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Commentary: Tobacco smoking and asthma: multigenerational effects, epigenetics and multilevel causal mediation analysis

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In this issue of the *Journal*, Accordini *et al*. document the findings from their study of the multigenerational asthma effects of tobacco smoking.[1] They found that grandmothers' tobacco smoking during pregnancy was

associated with their own children's asthma, and that the mothers' smoking was associated with asthma in the grandchildren. Importantly, they found that the grandmothers' smoking (in generation 1) when pregnant with the mothers (in generation 2) was linked to the grandchildren's asthma with nasal allergies (in generation 3), through pathways other than through the mothers' asthma or smoking during pregnancy. This is not entirely surprising. There is growing evidence that phenotypic risk factors can be subject to vertical or multigenerational inheritance. Furthermore, tobacco smoking is detrimental to health, having been linked to substantial morbidity and mortality from cancer, respiratory disease and heart disease, among others.[2] In pregnancy, tobacco smoking is known to lead to poor perinatal, pediatric and life-long outcomes, such as birth outcomes including low birth weight, small-for-gestational age, birth defects and many others.

The vertical transmission of the asthma effects of smoking within the maternal line will, at first, seem to suggest another reason for stopping or not initiating smoking during pregnancy in (grand)mothers. It is unclear whether telling smokers that their tobacco smoking will have deleterious health effects in their progeny will prove effective. Similar arguments could be made for the 'transmission' of the asthma effect of fathers' smoking during their reproductive development. Nonetheless, it is important to learn about the multigenerational asthma effects of smoking for the reasons outlined by Accordini *et al.*[1] The study provides important evidence that grandparents' health behaviour can have a lasting impact on their children's and grandchildren's health and, perhaps, further down the line. If this suggested mechanism proves to be durable, it offers an important early window for tackling risk factors of asthma. This study supports an epigenetic mechanism whereby (nicotine from) tobacco smoking leads to epigenetic variations that are transmitted from grandmothers to their grandchildren, through pathways other than through asthma phenotypes in their children.[3–5] Epigenetics has been gaining focus in studies of human health and disease, including asthma.[3–9] The study findings indicate the need for further investigation of epigenetic and other mechanisms that could be responsible for the links between ancestral tobacco smoking and asthma in descendants.

The authors should be commended for their thoughtfully executed study, especially for their multicenter, multilevel, multigenerational, multiple-exposure, single-mediator design and analysis, coupled with sensitivity analysis for uncontrolled confounding (see also the Supplementary Appendix of Accordini *et al*).[1] The study explored possible explanations of the multigenerational signals it found: multigenerational genetic, epigenetic or environmental mechanisms. The explanations also considered implications of information bias, collider-stratification bias due to unmeasured confounder(s) of mediator–outcome relations, and uncontrolled confounding of exposure–outcome relations. The authors[1] were rightly worried that such biases could explain part or all of their results. They used causal graphical theory to guide their choice of variables for confounding control for their assumed data generating process.[10,11] They also conducted probabilistic bias analysis[12,13] to assess the sensitivity of their results to an unmeasured common cause of the exposures, mediator and outcome. Taken together, these are important developments for a multigenerational epidemiological study.

What should we expect from future studies on this topic? First, we need more large multigenerational studies with prospectively collected repeated measurements on exposures, mediators, epigenetic markers, covariates and outcomes from diverse populations around the world. Clever, multistage designs with committed funding will be needed for feasible and well powered studies.

Second, we need modern mediation analysis with an eye on path-specific and heterogeneous effects to shed light on mechanisms involved in the multigenerational links from smoking to asthma phenotypes.[14–17] Attention should also be paid to the complexities of identification and estimation of mediated effects in multilevel, multiple-exposure, multiple-mediator and multiple-outcome studies of multigenerational effects of tobacco smoking and other exposures. I propose the use of a multiple-exposure, multiple-mediator and multiple-outcome (MEMMMO) framework in studies of multigenerational epigenetic inheritance. A well-developed MEMMMO framework consists of a structural causal model of the connections and the assumptions needed to identify and estimate the multiple mediational and interaction effects of multiple exposure interventions on multiple outcomes that have complex links over time. In this framework, effect decomposition for mediation analysis should consider other types of direct and indirect effects beyond controlled direct effects in multigenerational studies whenever the assumptions for natural, controlled or interventional effect decomposition appear defensible.[14,15] The causal mediation analysis of these studies within a MEMMMO framework will require further methods and software development, given the current limitations in the literature.[14,17–22]

Third, future studies should undertake multiple-bias modeling to address the impact of different combinations of uncontrolled confounding, selection bias and information bias on study results and conclusions.[12,14,23–29] Multiple-bias modeling can involve probabilistic sensitivity analysis conducted using Monte Carlo simulations and can be subsumed under an integrated general approach to causal mediation analysis (namely, g-computation via

Monte Carlo simulation) and record-level bias analysis (namely, generalized bias simulation, again using Monte Carlo methods).[15,23]

Indeed, epigenetic investigations can and should benefit from modern causal inference methods and conduct more mediation, interaction and bias analyses.

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