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Air Pollution and Autism Spectrum Disorders: Causal or Confounded?

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Abstract

In the last decade, several studies have examined the association between perinatal exposure to ambient air pollution and risk of autism spectrum disorder (ASD). These studies have largely been consistent, with associations seen with different aspects of air pollution, including hazardous air toxics, ozone, particulate and traffic-related pollution. Confounding by socioeconomic status (SES) and place of residence are of particular concern, as these can be related to ASD case ascertainment and other potential causal risk factors for ASD. While all studies take steps to address this concern, residual confounding is difficult to rule out. Two recent studies of air pollution and ASD, however, present findings that strongly argue against residual confounding, especially for factors that do not vary over relatively short time intervals. These two studies, conducted in communities around the US, found a specific association with air pollution exposure during the third, but not the first, trimester, when both trimesters were modeled simultaneously. In this review, we discuss confounding possibilities and then explain—with the aid of directed acyclic graphs (DAGs)—why an association that is specific to a particular time window, when multiple exposure windows are simultaneously assessed, argues against residual confounding by (even unmeasured) non-time varying factors. In addition, we discuss why examining ambient air pollution concentration as a proxy for personal exposure helps avoid confounding by personal behavior differences, and the implications of measurement error in using ambient concentrations as a proxy for personal exposures. Given the general consistency of findings across studies and the exposure-window-specific associations recently reported, the overall evidence for a causal association between air pollution and ASD is increasingly compelling.

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Conflict of Interest

Marc G. Weisskopf, Marianthi-Anna Kioumourtzoglou, and Andrea L. Roberts declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Keywords

Autism spectrum disorders; air pollution; particles; epidemiology; confounding; causality

Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder, characterized by difficulty in communication and social interaction, as well as restrictive and repetitive behaviors and interests [1]. The global prevalence of ASD is estimated at 6.2 to 7.6 per 1000 persons, although this estimate varies across studies, and ASD accounts for substantial social and financial burden across the lifespan [2,3]. In the U.S. the prevalence of autism is about one child in 68 [4]. Although heritability has been implicated in ASD etiology [1,5,6], recent evidence supports a greater environmental contribution than previously thought [7–10]. Several recent studies have indicated that perinatal exposure to air pollution may be an environmental risk factor for ASD [8,11]. While this seems at odds with rising ASD and largely declining air pollution, there are several reasons why this would be. Among others, examples include that such an association at the ecological level may not be seen with a single contributing factor when many factors contribute to a condition; or that air pollution could share a causal mechanism with many other factors, the sum of which could be rising. Ultimately, the best evidence for causality of a potential risk factor comes from rigorous individual level epidemiological studies rather than ecologic analyses. Below we discuss the state of the literature on air pollution and ASD, and why we believe the evidence for a causal association is increasingly compelling.

Air pollution is a mixture of gases and particles that are either primarily emitted (e.g. from industrial processes, biogenic sources, vehicular exhaust, combustion products, dust), or are secondarily formed in the atmosphere [12]. Three studies investigated whether exposure to any of several different hazardous air pollutants (HAP) was associated with ASD and reported significant associations, albeit with different HAPs, including metals, styrene, methylene chloride, volatile organics and others [13–16]. Diesel particulate matter (PM), a traffic-related air mixture, has been associated with ASD in two studies [13,15]. The association between traffic-related pollution and ASD diagnosis has also been reported in the literature using other proxy measures for traffic-related pollution such as distance of residence from road [17] or traffic tracers such as nitrogen dioxide [18–20]. However, in a study of twins in Stockholm County, Sweden, Gong et al. [21] observed no association between nitrogen oxides (also a traffic tracer), nor traffic-specific PM ≤ 10 μm in aerodynamic diameter (PM_{10}) and ASD, defined using an autistic traits scale cutoff. A European study combining four population-based cohorts from Sweden, the Netherlands, Italy and Spain did not find any associations between NO_2 (it did not consider PM) and higher ASD traits score [22]. These European studies are the only published studies to find no association between air pollution and ASD. Other studies have linked perinatal exposures to ozone [18,19] and PM ≤ 2.5 μm in aerodynamic diameter ($PM_{2.5}$) [18,20,23] with ASD.

All studies of air pollution and ASD have considered exposure in the perinatal period; several also considered more specific time periods of exposure. Although not always

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consistent for different pollutants and different time periods, elevated effect estimates have been observed for exposures during the entire gestational period, in the first year of life, and for different trimesters of pregnancy [18,20,23,24]. As air pollutant exposures across the different potential exposure windows are usually correlated, when different exposure time periods are modeled separately it would be expected that several would show associations even if only a single time period was causally related to the increased risk of ASD.

