Review

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Air pollution, aeroallergens and suicidality: a review of the effects of air pollution and aeroallergens on suicidal behavior and an exploration of possible mechanisms

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Abstract

Objective: Risk factors for suicide can be broadly categorized as sociodemographic, clinical and treatment. There is interest in environmental risk and protection factors for suicide. Emerging evidence suggests a link between environmental factors in the form of air pollution and aeroallergens in relation to suicidality.

Methods: Herein, we conducted a systematic review of 15 articles which have met inclusion criteria on the aforementioned effects.

Results: The majority of the reviewed articles reported an increased suicide risk alongside increased air pollutants or aeroallergens (i.e. pollen) increase; however, not all environmental factors were explored equally. In specific, studies that were delimited to evaluating particulate matter (PM) reported a consistent association with suicidality. We also provide a brief description of putative mechanisms (e.g. inflammation and neurotransmitter dysregulation) that may mediate the association between air pollution, aeroallergens and suicidality.

Conclusion: Available evidence suggests that exposure to harmful air quality may be associated with suicidality. There are significant public health implications which are amplified in regions and countries with greater levels of air pollution and aeroallergens. In addition, those with atopic sensitivity may represent a specific subgroup that is at risk.

Keywords: aeroallergens; air pollution; inflammation; pollen; suicide.

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Introduction

Suicide is a global phenomenon that represents one of the leading causes of death worldwide. Data collected in 2012 by the World Health Organization (WHO) (1) estimates that suicide accounts for 1.4% of deaths globally and is ranked as the second leading cause of death among individuals aged 15–29. Consequently, the WHO has made efforts to reduce these rates by identifying and implementing preventative strategies. The WHO (1) aims to continually implement and improve suicide prevention strategies (currently in place in 28 countries) through the use of several outlets (e.g. health care, media and education). Towards the foregoing aim, research has been conducted on the efficacy of various interventions for suicide prophylaxis. Effective suicide prevention strategies were found to be, physician education and restricting access to lethal means which could be used for suicide attempts (e.g. firearms, pesticides and gasses), while other preventative strategies (e.g. media reports and patient education) still require more rigorous assessments (2). The development of a successful and effective strategy towards suicide prevention relies heavily on the identification of suicide risk factors.

Risk factors for suicide are multivariate, consisting of both intrinsic and environmental factors (3, 4). The personal, cultural, societal and economic factors have been explored in detail previously and have been shown to vary greatly across these modalities and include, but are not limited to, age [high risk groups include youth (ages 15–19) and elderly (>75 years of age)] and gender [high risk groups

differ by location wherein Western nations have a large male to female suicide ratio (three- to five-fold)] (5). Rates of suicide are also higher among individuals diagnosed with mental illnesses [e.g. major depressive disorder (MDD), schizophrenia and post-traumatic stress disorder] (6, 7).

Recently, a number of environmental risk factors have also been considered. For example, the effect of meteorological factors on suicide has been examined, exploring the consequences of climate change (e.g. droughts), seasonality and air temperature on suicidality with many of these aforementioned factors (i.e. air temperature increases and increased droughts) demonstrating a significant positive association with suicide completion (8–10). In addition, it has been demonstrated that environmental factors, such as air pollution and aeroallergens (i.e. any airborne substance which can cause an allergic reaction) may have deleterious effects on mental health. A review conducted on environmental pollutants and psychosis by Attademo et al. (11) (n = 16 review articles; n = 13 original research articles) found evidence of a tentative positive association between exposure to environmental pollution and psychosis. Similarly, a review conducted by Kolves et al. (12), exploring the link between allergies and suicidal behaviors (n = 17 original research articles) found a positive association between the aforementioned factors. Suicide and decompensation of mental illness peak in spring and, to a lesser extent, in fall. This phenomena is represented in several recent studies wherein it has been reported that suicide and decompensation peaks coincided with spring and fall aeroallergen peaks (13). From low to high aeroallergen exposure, changes in anxiety symptom scores in patients with primary mood disorders are positively correlated with changes in allergy symptom scores (14).

The WHO defines air pollution as the modification of natural characteristics of the atmosphere through contamination of the environment by any chemical or agent. Furthermore, the WHO has developed standards reflecting the variability between pollutants, insofar as hazardous levels are dependent on respective pollutant concentration (15). Air pollutants do not act independently. For example, pollutants can also influence aeroallergens synergistically insofar as their atmospheric concentration may be increased, their allergenicity effects enhanced, and their transport in the air favored (16). While air pollution is a global phenomenon, higher levels are seen in low- and middle-income countries (17). The aforementioned trend is due to the primary use of unprocessed biomass fuels in developing countries; in contrast, developed countries tend to use cleaner fuels and methods of energy (e.g. petroleum and electricity) (18, 19). Dissimilarly, atopic diseases are more prominent in developed countries (20). There are various factors contributing to the increase of allergies, several theories established in the medical field include: the hygiene hypothesis wherein the immune system is affected due to decreased contact with microorganisms throughout childhood as hygiene standards are elevated, environmental contamination such as diesel exhaust particle pollutants and pesticides, and diverse diets in different countries (21). Notwithstanding global variation in levels of air pollution and atopic susceptibility, it is observed that these environmental urban factors at varying levels can have an impact on the population's health in a number of ways, including impaired lung function (e.g. increased wheezing and asthma cases) (22–24). Additionally, air pollution concentrations have also been associated with reductions in life expectancy (25).

Components of air pollution

Air pollution is caused by any agent capable of altering the characteristics and natural composition of the atmosphere, including a combination of gasses, particulate matter (PM), metals, and organic and inorganic compounds (26). The following list is not inclusive of all current air pollution agents; however, they are those that are targeted for reduction by the WHO, which include PM, ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2). Many air pollutants have been identified as health hazards, leading to negative health effects such as increased risk for cardiovascular diseases, and depressive symptomatology (27, 28). As such, the aforementioned agents are key targets according to the air quality guidelines, as lowering their levels could help lower the associated burden of disease (29). The air quality guidelines created by the WHO, are designed to offer guidance in the reduction of health impacts associated with air pollution. Given the detrimental health effects associated with air pollution, it is suggested these agents are not only able to penetrate into a variety of bodily systems; they are also exerting a negative effect on these systems (30).

