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Practice of Epidemiology

Interpretation and Potential Biases of Mendelian Randomization Estimates With Time-Varying Exposures

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Mendelian randomization (MR) is used to answer a variety of epidemiologic questions. One stated advantage of MR is that it estimates a "lifetime effect" of exposure, though this term remains vaguely defined. Instrumental variable analysis, on which MR is based, has focused on estimating the effects of point or time-fixed exposures rather than "lifetime effects." Here we use an empirical example with data from the Rotterdam Study (Rotterdam, the Netherlands, 2009–2013) to demonstrate how confusion can arise when estimating "lifetime effects." We provide one possible definition of a lifetime effect: the average change in outcome measured at time *t* when the entire exposure trajectory from conception to time *t* is shifted by 1 unit. We show that MR only estimates this type of lifetime effect under specific conditions—for example, when the effect of the genetic variants used on exposure does not change over time. Lastly, we simulate the magnitude of bias that would result in realistic scenarios that use genetic variants with effects that change over time. We recommend that investigators in future MR studies carefully consider the effect of interest and how genetic variants whose effects change with time may impact the interpretability and validity of their results.

bias (epidemiology); epidemiologic methods; instrumental variable; longitudinal studies; Mendelian randomization analysis

Abbreviations: *ALDH2*, aldehyde dehydrogenase 2 gene; BMI, body mass index; CI, confidence interval; *FTO*, fat mass and obesity-associated gene; IV, instrumental variable; MR, Mendelian randomization.

Mendelian randomization (MR) uses genetic variation as a proposed instrumental variable (IV) to estimate the effect of an exposure on an outcome (1). The increasing availability of genetic data and the perception that the assumptions required for valid causal inference with MR are more plausible than those required for traditional methods have contributed to its popularity.

To estimate the effect of an exposure, MR relies on classical (2) or more robust (3) versions of IV analyses. However, IV analyses have been developed to estimate the effect of exposure at 1 point in time, while MR is often interpreted as a longitudinal or lifetime effect of a time-varying exposure (1, 4–6). The rationale behind this difference in interpretation is likely that genetic effects begin at conception and are present throughout the life course, mimicking, to some extent, a longitudinal intervention. To our knowledge, the validity of this interpretation of MR as a lifetime effect has never been statistically justified with time-varying exposures.

The "lifetime effect" interpretation commonly seen in MR studies also lacks clarity (7). To be a well-defined causal construct, a lifetime effect requires specification of a time frame and a comparison of treatment regimens (8). Not only is the lifetime effect interpretation used in MR ambiguous, but in a recent review of MR contributions, Holmes et al. (9) pointed out that even an ambiguous interpretation would have many exceptions depending on the biological context. A less ambiguous, well-defined causal definition of the MR parameter would make its clinical importance clearer and help identify when MR approaches would be valid.

Here, we explore issues related to MR with time-varying exposures and the estimation of lifetime effects. We provide a definition of a lifetime effect and derive the conditions under which common approaches to MR estimates can be interpreted in this way. We begin with a simple empirical example to demonstrate a case where confusion arises in the interpretation of an MR study.

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AN EMPIRICAL EXAMPLE OF THE DIFFICULTY OF MR WITH TIME-VARYING EXPOSURES

Suppose our goal is to estimate "the" lifetime effect of body mass index (BMI; weight (kg)/height $(m)^2$) on systolic blood pressure using the rs9939609 variant within the fat mass and obesity-associated gene (*FTO*) as a proposed genetic instrument. By proposing this genetic variant as an instrument, we (and other investigators who have proposed this instrument) are assuming that the genetic variant is associated with BMI, has no effect on blood pressure except through its effect on BMI, and shares no causes with blood pressure. Additionally, to obtain an average treatment effect, we further assume effect homogeneity (10).

