Encouraging trends toward reduced risk of Alzheimer disease

What's good for the heart is good for the brain

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Alzheimer disease (AD) is a quintessential disease of aging. Onset before age 60 years is rare and is often attributable to one or more disease-causing genetic mutations. After age 60, the incidence of the disease doubles approximately every 5 years, at least until age 90.¹ If one survives to age 100, the cumulative incidence of AD probably exceeds 75%.^{2,3} Yet AD is clearly heritable, with twin studies suggesting that perhaps 70% of variability in its predisposition results from genes.⁴ *APOE* typically accounts for about half of the total genetic influence.⁵ *APOE*, and probably other genes, alters susceptibility for late-onset AD by modifying age at onset.²

At this point little can be done to alter genetic influences *per se*. But what about the other 30% of variability in predisposition? At least some of this may result from a combination of known risk factors. Factors such as head injury may be avoidable to some extent; one would probably want to avoid this even if it were not associated with risk of AD. But there may also be a “silver lining” in the cloud of genetic predisposition to AD. Because AD is usually not *caused* by environmental influences, it may be that modifying some of these influences could actually *defer* the onset of pathology or symptoms that are otherwise predicted by people's genetic makeup, thus reducing the age-specific incidence of the illness. A prominent group of modifiable risk factors can be summed up crudely in the statement “what's good for the heart is good for the brain.”

In the developed world at least, the last 50 years have witnessed an astonishing reduction in morbidity and mortality from atherosclerotic cardiovascular disease. Some of this change remains unexplained, but much of it is probably due to changes in diet and lifestyle factors, decreased smoking, medical control of blood pressure and lipids, and effective interventions for urgent cardiovascular syndromes. The last are unlikely to modify AD risk, but the others have all been identified as “protective” factors against AD. In this issue of *Neurology® Clinical Practice*, Christopher Filley⁶ points out that we have seen a substantial *decline* in the age-specific incidence and prevalence of AD in recent years, likely as a result of these risk-reducing factors. This decline will not suffice to offset the rapid growth in the numbers of very old in North America and Europe (age is, after all, the strongest risk factor for AD by far). There is

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little reason, therefore, to doubt the various estimates that numbers of individuals with AD will continue to increase rapidly over the coming decades.⁷ But the emerging decline in *age-specific* incidence of AD is encouraging nonetheless. This trend is likely to grow as people now in middle or early old age experience their later years. These “new arrivals” will probably have benefitted from more prolonged (and perhaps more intensive) measures to promote cardiovascular health and may therefore show an even greater reduction in age-specific rates of AD. Dr. Filley’s article cites recent studies that have identified these emerging trends and their likely benefits.

There is another group of risk or protective factors that may contribute to cognitive or brain reserve. These include physical activity, education, cognitive activity, and social stimulation. The effect of these lifestyle factors is less certain, but they are amenable to controlled studies to investigate their effects and potential mechanisms. For now, remaining physically and cognitively active is a reasonable goal in the absence of conclusive proof of its benefits for the brain.

We do have one reservation about Dr. Filley’s arguments. He indicates that AD has long been viewed as an immutable genetic illness. In fact, until the early 1980s it was believed that only a small fraction of AD was “familial” (we knew nothing of specific causal genes in those days) and that the majority was “sporadic.”⁸ The later 1980s and the 1990s were a time of rapid transformation in understanding of the familial nature of later-onset AD.^{9–11} But it was these same years that witnessed the emergence of substantial evidence that control of cardiovascular risk factors might also be protective, e.g., even in middle age.¹² Other risk factors such as sleep disturbance, infection/inflammation, and chronic stress are currently being investigated.

As we learn more about the genetic determinants of late-onset AD, the pathways that they implicate—e.g., lipid, metabolism, inflammation, and synaptic mechanisms—suggest additional possibilities for environmental modification of risk. Any particular genotype will predict a probability distribution around a central value for onset age. Some of the deviation around the central value may result from stochastic variation, but a good deal of it may be explained by specific risk-modifying exposures. At present, we have identified empirically only a few such exposures that accelerate onset and several that appear to retard it. We are fortunate today that plausible risk-modifying strategies are now available (hence our “new causes for optimism.”). But we still know little about the actions of the various risk genes themselves (including, after more than 20 years, *APOE*!) or the age-related brain changes that play roles in AD pathogenesis. Growing knowledge of genetic mechanisms and pathways should offer the potential for stronger, more rational pharmacologic interventions that may defer onset and reduce incidence. While we expectantly await these new drugs, risk factor assessment, appropriate counseling, and intervention appear to be worthwhile and will probably pay dividends for brain health.

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