PM is composed of a mixture of solid, liquid, inorganic/organic compounds and heavy metals suspended in the air. PM is often typified into two groups: PM equal to or less than 2.5 μm ($PM_{2.5}$) and PM equal to or less than 10 μm (PM_{10}). A third group, ultrafine particles (PM < 0.1 μm), causes a greater inflammatory response when inhaled in comparison to larger PM (31). PM is produced by two sources 1) primary sources emit PM in particle form (e.g. forest fires), and 2) secondary sources expel gasses which form PM through a series of chemical reactions (e.g. power plants, car exhaust) (32).

Ozone is a gas which is present in both the stratosphere, earth's upper atmosphere, and the troposphere, earth's lower atmosphere (ground level). The role of O_3 varies depending on the atmospheric layer, despite its identical molecular configuration in both layers. Ozone in the stratosphere, commonly known as the "ozone layer", allows for a reduction of harmful UV penetration from incoming sunlight. Stratospheric O_3 has had periods of localized and/or overall declines, and the reduction of this layer has been reported to have negative effects due to the important role of the ozone layer (e.g. UV protection) (33). In contrast, tropospheric O_3 is considered an air pollutant which occurs by UV reactions to hydrocarbons released from a variety of sources (e.g. fossil fuels, refineries, plants and soil) and the dissension of stratospheric O_3. Increased concentration of and exposure to the tropospheric O_3 is harmful, as O_3 is a highly oxidizing species associated with poor plant and human health (34). Specifically, O_3 affects vegetation and humans by entering internal systems through the stomata and lungs, respectively. In vegetation, cellular damage can occur which results in reduced growth and/or yield and in humans increased O_3 has shown a positive association with lung function in children (35, 36).

NO_2 is an irritant gas produced by the combustion of carbon dioxide (CO_2) and nitrogen monoxide (NO). NO_2 itself is toxic and also reacts with other air pollutants and the environment, contributing to tropospheric O_3, PM production, and lake acidification (37, 38). NO_2 has been associated with adverse cardiovascular health effects such as strokes (39).

SO_2 is a foul smelling gas produced by a variety of human sources (e.g. industrial activity and motor vehicles). SO_2 has been shown to adversely affect both humans and the environment (40). In humans, exposure has been associated with cardiovascular and respiratory difficulties (41, 42). Moreover, a significant association exists between SO_2 present in the atmosphere and the number of hospital admissions for ischemic heart diseases and cardiac diseases seen across seven European cities (i.e. Birmingham, London, Milan, Paris, Rome, Stockholm, and in the Netherlands) (41). Additionally, short-term exposure to SO_2 can result in bronchoconstriction in asthmatic populations (43).

Aeroallergens

Aeroallergens are particulates in the air which induce an atopic response. Agents commonly associated with inducing an atopic response include, but are not limited to, pollen, fungal spores, mold and animal dander. Aeroallergens are of particular interest in relation to air pollutants as they have an interactive effect wherein air pollutants can increase the development of pollen allergies and pollen in heavily polluted areas contain more allergenic proteins (16, 44). In addition the term "polluen" has been coined to describe the pollen/pollutant interaction and describe the make-up of pollen materials as they are often carriers of allergenic proteins and non-allergenic pollutants (45). Given the association with pollution and the fact that pollen grains are the major source of outdoor aeroallergens we explore them in particular in this review (46).

Pollen grains are male gametophytes of seed plants ranging from 10 μm to 100 μm in size that carry proteins which compose the allergenic material. Allergy symptoms (e.g. sneezing, nasal congestion and itching) are collectively referred to as allergic rhinitis (AR) and has been reported in variable prevalence, such as 8%–24% self-report in China and in contrast 11%–30% self-report in the US (47, 48). AR is an immunoglobulin E (IgE) mediated response, and can result in both localized or systemic inflammation (49). Pollen counts have also been positively associated with asthma-related hospital admissions (50). Pollen types and concentrations vary both spatially and temporally (51). The major airborne pollen groups have been summarized in detail elsewhere; however, pollen can be classified in an overarching fashion into tree, grass and weed (52).

The recent emphasis on suicide prevention and preliminary evidence demonstrating an association between air pollution, allergens and mental health provides the impetus for exploring the effects of air pollution and aeroallergens in relation to the risk for suicide. The effects of air pollution and aeroallergens on suicidality have been scarcely investigated; however, there is initial evidence suggesting a positive correlation between air pollution, aeroallergens and suicidality (53–66). Herein, the overarching aim is to provide a succinct review of the available literature on changes in air pollution, aeroallergens and their relationships to suicidal behavior, exploring potential mechanisms by which air pollution may influence suicide rates.

Methods

PubMed and Ovid MEDLINE, were searched from inception through May 15 2017 for published primary journal articles, reviews and meta-analyses exploring air pollution and aeroallergens in relation to attempted and completed suicide. The following keywords were used in various combinations for the search: air pollution, aeroallergens, pollen, suicide, suicide attempt, suicide completion, PM, NO_2, SO_2 and ozone. References from relevant reviews and the reference lists from included articles were screened manually. Articles selected for inclusion in this review were primary studies which discussed the

overarching topic herein, examining changes in air pollution and/or aeroallergens in relation to suicidal behavior.

Results

Results of our search criteria yielded 15 studies for review (Figure 1). Of the 15 studies, nine explored the relationship between air pollution and suicide, and six explored the relationship between aeroallergens and suicide, including both completed suicide and attempted suicide. The selected studies vary by length of study, location, and the components of air pollution and aeroallergens explored. Table 1 includes a summary of included studies investigating air pollutants and Table 2 includes a summary of studies investigating aeroallergens.

Air pollutants

All nine studies investigating the relationship between air pollution and suicide demonstrated a positive association between completed and attempted suicides with increased air pollution; however, the differences in design and methodology have produced variable results, insofar as not all components of air pollution explored [e.g. NO_2, O_3, PM_{10}, $PM_{2.5}$, SO_2 and carbon monoxide (CO)] are equally expressed in study findings with regards to their effects on suicide.

Studies which included PM_{10} and $PM_{2.5}$ as a measure (n = 7), collectively demonstrated that PM has a positive significant association with completed and attempted suicide (28, 53, 55–57, 59, 60). The effect size per pollutant was not consistent and varied by study and was dependent on a variety of differences in study design, methodology and analysis including covariates (e.g. holidays and temperature) and group stratifications (e.g. age group and suicide method). Increased NO_2 showed increase risk for suicide in four out of five studies (28, 56, 59, 60). Increased O_3 was associated with increased risk for suicide in three out of four studies (55, 57, 61). SO_2 increase demonstrated an increased risk for suicide in four out of five studies (28, 55, 56, 60). An increase in CO demonstrated a positive association with suicide risk in one out of three studies and a negative association in one of three studies (28, 55).