To estimate this effect, we used data from the Rotterdam Study, a prospective cohort study of people aged 55 years or older living in Rotterdam, the Netherlands (11). The medical ethics committee of Erasmus University Rotterdam approved the study, and informed consent was obtained from all participants. We included all participants who contributed to follow-up visits between 2009 and 2013 ($n = 5{,}123$). The MR estimate, derived via the IV ratio, can be obtained by dividing the per-allele effect of *FTO* on systolic blood pressure by the per-allele effect of *FTO* on BMI. On average in these participants, each high-risk allele was associated with an increase of 0.70 mmHg (95% confidence interval (CI): −0.16, 1.57) in systolic blood pressure and an increase of 0.32 units (95% CI: 0.15, 0.49) in BMI. Therefore, the IV estimate of the effect of BMI on systolic blood pressure is 0.70/0.32= 2.19 mmHg per BMI unit (95% CI: −0.65, 5.04).

Previous literature suggests, however, that the relationship between *FTO* and BMI changes with age (12–14). This time-varying relationship is also observed in the Rotterdam Study (Figure 1). Suppose that instead of using the average per-allele effect on BMI, which is composed of participants of different ages, we instead used information obtained at specific ages. The per-allele effect estimate at age 55 years is over 1 BMI unit (with wide confidence intervals), while the estimate at age 75 years is nearly null. Therefore, measuring the exposure at different ages would result in very different IV estimates because of changes in the denominator of the IV estimate even when the numerator remains the same. Therefore, if BMI were measured at age 55 years in all participants, the IV estimate would be approximately 0.70/1 = 0.70 mmHg per BMI unit. If BMI were measured at age 75 years, the denominator of the IV estimate would be very small—let us say, 0.1 BMI unit—and therefore the estimate would be 7.0 mmHg per BMI unit. Given that very different estimates can be obtained by measuring the exposure at different times, several questions arise: What "lifetime" effects are we actually estimating, and under what assumptions would one or all of these estimates be valid? From a public health perspective, addressing these questions is essential for these numerical estimates to be informative, as it would be important to discern whether changes in BMI would result in small or substantial changes in blood pressure.

This simple example brings up many important questions about using MR with time-varying exposures. In the following sections, we will explore how this can complicate MR analyses, how this can change the interpretation of MR estimates, and under what specific conditions MR estimates can be validly interpreted as well-defined effects.

A CLEARER DEFINITION OF LIFETIME EFFECTS

A clearer definition of what is meant by *lifetime effects* in the context of MR is required in order to determine whether

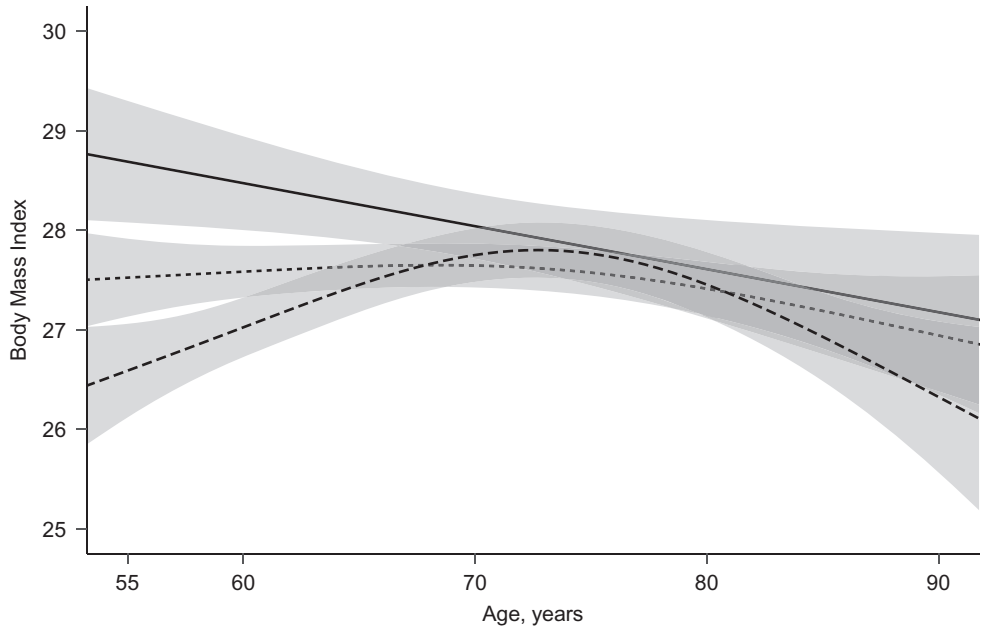

Figure 1. Relationship between body mass index (weight (kg)/height $(m)^2$) and age according to fat mass and obesity-associated gene (*FTO*) allele (rs9939609) among participants from the Rotterdam Study who were followed up between 2009 and 2013 ($n = 5{,}123$). The relationship was estimated using splines with 5 knots for each *FTO* allele. The solid line represents people with 2 A alleles; the short-dashed line represents people with an A allele and a T allele; and the long-dashed line represents people with 2 T alleles. The shaded regions show the 95% confidence intervals.

