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Lost in Translation: Epidemiology, Risk, and Alzheimer's Disease

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Abstract

There is increasing emphasis on interdisciplinary “translation” in biomedical research.¹ A major push towards prevention of Alzheimer's Disease is spawning translational research² that should span basic, clinical, and population investigations. Epidemiological studies, which address our understanding of risk and protective factors for disease at the population level, are contributing less than they could to translational research. In part, this is because the key concept of risk is being “lost in translation,” muddling interpretations and leading to interdisciplinary frustrations. Two epidemiologists offer a framework for resolving some of the confusion.

WHY THE DISCORD?

Many clinicians today see perplexing contradictions between the results of observational studies and those of interventional studies. For example, a carefully conducted prospective study of a large, community-based cohort showed the use of estrogen supplements to be associated with reduced subsequent occurrence of Alzheimer's disease (AD). That is to say, estrogens appeared to be potentially protective against the development of AD.³ Yet, a randomized clinical trial of estrogen conducted in women free of dementia did not reveal a protective effect; indeed, it was associated with a higher incidence of dementia.⁴ Hopes of prevention have also been dashed by nonsteroidal anti-inflammatory drugs (NSAIDs) which in randomized trials showed no protective effect,⁵ and possibly heightened risk in an older HMO-based cohort.⁶ Similar misfortunes have befallen antioxidant supplements,^{7, 8} and statins,⁹ whose apparently protective associations with AD in observational studies had raised hopes of preventing or delaying dementia. What is the clinician to make of this conundrum? Since the randomized controlled intervention trial is the accepted gold standard, are the epidemiologists leading him up the proverbial primrose path?¹⁰

The intuitively attractive principle called Occam's Razor is paraphrased as “all things being equal, the simplest solution is best.” It has however been challenged by Whitehead's caution “Seek simplicity and distrust it.” We will argue that the current climate of distrust and indeed dismissal of epidemiological data was caused by excessive simplification of epidemiological concepts, for which we epidemiologists ourselves must shoulder some of the blame.

KEY CONCEPTS

Prevalence is the proportion of a given population that has disease at a given point or brief period; a cross-sectional snapshot that reflects the public health burden of that disease at that time. Incidence is the rate at which new disease occurs in the population. Prevalence is in fact a product of both incidence and duration. In chronic conditions like AD, duration equals

survival. Thus, higher prevalence can result either from higher incidence, or from longer survival, or both. Incidence could be the same in two groups, e.g., women and men, but prevalence could be higher in women because of their longer survival. Simply put, prevalence reflects the burden of disease, while incidence reflects the risk of developing disease, in a given population or subgroup thereof.

But both prevalence and incidence depend on our definition of the “disease.”¹¹ If we define AD clinically, as present in those with dementia (further defined as deficits in several areas of cognition sufficient to disrupt social and occupational functioning) for which no sufficient cause other AD can be identified, we place one set of restrictions on whom we count as “cases” when estimating incidence or prevalence. If, instead, we define AD pathologically, as a requisite amount of amyloid plaque in specific brain regions, as noted by amyloid imaging, regardless of clinical cognitive functioning, we would obtain a different count. If it were possible to identify AD by detecting an excess of A-beta oligomers at the synapses of neurons, we would have yet another count. All of these case definitions are legitimate in context, are based on specific assumptions, and have their specific purposes. The narrower and perhaps more specific the definition, the lower the prevalence estimate will be. However, the relevance of case definition extends beyond counting cases, as we shall see below.

What has incidence to do with risk? If two groups or subgroups have different incidence rates for a disease, the group with the higher incidence rate is, by definition, at higher risk for the disease. A group free of dementia, when first assessed (baseline), can be followed over time to identify the subgroup that subsequently develops dementia. This subgroup's baseline characteristics, measured before the advent of dementia, may be compared with those of the rest who remained dementia-free. By convention, baseline characteristics observed in a significantly greater proportion of those who later became demented are considered putative risk factors for dementia. To clarify our usage here, a factor associated with a higher probability of dementia is called a risk factor; one associated with a lower probability of dementia is called a protective factor.

Clearly, risk/protection as described above is only a probabilistic statement. A risk factor for disease identified in this way is at best a signal. It is not necessarily the cause of the disease, or an intervention target for that disease. Failure to appreciate this distinction may be responsible for some of the confusion that has occurred in “translation.”

RISK VS. PREDICTION

We suggest that it is preferable to designate the broad category of factors associated with higher or lower future disease probability simply as *predictors*. Then, two sub-categories of predictors can be identified; (i) early *markers* or manifestations of the disease itself, indicating that preclinical disease has begun and (ii) *independent risk factors* that increase/decrease the likelihood that the pathological disease process will begin. Communication and translation will be enhanced by avoiding conflation of the two. We will illustrate this and subsequent points using the example of AD, or of dementia, according to the outcome reported in a given study. We will not provide examples of cardiovascular risk factors for dementia, important as they are, because the complex interactions between degenerative and vascular processes have been admirably dealt with by others.¹²

A predictor such as mildly impaired performance on a memory test, or the detection of amyloid deposits on brain imaging, may be found associated with higher probability of future dementia of the Alzheimer type. If so, it is more likely an early manifestation of the AD disease process itself rather than an independent risk factor for AD. Such markers may be useful in identifying individuals whose cognitive function is likely to decline further; they might help improve specificity of diagnosis, and perhaps help target candidates for early intervention. They might

even help signpost stages in the natural history of the disease. However, their role is conceptually different than those of independent risk factors that are not themselves part of the disease, but rather increase or decrease the likelihood of the disease-free individual eventually developing disease. The challenges of defining “disease-free” will be addressed later.