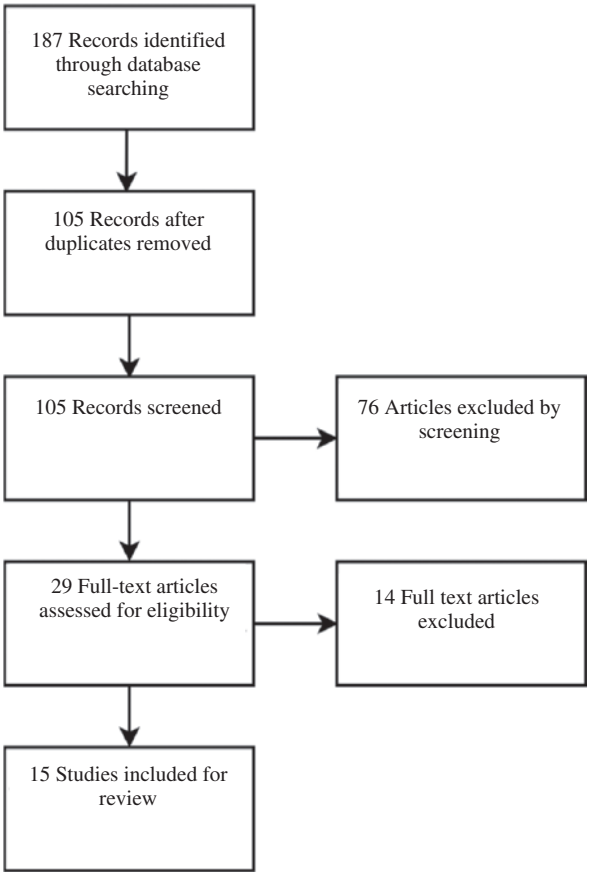

Figure 1: Flow diagram of article selection procedure.

Aeroallergens

Four studies that examined the association between pollen and suicide found an increase in suicides with increases in pollen; however, the studies were very heterogeneous with many different variations of pollen studied (e.g. tree-cypress pollen and tree-elm pollen) as pollen type is dependent on geographical location (62–64, 66). In addition, one study by Woo et al. contrasted their own previous findings wherein they initially found a relationship between increasing pollen and increased rates of suicide; however, it was then speculated that this relationship may be explained by socioeconomic factors (e.g. median income, number of psychiatrists in location of study and rural or urban setting) which vary by geographical location (62, 65). Pollen types were often segregated into tree pollen (n = 5), ragweed pollen (n = 4), and grass pollen (n = 2). Associations between suicide rates and pollen were mostly seen in tree pollen, where there was a significant positive association in three studies (62–64). Grass pollen had demonstrated a significant positive association with suicide risk in two studies; however, this relationship was not significant in Woo et al. after controlling for socioeconomic and demographic factors (62, 65).

Table 1: Summary of available studies on air pollutants.

Study	Characteristics	Air pollutants	Main findings
Bakian et al. (59)	Completed suicides (n = 1546) in Salt Lake County, Utah between January 1, 2000 and December 31, 2010. Time-stratified case-crossover design Examined relationship on day of suicide (lag 0) in comparison to 3 days prior to event (lag 3) and cumulative lags (e.g. average measure from lag 3 through lag 0). Confounding meteorological variable adjustments include: sunlight, temperature, dew point, and air pressure. Group stratifications included: age, sex, season of death and method (violent and non-violent)	NO_2, $PM_{2.5}$, PM_{10}, SO_2	Significant increases in pollutant concentration differences between case periods (days of suicide) and control period for NO_2 on lag day 2 and 3, and cumulative lag days 2 and 3. Mean pollution concentrations on days of case periods were higher than control periods for all pollutants at all lags excluding $PM_{2.5}$ and NO_2 on lag day 0 and 3, respectively, though this difference did not reach statistical significance Increase risk of suicide is associated with interquartile range increase in $PM_{2.5}$ on lag day 2 and NO_2 on lag day 2 and 3 and cumulative lag 3 Increased risk of suicide associated with exposure to $PM_{2.5}$ and NO_2 was strongest with males (all lag periods), age group 36–64 (lag day 3 and cumulative lag 2 and 3) and violent deaths (lag day 2 and 3, and cumulative lag day 3)
Biermann et al. (61)	Completed suicides (n = 1008) as well as suicide attempts (n = 917) in Bavaria/Germany from 2004 to 2007. Study examined monthly distribution of frequency of completed and attempted suicides in relation to measured O_3 values. Stratified by completed or attempted and typified by days with 0 or 1 suicide attempt/completion and 2 or more attempts/completions	O_3	Increased completed suicide rates are observed from July to September, which is not observed with suicide attempts. Ozone levels differed significantly between days where there were one or no completed suicides and days where there were two or more completed suicides. No statistically significant differences were observed with suicide attempts
Kim et al. (53)	Completed suicides (n = 4341) in Seoul, Busan, Incheon, Daejeon, Daegu, Gwangju and Ulsan in 2004. Time-stratified case-crossover design Examined relationship on day of suicide (lag 0) in comparison to 3 days prior to event (lag 3) and cumulative lags Meteorological variable adjustments include: sunlight, temperature, dew point, and air pressure. Group stratifications included: age, sex, season of death, socioeconomic status and underlying diseases (cardiovascular, diabetes mellitus, chronic obstructive pulmonary disease, cancer, and psychiatric illness)	PM_{10}, $PM_{2.5}$	Significant increases in pollutant concentration exist during case periods (days of suicide) compared to control period for $PM_{2.5}$ and PM_{10} during all lag and cumulative lag periods excluding lag/cumulative lag 3 where there is a decreased concentration between case periods and control periods Increase risk of suicide is significantly associated with interquartile range increase in $PM_{2.5}$ on lag day 1. Whereas risk of suicide is significantly associated with interquartile range increase in PM_{10} on lag days 0 through 2 When stratified by illness category, a statistically significant associated between PM_{10} and suicide risk was observed in those with cardiovascular disease. In contrast, the absence of all other diseases showed a significant association between PM_{10} and suicide risk. $PM_{2.5}$ showed no association with suicide risk for the absence or presence of any diseases Increased risk of suicide is significantly associated with exposure to $PM_{2.5}$ and PM_{10} in the age group 36–64, those of middle socioeconomic status, and seasonal transition periods. PM_{10} has an as additional significant risk association with males
Kim et al. (57)	Completed suicides in 16 regions in the Republic of Korea from January 1, 2006 to December 31, 2011. No explicit amount of suicides stated, average annual suicide rate of 29.1/100,000 per year. Examined relationship on week of suicide (lag 0) in comparison to 6 weeks prior to event (lag 6). Covariates controlled for included: sunlight, temperature, dew point, and air pressure. Group stratifications included: all air pollutants, temperature, sunlight, Korea Composite Stock Price Index, unemployment, consumer price index, average national monthly suicide number (past 5 years by month), celebrity suicides and weekly suicide rate (per 10 million by preceding week)	O_3, PM_{10}, NO_2, CO, SO_2	Ozone was significantly associated with suicide rates from lag 0 to lag 4. The greatest magnitude seen at lag 0 and the magnitude of the effect of O_3 on suicide rate decreased as lag time increased. PM_{10} also demonstrated significant associations with suicide rates at lag 0, 4 and 4. No other air pollutant showed significant associations with suicide rates at any time lags