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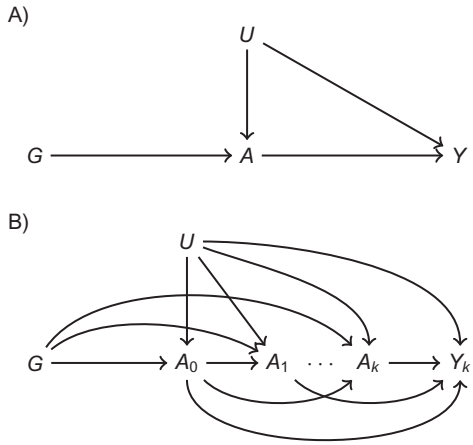

Figure 2. Causal diagrams depicting the relationship between a genetic variant (*G*), an exposure (*A*), and an outcome (*Y*) when the exposure is time-fixed (A) and when the exposure is time-varying (B).

common MR analyses are in fact estimating lifetime effects. The most common definition in the MR literature is "the effects of long-term differences in exposures on disease risk" (1, p. 12), but this lacks the clarity of a properly defined causal parameter (8). Does *long-term* necessarily refer to the effect from conception, or can it also refer to a shorter time period? Does *long-term differences* refer to differences in average lifetime exposure, differences induced by intervening on exposure at conception, or maintaining a fixed difference in exposure at all time points?

We will consider the canonical IV causal diagram with a single binary genetic variant G, a continuous exposure A, a continuous outcome Y, and unmeasured confounders U (Figure 2A). We will use counterfactual notation such that Y_k^a represents the outcome that would have been observed at age k had A been set to a. Using this notation, the effect of increasing a time-fixed exposure by 1 unit at age k would be $E[Y_k^{(a+1)}] - E[Y_k^a]$. In the context of MR with a time-fixed exposure (i.e., an exposure whose level is fixed at conception, such as eye color or blood type), this can be interpreted as the effect of increasing A by 1 unit over the entire lifetime on Y at age k.

With a time-varying exposure, A is not a single value but a vector $\bar{\boldsymbol{A}}_k = (A_0, A_1, \ldots, A_k)$ representing the value of A at each time point between conception ($k = 0$) and time k, at which the outcome is measured (Figure 2B). This vector can be thought of as the trajectory taken by A, similar to the allele-specific BMI trajectories depicted in Figure 1. Therefore, we propose the following definition for a lifetime effect of a time-varying exposure in the context of MR: the effect of shifting the entire exposure trajectory (denoted by the overbar ($\bar{\boldsymbol{A}}$)) by 1 unit on Y at time k. Another way to state this is the effect of increasing the exposure by 1 unit at every point in time. This particular definition of the lifetime effect can be written in counterfactual notation as $E[Y_k^{\bar{a}+\bar{1}}] - E[Y_k^{\bar{a}}]$.

Note the necessity of specifying the time at which the outcome is measured. For any exposure with cumulative effects starting at conception, the lifetime effects must be time- or age-specific, because older people will be exposed for longer periods of time. This means that cumulative effects can be very heterogeneous across age. For some types of noncumulative exposures or cumulative exposures incurred over shorter time periods, it is possible for lifetime effects to be constant across different age groups.

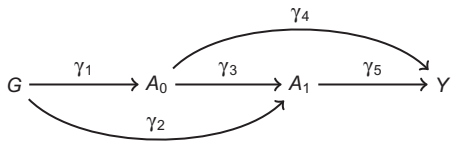

Figure 3. Causal diagram depicting the relationship between a binary genetic variant (*G*), an exposure (*A*) measured at 2 time points, and an outcome (*Y*). The γ_n values above the edges represent the parametric relationships between the variables joined by the edges. For readability, unmeasured confounding of the exposure-outcome relationship is omitted from the graph.