Only two recently published studies have calculated exposure-window-specific effects in analytic models simultaneously, an approach that is needed to isolate associations to specific time periods—as we will describe below. Kalkbrenner et al. [24] examined PM_{10} exposures in North Carolina and California, and Raz et al. [23] examined $PM_{2.5}$ and coarse particle ($PM_{10-2.5}$) exposures in a nationwide study (Table). In the Kalkbrenner et al. [24] study, when trimester exposures were separately examined, a protective association was observed for the first trimester and an elevated association for the third. In the Raz et al. [23] study, no associations were seen for $PM_{10-2.5}$, while elevated associations were observed for all trimesters for $PM_{2.5}$ when separately assessed. However, in both papers, when associations with the first and third trimesters were simultaneously estimated (Raz et al. [23] also included 2nd trimester exposure), the first trimester estimate became null (and the 2nd trimester in Raz et al.), while the third trimester effect estimate remained elevated and essentially unchanged. Raz et al. [23] also found associations with the 9 months before, during, and after pregnancy when each was modeled separately, but only an association with exposure during pregnancy when all were modeled simultaneously.

Determining whether the association between air pollution exposure and ASD is causal has important implications, because of potential insight into ASD etiology and also because air pollution exposures are modifiable through changes in both individual behaviors and public policy. Potential confounding must be carefully considered. Though all of the studies attempted to eliminate alternative explanations for air pollution-ASD associations, in epidemiological studies it can be very difficult to know whether one has sufficiently eliminated confounding and other forms of bias. Below, we first discuss potential confounders of the air pollution-ASD association that may introduce bias in these studies. Then, we discuss implications for potential confounding when associations are found with exposures during specific time periods (when more than one time period are modeled simultaneously) as the most recent two papers have done [23,24]. Finally, we discuss potential impacts of varying exposure measurement error across pregnancy periods.

Potential confounding in studies of perinatal air pollution exposures and ASD risk

Two types of confounding may be of concern in studying the association of air pollutants and ASD: confounding related to ASD ascertainment, and confounding by causal risk factors. Factors associated with ASD ascertainment may be associated with air pollution and so may bias associations between perinatal air pollutant exposure and risk of ASD. For example, urbanicity and high population density are strongly positively associated with most air pollutants [14,15,25,26]. Some characteristics of residential areas are also associated with the ascertainment of ASD. For example, residence more than 20 miles from a medical

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school is associated with ASD under-diagnosis, as is residence in a Health Professional Shortage Area [27]. Medical schools are overwhelmingly in or near a city center [28], and residents of rural vs. non-rural areas are nearly four times as likely to live in a Health Professional Shortage Area [29]. Thus, if these variables affecting ascertainment are not completely adjusted for, it is possible that more comprehensive autism ascertainment in more versus less urban areas could partly account for associations found between air pollutant exposures and ASD.

In contrast, other factors positively associated with air pollution can be negatively associated with ASD ascertainment. For example, in the US, low socioeconomic status (SES) is often associated with higher exposure to air pollution [30,31]. Indicators of lower maternal SES, including lower education, lower household income, and unmarried status, have been associated with under-diagnosis of ASD [27]. Thus, failure to adequately account for maternal SES may bias estimates of the association of air pollutants with ASD downwards – toward the null if the true causal association is positive, and toward a protective association if the true causal association is null.

In addition to factors affecting the ascertainment of ASD, potentially causal risk factors for ASD may also confound the association between perinatal air pollution exposure and ASD. For example, urbanicity is typically negatively associated with obesity and positively associated with air pollution. Maternal obesity is hypothesized to be a causal risk factor for ASD [32–34]. Features more common to cities, including mixtures of commercial, industrial, residential and office use, interconnected streets, and dense population, encourage physical activity and are associated with lower BMI [35]. In the US, states with higher percentages of rural residents tend also to have higher prevalence of obesity [36]. Thus, given differences in air pollution levels often found between urban and rural settings, failure to account for maternal BMI could lead to bias in estimates of the effect of perinatal air pollutants on ASD risk. The direction of this bias would depend on whether maternal BMI is negatively or positively associated with air pollution exposure in a given sample. Additionally, SES may confound the relation between ASD and air pollution due to the higher prevalence of obstetrical conditions in mothers of lower SES [37,38]; conditions such as low birth weight, short gestation, gestational diabetes, bleeding during pregnancy, low Apgar score, preeclampsia, and cesarean delivery have been associated with elevated risk of autism [33,39,40]. Air pollution has been associated with many of the above conditions [41–44], which could be intermediates on a causal pathway from air pollution to ASD. However, to the extent these conditions are caused by factors other than air pollution, for example, by maternal stress [45–48], incomplete adjustment for SES may potentially bias air pollutant-ASD associations away from the null in a positive direction in samples in which lower SES is associated with higher air pollution exposure.