Unfortunately, the plot thickens further. Even a seemingly independent risk factor could represent several different mechanisms. It could be truly a link in the chain of the causal pathway for AD.

Alternatively, it could serve as a mediator between a causal exposure and AD, or it could moderate or influence the effect of a causal exposure. The observed relationship could also be the result of confounding with another exposure, or a spurious finding related to a biased sample or a measurement artifact. In addition, the degree of risk could be a function of other phenomena, including the duration of exposure, the timing of exposure, and cohort effects.

TIME, AND TIMING, ARE OF THE ESSENCE

If our goal is identify causal risk factors, our first challenge is use a case definition of AD that incorporates the earliest indications of the disease process. This will allow us to accurately identify a truly disease-free individual, and specify the *temporal relationship* between risk factor exposure and development of disease. If our study design and available resources restrict us to examining exposures that occur more proximal to frank clinical manifestation of AD, we have a problem. We are now in danger of identifying associations that have little chance of being truly causal, because (at least in the degenerative dementias) the underlying pathological process likely started many years earlier. To be brutally honest, we still lack definitive information on the likelihood that subclinical pathology will in fact progress to clinical disease; and, further, the condition we now call AD is more heterogeneous than we usually acknowledge.

This temporal relationship between exposure and disease is the next step in understanding cause and effect, i.e., whether a particular exposure factor could have acted on individuals before the onset of the pathologic processes, in such a way as to influence (or even cause) the initiation (or prevention) of the disease. However, establishing the temporal relationship is less simple than it sounds. As with most chronic diseases, we do not know when the Alzheimer pathology begins. At present we only know when the disease process crosses an externally observable threshold, and when the clinical manifestations begin to interfere with the individual's functioning, i.e. when the person develops dementia or at least a characteristic pattern of lesser cognitive impairment.

Even an exposure that precedes the onset of disease may not affect risk consistently, depending on its timing. Long-term prospective studies in Scandinavia have shown that elevated cholesterol levels in mid-life increase risk of dementia in later life,¹³ while lower cholesterol is associated with dementia onset a few years later.¹⁴ In the Cache County Study, risk of dementia was reduced by estrogen use in proportion to both the timing and duration of use; women who had taken estrogens for at least ten years, during a period at least ten years before the onset of dementia, had the lowest risk of dementia.³ The Rotterdam study found a lower risk of dementia in individuals, aged 55 and older, who had taken NSAIDs,¹⁵ while a recent report from Seattle suggests an association in the opposite direction when NSAIDs are taken later in life.⁶ Taken together, these data suggest that for an exposure to raise or lower risk, it must occur during a certain critical period and perhaps for a certain length of time. A prevention trial of the same “protective” agent administered at older ages may be ineffective only because it is being delivered too late, i.e., after the risk was no longer modifiable, and possibly after the disease process had already begun in at least some of the trial participants.

MUST A RISK FACTOR BE MODIFIABLE?

Translation is further complicated by the fact that not all risk factors for chronic disease are potentially modifiable. Unlike infectious disease epidemiology, where in large part Koch's postulates still apply, we cannot require reversibility as a condition of causality. By analogy, there is little doubt that cigarette smoking is a risk factor for lung cancer; few would argue that cancer, once it has begun, can be reversed by smoking cessation. Most genetic risk factors are at present also not amenable to modification. However, identifying even non-modifiable risk factors can be valuable in two ways; they help understand aspects of disease mechanisms and they identify individuals at risk who can be targeted for appropriate interventions.

MUST RISK BE SIMPLE?

For non-familial AD, as for stroke, it seems improbable that a single factor acting in isolation can be the cause; rather, it seems more likely that disease initiation requires a perfect storm of many factors interacting with one another. The strongest risk factor for AD is greater age, an essentially unmodifiable factor which has been described as the elephant in the room.¹⁶ Gender is a less straightforward issue. Most cross-sectional surveys have found higher prevalence in women, but, as noted, prevalence does not directly reflect risk. Prospective studies have not found higher incidence (risk) in women except in the very oldest age groups. The most likely explanation is that longer survival in women inflates prevalence despite similar incidence. An exception is the aforementioned Cache County study in which older women who had not taken estrogen had higher rates than men.³ This apparent protective effect of estrogen was subjected to a randomized trial in older women (65 – 79 years) in which it showed no lowering and, in fact, an apparent elevation of dementia risk.⁴ However, to test the hypothesis actually suggested by the population data, the trial should have been conducted in middle-aged women and carried out over at least a decade. The fact that the appropriate trial design would have been virtually impossible to carry out does not disprove the hypothesis. The same arguments could be made about the statin and NSAIDs trials.