A SIMPLE EXAMPLE OF MR WITH A TIME-VARYING EXPOSURE

Applying the above definition of lifetime effects to a simple example with 2 time points clarifies what is happening in the previous empirical example. We assume the causal structure shown in Figure 3 with binary genetic variant G, continuous exposure A_k, which can take different values at $k = 0$ and $k = 1$, and outcome Y. The γ above each edge represents the causal effect of one variable on another, which, for simplicity, we assume is linear and constant for all causal relationships depicted. We have chosen 2 time points for simplicity, but in Web Appendix 1 (available at https://academic.oup.com/aje) we extend this logic to continuous time.

The lifetime effect of increasing the exposure trajectory $\bar{\boldsymbol{A}}$ by 1 unit in this example is simply the sum of the effects of A_0 and A_1 on Y_k: $\gamma_4 + \gamma_5$. The effect of G on Y, the numerator of the IV estimator, is the sum of the 3 possible pathways between them: $\gamma_1 \times \gamma_4 + \gamma_1 \times \gamma_3 \times \gamma_5 + \gamma_2 \times \gamma_5$. The effect of G on A can take 2 values in this example, depending on when A was measured. At time 0, the effect of G on A_0 is γ_1, and at time 1, the effect of G on A_1 is $\gamma_1 \times \gamma_3 + \gamma_2$. As such, there are at least 2 different IV estimates we may consider computing, by dividing the effect of G on Y by the effect of G on A at each time point:

$$\mathrm{MR}_0 = \frac{\gamma_1 \times \gamma_4 + \gamma_1 \times \gamma_3 \times \gamma_5 + \gamma_2 \times \gamma_5}{\gamma_1} = \gamma_4 + \gamma_5\left(\gamma_3 + \frac{\gamma_2}{\gamma_1}\right).$$

$$\mathrm{MR}_1 = \frac{\gamma_1 \times \gamma_4 + \gamma_1 \times \gamma_3 \times \gamma_5 + \gamma_2 \times \gamma_5}{\gamma_1 \times \gamma_3 + \gamma_2} = \gamma_4\left(\frac{\gamma_1}{\gamma_1 \times \gamma_3 + \gamma_2}\right) + \gamma_5.$$

For both MR_0 and MR_1, the terms inside the parentheses bias the estimates away from the true value. If we modify our example so the genetic effect on exposure is constant over time, the bias is eliminated. More specifically, if the genetic

