suicide risk in females gradually increased in line with increasing pollen counts.¹⁷

Woo *et al.*,¹⁸ who also used an ecological study design, analyzed the differences in prescription rates for intranasal corticosteroids and nonsedating antihistamines used in the treatment of AR compared with suicide rates in the United States. This analysis showed that, as prescriptions for intranasal corticosteroids increased, the suicide rate declined. This relationship remained significant when antidepressant use was taken into consideration. Results supported the investigators' hypothesis that successful treatment of allergies may act as a protective factor for suicide, results that contradict previous suggestions that suicidality in allergy sufferers may be associated with adverse effects of these medications.¹⁵ Woo *et al.*¹⁸ believe that the protective factors of treatment with intranasal corticosteroids could be due to the effect of these medications on reducing the intranasal production of cytokines. However, the prescription rates of nonsedating antihistamines (which have a limited effect on the production of inflammatory cytokines) were seen to rise in conjunction with suicide rates. This finding indicates that prescription rates of nonsedating antihistamines may indicate to the higher prevalence of allergies in the community but have little association with suicide rates.¹⁸

Two of the articles in the review, one from Finland and one from Denmark, included suicide mortality in individuals who had previously received hospital

treatment for atopic disorders. Both of these articles found associations between hospital-treated atopic disorders (AD, AR, and asthma) and subsequent death by suicide. The Finnish study found that individuals treated for atopic disorders died significantly more often during the first half of the year than during the second half of the year.¹⁹ However, suicide rates in patients without allergy followed an even distribution throughout the year. The Danish study presented that 1.17% of suicides in their sample of patients treated in the hospital had a history of allergies (AR with and without bronchial asthma) compared with 0.79% of controls who did not die by suicide (incidence rate ratio 1.59 [95% CI 1.41–1.80]).²⁰ Overall, AR predicted suicide in patients who had received inpatient treatment for their allergy and in those who had AR in combination with bronchial asthma.²⁰ The results were not significant for AD.

The Taiwanese study by Kuo *et al.*²² was the only study to measure suicide mortality in young people with AR of ages 11–16 years. By using a cohort design, an association between AR and an increased risk of death by suicide during a 12-year follow-up period was found. However, after controlling for current and previous asthma and smoking, AR lost its significance in the adjusted model, whereas current asthma remained significant.²²

A cohort study of students of the University of Glasgow linked with the National Health Service Central Register death records until 2012.²³ There was no evidence of an association between atopy without asthma, eczema-urticaria only, or hay fever only, and suicide. However, individuals with a combination of eczema-urticaria and hay fever showed a higher risk of suicide (hazard ratio [HR] 10.02 [95% CI 2.39–42.07]). This link remained significant after adjusting for sex, height, number of siblings, birth order, father's social class, body mass index, and current smoking (HR 9.51 [2.24–40.43]).

Limited research focused on the link between AD and suicide. A cohort study that used a nationwide data set of English Hospital Episode Statistics linked with mortality data from 1999–2011 included 267,788 individuals with eczema (L20-L30 by ICD-10).²¹ Persons with eczema were significantly more likely to die by suicide than those without (RR 1.4 [95% CI 1.1–1.8]). Although the study used age, sex, socioeconomic status, and residency-matched controls, the investigators were unable to adjust for other factors.²¹

Nonfatal Suicidal Behavior

Nine articles in this review measured nonfatal suicidal behavior in persons with allergy (five measured suicidal ideation, two suicide attempts, and two both ideation and attempts) (Supplemental Table 2). Seven

of the nine articles in this category used cross-sectional design (five were population based, two in clinical settings) and two used case-control design. Four of the articles included analysis of seasonal allergies and/or AR, four focused on AD, and one included both AR and AD. As with the articles on fatal suicidal behavior, multiple articles originated from the United States ($n = 3$), whereas one article originated from each Japan, Korea, the United Kingdom, Norway, and two articles were multicenter studies, one included 14 countries around the world and the other 13 European countries.