Table 1 (continued)

Study	Characteristics	Air pollutants	Main findings
Lin et al. (56)	Completed suicides (n = 1550) in the six original central urban districts in Guangzhou, China from 2003 to 2012. Time-stratified case-crossover design Examined relationship on day of suicide (lag 0) in comparison to 7 days prior to event (lag 7) and cumulative lags (e.g. average measure from lag 7 through lag 0). Confounding meteorological variable adjustments include: holidays, temperature, humidity, atmospheric pressure and sunshine. Group stratifications included: age, sex, season of death, method (violent and non-violent) and education	PM_{10}, NO_2, SO_2	Increased pollutant concentration differences exist between case periods (days of suicide) and control period for NO_2, SO_2 and PM_{10}. Largest effects of air pollution on suicide risk was seen with exposures to NO_2 and PM_{10} on lag day 2 and SO_2 at lag day 1, the effect size for all air pollutants gradually decreased over the 7 days. Dose-response curve shows the risk of completed suicide increases with levels of air pollutant concentrations The effects of all air pollutants on suicide risk were statistically significant in the cool season and showed greater effect sizes for males, those with high education levels and violent suicides. In addition, NO_2 and SO_2 showed statistically significant effects in persons <65 years of age
Ng et al. (60)	Completed suicides (n = 29,939) in Tokyo, Japan between January 2001 and December 2011 Time-stratified case-crossover design Examined relationship on day of suicide (lag 0) in comparison to 3 days prior to event (lag 3) and cumulative lags Confounding variable adjustments include: long-term trends, holidays, temperature, seasonality, and humidity. Group stratifications included: age, sex, season of death and marital status	$PM_{2.5}$, NO_2, SO_2, SPM	Marginal significant increases in pollutant concentration in case periods (days of suicide) compared to control period for NO_2 and SPM. No pollutant concentration changes per lag days and cumulative lag days were significant prior to stratification of groups. When stratified, an increased risk for suicide was associated with day of suicide concentration of NO_2 for those under 30 years of age. Increased risk for suicide was associated with $PM_{2.5}$ (lag 3 and cumulative lag 0–3), SPM (lag 3) and SO_2 (lag 1 and 2) for widowed subjects. In single subjects, a decrease in suicide risk was associated with SPM concentration at lag 3
Szyszkowicz et al. (58)	Suicide attempts/ideation (n = 1605) in Vancouver, Canada between January 1, 1999 and February 28, 2003. Time-stratified case-crossover design Examined relationship on day of suicide (lag 0) in comparison to 2 days prior to event (lag 2) Temperature, humidity, and date were also included in the model Separate analyses were included for all year (January–December), warm months (April–September) and cold months (October–March). The model was also further stratified by sex	O_3, PM_{10}, $PM_{2.5}$, NO_2, CO, SO_2	Positive statistically significant associations between emergency department visits for suicide and exposure to PM_{10} (lag 0 and 1), $PM_{2.5}$ (lag 0 and 1), NO_2 (lag 0, 1 and 2), CO (lag 0 and 1), SO_2 (lag 0). There were no statistically significant results for warm periods (April–September). The significant associations aforementioned between air pollutants and suicide attempts were only seen in the cold period (October–March) and all year (January–December)
Yackerson et al. (54)	Suicide attempts (n = 416) and persons hospitalized with schizophrenia (n = 1445) in Be'er-Sheva, Isreal between January 1, 2001 and April 30, 2002 Examined relationships of SSP in relation to western and eastern winds. Time registered in hospital is also included in the analysis	SSP	Significant positive correlations exist between the concentration of atmospheric SSP and suicide attempts during eastern desert winds in contrast to western desert winds wherein no correlations were found. A similar significant positive correlation is also apparent between psychotic attacks and particulate concentration with eastern winds. Peak SSP concentration was observed between ~20:00 and ~06:00 and periods with dominant eastern winds occur between ~04:00 and ~09:00
Yang et al. (55)	Completed suicides (n = 4857) in Taipei city, between January 1, 1991 and December 31, 2008. Empirical mode decomposition method used to de-trend and identify patterns in complex signals entitled IMFs. Six IMF cycles were found; IMFs 1 through 6: 2.7 months, 5.6 months, 11.9 months, 23.6 months, 63.3 months, 191.1 months	O_3, PM_{10}, NO_x CO, SO_2	Significant predictors for completed suicide include O_3, and SO_2 among other weather variables. In stratified cases, gender (both male and female) was positively associated with O_3. Only male gender was positively associated with SO_2. Violent means of suicide was positively associated with O_3, and in contrast non-violent suicide was negatively associated with CO and positively associated with SO_2 and PM_{10}. Elderly suicide (age >65 years) was positively associated with O_3

Table 1 (continued)

Study	Characteristics	Air pollutants	Main findings
	Predictor variables included weather and unemployment data Group stratifications included: age, gender, and means of suicide		

SPM, Small particulate matter – used instead of PM_{10} in Japan; SSP, solid air-suspended particulates – broken solid particles dispersed by air streams; IMF, intrinsic mode functions.

Ragweed pollen had positive significant associations with suicide risk in one study, which was no longer significant after controlling for socioeconomic and demographic factors (65).