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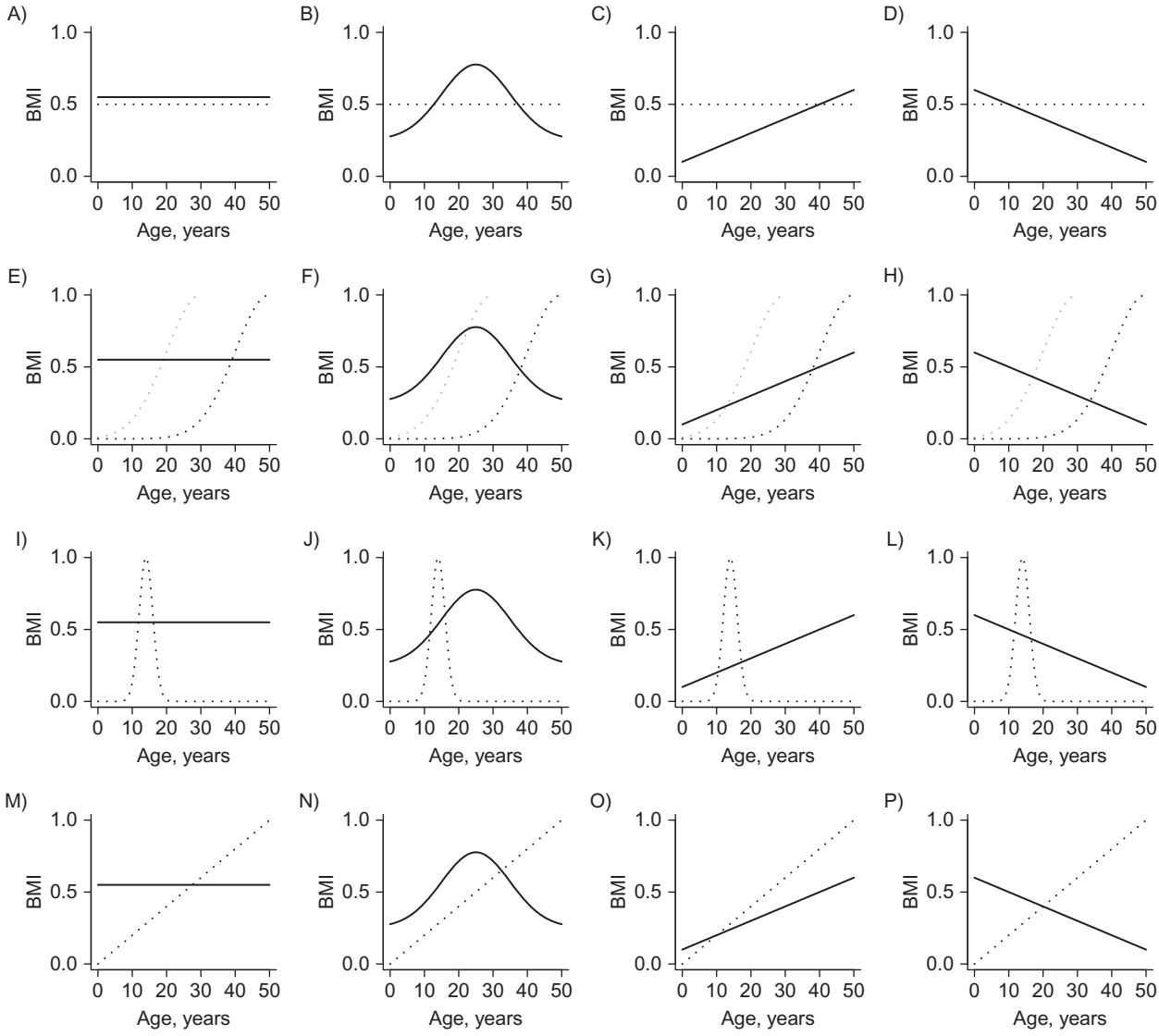

Figure 4. Sixteen hypothetical scenarios used to investigate possible magnitudes of bias in instrumental variable analyses. The solid line depicts the relationship between the genetic variant and body mass index (BMI; weight (kg)/height (m)^2). The first column shows results for a time-fixed genetic effect, the second column shows results for a time-varying effect similar to that of the fat mass and obesity-associated gene (*FTO*), the third column shows results for an increasing genetic effect, and the fourth column shows results for a decreasing genetic effect. The dotted line depicts the relevant exposure window. The first row shows results for a uniform exposure window, the second row shows results for an exposure window where recent exposure has a stronger effect, the third row shows results for a critical exposure window at age 13 years, and the fourth row shows results for an increasing exposure window. For the recent exposure scenario, the gray dotted line depicts the relevant exposure window at age 30 years. The black dotted lines are presented only to demonstrate the shape of the exposure window and are not drawn to scale.

effect is constant over time, then the effect of G on A_0 (γ_1) is equal to the effect of G on A_1 ($\gamma_1 \times \gamma_3 + \gamma_2$). This equality can be rewritten as $\gamma_3 = 1 - (\gamma_2/\gamma_1)$ and substituted into the equation for MR_0:

$$\begin{aligned}\mathrm{MR}_0 &= \gamma_4 + \gamma_5\left(1 - \frac{\gamma_2}{\gamma_1} + \frac{\gamma_2}{\gamma_1}\right)\\ &= \gamma_4 + \gamma_5.\end{aligned}$$

We can do the same with MR_1, substituting γ_1 for $\gamma_1 \times \gamma_3 + \gamma_2$:

$$\begin{aligned}\mathrm{MR}_1 &= \left(\frac{\gamma_1}{\gamma_1}\right) \times \gamma_4 + \gamma_5\\ &= \gamma_4 + \gamma_5.\end{aligned}$$

Therefore, even when A is time-varying, the IV estimate using either time point could potentially be a valid estimate of the

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lifetime effect of A on Y when the relationship between G and A is constant through time. However, when the effect of G on A changes over time, the IV estimate will be a biased estimate of the lifetime effect. The intuition behind this result is simple: If the relationship between G and A changes over time, it cannot be adequately summarized by measuring it at 1 time point.

