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Time, sex, gender, history, and dementia

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A growing body of epidemiologic evidence indicates a decline in the incidence or prevalence of dementia in high income countries in the past 25 years. Following the report in early 2016 of a decline in the incidence rates of dementia in the Framingham study (Framingham, Massachusetts),¹ another study confirmed a declining trend in incidence rates in the United Kingdom,² and a third study confirmed a declining trend in the prevalence of dementia in a sample representative of the entire United States.³ Several experts have written commentaries or reviews on these declining trends and have discussed the possible role of vascular risk factors, education, wealth, and other personal or social factors.^{4–10} Of particular interest is the commentary by Jones and Greene, two experts of the history of medicine, who have framed the declining trend for dementia within the broader context of trends for cardiovascular diseases. Cardiovascular diseases (in particular, coronary artery disease) have declined for several decades, reached a plateau, and started to increase again in some countries.⁴ Jones and Greene concluded that the burden of disease is malleable and may change; therefore, history offers reasons for hope.^{4,11} However, they also stated that an increase in the incidence or prevalence of obesity, diabetes, and hypertension could undermine the gains achieved through improved education, wealth, and control of vascular risk factors in the second half of the last century. Therefore, even if a dementia decline has begun, it might not last, and the future trends depend on the balance of diverging trends in multiple factors.⁴

In this commentary, I expand on the observations made by Jones and Greene and I make a number of additional observations. First, I suggest that the decline in the incidence or prevalence of dementia is not explained completely by the factors considered so far, and that a broader historical perspective may be needed. Second, I suggest that the overall declining trend may conceal trends in opposite directions for the two major subtypes of dementia, the neurovascular and the neurodegenerative type. Third, I suggest some areas of future research to further elucidate the trends. I restrict my consideration to countries with higher income, primarily from Europe and North America, because the time trends of neurological diseases, and of dementia in particular, may be different in other parts of the world with different demographic, social, cultural, and economic characteristics.^{12–15}

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The trends in dementia incidence or prevalence remain partly unexplained. For example, in the study by Langa et al, the prevalence of dementia declined even though the cardiovascular risk profile worsened (e.g., increased prevalence of hypertension, diabetes, and obesity over time).³ These findings suggest that the increase in prevalence of cardiovascular risk factors was probably counterbalanced by an improvement in treatment (better treatment of hypertension and diabetes). The increasing trends in late-life obesity and overweight in relation to dementia risk need further study. It is possible that overweight and obesity in late life may protect against dementia rather than increase the risk. The OR of 0.69 (31% reduction comparing the prevalence in 2012 to the prevalence in 2000) only increased to 0.82 after accounting for all of the factors considered (age, sex, race/ethnicity, education, net worth, cardiovascular risk factors and diseases, and body mass index). Therefore, a large segment of the decline remained to be explained by yet unknown factors.³

The trends for dementia incidence and prevalence have occurred within the context of large-scale historical events. Important dynamic interactions between sex, gender, socioeconomic factors, and cultural factors have occurred over historical epochs of the last century. For example, the people who have developed dementia in the last 20 to 30 years in Europe and North America have lived through World War I (1914–1918), the Spanish flu pandemic (1918–1920), the Great Depression (1929–1937), World War II (1939–1945), the polio epidemic (1949), the Korean War (1950–1953), the Vietnam War (1955–1975), political protest movements in the 1960's, the end of the Cold War (1991), the Yugoslav Wars (1991–2001), and the more recent conflicts in the Middle East. Some of these events have caused food restriction or famine, massive migrations, incarceration, persecution, violence, and stress. Patients with dementia have also lived through natural catastrophes, such as earthquakes and floods. They have lived through changes in access to information (e.g., widespread use of radios and televisions, and more recently of the internet), changes in the physical environment (e.g., increase in urbanization and population density, mechanization of agriculture and increased use of herbicides and pesticides, increase in air and water pollution), changes in food availability (e.g., introduction of frozen food, distant transportation of fruit and vegetables) and diet (e.g., reduced time spent in preparing food, use of food additives to increase shelf life), and changes in life habits (e.g., the initial increase and later decrease in cigarette smoking, the increase in sedentary lifestyle). Finally, they have lived through changes in medical care (e.g., introduction of antibiotics, anti-hypertensive drugs, diabetes drugs, dyslipidemia drugs, anticoagulant drugs, and psychiatric drugs). The impact of these large scale historical events on health and diseases remains poorly understood.

