Invited Commentary

Invited Commentary: When Bad Genes Look Good—APOE*E4, Cognitive Decline, and Diagnostic Thresholds

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Scientific interest frequently focuses on how factors that influence disease onset subsequently affect disease progression. In this commentary, the author discusses four sources of bias that arise in such work. The focus is on Tyas et al.’s analyses (Am J Epidemiol 2007;165:1231–1238) of how the apolipoprotein E *E4 allele, a well-documented risk factor for Alzheimer’s disease, influences progression of cognitive impairments from mild or global cognitive impairment to dementia or death. The author addresses four phenomena that can lead to spurious (noncausal) associations between apolipoprotein E *E4 status and rate of progression of cognitive impairments: beginning observations in the middle of a developing pathologic process, survivor bias, uncertainty in the timing of disease diagnosis, and nonlinear disease progression trajectories. Because these sources of bias are potentially relevant in any study of how risk factors for disease onset influence disease progression, the author advocates assessing their likely magnitude in specific contexts when interpreting results.

Research on determinants of disease progression poses a fundamental methodological challenge in that it can be conducted among only those individuals who were vulnerable to the disease. Although it is conceptually possible that a risk factor that prevents disease onset would perversely hasten disease progression were it to occur among the diseased, we cannot study this possibility directly. The stronger the protection against the disease that an exposure confers, the more difficult it is to study how that factor affects disease progression. For the same reasons, it is equally difficult to study how risk factors that increase vulnerability to a disease affect progression of that disease.

Tyas et al. (1) have written a thoughtful and ambitious paper examining risk factors for transition from intact cognition to impaired states and whether those risk factors influence progression from transient impaired states (mild cognitive impairment [MCI]) or global cognitive impairment) to permanent states of dementia or death. This latter question is the topic of my commentary; it is a specific example of research on how risk factors for disease onset affect disease progression. I focus on four phenomena that can lead to spurious (noncausal) associations between risk factors for disease onset and the rate of disease progression: beginning observations in the middle of a developing pathologic process, survivor bias, uncertainty in the timing of diagnosis, and nonlinear disease progression trajectories (table 1). I argue that the first of these phenomena is especially relevant to Tyas et al.’s results. Some special issues arise because of dementia’s chronic nature and insidious (nonacute) onset. Most of the methodological problems, however, occur when studying how time-constant exposures (risk factors whose values do not change, e.g., genes, race, or sex) that affect disease onset subsequently modify disease progression. Each bias can be demonstrated by using directed acyclic graphs showing how design or analysis decisions result in noncausal associations (paths) between the exposure and

Abbreviations: APOE, apolipoprotein E; MCI, mild cognitive impairment; QP, quickly progressing; SP, slowly progressing.

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rate of decline (figure 1). Beginning a study at disease diagnosis is similar to baseline adjusting in longitudinal data analyses, and many of the biases are analogous (2–4).

For illustration, I focus on estimating the effect of the apolipoprotein E (APOE) *E4 allele, a well-established risk factor for Alzheimer’s disease (5), on progression to dementia after the onset of MCI. That is, would progression to dementia after MCI onset occur more quickly if a patient carried the *E4 allele than if he or she did not carry this allele? As Tyas et al.’s (1) findings suggest, I assume that APOE*E4 increases risk of incident MCI and that MCI is an early stage in a trajectory of declining cognition culminating in dementia. Similar questions are addressed in several prior studies examining the effects of *E4 status on rate of cognitive decline after dementia diagnosis (6–11). Tyas et al.’s findings shed light on some challenges encountered in this research.

BEGINNING OBSERVATIONS IN THE MIDDLE OF THE DECLINE TRAJECTORY

MCI presumably is diagnosed in the middle of an ongoing, accumulating, pathologic process, which introduces problems if unmeasured factors influence both MCI onset and rate of disease progression and we model change from time of diagnosis (rather than from initiation of the pathologic process). For example, among newly diagnosed MCI cases, *E4 status may be associated with unmeasured causes of MCI, even though they were independent in the population. The unmeasured factors will therefore confound analyses of the association of disease progression and *E4 status.