Four studies presented self-reported diagnosis of AR or AD,^{24–27} four studies used physician diagnoses (one used ICD-10²¹), for the other studies, criteria of diagnosis were not presented,^{28–30} and one study used immunoglobulin E antibody analysis.³¹ Eight articles used self-reported suicidal ideation and/or attempts, and one study used hospital presentations for self-harm (ICD-9 and ICD-10).²¹

AR Studies

A multicenter study, which included 14 countries combined, found no association between AR and suicidal ideation or attempts in the past 12 months.²⁴ Similarly, Postolache *et al.*³¹ found no significant association between sensitivity to seasonal aeroallergens and lifetime suicide attempts in patients with a major depressive disorder or a bipolar disorder in a small convenience sample in the United States. The U.S. study by Gupta and Gupta²⁸ used data from several exploratory studies, which provided information on suicidal ideation in patients with AD and various other skin conditions; however, they did not have a comparison or control group without skin conditions. Overall, 2.1% of patients with AD reported suicidal ideation, which was lower than all other groups with skin conditions except for alopecia areata.

However, a U.S. survey on suicidal ideation and attempts by adults with seasonal allergies by Messias *et al.*²⁶ showed the presence of an association between allergies and suicidal ideation, which remained statistically significant after controlling for age, sex, race, lifetime depression, history of seasonal allergies, asthma, and smoking status. Although allergies were initially associated with suicide attempts, this result no longer remained significant when accounting for the abovementioned factors.

AD and Mixed Studies

A European multicenter study reported that people with atopic eczema had significantly higher odds of suicidal ideation (OR 2.03 [95% CI 1.20–3.45]), nevertheless, it did not remain significant after adjusting for other skin conditions, sex, age, socioeconomic status, stress, comorbidities and depression (OR 1.32 [95% CI

0.75–2.33]).³⁰ However, eczema (unspecified) and hand eczema were not significantly linked to suicidal ideation.³⁰ Similarly, a cohort study that used a nationwide data set of English Hospital Episode Statistics showed that eczema was associated with an increased risk of self-harm (RR 1.4 [95% CI 1.3–1.5]), the highest risk being in those ages 45–64 years (RR 1.7 [95% CI 1.5–1.8]). This investigation used age, sex, socioeconomic status, and residency matched controls but was unable to adjust for other factors.²¹

The only study that analyzed the link between both AD and AR and lifetime suicidal ideation was a Japanese case-control study.²⁹ The investigator found that the prevalence of suicidal ideation increased with the severity of AD, 0.2% of patients with mild AD, 6% of patients with moderate AD, and 19.6% of patients with severe AD, which was more common in female patients than in male patients. Only 0.14% of patients with AR experienced suicidal ideation, which was similar to the general population sample (0.08%).²⁹ A major strength of this article was the inclusion of patients with different levels of AD severity (including severe AD), a factor not considered in other studies.

Youth Studies

There were two studies among school students, one focused on AR²⁵ and one on AD²⁷ and the link to suicidal ideation. A large Web-based survey of school students ages 12–18 years in Korea found a statistically significant association between AR and suicidal ideation in both boys and girls after adjusting for age, smoking status, alcohol consumption, parental education, economic status, type of city, stress, and depression.²⁵

A study from Norway analyzed the link between suicidal ideation and AD in adolescents ages 18–19 years.²⁷ The investigators distinguished between current and past eczema, and reported that youth with current eczema had a significantly higher risk compared with those without eczema (never had eczema). This was significant for both sexes and remained so after adjusting for ethnicity, family income, and sex. Furthermore, current eczema with itch was significantly associated with suicidal ideation compared with cases without eczema but not for cases of eczema without itch.²⁷

DISCUSSION

The exact reason for the potential link between allergies and suicidal behaviors is not clearly understood. It has been hypothesized that increased suicide risk in persons with allergy may share a link with the well-established seasonality of suicide, with peaks in suicide mortality during spring time (when aeroallergens are at their highest) being reported consistently in the literature.^{32,33} Reasons for this may be that increased pollen in the air during spring causes sensitized people

to feel unwell and triggers the immune-related expression of inflammatory cytokines, which may be responsible for feelings of anxiety, depression, aggression, and sleep disturbances.³⁴ A recent systematic review showed that altered levels of some inflammatory cytokines (more specifically interleukin 2, interleukin 6, interleukin 8, tumor necrosis factor α , and vascular endothelial growth factor) seem to be related to suicidal behavior.³⁵ However, it is important to note that there can be other reasons for a seasonal peak in spring, including changes in bioclimatic factors, which have an impact on melatonin, cortisol, serotonin, and l-tryptophan levels, but also economic factors, including the “broken promise” theory.³⁶ A further explanation for suicidality in persons with allergy may be the adverse effects of common medications used in the treatment of atopy. In particular, pseudoephedrine and systemic corticosteroids have been linked to mood disturbances, including agitation, anxiety, and depressive episodes.¹⁵