In addition to the factors cited here, other potential causal risk and protective factors for ASD are socially patterned (with prevalence of risk factors generally more common among persons of lower SES and prevalence of protective factors more common among persons of higher SES), and may be associated with air pollutants in certain geographic regions. Some examples include prenatal vitamin intake [49], exposure to stressors, including intimate

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partner violence [45,50], exposure to indoor toxicants [51], and quality of maternal prenatal diet [52].

Overall, because confounding arises from common causes of air pollution levels and ASD, the factors of greatest concern for confounding relate largely to SES and place of residence. While it can be difficult to completely capture such variables, we describe below how the findings of two of the most recent air pollution-ASD studies provide the strongest evidence yet that the observed associations are not the result of confounding. It is also possible that personal behavior differences could be related to both ASD and how a mother comes into contact with air pollution, thus possibly introducing confounding. However, we describe below how using ambient air pollution levels as a proxy for personal exposures, rather than directly measuring personal exposures, helps avoids this concern.

The importance of critical windows of exposure

Associations between exposures and health outcomes are sometimes specific to exposures during particular time windows. When this is the case—for example the findings in two of the most recent studies of PM and ASD of an association between exposure during the third trimester of pregnancy and ASD, but not exposure in the first trimester [23,24]—there are important implications for causality. First, specific time windows of vulnerability to a given exposure can suggest the involvement of certain time-specific biological events. For instance, the third trimester of pregnancy is a period when cortical synaptogenesis is peaking [53,54]. Thus, the exposure-window specificity in recent ASD studies for associations with air pollution exposures during the 3rd trimester could focus attention on biological events like these. Second, from the epidemiological perspective, simultaneous examination of different time periods of exposure can provide a check on the presence of confounding bias, thereby greatly increasing the likelihood that the association found is truly causal when this check suggests no confounding.

Time-Invariant Confounding

Figure 1 is a Directed Acyclic Graph (DAG) representing different possible sets of basic assumptions about the causal relationships among key variables in the two recent studies of PM exposure and ASD [23,24]. A full explanation of DAGs and the theory underlying them is beyond the scope of this review, but we refer the reader to a key text on the topic [55]. As drawn, the DAG in figure 1A makes the assumption that neither PM during the 1st trimester of pregnancy (PM_{1st}) nor PM in the 3rd trimester (PM_{3rd}) causes ASD, but that an uncontrolled time-invariant variable U is causally related to ASD and also related to both PM_{1st} and PM_{3rd}. For example, U could be some aspect of SES, which, as described above, is related both to PM levels and the likelihood of getting an ASD diagnosis. More generally, the U indicated in Figure 1 could be any confounder that is time-invariant over the time period covered by the exposure windows (and thus affects both PM_{1st} and PM_{3rd} equally). We will examine the possibility of time-varying confounding variables that relate to PM in only one exposure window (or to PM in multiple windows, but differently in different windows) below; these are not included in Figure 1.

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If the DAG in Figure 1A is correct, then a non-causal association would be seen between ASD and both PM_{1st} and PM_{3rd} (whether or not they are modeled together) induced by confounding through the uncontrolled variable U. However, if an association is found that is specific to a particular time window—in our case, for example, PM_{3rd} and not PM_{1st}—when both time windows are in the model together, then U cannot be confounding the association of ASD with PM_{3rd}. If U were confounding the association with PM_{3rd}, we would also see the association of ASD with PM_{1st}. In this situation, PM_{1st} acts as a negative control exposure, i.e. an exposure that suggests uncontrolled confounding if it is associated with the outcome (see [56–59] for details on this concept). Importantly, confounding is ruled out even if U leads to ASD through an event specific to only one time window (or to different effects in different windows), e.g., women of higher versus lower SES may be more likely to be taking folate supplements in the 1st trimester, but not the 3rd (Figure 1B). This trimester-specific effect of SES would be one of the reasons there is a causal relation between SES and ASD (represented by the arrow; there could be other reasons as well), but that part of the confounding path between PM and ASD is the same for both PM_{1st} (PM_{1st}←SES→folate supplements in 1st trimester →ASD) *and* PM_{3rd} (PM_{3rd}←SES→folate supplements in the 1st trimester →ASD) because SES is invariant over the pregnancy period and so has the same relation with PM_{1st} as with PM_{3rd}. Thus, an association of ASD only with PM_{3rd} but not PM_{1st} in a model containing both PM_{3rd} and PM_{1st} suggests that the causal structure is as shown in Figure 1C.