Imagine a simple world in which there are two types of Alzheimer’s disease: quickly progressing (QP) and slowly progressing (SP). The type of Alzheimer’s disease may result from unmeasured genetic differences (something besides APOE alleles), comorbid conditions that hasten decline, or any unmeasured factor that exacerbates rate of decline and occurs independently of APOE allele status. Consider hypothetical decline trajectories for four types of people: QP/*E4C255, QP/*E4*/C255, SP/*E4C255, SP/*E4*/C255. Everyone begins with a cognitive function test score of 30 and declines at different rates (figure 2), until crossing a diagnosis threshold at 24, at which point they are diagnosed with MCI; after declining below 15, they are diagnosed with dementia. Assume decline is linear and

| TABLE 1. Bias in studies of risk factors for disease progression when risk factor influences disease occurrence |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Source of bias | Conditions under which bias is likely | Likely direction of bias | Tests for importance or sensitivity analyses |
| Observations begun at diagnosis, in the middle of trajectory of decline | • Decline occurs prior to diagnosis, but research focuses on rate of decline after diagnosis. • Unmeasured factors influence both disease onset and rate of decline after diagnosis. | Disease onset risk factors spuriously associated with slower progression | • Effect of *E4 on disease onset • Effect of unmeasured risk factors on disease onset • Interactions between *E4 and unmeasured risk factors in determining disease onset • Effect of unmeasured risk factors on rate of decline postdiagnosis |
| Survivor bias | • Disease progression is studied in only a subgroup of survivors. • Unmeasured factors influence both disease onset and survival. • The risk factor under study influences survival (directly or via rate of disease progression). | If risk factor reduces survival likelihood, risk factor spuriously associated with slower progression | Fraction of sample surviving • Association of risk factor with survival |
| Uncertainty in timing of diagnosis | • Diagnosis is based on symptom severity. • Symptom measures fluctuate transiently. | Disease onset risk factors spuriously associated with faster progression | Effect of risk factor on disease onset • Instability in symptom measures |
| Nonlinear declines | • Rate of progression is nonlinear over time or the measurement properties of the instrument render progression apparently nonlinear. • Individuals enroll in the study at different points in the trajectory. | If trajectory flattens at the bottom, risk factor for early onset associated with slower rate of progression | Shape of decline trajectory over time • Strength of association between risk factor and starting point (baseline) |

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constant from the moment the pathologic process begins to
the moment of death. The effect of *E4 on rate of decline
is 2.5 units/5 years. The effect of QP versus SP-type
Alzheimer’s disease is 2 units/5 years. Figure 1A shows the
causal structure that could generate data such as that shown
in figure 2.

If we begin to follow rates of change at MCI diagnosis,
we will never consider the SP/*E4/C255 group because they will
remain undiagnosed during our observation period. At any
given age, people without *E4 alleles who are diagnosed
with MCI will tend to carry the QP risk factor. Slow de-
cliners without *E4 are unlikely to reach the MCI diagnostic
threshold. Excluding the SP/*E4 group by restricting to
those who were diagnosed introduces an association be-
 tween *E4 and U, resulting in underestimation of the effect of *E4 status on transition to dementia. This is the essence of selection bias: conditioning on a
causal factor that is a consequence of the pathologic process.

This situation is a consequence of the “horse-racing
effect” (12) or, more generally, collider bias (13). This
phenomenon obscures the causal effect of *E4 on rate of
decline among diagnosed patients even though QP/SP
disease type is independent of *E4 status in the population.