Duration

Air pollution studies vary in length from day of suicide to 191.1 months before suicide. The difference between effects of acute (i.e. less than or equal to 7 days before suicide) and prolonged exposure to air pollutants (i.e. greater than 7 days before suicide) on suicidality have not been explored in depth, such that the majority of the studies have explored acute effects, with few studies employing longitudinal designs examining prolonged exposure (59). There is evidence for both acute and prolonged exposure effects on suicide rate in air pollution. For example, one longitudinal study conducted by Yang et al. (55) found that exposure to gaseous pollutants SO_2, O_3 and CO continued to be a predictor of suicidality up to 15.9 years ($r = 0.365$, $p < 0.001$; $r = 0.338$, $p < 0.001$; $r = -0.236$, $p = 0.001$, respectively). In contrast, there is evidence that acute exposure, even in very brief durations, has an influence on the risk of suicide. In particular, Bakian et al. (59) demonstrated that a single day of exposure to $PM_{2.5}$ and NO_2 on 2 days prior to suicide conferred an increased risk of suicidality [odd ratio (OR) = 1.05, 95% confidence interval (CI): 1.01, 1.10; OR = 1.13, 95% CI: 1.01, 1.27]. A trend exists in that increased air pollution lag days show decreased suicide risk (56, 60). However, the long-term impact of exposure to air pollution has yet to be fully elucidated and may have greater cumulative effects when combined with other risk factors for suicide.

Duration in aeroallergen studies was measured differently as pollen exposure is often typified into seasons. However, acute effects were initially demonstrated with grass-pollen wherein same-day or prior-day pollen counts predict the amount of daily emergency department events for self-directed violence (63). Interestingly, no aeroallergen studies looked specifically at long-term lag, perhaps given that atopic conditions are generally classified by seasons (e.g. tree pollen allergy season vs. grass pollen allergy season).

Seasonality

The effects of air pollution on suicide have a seasonal variation as demonstrated by trends seen typically divided by North American hot (i.e. April–September) versus cold months (i.e. October–March). When segregated by season, the effects of air pollutants on suicide risks were statistically significant in the cooler months, in contrast to no statistically significant trends seen in the hot months (56, 58). There also appears to be a critical transition period between spring and fall, where there is increased suicide risk with PM_{10} and $PM_{2.5}$ (53, 59). This transition period may be reflective of the suicide trends seen in pollen as pollen levels demonstrate seasonal variation with increases in pollen counts occurring during their respective on-seasons which also vary spatially and temporally.

Systems and effects

The respective ability of these components of air pollution to affect human health is dependent on their respective abilities to enter the body (Table 3), where they deposit in our bodies, and the methods by which they interact with their surroundings once they gain entrance. Primary routes of entry of air pollutants and aeroallergens for humans include ingestion and inhalation. In addition, air pollutants may affect a number of bodily systems (e.g. respiratory, cardiovascular, nervous, urinary and digestive), reviewed in detail elsewhere (69). Furthermore, aeroallergens are most often associated with detrimental effects to the immune system, cardiovascular system and respiratory system (70–73). Of particular interest are the systems which have known effects on processes associated with

Table 2: Summary of available studies on aeroallergens.

Study	Characteristics	Aeroallergen	Main findings
Postolache et al. (62)	Data on completed suicides [n = 4228 (2417 tree season and 1811 ragweed season)] were obtained in the US. Suicides were then stratified by county/state, date, sex, age and method (violent and non-violent). Tree and ragweed pollen data were obtained from 1995 to 1998. Pollen concentrations were typified into three periods, prepollen (tree pollen: <10 p/m^3; ragweed <mid-way on log scale between 10 p/m^3 and 100 p/m^3), peak-pollen (tree pollen: >100 p/m^3; ragweed >mid-way on log scale between 10 p/m^3 and 100 p/m^3), and postpollen wherein levels return to those of prepollen Relative rates were calculated for each allergen period, pollen-level period, and suicide type Confounding adjustments include: light (measured by sunshine)	Tree and ragweed pollen	Significant increases in the relative rate of nonviolent suicides amongst young women were seen in the tree-pollen season during peak-pollen period in comparison to the prepollen period. In contrast, in older females, there was a significant increase in the relative rate of nonviolent suicides during the tree-pollen season in the postpollen period in comparison to the prepollen period. It is possible that in older women, greater light exposure could have inflated the relative rate of suicide during this period There were no other significant associations between aeroallergens and suicides
Jeon-Slaughter et al. (63)	Time series study examining the temporal relationship between seasonal pollen and the number of nonfatal self-directed violence events between January 2, 2000 through December 28, 2003 (n = 1995), in Dallas County, US. Data was stratified by sex. Daily pollen count in the Dallas area was also extracted. Pollen was examined in two ways, an overlapping period which was 16 h pre- and 8 h post-data collection from the emergency department; and a 1 day prior period which was 40 h pre- and 16 h post-data collection from the emergency department	Pollen – tree (elm, cedar, sycamore, ash, mulberry, hackberry, willow, pecan, walnut, hickory, mountain cedar, oak, cottonwood, juniper, and maple), grass and ragweed	Significant positive association between self-directed violence in women and same day and/or prior day tree pollen counts. This was not seen in men In both genders, grass pollen at same-day or prior-day counts predicted the amount of daily emergency department presentations for self-directed violence No significant correlations were found for ragweed pollen
Stickley et al. (64)	Time-stratified case-crossover analysis where data was collected on completed suicides (n = 7517) that occurred in Tokyo between February 1, 2001 and April 30, 2011 Suicides were stratified by sex and age. Daily pollen levels were obtained from nine monitoring posts across Tokyo. Daily air pollutant values were also measured across 10 sites Confounding meteorological values recorded included: temperature, humidity, wind speed, and rainfall. Public holidays were also included Exposure of pollen during the control periods (same days of the week within the same month as before and after event) compared to daily exposure of pollen Examined the lag effect of pollen up to three days before the event (lag 0–lag 3), this model was also adjusted to include the air pollutants	Tree pollen: Japanese cedar and cypress Air pollutants: $PM_{2.5}$, SO_2, NO_2, O_3	There was a statistically significant difference between men and women; for women, higher levels of same-day pollen levels was associated with an increase in the odds for completed suicide. This association remained when SO_2, NO_2 and O_3 were included in the analysis for women. When $PM_{2.5}$ was controlled for, all levels of pollen were significantly associated with suicide No concentration of pollen was associated with increased odds for suicide in men

Table 2 (continued)