Figure 1C makes clear why PM_{3rd} and PM_{1st} need to be estimated together: if they are not, then PM_{1st} would be associated with ASD because of its correlation with PM_{3rd} via the path PM_{1st}←U→PM_{3rd}→ASD. This path is blocked by conditioning on PM_{3rd}. A similar situation could be described for exposure during the entire pregnancy vs. the 9 months before or after, as in our recent study [23]. Note that as originally described, ideal negative control exposure variables are known *a priori* to not cause the outcome under study [56]. However, we recently described how under reasonable assumptions, exposures for which a causal effect on the outcome is uncertain (such as PM exposure in different time windows) can also act as negative control exposures if, when included in a model with other exposure time windows, their association with the outcome is null [59].

Time Varying Confounding

In our example, the described negative control exposure approach implies that there is not uncontrolled confounding by factors that are time invariant over the exposure windows considered (here the 9 months of pregnancy). This point is very important, in that it implies that confounding by, for example, variables related to socioeconomic status (SES) or case ascertainment—that otherwise can be quite problematic for studies of air pollution and ASD [27,60] as described above—is not occurring. In contrast, a time-varying variable V that could be differentially related to PM_{3rd} (V_{3rd}) and PM_{1st} (V_{1st}) could still confound the association between PM_{3rd} and ASD in analyses including PM_{1st} (via the path PM_{3rd}←V_{3rd}→ASD; Figure 2A). In air pollution studies, however, there are very few factors that could conceivably generate this type of time-varying confounding. One possibility is time-varying meteorological factors associated with air pollution, such as wind patterns and temperature. It is unclear, however, how these meteorological factors could be

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causal risk factors for ASD. If they are not causal risk factors for ASD, they do not introduce confounding (although some recent studies have reported associations between temperature and known ASD risk factors, such as preterm birth and birth weight [61–64]). On the other hand, other air pollutants (M)—for example, traffic-related gases—are more plausible candidates for time-varying confounders of PM (with a causal structure more likely like that depicted in Figure 2B). Therefore, other air pollutants cannot be ruled out as confounding the PM-ASD association, but in this case, some air pollutant would still be implicated in causing ASD (and the strength of causal inference from the negative control exposure described above would still apply to the offending, confounding other air pollutant for which PM would in this case be a proxy).

One potential concern that should be noted is that if a woman changes address during her pregnancy, then what was a time invariant covariate, for example neighborhood median house value, could become a time varying one (if she moves to a neighborhood with a different median house value). However, in this case, a slight weakness of the Kalkbrenner et al. paper becomes an advantage [24]. Pregnancy address in the main analyses of that study was determined from the birth certificate and so, if a woman moved after the 1st trimester, the exposure assignment for the 1st trimester would be incorrect. But that makes the 1st trimester exposure assignment based on the birth address an even better negative control exposure for the 3rd trimester, because it cannot be causally related to the outcome while still being associated with the same median house value that could confound the 3rd trimester estimate [56–59]. Thus, in this case, variables that might be time varying because of changing addresses during pregnancy are not the problem they could be in other settings. To be clear, this would be a problem for the interpretation of the effect estimate for the 1st trimester (related to how well the assigned ambient concentration predicts personal exposure, discussed in “The trouble with measurement error” section below), but it would in this case not be a time-varying variable that could create a spurious association with the 3rd trimester estimate. Also suggesting this is the fact that in the Raz et al. study, and a subanalysis of the Kalkbrenner et al. study, the results were similar when analyzing all women or just those that did not move during pregnancy [23,24].

Use of Ambient Concentrations vs. Personal Exposures of Air Pollutants

Another factor that can vary over short time periods is personal behavior. However, perhaps counter-intuitively, examining associations with *ambient* air pollution concentrations rather than *personal* air pollution exposures—while introducing exposure measurement error [65]—helps avoid confounding biases that could stem from differences in personal behaviors. This occurs because 1) ambient air pollutant concentrations are used as proxies for personal exposure (as any causal biological mechanism would be acting through actual personal exposure), and 2) because individual behaviors that could differ over time (e.g. 1st vs. 3rd trimester) affect personal exposure directly, but not estimated ambient concentrations (Figure 3).

In Figure 3 we distinguish between ambient PM concentrations (^{amb}PM) and personal PM exposure (^{pers}PM) either during the 1st or 3rd trimester of pregnancy (this could also be applied to the 9 months before, during, or after pregnancy). It is possible, for example, that

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in the 1st trimester of pregnancy a woman works away from home more often than during the 3rd trimester. This change in work patterns could in turn affect her personal PM exposure. If these different activity patterns (depicted by $^{pers}V_{1st}$ and $^{pers}V_{3rd}$) are also somehow related to ASD, then they could introduce a bias in the association between ^{pers}PM and ASD, e.g. along the path $^{pers}PM_{3rd} \leftarrow ^{pers}V_{3rd} \rightarrow ASD$, that could differ for the 1st and 3rd trimesters. However, this potential confounding from differences in individual behavior in the two exposure time windows could not confound estimates of the *ambient* PM–ASD association.

