Published Ahead of Print on November 22, 2019 as 10.1212/WNL.0000000000008680

ARTICLE

Prion disease incidence in the United States, 2003–2015

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Neurology® 2020;94:1-5. doi:10.1212/WNL.0000000000008680

Abstract

Objective

To report the incidence of prion disease in the United States.

Methods

Prion disease decedents were retrospectively identified from the US national multiple cause-of-death data for 2003–2015 and matched with decedents in the National Prion Disease Pathology Surveillance Center (NPDPSC) database through comparison of demographic variables. NPDPSC decedents with neuropathologic or genetic test results positive for prion disease for whom no match was found in the multiple cause-of-death data were added as cases for incidence calculations; those with cause-of-death data indicating prion disease but with negative neuropathology results were removed. Age-specific and age-adjusted average annual incidence rates were then calculated.

Results

A total of 5,212 decedents were identified as having prion disease, for an age-adjusted average annual incidence of 1.2 cases per million population (range 1.0 per million [2004 and 2006] to 1.4 per million [2013]). The median age at death was 67 years. Ten decedents were <30 years of age (average annual incidence of 6.2 per billion); only 2 of these very young cases were sporadic forms of prion disease. Average annual incidence among those ≥65 years of age was 5.9 per million.

Conclusions

Prion disease incidence can be estimated by augmenting mortality data with the results of neuropathologic and genetic testing. Cases <30 years of age were extremely rare, and most could be attributed to exogenous factors or the presence of a genetic mutation. Continued vigilance for prion diseases in all age groups remains prudent.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Glossary

CDC = Centers for Disease Control and Prevention; **CJD** = Creutzfeldt-Jakob disease; **CWD** = chronic wasting disease; **ICD-10** = International Classification of Disease, Tenth Revision; **NCHS** = National Center for Health Statistics; **NPDPSC** = National Prion Disease Pathology Surveillance Center; **vCJD** = variant Creutzfeldt-Jakob disease.

Human prion diseases such as Creutzfeldt-Jakob disease (CJD) are invariably fatal, and the majority of patients die within 1 year of onset.[1] As a result, national multiple cause-of-death data can be a useful tool in estimating prion disease incidence in the United States.[2] However, there are limitations inherent to the use of these data alone, including the possibility of diagnostic and coding errors.[1] Previous active surveillance has indicated that death certificate review may not capture 14% of CJD cases.[3] Neuropathology is necessary for prion disease confirmation, and results of such testing may not be available at the time a death certificate is completed.[2] As a result, some prion disease cases may not be indicated as such in multiple cause-of-death data. Autopsy findings may also provide evidence that decedents with prion disease coded as a cause of death did not actually have the disease. The National Prion Disease Pathology Surveillance Center (NPDPSC) was established in 1997 by the Centers for Disease Control and Prevention (CDC) in collaboration with the American Association of Neuropathologists to provide state-of-the-art confirmation of prion disease for clinically diagnosed or suspected cases.[4] By using results from NPDPSC testing in combination with national multiple cause-of-death data, we sought to more accurately calculate prion disease incidence in the United States.

Methods

Prion disease decedents were identified for 2003–2015 from restricted-use US national multiple cause-of-death data via a data use agreement with the National Center for Health Statistics (NCHS); these decedents were selected based on the presence of the CJD ICD-10 code of A81.0 or literal text indicating CJD or CJD-related terms. The use of literal text searches, described previously,[1] allows for the inclusion of prion disease cases coded with an incorrect ICD-10 code as well as the exclusion of miscoded non–prion disease cases (e.g., JC virus). The year 2003 was selected to start the surveillance period because it was the first year that literal text data were available for all 50 states. The prion disease decedents were then cross-checked with specimen test results in the NPDPSC database. Because decedent names are not included in the NCHS data, an algorithm was used to determine likely decedent matches between the 2 databases based on demographic variables including sex, race, date of birth, date of death, and state of residence.

When specific demographic data (age, date of death) were confirmed through an online obituary or death record search, NPDPSC decedents with neuropathologic or genetic test results positive for prion disease for whom no match was found in the NCHS data were added as cases for incidence calculations; those with NCHS data indicating prion disease but with negative neuropathology results were removed. Age-specific and age-adjusted average annual incidence rates were then calculated using the corresponding US census population estimates for each year as the denominator; age-adjusted rates were calculated by the direct method and used the year 2000 standard US population.[5] Poisson regression analysis was used to calculate risk ratios and associated p values for comparison between groups and to test for trend over time.[6]

During the surveillance period, CDC or NPDPSC sought to improve the diagnosis and reporting of prion diseases in multiple ways, including (1) providing funds to selected state health departments (e.g., states with large populations or long presence of chronic wasting disease [CWD] in free-ranging cervids); (2) corresponding with neurologists and neuropathologists via professional organizations; (3) publishing scientific articles, providing free expert consultations, and maintaining prion disease–related websites; (4) assisting the CJD Foundation support group with educational workshops and conferences; and (5) expanding the use of CSF tests and brain MRI to increase earlier and more sensitive and specific diagnoses.