With genes, there is little concern about establishing the temporal relationship between the exposure and disease onset. The only genetic risk factor that has been consistently identified for late onset AD is the $\epsilon 4$ allele of the Apolipoprotein E gene (*APOE*4*) on chromosome 19. Yet, even this relationship is complicated. It is not an autosomal dominant, deterministic gene; rather, it is a marker of susceptibility. The presence of this gene increases the probability of an individual's developing AD, but is neither necessary nor sufficient to cause the disease. Further, it does not appear to influence risk of AD in native African¹⁷ or African American populations¹⁸ which have higher $\epsilon 4$ allele frequencies than Caucasian or East Asian populations. What could this mean? One possibility is that cardiovascular disease is a "competing risk" in African populations; vulnerable individuals with *APOE*4* may succumb to cardiovascular disease before they grow old enough to manifest dementia. *APOE*4* also appears to interact with other risk factors, with some but not all studies showing that it acts synergistically with head trauma^{19,20} and hypertension²¹ to elevate AD risk. To complicate matters further, *APOE*4* appears associated with earlier onset of dementia; its effect on incidence interacts with age such that it has diminished effect on incidence in the oldest age groups.

Depression provides another complex challenge.^{22 - 26} Case-control studies of AD have shown history of previous major depression to be more common in cases than in healthy controls. Many clinical studies have shown depressive symptoms or illness to be associated with cognitive deficits, which are at least partly reversible with treatment of depression. Population studies have largely confirmed these cross-sectional associations, but diverge with regard to whether depression predicts cognitive decline in prospective studies. It appears plausible that depression appearing shortly before the onset of cognitive decline in AD is a prodromal stage

of the dementia, while depression appearing many years before may be an independent risk factor for AD. One proposed mechanism involves mediation by hippocampal damage secondary to the prolonged hypercortisolemia associated with depression.²⁷ While details are beyond the scope of this commentary, this example illustrates a potentially testable hypothesis: early and vigorous treatment of depression may reduce the risk of subsequent dementia.

TRANSLATION INTO TRIALS

While clinical trials are the accepted gold standard for risk modification, they are complemented by observational population studies without which the clinical picture is incomplete. For example, only long-term prospective population studies could show the relationship of disease risk to duration and timing of exposure.²⁸ The feasibility of clinical trials of sufficient scope and duration to test epidemiologically-derived hypotheses remains elusive. We need to discuss a standard for when clinical trials are not practical but sufficient epidemiological evidence exists to move to expert consensus and communication with the public. For example, it is neither feasible nor ethical to conduct a randomized clinical trial of cigarette smoking to observe its effect on the incidence of cancer or heart disease. It is also not practical to design a 30-year randomized trial of even a relatively harmless intervention, such as a carefully regulated diet rich in antioxidants, to compare disease incidence with those on “usual” diet. Attrition and non-adherence would plague the implementation and interpretation of such a study, even if an agency could be found to fund it.

What, then, is the value of risk factor studies, if for logistic or financial reasons they cannot be immediately translated into randomized clinical trials? It has been noted that “black-box epidemiology” is denigrated by some as an empty search for associations, unguided by underlying theory.²⁹ However, it can also be viewed as a “valuable source of seemingly unrelated facts that await coherent explanation by novel theories, and that provide empiric tests of theories.”²⁹ Identifying factors that raise or lower the probability of disease is the first step towards generating hypotheses about pathogenic mechanisms. Observations about the apparent protective effects of NSAIDs against AD have led to the recognition of inflammatory mechanisms in AD; this knowledge has been useful even though the trials have not yet been successful.

The above are merely some of the risk or protective factors reported from epidemiologic studies of AD. They exemplify the complexities and interrelatedness of factors that are not always obvious to casual observation. When different approaches, including laboratory, clinical, and epidemiologic studies, converge on a consistent finding, the challenge of translation is minimal. When different approaches yield differing observations, they should be viewed as a body of facts demanding explanation by proposed causal theories.²⁹ Underlying mechanisms as well as the critical issues of timing and duration should be carefully examined before trials are undertaken. Newer hybrid analytic methods show potential for fruitfully combining elements of observational and interventional approaches.³⁰ Collaborative, interdisciplinary studies offer the best hope for disentangling the web of causation.

TRANSLATION FOR NON-SCIENTISTS

Finally, a major challenge for researchers as well as funding agencies today is communicating appropriately with the public, with legislators, and the mass media. It is difficult to responsibly discuss levels of certainty and quality of the evidence with the public, and unrealistic to expect the requisite caveats and nuances to make the evening news. It seems particularly critical to educate health care providers, who must answer patients' and families' questions about what they have just seen on the Internet or heard on talk radio. This task is too important to be squeezed out of individual investigators' public relations budgets. Rather, this final step in

translation should be recognized as the shared responsibility of investigators, funding agencies, advocacy groups, community organizations, and the media.

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