In Figure 3, the ^{pers}PM variables ($^{pers}PM_{1st}$ and $^{pers}PM_{3rd}$) are common effects of ambient PM concentrations ($^{amb}PM_{1st}$ and $^{amb}PM_{3rd}$) and personal V variables ($^{pers}V_{1st}$ and $^{pers}V_{3rd}$). In DAG terminology this is referred to as a "collider" – a variable into which two arrows point. Colliders block the association between the variables that collide on them [55]—in our case between $^{amb}PM_{3rd}$ and $^{pers}V_{3rd}$. Therefore, a (non-causal) statistical association between $^{amb}PM_{3rd}$ and ASD cannot occur along the path $^{amb}PM_{3rd} \rightarrow ^{pers}PM_{3rd} \leftarrow ^{pers}V_{3rd} \rightarrow ASD$ because $^{pers}PM_{3rd}$ is a collider. This would be true not just for differences in time spent away from home during the different exposure time windows, but also for any other such personal behavior differences. If individual behaviors directly affected the ambient concentrations (an arrow from, e.g., $^{pers}V_{3rd}$ to $^{amb}PM_{3rd}$), then those behaviors could confound estimates for the ^{amb}PM measures, but this is largely not plausible (nor could such behaviors affect the modeling of ambient air pollution concentrations). If individual behaviors and ambient concentrations share time-varying common causes, then this could introduce time-varying confounding, but this is both somewhat unlikely and, if it is present, is likely weak and so would introduce little confounding. Note that while this time-varying confounding could in general be the result of changing address during pregnancy (causing a time invariant variable to become time varying), this does not appear to account for the trimester specific ASD findings for the reasons given in the preceding section. Under these conditions, estimates of ambient air pollution concentrations are effectively acting as instrumental variables for personal exposures and so avoid the problem of confounding of personal air pollution exposure and ASD by individual behaviors (see [66,67] for discussion of instrumental variables).

It is conceivable that that ambient PM (^{amb}PM) could affect personal behavior (^{pers}V)—for example, a mother knows of high ambient pollution on a given day and decides to stay inside—which in turn could affect personal exposure (^{pers}PM), and that could differ by trimester. In this structure, ^{pers}PM is not a collider, but ^{pers}V still cannot confound the $^{amb}PM \rightarrow ASD$ association because ^{amb}PM causes ^{pers}V not vice-versa (there is no arrow into ^{amb}PM from ^{pers}V). In this case, the difference in personal behavior by trimester could differentially affect estimates for ^{amb}PM by trimester, but only if there is truly a causal association between ^{pers}PM and ASD as discussed in the following section.

The trouble with measurement error

There are many different potential sources of measurement error, e.g. [68–71], but it is beyond the scope of this paper to review the impact of all different error types on the association between air pollution and ASD. In this section we focus on error that is more

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likely to be different for different time windows (e.g. 1st vs 3rd trimester), specifically that induced by use of exposure predictions based on estimated ambient concentrations at a residence that ignore personal behavior and activity patterns. We do, however, assume that the estimated ambient concentrations at the mother's residential address are equally accurate measures of the true ambient concentrations at the address in the different exposure windows (independently of where the mother actually is), and there is no reason to suspect otherwise. Although error in the estimation of individual air pollution exposures by ambient air pollution concentrations will not introduce confounding bias from personal behavior differences into the effect estimates for the ambient concentrations, as described in the previous section, this error can attenuate the ambient air pollution effect estimates [65]. For example, when using methods to assign an ambient air pollutant concentration estimate at a woman's residential address, either by using concentrations measured at some nearby monitor(s) or by model predictions (as is typically done, e.g. [23,24]), if a woman spent much of her time at home during the 3rd trimester of pregnancy but not during the 1st trimester, $^{amb}PM_{3rd}$ would be a more accurate measure of $^{pers}PM_{3rd}$ than would $^{amb}PM_{1st}$ of $^{pers}PM_{1st}$. If there were true causal effects of both $^{pers}PM_{1st}$ and $^{pers}PM_{3rd}$, then the effect estimate for $^{amb}PM_{1st}$ would be attenuated compared with that of $^{amb}PM_{3rd}$. (A similar scenario could be described to explain a stronger result for, e.g. the 9 months of pregnancy vs. the 9 months after). Although measurement error could account for different effect estimates of ambient PM with ASD in different exposure time windows, this difference in measurement error in the two time periods does not nullify the negative control exposure argument against residual confounding by time-invariant U outlined in Figure 1. The measurement error we are discussing affects how well ^{amb}PM predicts ^{pers}PM, *not* how well we estimate ^{amb}PM concentrations. The confounding that negative control exposures can reveal (the U in Figure 1) is confounding of the ^{amb}PM-ASD association; it is independent of the association between ^{amb}PM and ^{pers}PM, and would exist regardless of what the $^{amb}PM \rightarrow ^{pers}PM$ association was. In DAG path terms, the measurement error affects the strength of the arrow between ^{amb}PM and ^{pers}PM ($^{amb}PM \rightarrow ^{pers}PM$), but that arrow is not in the potential confounding path $^{amb}PM \leftarrow U \rightarrow ASD$. Thus, despite the potentially different attenuation of $^{amb}PM_{1st}$ and $^{amb}PM_{3rd}$ effect estimates for ASD from errors in approximating personal exposure from ambient pollution concentrations, an ^{amb}PM-ASD association that is specific to a particular exposure time period still implies that confounding by the U variables described in Figure 1 is not present. Note, however, that while this increases our confidence in the causality of the association seen with PM exposure in the 3rd trimester, we cannot rule out that exposure during the 1st trimester (or another period) is *also* causally related to ASD. For example, in the two recent studies in which exposure in different time periods were modeled together [23,24], it is possible that a true causal effect of PM exposure in the 1st trimester could have been completely attenuated by error in estimating personal exposure from ambient concentrations in the 1st trimester.

