

**Commentary on Chan et al (2020): Urgent need for more sophisticated research designs to examine the association between adolescent e-cigarette use and future smoking initiation.**

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Concise summary (50 words): *"In order to determine the relationship or relationships between adolescent e-cigarette use and future smoking, there is an urgent need to triangulate results across different study designs. We propose use of observational cohorts and population-level data in order to facilitate stronger ways of testing hypotheses regarding causal mechanisms."*

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There is a strong association between e-cigarette use amongst non-smoking adolescents and subsequent cigarette smoking(1). The debate around the causal nature this association is ongoing. Some argue that e-cigarettes act as a gateway to tobacco addiction, causing those who might not otherwise have smoked tobacco to become addicted, i.e., the "gateway hypothesis". Others argue that those who experiment with e-cigarettes would have used tobacco regardless of initial e-cigarette use, and that a third variable causing e-cigarette and tobacco use to co-occur, i.e., "common-liability hypothesis"(2).

E-cigarette and tobacco use in adolescence overlaps with other risk-taking behaviours, like drug and alcohol use, and are not isolated from socioeconomic, social and individual factors. The inter-relationship between these variables makes causal inference using traditional epidemiological approaches extremely challenging. It could be that there is a true causal explanation, allowing us to conclude 'on average x causes or does not cause y'. Alternatively, it could be that the "effect" varies in strength, precision or directionality based on risk factors like regulatory and marketing environment, socioeconomic position (SEP) or genes, for example. To date, efforts to address these factors have been inconclusive, and/or have not been able to rule out the presence of residual confounding.

In this issue, Chan et al(3) report an interesting approach to measure residual confounding in their systematic review and meta-analysis of longitudinal cohort studies examining the association between adolescent e-cigarette use and later tobacco use. They calculated "e-values" for each study to see if studies were sensitive to unmeasured confounding(4). The e-value analyses indicated that the "effect" of vaping on later tobacco use could be fully explained by confounding in at least half of the studies.

In recent years, leading epidemiologists have recommended that researchers should triangulate results from epidemiological studies by comparing estimates derived from approaches which allow varying levels of causal interpretation(5). As Chan and other systematic reviewers(1) have identified, there are currently at least 11 longitudinal studies that have examined the association in question, however these studies have used traditional multi-variable approaches in attempt to overcome confounding, and causal inference is not possible. Clearly, there is an urgent need to triangulate

results derived from traditional approaches with approaches that are stronger in their ability to make causal inferences. We propose three types of approaches that could be used.

Firstly, researchers can improve adjustment in traditional multivariable regression analyses. Studies could adjust models for time-varying confounders like stress, other drug and alcohol use, or peer-group factors. Similarly, researchers could adjust models for important genetic and psychological risk factors of tobacco/nicotine use, e.g., CYP2A6, “novelty seeking”, “risk-taking”(2,6). Furthermore, as we know that tobacco use is largely structured by factors like SEP, one approach could be to stratify analyses by SEP, or adjust models for the interaction between exposure and SEP. To strengthen multivariable adjustment, effect estimates could be compared between multivariable adjusted and propensity score adjusted regression approaches.

Secondly, population-level data could be harnessed to investigate relationships between e-cigarette use and/or availability and subsequent smoking rates in young people. For example, interrupted time-series designs combining longitudinal and prevalence data could be used to corroborate or contest findings from longitudinal cohorts. If e-cigarettes cause smoking uptake, this could be tested for in population-level data, using either data on e-cigarette use at a population level or on e-cigarette availability. As e-cigarette regulations continue to change at country-level, there are clear opportunities for research in this area. Interrupted time-series design could be used with readily available data sources; a number of studies have successfully used this approach in the field of addiction(7).

Other novel approaches could be used, but development work is needed first. One approach could be to use instrumental variables as a proxy for e-cigarette use. Instrumental variables are variables that are strongly associated with the exposure, but not with confounders of the exposure and the outcome(8). In tobacco control instrumental variables have been developed for examining the impact of smoking cessation treatments like varenicline and nicotine replacement therapy on future smoking cessation and mental health outcomes(9,10), and these instrumental variables have been shown to produce effect estimates for smoking cessation medicines that are comparable to estimates derived from RCTs of the same medicines(10). However, development work is required first to develop a robust instrument for e-cigarette use. Previous instruments have been established using data available from the Clinical Practice Research Datalink(11). To permit development of a suitable instrument for e-cigarettes, regular recording of e-cigarette use and clinician recommendations of e-cigarettes for smoking cessation should be incentivised in primary care.

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