

Age and Variant Creutzfeldt-Jakob Disease

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The young and stable median age of those who die of variant Creutzfeldt-Jakob disease has been attributed to age-dependent infection rates. This analysis shows that an influence of age on risk for death after infection better explains age patterns, suggesting that biologic factors peaking in the third decade of life may hasten disease.

The epidemic of variant Creutzfeldt-Jakob disease (vCJD) in Great Britain is now thought to be caused by the same prion responsible for bovine spongiform encephalopathy (BSE) in cattle (1). A striking feature of the human epidemic has been the young age of most patients and the lack of any trend toward older ages in patients dying later in the epidemic. Investigations of this stability have agreed that age must influence risk for infection (2,3), and studies projecting future numbers of cases have assumed that age only influences infection risk and does not influence risk for disease after infection (3–5). By extending previous methods to model age as a time-dependent covariate, I show here that the stable age distribution over time is in fact better explained by an influence of age on risk for disease after infection.

As was done in previous studies (2–5), I used methods to exploit the relation among date of infection, incubation time, and date of disease. The incubation period is defined as the time from infection to disease, which can be onset, diagnosis, or death. I focused on death from vCJD because no measurement error exists in the date of death, and ascertainment delay is less of an issue for this than for the date of disease onset. These methods were developed extensively for analyzing the HIV epidemic, both for estimating past infection rates, assuming a known incubation period distribution (6,7), and for estimating incubation, assuming a known infection pattern (8,9). To match the last approach, I assumed that the shape over time of the infection hazard (the risk for infection among uninfected persons) is determined by what is known about the BSE epidemic (10) and that the scale of the infection hazard is large enough so that the total number of infections (approximately 1.2 million) is much larger than the number of deaths to date. (This large number of infections implies that risk of developing disease after infection must be very low, so most of those infected will die of other

causes, and disease will never develop.) I assumed that age has a multiplicative effect on the risk for infection or on the risk for disease after infection, corresponding to the proportional hazards assumption (11) frequently used in survival analysis. Detailed statistical methods are described in an online Appendix (available from: URL: <http://www.cdc.gov/ncidod/EID/vol9no12/03-0361-app.htm>).

Using the 121 reported deaths from 1995 to the end of 2002, I obtained similar shapes for the estimated influence of age on risk for infection (Figure a) or on risk for death (Figure b), with both showing strong peaks. The model of Figure b, where age influenced only risk for death, had a log likelihood that was better by 1.91 than the model of Figure a, where age influenced only risk for infection. A simulation test using data generated under the model of Figure a found differences this large 75 times in 2,000 runs ($p = 0.038$), indicating that the data are more compatible with an influence of age on risk for death. This age model appears to better explain the observed stability of ages at death over time. A simple regression of age at death on quarter of death estimates that the mean age has remained nearly constant at around 29 years, with an average increase of 26 days for each year of the epidemic. (A robust regression [12] of age at death on quarter of death found an increase of 20 days per year, nearly identical to the 26 days found by ordinary least squares regression.) The model in Figure b matched this finding with an estimated overall increase in mean age of 34 days per year, but the model in Figure a predicts an increase of 214 days per year.

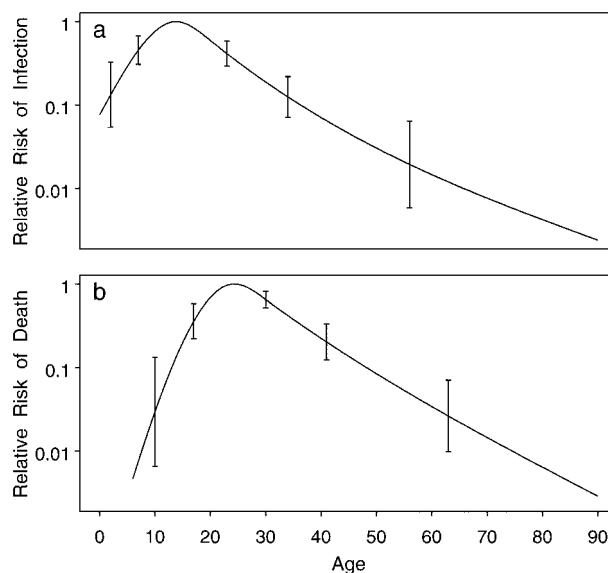


Figure. Estimated influence of age on a) risk for infection with the variant Creutzfeldt-Jakob disease (vCJD) agent and b) risk for death from vCJD after infection. Vertical bars are pointwise 95% confidence intervals for selected ages.

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The shapes in the Figure contrast with those assumed by previous studies. One study assumed constant infection risk up to age 15, which is ruled out by the confidence intervals shown on the left in Figure a (3). Another study modeled the influence of age on both risk for infection and risk for death from vCJD after infection, but it imposed a mathematical form for the influence on risk for death that can only be monotonic, an assumption incompatible with the peaked shape in Figure b (2). That study's finding that age must influence risk for infection rather than only influencing risk for death is therefore suspect. In addition, a later analysis (13) claiming to confirm the impact of age on risk for infection did so only by assuming that age had no influence on subsequent risk for death.

In the Figure b model, younger persons' risks for death increase as they age (moving up the left slope), while older persons' risks decrease (moving down the right slope). Therefore, the highest risk moves toward younger and younger age cohorts over time, counteracting the aging of the entire infected population and thereby matching the observed stability in ages at death. Nothing counteracts the aging of the infected population if age is assumed to influence only risk for infection. This finding and reasoning contrast with an argument (3) that an influence of age on risk for death would result in a shift toward older cases later in the epidemic because most younger persons would have died earlier. This argument relies on the unstated assumption that the total number of infections is small enough that cases to date constitute a substantial fraction of the total infected in younger age cohorts. I have considered here the case that many more were infected. Even if the unstated assumption were true, this finding would not explain the observed stability because aging of the entire infected cohort should still produce an upward trend.

The estimates in the Figure assume that total infections were much greater than deaths reported to date but not so large that the pool of >20 million persons with the susceptible genotype became noticeably depleted before measures were implemented at the end of 1989 to keep contaminated beef out of the human food supply. I evaluated such a scenario, with most susceptible persons infected by 1989, and found even stronger evidence in favor of an influence of age on risk for death rather than risk for infection. The log likelihood was better by 3.13, and only 12 of 2,000 iterations in a simulation test produced a difference this large ($p = 0.006$).

The reasons for the age distribution of vCJD cases and its stability over time remain unclear, and epidemiologic analyses can provide limited insight. Previous assertions

that age must influence risk for infection and that age does not influence development of disease may have been incorrect. Our findings suggest that the possibility should not be discounted that biologic factors peaking in the third decade of life may promote vCJD prion replication and consequent development of disease.

Acknowledgment

I thank the United Kingdom's Creutzfeldt-Jakob Disease Surveillance Unit for providing the data on variant Creutzfeldt-Jakob disease cases.

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