Conclusions

The direction and magnitude of the association between perinatal air pollution exposures and risk of ASD has been relatively consistent across several studies in different settings. SES and residence-related factors are the elements most likely to confound this association,

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and they can be difficult potential confounders to completely capture and rule out. Two of the most recent studies of air pollution and ASD, however, found associations specific to the 3rd trimester of pregnancy, with null associations for the 1st trimester when both were estimated simultaneously. This exposure-window specificity of findings is an important new contribution and implies that uncontrolled confounding by exposures that do not vary over the time frame examined—such as SES and residence-related factors—cannot account for the estimate seen with 3rd trimester exposure. Given the largely consistent results across the many studies that have explored aspects of air pollution and ASD, the new findings of exposure-window-specific effects suggest either that time-invariant confounding is not as problematic as we might think, or that studies have done a reasonable job of accounting for them. In addition, the use of ambient concentrations rather than personal exposure measures also helps avoid confounding by behavioral differences that could impact personal exposure levels. Thus, while questions still remain about which specific component of air pollution (although there could be several) is the most relevant, we believe the overall evidence for a causal association between exposure to air pollution and risk of ASD is increasingly compelling.

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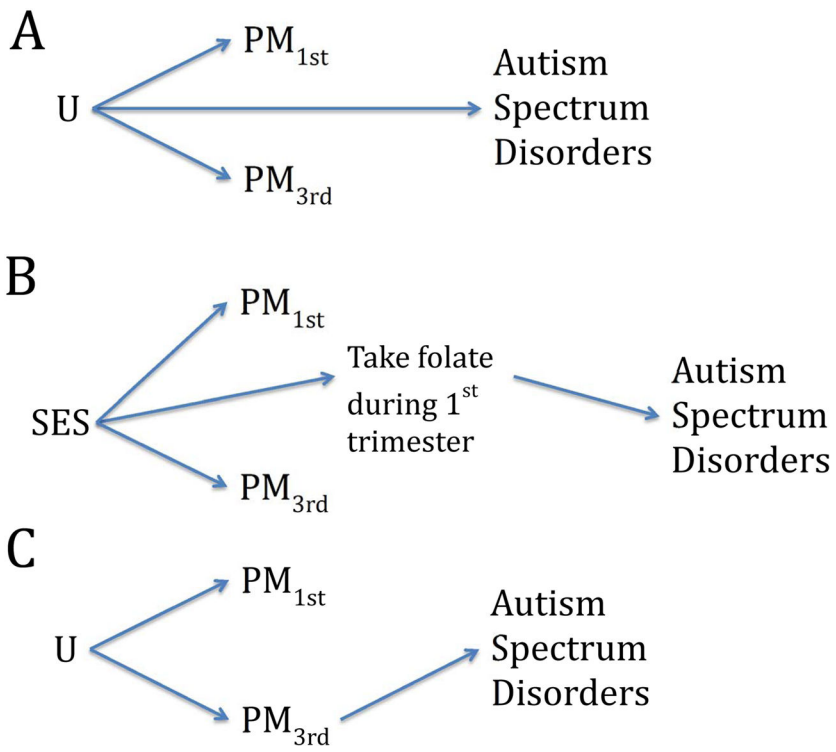

Figure 1.

Directed acyclic graphs (DAG) representing possible confounding of the particulate matter (PM)—autism spectrum disorders (ASD) association by time-invariant factors (U). The subscripts indicate different trimesters of pregnancy. Each panel depicts a different set of assumptions about the underlying factors that give rise to the data. **A)** There is no causal effect of PM on ASD, but some U variables confound the PM-ASD association. **B)** Same as A, with addition of folate consumption during 1st trimester of pregnancy as one way that SES (as one possible U variable) causes ASD. **C)** Only PM_{3rd} is causally associated with ASD, while U and PM_{1st} are not. See text for additional discussion.