The results of articles about suicide mortality in the current review lend support to the hypothesized link between atopy and elevated suicide risk for both adults^{18–21} and children.²² However, two ecological studies from the United States^{15,16} on fatal suicidal behavior found limited or no links between allergy suffering (increased aeroallergen exposure) and a higher prevalence of death by suicide. Nevertheless, a Danish ecological study demonstrated the link between allergenic pollen and increased suicide mortality.¹⁷ Ecological studies may be subject to the ecological fallacy due to the risks of using aggregate level data on groups to make inferences about people at the individual level. As already noted, individual level studies supported the link^{19–22}; only one study showed that there is no link between eczema-urticaria only or hay fever only and suicide²³; however, individuals with a combination of eczema-urticaria and hay fever were associated with higher risk of suicide. The majority of studies measured AR or mixed AR and AD; only one study focused on AD, therefore, it is not possible to determine suicide risk by different types of allergic conditions. Further research that provides separate analysis of these conditions could provide a clearer picture.

However, the results of individual level studies on nonfatal suicidal behavior showed more mixed results. Interestingly, significant increases in suicidal ideation were found in individuals with AD, adults^{21,29} and adolescents²⁷; nevertheless, in one study, it lost significance after adjusting for other skin conditions and depression.³⁰ The link between AR and nonfatal suicidal behaviors seems to be more questionable because three studies did not support that link^{24,29,31}; still, one study among children²⁵ and one among adults²⁶ supported an association with suicidal ideation but not with suicide attempts.²⁶

With regard to differences in subgroups, a small number of articles seem to indicate possible sex differences in

the impact of allergies on suicidal behavior. The findings of Postolache *et al.*,¹⁵ who noted that increases in suicide were only present in females, are consistent with previous findings that allergy is associated with increased depression in women but not in men.³⁷ This may be because atopy is more prevalent in women than in men or that effects of allergies on suicide could be partly mediated by hormonal systems.³⁴ Similarly, Kimata²⁹ reported a higher prevalence of suicidal ideation in female patients with AD than in male patients with AD. Again, these results should be interpreted with caution due to the small number of studies in the review and the fact that other investigations did not demonstrate similar sex differences.^{25,28} Singhal *et al.*²¹ indicated that the risk of self-harm was highest in the middle-aged group (45–64 years) with eczema. Nevertheless, Qin *et al.*²⁰ found a stronger effect in the older adults (≥ 60 years) and in individuals with multiple hospital admissions; furthermore, suicide risk was heightened during the first 3 months after hospitalization for allergies.²⁰ The three studies that focused on younger age groups did not present any clear differences from those that involved adults.^{22,25,27} In addition, it is important to note that a study in adolescents showed an increased risk of suicidal ideation with current eczema and, in particular, eczema with itch.²⁷

Despite the potential adverse effect of certain allergy medications,³⁴ only one ecological study that analyzed the potential effect of these drugs was identified¹⁸; however, it should be further tested on individual level.

Limitations

The current review was limited by the small number of studies on the topic, and it was restricted to English-language articles. In particular, there was a limited number of articles that focused on children and adolescents, and the majority of the articles originated from North America and Scandinavia; when considering the differences in climates, seasonal conditions, and prevalence of allergies, those results may not be transferrable to other countries.

In addition, the individual studies examined had a number of limitations themselves. A number of articles in the review used either ecological design ($n = 4$)^{15–18} or the cross-sectional design ($n = 6$); these designs do not allow determination of causality.^{24–28} The studies that used data from hospitals or other treatment services may have excluded a number of persons with allergy because many minor cases of allergies may not present serious enough health risks to warrant treatment.^{19–21,29,30} However, a number of studies relied on self-report data, which may not always be completely accurate.^{22,25–29,31}

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