

## Response

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# Ignoring the Evidence Will Not Stop the Alzheimer's Disease/Diabetes Pandemic

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The preceding commentary [1] makes important and valid points about the potential pitfalls of analyzing summary databases, particularly those representing changes in mortality rates over time. All databases are flawed because of imperfect and not entirely consistent means of data collection and time-dependent shifts in disease recognition. True, mortality rates are not the same as incidence or prevalence rates, but it is noteworthy that the prevalence rate of Alzheimer's disease has increased over time, and, as there are no effective treatments or cures, survival has not significantly changed. Ergo, changes in mortality rates in this case reflect changes in prevalence. Another matter is that correlative data analyses can be flawed because of the simple fact that events and conditions may be correlated but this does not prove causality. For example, the finding that trends in mortality rates from Alzheimer's and Parkinson's diseases increased along with consumption of certain foods and use of nitrate-containing fertilizers, although interesting, is open to debate regarding the relationships [2]. One could simply argue that those trends in mortality might have been due to increased exposure to computer games or cell phones. It is true that life expectancy in the US has increased over time, but for that very reason we analyzed the database by comparing mortality rates within specific age groups,

over time. This approach removes bias associated with aging of the population because it compares death rates from lung cancer among 55–64 year olds in 1980 to death rates in the same age group in 2005. If a fatal disease were genetic in etiology, then death rates would not be expected to increase among 65–74 year olds over a 30-year interval.

All of that said, it is curious that in the same study using exactly the same database, other analyses and conclusions are quite easily accepted as logical, based upon known medical advances or public health interventions. For example, no one would dispute the progressive increases in HIV/AIDS mortality rates observed in nearly all adult age groups in the 1980s, and no one would have difficulty attributing the subsequent sharp declines in age-specific mortality rates from HIV/AIDS to increased availability of effective anti-retroviral therapy. Similarly, death rates from lung cancer increased in all age groups over time, until after a period of implementing public health efforts to curb cigarette smoking. Declines in age-adjusted mortality rates from heart attacks could be explained on the basis of public health interventions as well. However, with regard to diabetes mellitus, it was most curious to observe the steady decline in age-adjusted mortality from the 1960s through the early 1980s, followed by a shocking increase in mortality rates within all age groups during subsequent years [2]. Certainly no one would argue that medical treatment for diabetes mellitus is less advanced today than it was in the 1960s, yet what explanation do we have for the worsened outcomes in all age groups?

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Although epidemiological studies and analysis of mortality databases are not perfect, they are useful for re-evaluating hypotheses about disease pathogenesis and assessing roles for genetic versus environmental mediators of fatal disease. In this regard, the relatively rapid increases in mortality rates from diseases that most investigators consider to be genetic, familial or idiopathic in nature deserve scrutiny and fresh assessments about their potential pathogenesis because such dramatic shifts in mortality rates are more characteristic of exposure-mediated disease such as HIV/AIDS or lung cancer.

Three important pieces of information led us to the hypothesis that increased human exposure to nitrosamines could be responsible for the growing increases in rates of Alzheimer's, Parkinson's and perhaps other related neurodegenerative diseases: 1) human postmortem brains with Alzheimer's or Parkinson's diseases were found to have significant impairments in insulin and insulin-like growth factor signaling mechanisms and gene expression, similar to the abnormalities that characterize diabetes mellitus, metabolic syndrome, and non-alcoholic steatohepatitis (NASH) [3–6]; 2) clinical studies have demonstrated that Alzheimer's disease is associated with brain insulin resistance and deficiencies in glucose utilization [7–12]; and 3) Streptozotocin, which is a nitrosamine-related compound, causes diabetes mellitus, peripheral insulin resistance, NASH, and neurodegeneration and has many features in common with Alzheimer's disease [13–16]. By the time the manuscript under discussion was accepted for publication, we had already demonstrated that low-dose NDEA treatment produces the same abnormalities that occur with Streptozotocin, and that the addition of high dietary fat intake, exacerbates NDEA-induced insulin-resistance diseases, including neurodegeneration [17–19]. Moreover, evidence suggests that prenatal exposure to nitrosamines through diet lead to obesity in the offspring [20], suggesting that epigenetic factors also play a role in the pathogenesis of insulin resistance diseases. Furthermore, earlier studies linked increased dietary nitrite or nitrosamine exposures to increased risk for developing diabetes mellitus in humans [21,22]. Therefore, while we agree that epidemiological studies are generally subject to criticism and varied interpretation, it is important to realize that our hypothesis is supported by relevant experimental data showing that exposures to low, sub-mutagenic doses of nitrosamines, with or without superimposed high dietary fat intake cause insulin-resistance diseases similar to those that are currently epidemic in our society.

The bottom line is that deliberate addition of any substances that could increase human exposure to nitrosamines via food sources is problematic, if not irresponsible. Certainly, one of the greatest advances in society has been efficient food production through improvements in agricultural technology and, for this, all of us should be thankful. Nonetheless, the epidemiological data are alarming in that they strongly suggest exposures are the principal factors mediating insulin resistance diseases in the US. The roles of nitrosamines and high dietary fat intake are supported by experimental and human studies data. The matter could be resolved by eliminating unnecessary exposures. There are already several US companies that produce fertilizers devoid of components that could result in increased nitrosamine exposure through diet. My question is simple—what plausible explanation could there be for not doing whatever it takes to lower our risks and potentially help prevent exposure-mediated insulin-resistance diseases?

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