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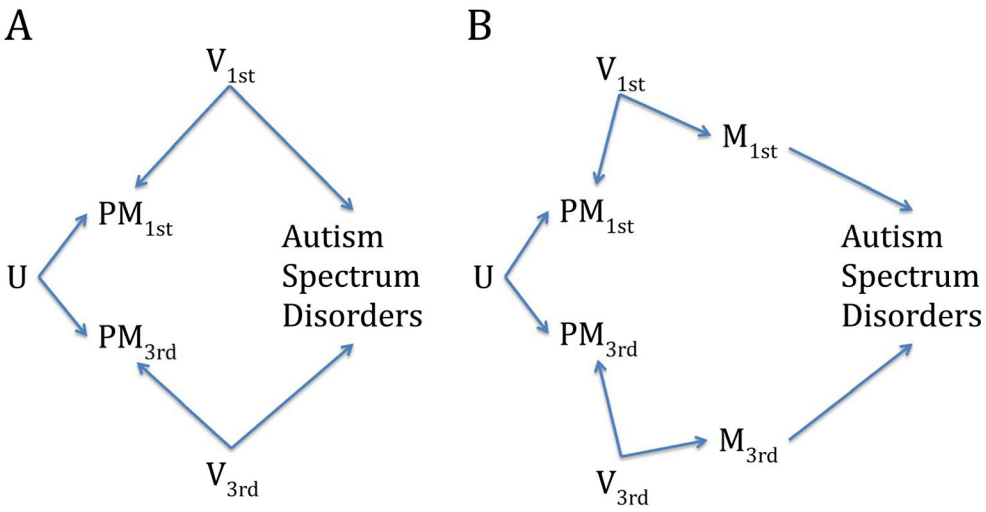

Figure 2.

Directed acyclic graphs (DAG) representing possible confounding of trimester specific associations by time-varying factors. **A)** Factors that vary from the 1st to 3rd trimester of pregnancy (V) could introduce confounding of the particulate matter (PM)—autism spectrum disorders (ASD) association that is specific to one of the trimesters. **B)** Other aspects of air pollution (M) than PM are possible time-varying confounders because they can be correlated with PM in a time-varying way because of factors that predict both (V). See text for additional discussion.

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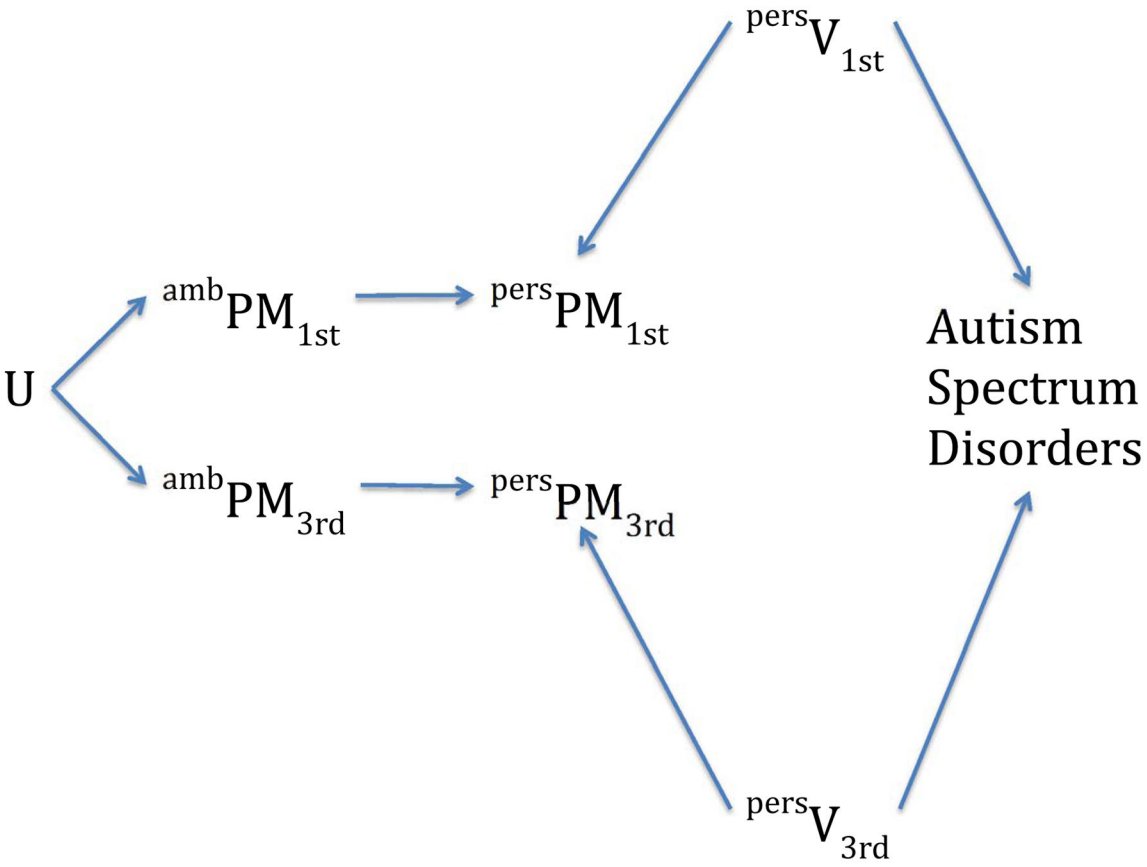