Study	Characteristics	Aeroallergen	Main findings
Woo et al. (65)	Completed suicides between the years 1999 and 2001 in continental US. Confounding variables were controlled for in two fashions; between-county and within-county effects. Within-county effects included time of the year, age, sex and race. Between-county effects included type of location (i.e. metropolitan or non-metropolitan), number of local psychiatrists and socioeconomic status	Tree, grass and ragweed	Significant association of suicides with grass and ragweed pollen were found in between-county effects; however, after controlling for location type, number of psychiatrists and socioeconomic status, the initial association was no longer significant No significant within-county associations were found
Qin et al. (66)	Completed suicides (n = 13,700) in Denmark (Middle Jutland or Capital region) from January 4, 1982 through December 31, 2006. Daily pollen data from two stations were recorded, meteorological conditions were also collected (e.g. temperature, cloud cover and humidity) Average pollen counts per week were typified into five levels: no pollen (0), very low level (<10), low level (10 to <30), middle level (30–100) and high level (>100) Variable adjustments include: region, calendar weeks, weekly average of temperature, cloud cover, and humidity Group stratifications included: sex, age group and history of mood disorders	Pollen grains non-typified	Increased relative risk for completed suicide with increasing pollen counts, seeming to increase linearly with large number of pollen counts. Associations remained after controlling for meteorological conditions, regional and calendar effects Significant gender differences were detected. In women, relative suicide risk increased gradually with pollen counts until the concentration reached the middle level varying marginally by age, particularly in those women under 35 and over 60. In contrast, in men, the relative risk of suicide increased significantly with a small increase of air pollen count (i.e. from zero to a very low level). This phenomenon was especially apparent in young men (<35 years) When stratified by the presence of a history of mood disorders stronger influence of air pollen on the relative risk of suicide was apparent in both genders, but was more dominantly represented in males
Postolache et al. (13)	A convenience sample of 80 patients with major depressive disorder and bipolar disorder with a history of suicide attempts in the Southern mid-Atlantic region of the US. Participants were stratified by allergy sensitive group and non-allergy sensitive group by IgE analysis. Retrospective suicide attempts were measured using the Columbia Suicide History form and the NIMH life chart methodology	Tree and ragweed	No statistically differences were seen in suicide attempts between those with or without IgE sensitivity in any pollen season.

suicidal ideation, specifically the respiratory system, immune system, and cardiovascular system.

Air pollutants

Respiratory system

The respiratory tract is the main route of entry for air pollutants in humans. As such, there are many studies exploring the effects of air pollution on respiratory health. It has been proposed that air pollutants, particularly transitional metal particulates, disturb the airway by causing inflammation, as demonstrated by increased levels of C-reactive protein (CRP) in the circulatory system. CRP is an indiscriminate marker of inflammation produced by the liver (74). The inflammatory marker CRP has demonstrated a positive association with recent suicide attempts in the psychiatric population, wherein a higher concentration of CRP has been found in recent suicide attempters compared to those who have not recently attempted

Table 3: Methods by which particles enter the lungs.

Method	Element of pollution	How
Diffusion[a]	<0.05 μm	Follows Brownian motion – the erratic movement of microscopic particles due to molecular bombardment Particles depositing into lungs by chance
Electrostatic precipitation[b]	Charged particles	Inhaled electrically charged particles produce larger deposition than expected due to dispersion by their charge
Inertial impaction[b]	>1.00 μm	Particles are able to keep their original trajectory despite changes in airstream thus depositing themselves with surface contact
Interception[b]	Fibrous particles	Particles travel close to airway passage where an edge of the particle touches the airway passage surface and is deposited
Sedimentation[b]	>0.05	Particles deposit due to influence of gravity

[a](67), [b](68).

suicide (75). In addition, high CRP levels have also been associated with risk of depression and psychological distress in the general population (76). Therefore it is possible that increased levels of CRP caused by air pollutants may contribute to a suicidal state in certain populations.

Additionally, the pathogenesis of airway inflammatory disease may be mediated by the endoplasmic reticulum (ER) stress pathway, which has shown links to activation of major inflammatory pathways (e.g. NF-κB-IKK) (77). A study conducted by Bown et al. (78) demonstrated that subjects who died by suicide with MDD had higher levels of ER stress proteins (GRP78, GRP94, and calreticulin) present in their temporal cortex. Furthermore, the ER stress pathway has shown to have genetic variation, as such the susceptibility to deleterious effects of air pollution are not consistent across the whole population (79).

Prolonged exposure to air pollutants, specifically O_3 and PM, has also been associated with reduced lung function and associated chronic illnesses which can result in reduced oxygen (e.g. asthma and emphysema) (69). It has been demonstrated that suicide rates are elevated in populations located at higher altitudes, where levels of hypoxia – oxygen deficiency – are high (80). This phenomenon has also been observed in other medical conditions associated with hypoxia, including smoking, asthma and chronic obstructive pulmonary disease (81). In contrast, it has been demonstrated that former episodes of hypoxia (e.g. former asthma) are not associated with suicidal ideation or attempts (82). Goodwin et al. (82) suggest that current asthma reflects an active disease whereas former asthma is an inactive disease, and the active state of the disease could be contributing to suicidal ideation. Hypoxia can alter a variety of systems including serotonin synthesis, wherein decreased oxygen is correlated with lower serotonin synthesis levels, possibly explaining the positive relationship suggesting that hypoxia may also be related to mood disturbances resulting from decreased serotonin (80, 83, 84). The affective disturbances present in MDD are mediated by disruptions in the neural serotonergic system; particularly a deficiency in serotonin (85).

Cardiovascular system

$PM_{2.5}$ and O_3 have been shown to affect systemic vasculature and cardiovascular processes (86). Affected cardiovascular processes include increased heart rate variability (i.e. interval between heartbeats), ectopic beats (i.e. disturbance of cardiac rhythm), blood inflammatory and coagulation markers, and mean red blood cell hemoglobin concentration (87). As such, a variety of cardiovascular ailments have been associated with exposure to air pollutants (e.g. anemia, myocardial infarctions and angina) (88, 89). Moreover, individuals with mood disorders, including a diagnosis of MDD, bipolar disorder, and those experiencing acute major depressive episodes, are more likely to experience suicide attempts and/or completion and are also more likely to experience cardiovascular diseases (90–92). In addition, several cardiovascular diseases have been found to have mood-altering side effects including adjustment disorder with depressed mood and, to a lesser extent, MDD (92).