SURVIVOR BIAS

The bias resulting from selecting those with enough im-
pairment to be diagnosed with MCI is similar to the bias
induced by selecting only long-term survivors. Figure 3 dis-
plays hypothetical trajectories, assuming that when cognitive
function declines below a certain threshold, the individual
dies or leaves the study. Imagine that we are able to include
only those individuals who survive past age 80 years (e.g., if
genotyping is delayed until this point). We are thus likely to
omit from our study the very worst performing group, QP/
*E4+, who die earlier. The consequence is similar to that
described above: omitting the SP/*E4− patients makes the *E4 allele look (relatively) benign, and omitting the QP/*E4+ group also makes the *E4 allele appear harmless. Again, this phenomenon occurs only if unmeasured factors influence selection (in this case, survival) and also influence decline.

FIGURE 2. Hypothetical decline trajectories for four types of individuals: restricting to the diagnosed cases excludes the best-performing individuals without an apolipoprotein E gene (APOE) *E4 allele. Average rate of decline among the APOE *E4 carriers who are diagnosed with mild cognitive impairment (MCI) (including quickly progressing (QP)/*E4+ and slowly progressing (SP)/*E4+) is 4.0 points per 5 years, while average rate of decline among the noncarriers who are diagnosed is 2.5. The estimated effect of APOE *E4 among those who are diagnosed is 1.5 per 5 years, substantially less than the magnitude of the true causal effect (2.5) defined in these hypothetical data.

FIGURE 3. Hypothetical decline trajectories for four types of individuals: restricting to survivors excludes the lowest performing individuals with an *E4 allele. MCI, mild cognitive impairment; SP, slowly progressing; QP, quickly progressing; APOE, apolipoprotein E.
UNCERTAINTY IN THE TIMING OF DIAGNOSIS

Ideally, MCI would be diagnosed immediately after an individual crossed the impairment threshold. This threshold would be defined identically for everyone in the sample, and the moment it was crossed would be precisely demarcated. Unfortunately, this ideal situation does not correspond with clinical reality. Observed functioning in patients with incipient MCI fluctuates for many reasons: patients have good and bad days, intermittent bouts of depression, medication changes, and so forth. As a result, individuals may be prematurely diagnosed with MCI during brief periods of impaired functioning that subsequently remit (or may remain undiagnosed because they were assessed on a particularly lucid day). Tyas et al.’s data (1) indicate that “back-transitions,” or improvements in cognitive status, are fairly common (~15 percent of transitions from MCI or global impairment were to less impaired states). Furthermore, MCI diagnosis is usually based on symptoms (e.g., memory loss, declines in other cognitive functions) that are the same as or correlates of those symptoms subsequently used to assess progression to dementia. The consequence of premature diagnosis is that the apparent decline trajectory post-diagnosis (figure 4, dotted line) will appear flatter than the true decline trajectory (figure 4, solid bold line). Similarly, premature MCI diagnosis makes the time to dementia appear longer. Protocols that initiate follow-up at diagnosis date will begin monitoring some patients during transient bad periods and thus underestimate their long-term rate of change.

The tendency to underestimate rate of decline affects *E4 carriers less than it affects non-*E4-carriers. If two patients, one *E4+ and the other *E4−, each score below the diagnosis threshold, on average the *E4+ patient’s true functioning is lower (the *E4+ patient is more likely to truly have MCI). In other words, the false-positive rate of MCI diagnosis is higher for those without APOE*E4. Figure 1C illustrates a data-generating process that could give rise to such a bias: *E4 status influences true functioning, and true functioning influences both MCI diagnosis and subsequent dementia diagnosis. However, MCI diagnosis is also influenced by transient fluctuations in test performance, so restricting to individuals with diagnosed MCI leaves uncontrolled variation in underlying cognitive function. In directed acyclic graphs terminology, restricting analyses to individuals with MCI diagnoses does not fully block the path from *E4-status → cognitive function → dementia diagnosis.