Figure 3.

Directed acyclic graph (DAG) representing the relations between ambient (amb superscripts) particulate matter (PM) concentration estimates, personal (pers superscripts) PM exposure estimates, time invariant factors (U) that affect ambient PM, time-varying factors (V) that affect personal PM exposure, and autism spectrum disorders. The subscripts indicate different trimesters of pregnancy. The personal PM exposures are colliders. See text for additional discussion.

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Table

Comparison of the two papers that examine exposure time period specific associations while adjusting for multiple time periods within individuals

Author	Raz [•• 23]	Kalkbrenner [•• 24]
Publication Year	2015	2015
Population	Nested case-control study of children of the Nurses' Health Study II, a prospective cohort of Nurses enrolled in 1989	Population-based case-cohort of children born in San Francisco Bay Area and North Carolina.
N (cases, controls)	1767 (245 cases, 1522 controls)	15,645 (979 cases, 14,666random sub-cohort identified from birth records)
ASD definition	Autism, Asperger's syndrome, or other autism spectrum disorder, and excluding genetic syndromes	DSM-IV-TR Autism spectrum disorder
ASD ascertainment	Maternal report, validated with the Autism Diagnostic Interview-Revised in a subsample and with the Social Responsiveness Scale in most participants	The Autism and Developmental Disabilities Monitoring Network: active records-based surveillance based on children's developmental records from health and educational agencies
Air pollution definition	Monthly averages of particulate matter (PM), diameters ≤2.5 μm ($PM_{2.5}$) and 2.5–10 μm ($PM_{10\text{-}2.5}$), predicted from a continental US spatiotemporal model and linked to residential addresses. Data from USEPA's Air Quality System and other sources	Daily PM_{10} concentrations were estimated with a moving-window kriging approach using the Bayesian Maximum Entropy geostatistical method linked to residential address. Data from USEPA's Air Quality System
Residency ascertainment	Multiple maternal reports, accounting for moving during pregnancy	Address on birth certificate; address history via LexisNexis to ascertain moving during pregnancy on a subset
Potential confounders examined	Child's birth year, child's birth month, child's sex, maternal age, paternal age, paternal education, maternal grandparents' education premature birth, birth weight, gestational diabetes, preeclampsia, smoking during pregnancy, state, maternal marital status, Census tract median income, Census tract median house value	Child's state of birth, year of birth, state by year, season of birth, race/ethnicity, maternal education, maternal age, Census block median household income, Census block urbanization, maternal marital status, tobacco use during pregnancy
Effect estimates*	No association found for $PM_{2.5\text{–}10}$	
	$PM_{2.5}$	**PM_{10}**
	Adjusted odds ratio (95% CI), per IQR increase (4.4 μg/m^3)	**Adjusted odds ratio (95% CI), per 10 μg/m^3 increase**
1st trimester#	1.23 (1.01, 1.49)	0.86 (0.74 0.99)
2nd trimester#	1.27 (1.05, 1.54)	0.97 (0.83 1.15)
3rd trimester#	1.49 (1.20, 1.85)	1.36 (1.13 1.63)
1st trimester, adjusted for other exposure periods	1.06 (0.83, 1.35), adjusted for exposure in the 2nd and 3rd trimester	1.01 (0.81 1.27), adjusted for exposure in the 3rd trimester
2nd trimester, adjusted for other exposure periods	1.00 (0.78, 1.30), adjusted for exposure in the 1st and 3rd trimester	0.93 (0.79 1.09), adjusted for exposure in the 3rd trimester
3rd trimester, adjusted for other exposure periods	1.42 (1.09, 1.86), adjusted for exposure in the 1st and 2nd trimester	1.38 (1.03 1.84), adjusted for exposure in the 1st trimester

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* Due to the large number of effect estimates presented in the two papers, only an illustrative sample is included here.

Not adjusted for other exposure period.