The overall declining trend in dementia incidence or prevalence may conceal trends in opposite directions for the two major subtypes of dementia, the neurovascular and the neurodegenerative type. Let us first consider some important trends in other neurological diseases. The incidence of stroke has declined over four or five decades in the United States and Canada.^{16–18} In addition, the incidence of parkinsonism and Parkinson's disease has increased over the last 30 years in a United States population.¹⁹ At the same time, drug-induced parkinsonism, a disease strictly linked to medical practices, declined in the same population.²⁰ Finally, the incidence of amyotrophic lateral sclerosis has increased from 1982 to 2009 in Denmark.²¹

At the risk of some oversimplification, we can group the neurological diseases discussed above in three groups: 1) diseases that involve neurovascular mechanisms (e.g., large strokes, small strokes, white matter lesions) such as stroke and vascular dementia or mixed dementia, 2) diseases that involve degenerative mechanisms (e.g., the accumulation of plaques, tangles, or Lewy bodies; the development of atrophy of specific regions or of the full brain) such as the degenerative dementias (primarily Alzheimer's disease), Parkinson's disease, and amyotrophic lateral sclerosis, and 3) diseases that are independent of both neurovascular or neurodegenerative mechanisms such as drug-induced parkinsonism. Dementia as a syndrome includes patients who have primarily neurovascular lesions, patients who have primarily degenerative lesions, and the full spectrum of mixed cases in between.²² Therefore, a decline in the occurrence of dementia may be explained by a decline in neurovascular mechanisms, in neurodegenerative mechanisms, or in both mechanisms at the same time. However, it is also possible that the two underlying mechanisms are trending in the opposite direction.

The concurrent decline in the incidence of stroke supports the hypothesis that the incidence of dementia is declining because of the reduction over time in the neurovascular component of dementia.¹⁷ On the other hand, the concurrent increase in the incidence of Parkinson's disease and amyotrophic lateral sclerosis suggests that the neurodegenerative component of dementia may be increasing over time. It can be hypothesized that dementia with earlier onset, with familial aggregation, and with predominant neurodegenerative lesions is increasing over time, whereas dementia with later onset, limited familial aggregation, and with predominant neurovascular lesions is decreasing over time. These opposing trends will be evident if we consider age-specific time trends; however, the decrease in the vascular mechanisms of dementia would overpower the opposite trend of increase in neurodegeneration in the overall population (time trends for all ages combined). This is because the risk of dementia increases steeply with advancing age, and the majority of patients will develop a vascular or mixed type of dementia.

I suggest that it is important to consider the declining trend in dementia incidence and prevalence in the broader context of time trends for other related neurological disorders. In addition, these trends for brain disorders should be considered within the broader context of trends for other important disorders of the cardiovascular system, the respiratory system, and the urinary system.^{4,11} Finally, all of these trends should be considered part of the general trends in aging.

The trends for dementia incidence or prevalence may vary by sex. The decline in the incidence of dementia in the Framingham study and in Germany was more pronounced in women than men.^{1,23} By contrast, the decline in the incidence of dementia was almost completely restricted to men in the United Kingdom study and was greater in men in Spain.^{2,24} The declining trends of dementia for men and women may vary across countries and across time periods because of the interaction of sex and gender factors with a changing physical, social, and cultural environment (e.g., interaction of sex and gender with "living conditions"). The dramatic historical changes that occurred in the second half of the last century have impacted women differently from men. For example, men went to war in 1939–1945, whereas women stayed home with the elderly and children, and took on new

roles to support the war efforts (many women started working in industry or agriculture). Men started to smoke cigarettes earlier than women, men reached much higher percentages of use, and men experienced a steeper decline in smoking in more recent decades. Attention to sex related factors (chromosomal, endocrine, and reproductive factors) or to gender related factors (social and cultural factors) may help us to interpret the time trends. These sex and gender factors may be part of the missing explanation of the decline in the incidence or prevalence of dementia. We and others have recommended looking at risk and protective factors for dementia separately in men and women.^{25–27}