Vascular depression, while absent from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, is conceptualized as depressive symptoms with the accompaniment of vascular pathogenesis (93). One such factor postulated to be involved in the pathogenesis of vascular depression is brain lesion localization. Two theories have hypothesized different roles for brain lesion localization: 1) small lesions disrupting critical pathways related to depression (e.g. "lesion-depression pathway" – lesions

involving left hemisphere prefrontal or basal ganglia structures, which have been shown to be associated with depressed moods), and 2) an accumulation of lesions exceeding a threshold [e.g. white matter hyperintensities (WMH) >10 cm^2] (93, 94). Specifically, large quantities of WMH have been shown to be a factor in predicting future depression as WMH have been associated with the development of depressive symptoms (95, 96). Development of WMHs have further been associated with exposure to $PM_{2.5}$ and O_3 (97). Notwithstanding the aforementioned associations, there is a paucity of literature investigating the role of PM exposure in the development of vascular depression, either by changes in vasculature or by association with brain lesions.

Immune and neurological system

PM, particularly the heavy metals, interacts with the immune system in an antigen nonspecific fashion (69, 98). As such, these metals can lead to malfunction or disruption of regulatory systems (98). Specifically, lead exposure has been shown to result in changes to the dopaminergic and glutamatergic systems in the brain. For example, the density of N-methyl-D-aspartate receptors (NMDAR) has been reported in animal models to be elevated with exposure to lead (99). In addition, other neurological factors which are known to mediate the pathophysiology of mood disorders [e.g. serotonin (5HT) and brain-derived neurotropic factor (BDNF)] are also susceptible to dysregulation with air pollutants (100, 101).

The NMDAR is a glutamate receptor whose dysregulation is implicated in many mental disorders. Observed dysregulation of NMDAR systems across different disorders has included both an increase and a decrease in receptor densities. For example, Nudmamud and Reynolds (102) reported increases of NMDAR density bilaterally in the superior temporal cortex in schizophrenia patients. In contrast, Nudmamud-Thanoi and Reynolds (103) reported a decrease in NMDAR density in patients with MDD and bipolar disorder in the superior temporal cortex. Given the observed NMDAR dysregulation in various mental disorders, those exposed to particulate metals could be at risk for entering a state which promotes suicidal ideation.

Pro-suicidal ideation states are often associated with depressed mood and a deficiency in 5HT (104). In contrast to what would be expected by the monoamine hypothesis of depression [i.e. a deficit in certain neurotransmitters (e.g. 5HT) are responsible for depressive symptomatology], exposure to air pollutants, specifically O_3 results in increased 5HT and its metabolites [i.e. 5-hydroxy-indole-acetic acid (5-HIAA)] in pre-clinical models (105, 106). While this increase would appear beneficial, it has been demonstrated that increased 5HT is associated with anxiety and decreased sleep quality (the latter through increased 5-HIAA) (106, 107). Sleep disturbances independent of mood symptomatology are demonstrated to be a risk factor for suicidal thoughts and behaviors as demonstrated in a meta-analysis conducted by Pigeon et al. (108) (adjusted effect size, risk ratio: 1.91, 95% CI: 1.64–2.23; $p < 0.001$). Furthermore, anxiety disorders (e.g. panic disorder, post-traumatic stress disorder, social phobia, and agoraphobia) have been associated with increased odds of suicidal ideation in Canadian (unadjusted odds ratio 5.63, 95% CI: 4.59–6.90) and American (unadjusted odds ratio 8.36, 95% CI: 6.06–11.54) populations (107).

It has been suggested that decreases in BDNF reduces neural plasticity and the ability for coping with crisis situations (109). Various neuroprotective actions such as exercise and antidepressant pharmacological agents have been known to increase BDNF production (110, 111). The foregoing observations are further substantiated by reports indicating that BDNF is markedly downregulated among those who have completed suicide, independently of mood symptoms (112). Notable, it has been demonstrated that when exercising in air polluted conditions, specifically traffic-related air pollution, levels of BDNF are not increased compared to those exercising in a room with clean air (101). Despite exercise being known to increase BDNF this increase was only seen in those that exercised in a clean room. It has been further suggested that BDNF production is epigenetically mediated, wherein increased DNA methylation results in lower BDNF mRNA levels. Moreover, preliminary research has demonstrated that traffic-related air pollutants moderate DNA methylation (113, 114).

Aeroallergens

Respiratory and immune system

Similar to air pollutants, inhalation is the most common method of allergen entry into the human body; however, deposition of allergenic compounds along the respiratory tract is variable and is mediated by both particle diameter and breathing types (e.g. heavy through nose, light through mouth) (49). Ultimately, many pollen particles are too large to deposit in the lungs, although certain pollens, such as rye-grass pollen have demonstrated the ability to induce asthmatic effects similar to air pollutants. This is of relevance because asthma has shown positive associations with suicidal behaviors (115, 116). Interestingly it has

been demonstrated that in contrast to air pollutants, non-allergic asthma has been associated with higher levels of CRP than allergic asthma (117). As such, there exists differences in the inflammatory pathways between air pollutants and aeroallergens.

Aeroallergens result in an IgE mediated immune response that is often localized and chronic (118, 119). Cytokines play a regulatory role in IgE-mediated atopic responses whereby increased interleukin-4 (IL-4) has a major role in IgE synthesis (120). Interestingly, the role of cytokines in suicidal behavior is contrary to what would be expected; previous evidence has suggested increases in interferon gamma (IFN)-γ, which down regulates the production of IgE. Moreover, an association between increased levels of IL-4 and suicide was only demonstrated in one study (121). Notwithstanding the foregoing results, IgE status has been associated with increased depression scores indicating worse mood symptoms (122).

Allergen-associated inflammation may also affect the brain. While the effects of this phenomenon in humans is poorly understood, there have been demonstrations of allergy-related neurological changes in murine models (49). For example, one study found that mice sensitive to allergies were found to have increased brain levels of IgE and immunoglobulin G. Furthermore, the presence of allergies was also found to increase phosphorylation of the tau protein which is a detrimental process towards the formation of Alzheimer's disease (123). The aforementioned murine study made reference to Eriksson et al. (124), who demonstrated that atopy is associated with increased risk for Alzheimer's disease and dementia in humans. Phosphorylated tau is associated with Alzheimer's disease, it has been also associated with mild cognitive impairments (125). Interestingly, suicide has been positive associated with both Alzheimer's disease and cognitive impairments (49). Collectively, these findings suggest that allergenic rhinitis may account for at least some of the increased risk of suicide seen in both Alzheimer's disease and mild cognitive impairments, although this hypothesis warrants further investigation. In addition, the ability for allergens to influence brain function has been documented by Reeves et al. (126) where they proposed that alcohol disrupts the blood-brain barrier and, as such, allows the brain to be exposed to immune cells and cytokines which can influence mood symptomatology and result in behaviors such as suicide. Furthermore, in contrast to increases in 5HT seen with air pollutants, atopic rhinitis is associated with decreased 5HT (127). The aforementioned trend of 5HT under atopic rhinitis conditions is aligned with the monoamine hypothesis of depression, and may contribute to mood disturbances in this population.