MR AND TIME-VARYING EXPOSURES: A SIMULATION

To learn about the magnitude and direction of bias with realistic parameters, we performed analytical derivations for the following series of simulated scenarios. We simulated a longitudinal relationship between a binary genetic variant G, an exposure A, and an outcome Y, running the simulations to age 30 years and age 50 years, with relationships between variables informed in part by prior literature on *FTO* and BMI (14). We used 4 different gene-exposure relationships, depicted in each column of Figure 4, where the solid line is the per-allele effect at different points in time. The first column represents a constant genetic effect, where the per-allele effect of G is constant over time. The second and third columns represent genetic variants whose effects increase and decrease over time, respectively. The last column roughly emulates the relationship between *FTO* and BMI, where the largest per-allele difference occurs around age 20 years and decreases thereafter. Where the per-allele effect varied with time, the maximum change was 0.5 BMI units, to match a conservative estimate of the greatest change observed in the effect of *FTO* on BMI (15).

Each row in Figure 4 represents one of the 4 different exposure window scenarios we used. Here, an exposure window is defined as the time period during which the exposure is relevant to the etiology of the outcome (16). In other words, only changes in exposure during the exposure window will affect the outcome, holding exposure at other time points constant. The dotted lines represent the instantaneous effect of exposure at different points in time on Y_K. The first row represents a pure cumulative effect, where exposure at any time point has the same effect on Y_K. In the second row, the effect of recent exposure is stronger and is roughly limited to 30 years before K, though most of the effect comes from the last 10 years. Note that in the recent exposure scenario, the exposure window is relative to the age at which the outcome is measured. The dotted gray line, therefore, represents the exposure window when the outcome is measured at age 30 years. The third row represents a critical exposure window where only exposure around age 13 years (i.e., slightly before the available initial measurement of exposure) affects Y_K. The last row is a simple increasing exposure window where later exposure has a larger effect on Y_K. All exposure windows were scaled to make the lifetime effect at age 50 years equal to 2, and the lifetime effect at age 30 years was calculated by taking the area under the solid line in Figure 4 from birth to age 30 years. Altogether, we selected these scenarios to represent some biologically plausible relationships between *FTO*, BMI through midlife, and blood pressure (15) while they are nonetheless relevant for an arbitrary MR genetic variant, exposure, and outcome combination.

The IV numerator, the effect of G on Y_K, was calculated by multiplying the genetic effect on exposure (dotted line in Figure 4) by the effect of exposure on the outcome (solid line) and taking the area under the resulting curve from birth to age 30 years or age 50 years. The denominator of the IV estimate was the value of the difference in BMI at age 30 years or age 50 years (dotted line). The final IV estimate was obtained by dividing the IV numerator by the denominator. The R software code for these derivations (R Foundation for Statistical Computing, Vienna, Austria) can be found in Web Appendix 2.

When the instrument strength was constant over time, the estimates were unbiased with respect to the lifetime effect at both ages, regardless of the shape of the exposure window (Table 1). The estimate was biased in all other scenarios, and the bias was sensitive to not only the type of relationship between the genetic variant and the exposure but also the exposure window and the age at which the outcome was measured. For example, in the *FTO* scenario, the IV analysis underestimates the true effect at age 30 years but overestimates the effect at age 50 years.

When the *G-A* relationship changes with time, the bias is minimized to the degree that the measured *G-A* relationship is a good summary of the average *G-A* relationship within the exposure window. For example, in the scenario with the lowest bias—the *FTO G-A* scenario with the recent exposure window at age 30 years—the *G-A* relationship at age 30 years is relatively close to the average *G-A* difference in the most important part of the exposure window. In the scenarios with the highest bias, such as the *FTO G-A* scenario and a critical exposure window at age 50 years, the *G-A* relationship when measured at age 50 years is much smaller than the level in the exposure window.