The trends for dementia incidence or prevalence may vary by race and ethnicity. Major variation in the incidence of dementia within a given time period have been reported across African Americans, American Indian and Alaska Natives, Latinos, Pacific Islanders, Whites, and Asian Americans living in California.²⁸ These differences suggest that genetic differences and linguistic, religious, and cultural differences linked to race and ethnicity may interplay with the shared natural environment and the shared social and political environments in modifying the risk of dementia. A recent study showed a decline in the incidence of dementia in African Americans living in Indianapolis, Indiana between 1992 and 2001. However, no decline was observed over the same time period and using the same study design and procedures for Yoruba Africans living in Ibadan, Nigeria.¹² These findings suggest that environmental, social, and cultural factors may be the driving forces underlying time trends in different countries even when the genetic background is common.

The trends for dementia incidence or prevalence may vary by country or region. Because sex, gender, race and ethnicity, language, religion, diet, medical system, and culture interact with each other within a given political and legal system, we expect different countries (or regions) to experience smaller or bigger time trends, or similar time trends but earlier or later (non synchronous trends).^{12,14,15} Different countries may also undergo a bigger trend in men or in women as discussed in the comparison of trends in the United Kingdom and Spain versus the United States and Germany.^{1,2,10,23,24}

The trends for dementia incidence or prevalence may vary by birth year (or birth cohort). An alternative way of studying the impact of time on the risk of dementia is to consider the year of birth. If we hypothesize that important environmental effects can take place during the period of maximum vulnerability of the brain, the nine months of intra-uterine development are crucial.²⁹ Children exposed intra-uterine to a specific infectious agent (e.g., a virus), a specific toxin (e.g., mercury), or to a dietary deprivation (e.g., total caloric deprivation or a particular vitamin deficiency) may experience an inadequate development, and may be born with a brain particularly susceptible to neurological diseases. Some of these diseases may become manifest only several decades after birth when the normal aging-related decline in the number of brain cells and in the function of brain cells will interact with the congenital deficits. We reported some examples of cohort analyses conducted in the population of Olmsted County, Minnesota. Our cohort analyses for dementia or Alzheimer's disease did not reveal a birth cohort effect.^{30,31} However, these types of analyses should be repeated in other populations.⁸ In a more recent study, and using a more sophisticated method of analysis (age-period-cohort models), we showed an increased risk of Parkinson's disease for both men and women born in the 1920 cohort (1915–1924) in the same Olmsted County

population.^{19,32} Age-period-cohort models have also been used to study time trends for amyotrophic lateral sclerosis.²¹

The future of dementia remains somewhat unclear. There is reasonable evidence for more optimistic projections. However, even if the incidence continues to decline, the prevalence (percent of the population affected at one given point) may remain the same or increase if survival of persons affected by dementia increases. In addition, even if the prevalence declines, the total number of persons affected by dementia may remain the same or increase if the size of the elderly population expands (population aging).^{4,13} Finally, we cannot be sure that the trends of reduced incidence will continue in the coming decades.^{4,31} Living conditions and diseases occur in an environmental, social, and cultural context that evolves historically. Therefore, the burden of disease can be modified over time by human practices such as public health, medicine, and politics. Diseases can rise and decline (appear and disappear) over time; however, these trends reflect complex interactions and are delicate (contingent and ephemeral).

The decline in the incidence of dementia reminds us that investing some of our societal money in improving education, improving general living conditions, and strengthening the primary prevention of diseases may be more prudent than putting all of our resources in the search for a magic treatment for Alzheimer's disease or in the development of expensive and invasive biomarkers to predict the future occurrence of disease.^{2,6} Our narratives should be cautiously optimistic and pragmatic.^{4,11}

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