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Ambient air pollution: How much of estimated "prenatal exposure" is truly attributable to pre-birth exposures?

In the September 2017 online issue of Environmental Research, Hehua et al. (2017) concluded that prenatal exposure to NO_2, SO_2, and PM_{10} is significantly associated with wheezing and asthma development in childhood, after conducting a systematic review and meta-analysis. However, this paper has several methodological shortcomings which render its overall conclusions questionable.

First, the authors selected papers that reported prenatal exposure effects on wheeze and asthma and interpreted the resulting pooled effects as being true consequences of prenatal exposures. None of the included studies adjusted for postnatal exposures and those that did report correlations between prenatal and postnatal exposures for NO_2 found them to be very high [0.94 (Aguilera et al., 2013), 0.97 (Liu et al., 2016)] or moderate [0.53 (Clark et al., 2010), 0.5 (Esplugues et al., 2011)]. With the exception of only one study (Esplugues et al., 2011), the studies that compared postnatal and prenatal exposure effects found the latter ones to be highest for asthma (Liu et al., 2016; Clark et al., 2010) and wheeze (Aguilera et al., 2013). Thus, the data on impacts of prenatal NO_2 exposure on asthma development and wheeze by Hehua et al. (2017) cannot rule out a potential postnatal effect.

Second, not all relevant studies were included in the systematic review and meta-analysis, in particular with respect to NO_2 exposure during the whole pregnancy period and early life asthma onset and wheeze. While the findings from Sbihi et al. (2016) were included, in which the birth address exposure was interpreted as a whole pregnancy exposure among non-movers, several other papers that also used this strategy were ignored (Heinrich et al., 2016; Mölter et al., 2015). A recent systematic review (Heinrich et al., 2016) and meta-analysis (Mölter et al., 2015) reported slightly increased risks for wheeze and asthma but no associations reached statistical significance for NO_2 or particulate matter.

Third, the calculated overall estimates for prenatal air pollution exposure effects on asthma and wheeze, shown in Figures 2–4, included all reported effect estimates, even if more than one estimate was provided per study. This strategy is not justified as it leads to the inclusion of several effect estimates that are not independent. Consequently, the obtained pooled estimates of the meta-analyses are biased. For example, the correct pooled estimate for NO_2 and asthma is 1.05 (0.96–1.14), $p = 0.282$, which summarizes the effect estimates for the whole pregnancy period from Deng et al. (2016) and the Land Use Regression (LUR) based estimates derived in Sbihi et al. (2016) and Clark et al. (2010) (the corresponding reported effect estimate in Hehua et al. (2017) was 1.12 (1.04–1.19)). In these last two studies, the LUR exposure estimates should be used because these were considered to be more precise and to have a higher spatial resolution than the estimates derived using the Inverse Distance Weighted exposure assessment strategy. The given pooled effect estimates for wheeze in Figure 2 and asthma in Table 3 are also incorrect. Once re-calculated, the correct effect estimates are overall more conservative than the conclusions reached by Hehua et al. (2017), which is also supported by a recent systematic review on the effects of life-long exposure to NO_2 and particulate matter on asthma development and wheeze using published birth cohort data (Heinrich et al., 2016).

Fourth, there are some minor mistakes regarding citations for the incidence of wheeze and asthma from Khreis et al. (2017), Fan et al. (2016) and Veras et al. (2017), although these studies summarized findings from cross-sectional studies and from hospital admissions in relation to air pollution exposure.

Overall, the health impact assessment of exposure to ambient air pollutants during pregnancy on asthma and wheeze is more complex than presented by Hehua et al. (2017). Exposures pre and post birth in cohort studies are almost always highly correlated. This universal challenge in most birth cohort studies hinders the ability to distinguish with confidence which window of time represents the vulnerable time period where environmental exposures play a role in the etiology of the disease of interest. However, a smart strategy was recently suggested for second-hand smoke exposure and asthma (Neuman et al., 2012); exposure could be categorized as never exposed, prenatally exposed only, postnatally exposed only and either prenatally or postnatally exposed. This grouping might better reflect the complexity of the topic. A similar strategy could be applied to prenatal ambient air pollution exposures and is highly warranted. Alternatively, models should at least be adjusted by postnatal exposures. Moreover, advances in modeling exposures are also allowing to obtain a high level of spatio-temporal granularity that may help analysis and re-analysis of birth cohort studies.

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