



Relationship between traffic-related air pollution particle exposure and asthma exacerbations

Association or causation?

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Introduction

Clinicians are often asked about articles in the media proclaiming new and unexpected causes of disease. Often, these headlines are based not on randomized clinical trials but rather on associations discovered in observational studies. Most clinicians realize that a *P* value less than .05 does not prove causation but do not necessarily know how to critically judge whether a reported association should be considered a true cause of the disease. In 1965, Austin Bradford Hill published “The Environment and Disease: Association or Causation?”¹ Dr Hill, an occupational physician, asked, “... we see that the event B is associated with the environmental feature A, that, to take a specific example, some form of respiratory illness is associated with a dust in the environment. In what circumstances, can we pass from this observed association to a verdict of causation? Upon what basis, should we proceed to do so?” He proceeded to list criteria to consider in determining whether an association is due to causation. These criteria (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) have since become fundamental tenets of causal inference in epidemiology. In this perspective, we will ask the same question as Dr Hill did more than 50 years ago. Does traffic-related air pollution particle matter (TRAP particle) exposure (“dust in the environment”) cause asthma exacerbation (“respiratory illness”)?

In this perspective, we use Hill's criteria to (1) systematically review different types of studies recently published on this question, (2) assess the strength of evidence supporting a causal role, (3) integrate the dataset to offer a plausible biological explanation

for this association, and (4) present some implications of this explanation for the clinician.

Evaluation with Hill's Criteria

Criterion 1: Strength of the Association

Hill suggested that associations with small effect sizes could more conceivably be attributed to other underlying contributors (ie, bias or confounding) and, therefore, were less indicative of causation. For example, an increase of 850 exacerbations when exposure A is high vs low has a greater effect magnitude than an increase of 25 exacerbations, although both might be statistically significant. As such, the original Hill's criterion would assume that exposure A is more likely to be causal than exposure B. With the advent of new techniques for aggregated large datasets and the realization that complex diseases often have multiple triggers sometimes only contributing a small percentage to the overall effect, statistical significance, not the magnitude of association, is the accepted benchmark for judging the strength of an observed association and thus its potential causality.² Using the previous example, if the association between exposure B levels and asthma exacerbations has a *P* value of .004 and that of exposure A has a *P* value of .04, exposure B is more likely to be causal even if the effect magnitude is relatively small.

Recent large population analyses have provided compelling data describing the strength and magnitude of the association between TRAP particle exposure and asthma exacerbations in time-series studies.^{3,4} By pooling large datasets, researchers could demonstrate strong (often *P* < .001) temporal associations between daily fluctuations in regional TRAP particle concentrations and increased asthma exacerbations requiring emergency department visits or hospitalizations. Although the association was statistically significant, a modest (1%–15%) fraction of asthma exacerbations could

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be attributed to TRAP particle exposure.^{3,4} Put another way, these data imply that TRAP particle exposure is a cause of asthma exacerbations in a measureable but select fraction of cases.

Under what conditions does TRAP particle exposure play a role in exacerbations? There are a number of time studies reporting that the association between regional TRAP particle levels and asthma exacerbations is stronger in the warmer months,^{3,5} although TRAP particle concentrations are generally higher in the winter months. This obscuring of a relation between TRAP particle levels and asthma exacerbations in the colder months is likely due to the high frequency of upper respiratory infections (URIs) in wintertime and the fact that URIs have much stronger effects on exacerbations compared with TRAP particle exposure.⁶ Because respiratory viruses account for approximately 85% of asthma exacerbations,⁷ a significant role for TRAP particles is likely limited to the fraction of exacerbations caused by non-URI exposures (see discussion below).

Criterion 2: Consistency

Traditionally, Hill's consistency criterion is upheld when multiple epidemiologic studies using different locations, populations, and methods show a consistent association. With the advent of meta-analyses, it is clear that failure to demonstrate statistical significance in a single study (especially small studies) does not necessarily preclude the possibility of a meaningful exposure-response relation.² Because of the small effect size, very large studies and/or a pooling of multiple studies are required to observe the association between TRAP particles and asthma exacerbations with confidence.

The population fraction of exacerbations attributable to TRAP particles theoretically could be substantially larger if TRAP particle exposure causes asthma to develop.⁴ In contrast to exacerbations, the evidence that TRAP particle exposure is a cause for asthma is inconsistent. Recent studies in large populations such as the ESCAPE study reported no association,⁸ whereas other studies reported a positive relationship.^{9,10} As noted earlier, the failure to achieve statistical significance in some studies does not necessarily rule out a role for TRAP particle exposure in the development of asthma but does make the argument for causation weaker until further data are available. Similarly, if TRAP particle exposure increases the incidence or severity of URIs as some studies suggest,¹¹ the attributable risk for TRAP particle exposure on exacerbations would increase substantially but more study is needed to assess this interaction.

Criterion 3: Specificity

Hill suggested that associations are more likely to be causal when they are specific, meaning the exposure causes only 1 disease. This criterion is considered the weakest for determining causality² because exposures such as cigarette smoke are known to cause multiple diseases. Similarly, TRAP particle exposure has been associated not only with asthma exacerbations but also with morbidity and mortality in patients with emphysema, cardiovascular disease, and lung cancer.