Figure 5 compares (hypothetical) trajectories of an *E4+ and *E4− individual that diverge at age 67 years, when the *E4+ patient begins declining. At each assessment, patients score in a distribution around the true functional level because of transient fluctuations or instability. If the *E4− individual is diagnosed with MCI in his or her early seventies, it is likely because he or she had a particularly poor assessment day, while an *E4+ individual diagnosed at the same age is more likely to have a true functional level below the threshold. At the next assessment, we expect regression to the mean or true functional level, leading us to overestimate the amount of time between MCI diagnosis and dementia diagnosis (and the slope of the decline trajectory) for the *E4− carrier. The same bias will occur whenever MCI is diagnosed, if the *E4+ carriers have an average true function lower than that of the *E4− patients.
This bias is proportional to the transient variability in scores and will make any risk factor that hastens disease onset appear to hasten disease progression. It is reduced but not eliminated by using multiple tests for diagnosis, requiring patients to meet diagnostic criteria at two consecutive visits, or excluding patients who do not remain below diagnostic criteria at all subsequent visits. It is common to ignore back-transitions or to exclude patients who appeared to recover in studies of MCI and dementia. Tyas et al.’s findings (1) highlight the prevalence of back-transitions and thus the importance of explicitly considering how they affect results.

NONLINEAR TRAJECTORIES

Nonlinear trajectories are a major concern in prior research on APOE*E4 and dementia progression (6, 14). Tyas et al.’s approach (1) circumvents this problem. Nonlinearities may result if compensatory or resilience processes buffer functional consequences of neurologic damage in early disease. Neurologic damage may accumulate until the brain loses resilience to further damage and decline. The decline trajectory will be relatively flat in early stages and then suddenly collapse. Alternatively, the trajectory may flatten at the end stages of disease, when there is little function remaining to lose. Although conceptually distinct, scaling characteristics of the cognitive measure can produce the same phenomena if they are insensitive to changes at the low or high end of the scale.

When the decline trajectory is nonlinear, variables associated with where in the trajectory an individual is first observed will tend to predict subsequent rate of change. If *E4 carriers tend to be further along the decline trajectory at first assessment, their slopes may appear to be relatively flat during follow-up (figure 6). Conceptually, the true function at one point in time influences the rate of change over follow-up (figure 1D), and this relation could plausibly be in either direction. Average slope of decline is not always the outcome of substantive interest. If rate of change after reaching beyond a severe impairment level is no longer relevant, the outcome might be more appropriately modeled as time to impairment threshold or absolute level of function. Handling nonlinearities is one justification for restricting to newly diagnosed individuals or otherwise matching on initial cognitive status. Tyas et al.’s approach (1)—modeling transition to dementia as a function of prior cognition without attempting to measure rate of decline directly—helps circumvent this problem. Such restrictions introduce their own set of problems but help simplify interpretations when decline trajectories are likely to be nonlinear. Examining the shape of average trajectories, for example, using growth curves with flexible time specifications, is a first step in...
assessing whether nonlinear trajectories substantially bias the estimates.

**IMPLICATIONS FOR TYAS ET AL.'S RESULTS**

Tyas et al. (1) find that APOE*E4 is independent of transition from MCI to dementia but, in contrast, that *E4 predicts transition from global impairment to dementia. Before accepting etiologic explanations for these findings, it is worth considering whether the results partially reflect the biases discussed in this commentary. The two most relevant biases are likely due to uncertainty in diagnoses and beginning observations in the middle of the decline trajectory. The former is easier to quantify (table 1). It would be especially interesting to know whether the reliability of the MCI assessment compared with the global impairment assessment could account for the divergent results with respect to transition to dementia.

Examining the full trajectory of change from intact cognition through dementia, without conditioning on prior cognitive state, helps avoid bias when MCI diagnosis is a common effect of *E4 and unmeasured risk factors. One option is to use growth curves (with test scores as outcomes and a flexible model of time), although doing so does not directly address time to dementia diagnosis. This approach avoids some biases raised by Tyas et al.’s conditional models (1), but it introduces others. Neither approach alone can adequately address the research question, but contrasting results from these two approaches can lend insight into which biases are likely to be most influential in the current data set.

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