Cardiovascular system

Atopic inflammatory processes have also been shown to influence vascular health insofar as factors associated with allergic diseases (e.g. increased IgE, cytokine secretion and low vitamin D concentration) can add to cardiovascular disorder pathogenesis (128). Further contributing to cardiovascular disease is the prolonged use of glucocorticoids, often used to control AR, as this treatment has been associated with metabolic dysregulation in the form of weight gain (128, 129). This is of significance as obese individuals are more likely to commit suicide than those with normal or low weight (130).

Discussion and conclusion

This review examined the relationship between air pollution, aeroallergens and suicide. We further explored the possible mechanisms by which exposure to air pollution and aeroallergens can lead to suicide attempts and/or completions. It is apparent that components of air pollution, particularly $PM_{2.5}$, have the ability to negatively affect a variety of bodily systems (e.g. respiratory, cardiovascular and immune), ultimately resulting in alterations that are consistent with differences seen in those with mental disorders and/or in individuals who have attempted and/or completed suicide. In addition, it has been demonstrated that pollen alone can induce an immune response, which is potentially conducive to a suicidal state. However, the effects of pollen are exacerbated by the presence of air pollutants, as explained by the concept of "polluen" (45).

With the similarities and differences of the pathways affected by both air pollutants and aeroallergens, polluen may attack various systems simultaneously. It has been demonstrated that when pollen is exposed to specific air pollutants, it becomes more allergenic as more allergens are released from the pollen grain. In contrast SO_2 resulted in decreased release of allergens from the pollen grain (46). Thus, it is possible that under certain pollution conditions the allergenic potential of aeroallergens is increased, potentially resulting in increased cases of allergenic rhinitis. In addition, there is also the concept of air pollutants carrying allergenic material, which could be activating both series of immune and system responses, contributing to a pro-suicidal internal environment.

There is a growing interest in ecological factors and their influence on suicidal behavior. While this review

mainly focuses on pro-suicidal factors, there are also environmental factors that have been shown to reduce the rates of suicide. For example, lithium is a mood stabilizing agent and is known to have suicide protective effects. Trace amounts of lithium are found in drinking water; areas with higher lithium content in the drinking water have shown lower suicide rates in many existing studies (131, 132). For example, Kapusta et al. (133) explored the relationship between lithium in drinking water and suicide rates across 99 Austrian districts (average population 8,297,964, SD = 65,050). The overall suicide rate was found to be inversely associated with the lithium levels in drinking water ($B = -0.41$, $p \geq 0.0001$) (133). While the existing literature regarding air pollution, aeroallergens and suicide is very limited, the trends in the current literature would suggest that these ecological factors and their components demonstrate a pro-suicidal ecological effect.

The components of air pollution explored largely varied across studies. The recurring trend of the association between PM and suicide in the aforementioned studies and its systematic reappearance in suggests that it is an important component of air pollution with respect to suicidality. However, studies carried out prior to 2005 did not consider the effect of $PM_{2.5}$, as this measurement was only implemented after this time. As PM is diverse in its composition, there could be a variety of components that affect suicidality. Exposure to heavy metals in the environment has been related to immunotoxic effects and has been targeted for direct reduction in consumption (e.g. consuming less foods with trace amounts of metals) (134). Heavy metals present in PM appear to be the main culprits impacting mental health via the respiratory system, cardiovascular system and immune system (69, 74, 86).

Available literature on the topic is limited insofar as the risk factors for suicide are multiplicative, involving a variety of different processes and systems, and direct inferences about the causal role of air pollution and aeroallergens in suicidality cannot be made at this point in time. Additionally, the possibility remains that there may have been pre-existing mental disorders among existing study samples. Interestingly when the aforementioned factor was controlled for by Postolache et al. (13), no differences were seen in suicide attempts in patients with MDD and bipolar disorder with or without allergy sensitivity in any pollen season. Moreover, only a limited number of locations were explored for air pollutants, excluding many of the cities with the highest amount of air pollution worldwide (e.g. Tokyo, Shanghai and Delhi) (135). Also, given the recent change in reporting standards (e.g. the introduction of $PM_{2.5}$ in 2005), many historic data is incomplete, making it difficult to consider the effects of major pollution events such as the industrial revolution and the Bhopal gas leak on suicide rates. Large pollution events are important to analyze as they often have large effects on the population's health, such as the Beijing fog in 2013 (136).

Limitations in the current studies include the lack of consistency in reporting air pollutants given the recent introduction of $PM_{2.5}$, and the lack of many long-term exposure studies for both air pollutants and aeroallergens. Studies which reported on aeroallergens were also limited in diversity as there exists a large variety of aeroallergens. Additionally, only one study examined the effects of both pollen and air pollutants together. Future directions include exploring suicide statistics following major pollution events, exploring trends between studies comparing areas with high amounts of pollution to those with low pollution, and further exploring the specific composition of PM as a factor for suicide. Guo and Barnett (137) have completed a criticism on the methodology used for Bakian et al.'s study expressing the time-stratified case-crossover design with long strata durations (which has been widely repeated across other studies) is not as sensitive as desired and may not accurately control for pollutant seasonality. In addition gaps exist in the lack of controlling for the potential confounding variable of precipitation, and averaging air pollutant data across many stations (a practice which was repeated frequently) (137). It is possible that more accurate and representative studies of the interaction between air pollutants and suicide could be achieved if the aforementioned criticism was addressed.

Furthermore, studies are required that explore the effect of other aeroallergens on suicide and studies which explore combinatory effects of air pollutants and aeroallergens, also known as polluens. IgE mediated allergic reactions are not only seen with aeroallergens but also seen with some food allergies, which are recognized as the most common chronic non-communicable disease in children. With increasing global prevalence, there's impetus for exploring the impact on suicide (138, 139).

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