Criterion 4: Temporality

Hill explained that for an exposure-disease relation to be causal, exposure must precede the onset of disease. Time-series studies generally report that asthma exacerbations are increased on the same day or day after TRAP particle exposure, with some reporting associations lagged by a few days. The same-day associations suggest that TRAP particles can worsen asthma fairly quickly and recent studies using near real-time data support the proposition that TRAP particle effects can occur within hours of exposure.¹²

Criterion 5: Biological Gradient

Hill wrote that, "if a dose response is seen, it is more likely that the association is causal." This criterion has been fulfilled through many studies demonstrating a dose-response relation between TRAP particle exposure and asthma exacerbations.

Criteria 6 and 7: Biological Plausibility and Coherence

Hill's criterion of biological plausibility is satisfied if the relation is consistent with the current body of knowledge regarding the etiology and mechanism of disease. Coherence has been viewed as being similar to biological plausibility, in that the cause-and-effect story should make sense with all knowledge available to the researcher.² Based on the findings described earlier, a coherent mechanism should be consistent with relatively small but statistically significant effects of TRAP particles on asthma exacerbation primarily occurring in the warmer months. A biologically plausible mechanism of TRAP particle-induced exacerbation would be expected to involve increased T-helper type 2 or type 2 lymphoid cells, known to increase eosinophilic airway levels, because airway eosinophils are believed to be the primary mediator of asthma exacerbations. Although there is little evidence that TRAP particle exposure alone activates T-helper type 2 or type 2 lymphoid cells, there is increasing evidence from animal¹³ and human¹⁴ challenge studies that TRAP particle co-exposure can augment eosinophilic inflammation induced by allergen alone. Recent studies have suggested that TRAP particle exposure might act as an adjuvant upregulating T-helper cell type 2 responses through the production of interleukin-17¹⁵ and/or by activating type 2 lymphoid cells.¹³ These adjuvant effects suggest a biologically plausible and coherent explanation for how TRAP particle exposure might induce asthma exacerbations occurring in the warmer months.¹⁶

Criterion 8: Experiment

Hill explained that evidence drawn from epidemiologic studies demonstrating declines in disease risk after cessation of exposure might be the strongest support for causal inference. Largely as a result of the Clean Air Act, aggregate emissions and regional TRAP particle concentrations have decreased across the country by more than 70% since the 1970s. Is there any evidence that there has been a concomitant decrease in asthma exacerbations? Berhane et al¹⁷ examined whether improvements in ambient air quality in Southern California from 1993 through 2012 were associated with decreases in bronchitis symptoms in children. They reported significant decreases in persistent symptoms of cough, congestion, or phlegm (measured by questionnaire) related to air pollution in children with asthma (interestingly, the degree of air pollution-related symptom decrease was greater in children living in households with dogs, potentially supporting the notion of interaction between TRAP particles and allergen exposure). As such, there is evidence that decreasing levels of TRAP particles have resulted in improved asthma control in children. Further studies are needed to examine whether similar trends have occurred with asthma exacerbations.

Criterion 9: Analogy

Analogy has been interpreted to mean that when 1 causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way.² For TRAP particle exposure and asthma exacerbation, the effect of secondhand cigarette smoke exposure might be the most instructive analogy. It is generally accepted that secondhand tobacco smoke exposure is associated with

increased asthma severity.¹⁸ Similar effects should be expected because tobacco smoke and ambient TRAP particles contain polycyclic aromatic hydrocarbons that activate the aryl hydrocarbon receptor, resulting in upregulation of some of the same biological pathways.¹⁹

Conclusion

In this Perspective, we have presented evidence that implicates TRAP particles as a cause of asthma exacerbations. Dr Hill wrote, “None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question, is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”¹ Based on a systematic up-to-date review of the literature, the most likely explanation for this association is clearly cause and effect. At this time, the epidemiologic literature suggests that only a fraction of asthma exacerbations is caused by TRAP particle exposure. Integration of the current epidemiologic and experimental data suggests that asthma exacerbations in the warmer months when URIs are less frequent might be mediated by TRAP particles together with allergen co-exposure.

Implications for the Clinician

If this understanding is correct, clinicians should consider the effects of TRAP particles especially in their patients who have asthma exacerbations during the warmer months. Instead of taking a “medication holiday,” these patients should continue to receive inhaled corticosteroids throughout the summer to modulate effects from allergen and thereby decrease effects from TRAP particle exposure. The effect of TRAP particle exposure also should be considered in patients with indoor allergen sensitization and exposure who report exacerbations unrelated to URIs during the winter months. Physicians should counsel such patients to minimize outdoor activity when regional TRAP particle levels are increased and avoid exposures to indoor pollutants such as tobacco smoke that act in a similar fashion. Clinicians also should be aware that significant localized exposures to car and bus emissions can worsen asthma, even on “low air pollution days,” in susceptible patients.⁴

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