HOW COMMON IS IT FOR GENETIC EFFECTS TO VARY WITH AGE?

Despite the widespread use of genome-wide association studies, few researchers have investigated how genetic effects change with age. This is probably because genome-wide association studies require large sample sizes to achieve adequate statistical power and investigating effect modification by age would require even larger sample sizes. One recent, large meta-analysis of genome-wide association studies of BMI found 15 loci that demonstrated different effects by age, including *FTO* and the melanocortin 4 receptor gene (*MC4R*), which are commonly used in MR studies of the effect of BMI (17). A variety of other studies have also found effect modification by age for the effect of genetic variants on BMI (13–15). The same phenomenon has been observed with other phenotypes such as low-density lipoprotein cholesterol (18, 19), Alzheimer disease (20), and blood pressure (21–23).

For many genetic variants used in MR studies, there has been no investigation into whether age modifies the relationship between the genetic variant and the exposure. For some complex phenotypes, we can infer effect modification by age. For example, consider the aldehyde dehydrogenase 2 gene (*ALDH2*) and alcohol consumption. The *ALDH2* genetic variant cannot have any effect on alcohol consumption until a person initiates alcohol consumption. Therefore, the effect of *ALDH2* on alcohol consumption changes from zero before

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Table 1. Results From the 16 Hypothetical Scenarios Described in Figure 4, Comparing the True Lifetime Effect of Exposure on the Outcome With a Mendelian Randomization Estimate When the Instrument Strength Varies Over Time

Exposure Window[a]	Age at Which Exposure Is Measured							
	Age 30 Years				Age 50 Years			
	True Effect	MR Estimate	Absolute Bias	Relative Bias, %	True Effect	MR Estimate	Absolute Bias	Relative Bias, %
Constant genetic scenario								
Uniform[b]	1.2	1.2	0.0	0	2.0	2.0	0.0	0
Recent[c]	2.0	2.0	0.0	0	2.0	2.0	0.0	0
Critical[d]	2.0	2.0	0.0	0	2.0	2.0	0.0	0
Increasing[e]	0.7	0.7	0.0	0	2.0	2.0	0.0	0
Increasing genetic scenario								
Uniform	1.2	1.0	−0.2	−18	2.0	1.5	−0.5	−25
Recent	2.0	1.8	−0.2	−10	2.0	1.8	−0.2	−8
Critical	2.0	1.6	−0.4	−20	2.0	1.3	−0.7	−36
Increasing	0.7	0.6	−0.1	−12	2.0	1.7	−0.3	−16
Decreasing genetic scenario								
Uniform	1.2	1.5	0.3	22	2.0	3.0	1.0	50
Recent	2.0	2.2	0.2	11	2.0	2.3	0.3	16
Critical	2.0	2.5	0.5	23	2.0	3.4	1.4	72
Increasing	0.7	0.8	0.1	14	2.0	2.7	0.7	34
FTO genetic scenario								
Uniform	1.2	0.9	−0.3	−22	2.0	3.7	1.7	85
Recent	2.0	2.0	0.0	−2	2.0	2.9	0.9	46
Critical	2.0	1.5	−0.5	−24	2.0	3.9	1.9	95
Increasing	0.7	0.7	−0.1	−8	2.0	3.7	1.7	85

Abbreviations: *FTO*, fat mass and obesity-associated gene; MR, Mendelian randomization.
[a] Constant, increasing, and decreasing genetic scenarios refer to constant, increasing, and decreasing genetic effects, respectively.
[b] Exposure at any time has the same effect on the outcome as exposure at any other time.
[c] Only exposure during the 10 years before the outcome is measured has an effect on the outcome.
[d] Only exposure around age 13 years has an effect on the outcome.
[e] The effect of the exposure on the outcome increases linearly with time.

initiation of alcohol consumption to a nonnull effect in adult populations. If the effect of *ALDH2* on alcohol consumption were constant with age after initiation, the MR estimate would correspond to a lifetime effect starting at initiation rather than conception. However, people who are homozygous for the *2 allele are almost all never drinkers (24); therefore, for the effect of *ALDH2* to be constant over time, people with at least one *1 allele would have to drink the same amount regardless of their age. Alcohol consumption peaks around age 20 years and declines with age (25), meaning that the effect of *ALDH2* on drinking necessarily decreases with age. In Web Appendix 3, we also demonstrate that genetic effects are almost guaranteed to change with time when there are bidirectional effects between 2 variables. Therefore, when there are bidirectional effects between 2 variables, including the more general and common situation of treatment-confounder feedback, the effect estimate will be biased (but the test of whether one variable causes the other will be valid in both directions).

DISCUSSION

MR is still a relatively new method, having risen in popularity only in the last 20 years (1). The method has spread rapidly from exposures that are direct gene products (e.g., proteins) to complex phenotypes (e.g., BMI, alcohol consumption). While investigators who use MR continue to develop new robust methods to address certain violations of the IV assumptions, little attention has been paid to issues that differentiate MR from classical IV analysis, such as the estimation of lifetime effects and the (often unacknowledged) use of time-varying exposures.

We have demonstrated that genetic variants whose genetic effect on the exposure of interest changes over time cannot typically be used to validly estimate lifetime effects with MR. We show this by deriving a bias formula in a simple case, deriving bias in several hypothetical scenarios, and computing inconsistent estimates in an empirical example. Indeed, when the genetic effect on exposure changes with time, the MR

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estimate does not intuitively correspond to any causal parameter and certainly is not a valid estimate of the lifetime effect defined here. Our results, and the potential ubiquity of such genetic variants, calls into question the numerical estimates from many MR studies. Moreover, our results corroborate the intuition of prior skeptics that variations in genetic effects over the life course complicate, if not invalidate, MR analyses (26). One silver lining to this conclusion is that, even if the numerical results are not interpretable due to time-varying genetic effects, such MR studies can still potentially provide a valid test of certain causal null hypotheses (27).

Whenever the goal of an MR study is to estimate a lifetime effect, investigators should ideally limit their analyses to genetic variants whose effects on exposure are constant over time or carefully consider how the time-varying genetic effect might impact the effect estimate. In many contexts this is verifiable and can be achieved by looking for a statistical interaction between the genetic variant, age, and the exposure or by plotting the relationship between exposure and age stratified by allele in samples with sufficient variation in age. One possible sensitivity analysis for the importance of variation in the effect of a genetic variant would be to calculate the MR estimate with more than 1 of the possible denominator estimates, as we did in our empirical example based on the Rotterdam Study data. If the MR estimate is not sensitive to the differences, the investigators may perhaps argue that their conclusions are unlikely to be affected. Note, of course, that such sensitivity analyses depend upon having longitudinal data. Researchers may also consider adapting our provided code to investigate other hypothetical scenarios that map onto their beliefs about their particular genetic variant, exposure, and outcome relationships as a means for investigating possible magnitudes of bias.

We have proposed one definition of a lifetime effect in MR, but certainly other interpretations could be given. One possible alternative is the effect of a point intervention at conception. Our interpretation and this interpretation are equivalent with time-fixed exposures or genetic variants whose relationship to the exposure does not change with time. We demonstrate in Web Appendix 4 that estimating this effect usually requires that the genetic variant affect the exposure only at conception and at no future time point, which is biologically implausible in most MR settings. Another possible reading of the prior literature is that MR estimates the effect of an *average* 1-unit change in exposure across the lifetime, as opposed to the exact 1-unit change at all time points proposed in the current paper. This definition is further complicated by multiple versions of treatment: An average 1-unit change can result from many different exposure trajectories and would not necessarily result in the same effect size. More generally, this and recent work (7) suggests the importance of MR investigators' providing unambiguous interpretations (and the assumptions upon which such interpretations rest) of their numerical estimates: If the investigators suggest that they are not trying to estimate the lifetime effect as defined in the current paper, they should clarify what causal parameter they indeed are trying to estimate instead.

In conclusion, we have provided a definition of lifetime effects that can be used in MR studies. In so doing, we have also demonstrated that many genetic variants used in MR studies cannot be leveraged to validly estimate this definition of lifetime effect. We recommend that investigators in future MR studies carefully consider the effect of interest and how genetic variants whose effects change over time may impact the interpretability and validity of their results.

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