Data availability

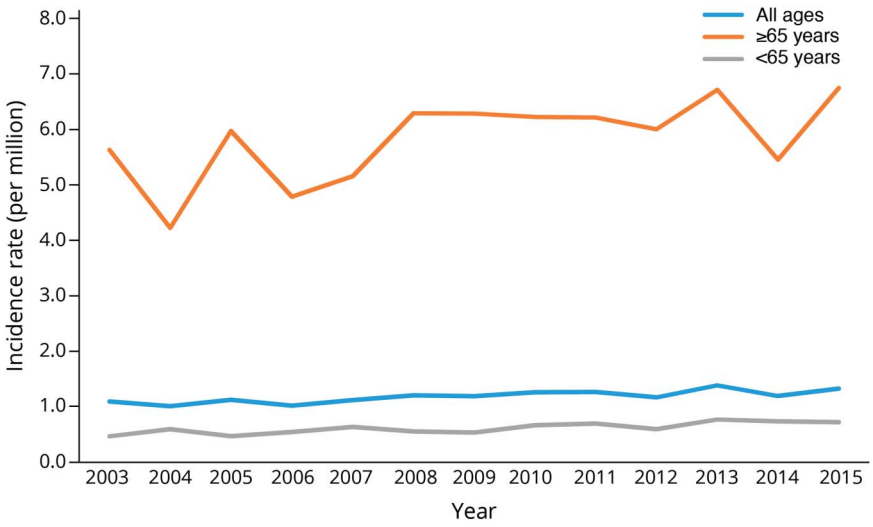
National multiple cause-of-death data may be requested through the National Association for Public Health Statistics and Information Systems (naphsis.org/research-requests). A search of these data using ICD-10 code A81.0 would not include decedents that were added to our case count based on the results of literal text searches or testing performed at NPDPSC.

Results

A total of 5,212 decedents were identified as having prion disease during 2003–2015 for an age-adjusted average annual incidence of 1.2 per million population. The age-adjusted annual incidence ranged from 1.0 per million (2004, 2006) to 1.4 per million (2013) (figure 1). There was an increasing trend in incidence over the entire 2003–2015 period ($p < 0.0001$); however, there was no significant increase when looking only at the second half of the period (2010–2015, $p = 0.2$). An average of 1 death per 6,239 all-cause deaths annually was attributed to prion disease (range 1:5,102–1:7,835); among those ≥65 years, the annual average was 1 per 7,700 (range 1:6,187–1:11,475).

While the percentage of male (49.8%) and female (50.2%) prion disease decedents was similar, the difference in age-

Figure 1 Prion disease incidence, age-adjusted (all ages) and age-specific (<65 and ≥65 years), United States, 2003–2015



adjusted incidence (1.3 and 1.1 per million per year, respectively) was significant ($p < 0.0001$) (table). The age-adjusted average annual incidence among white decedents (1.3 per million) was more than double the incidence among black decedents (0.6 per million). The highest age-adjusted incidence was found among residents of the Midwest (1.3 per million per year); significantly lower rates were seen in the South (1.1 per million, $p < 0.0001$) and West (1.2 per million, $p = 0.006$). These regional differences remained when the analysis was limited to white decedents.

The median age at death was 67 years. Ten cases were <30 years of age, for an age-specific average annual incidence of 6.2 per billion; only 2 of these very young cases had sporadic forms of prion disease (1 sporadic CJD, 1 sporadic fatal insomnia) for an age-specific average annual incidence of 1.2 per billion. Five of the remaining young cases were familial (3 Gerstmann-Sträussler-Scheinker syndrome, 1 fatal familial insomnia, 1 familial CJD), 2 were variant CJD (vCJD), and 1 was iatrogenic CJD (dura mater–associated). The age-specific average annual incidence among those <55 and ≥55 during the time period was 0.2 and 4.7 per million, respectively; among those ≥65, it was 5.9 per million. In addition to the 2 vCJD cases <30 years of age mentioned previously, 2 more young (<50 years) vCJD cases were identified in the United States during the surveillance period. Investigations of all 4 of these vCJD cases indicated they were most likely exposed to the infectious agent outside of the country.[7]

For decedents with a specific prion disease diagnosis from the NPDPSC based on both neuropathologic and genetic testing, 89% were classified as having a sporadic prion disease, 10% as having a familial prion disease, and <1% as having iatrogenic prion disease. Approximately 13% (range 9%–18%) of the total prion disease cases each year were the result of additions based on positive neuropathologic findings (figure 2); 5% (range 3%–6%) of the death certificate cases were removed. Of the 2,312 cases identified in the NCHS data for which physicians obtained neuropathologic results from the NPDPSC, 2,096 (90.7%) were confirmed, while 216 (9.3%) were falsely classified as prion disease.

Analysis of multiple cause-of-death data is an efficient means of conducting CJD surveillance. Incorporating findings from neuropathologic and genetic testing into these data enhanced surveillance by providing better estimates of the true disease incidence. Matching NCHS and NPDPSC data was successfully accomplished through comparison of key demographic variables. The rarity of a prion disease diagnosis, coupled with the use of multiple variables in the matching process, allowed for a high level of certainty in patient matches; 2 decedents matching by state of residence, sex, and date of death, for example, but with a minor discrepancy in date of birth, would be flagged and the match subsequently verified or ruled out through confirmation of the correct birth date. Given the absence of (1) a highly specific antemortem test during the surveillance period and (2) results of neuropathologic analyses at the time of death certificate completion, the identification of deaths in the NCHS data that were misclassified as being due to prion disease was not surprising. With the recent introduction of the real-time quaking-induced conversion test, diagnostic accuracy prior to death will improve, which should lead to a corresponding improvement in the accuracy of death certificate data.[8]

The age-adjusted average annual incidence of 1.2 per million population during 2003–2015 is consistent with the rates reported in many other countries where prion disease surveillance is conducted.[9] The relatively low incidence in the

Table Prion disease incidence, United States, 2003–2015[a]

Characteristic	Incidence[b]	Risk ratio (*p* Value)
Age group, y		
<55	0.2	Reference
≥55	4.7	21.8 (<0.0001)
<65	0.6	Reference
≥65	5.9	9.5 (<0.0001)
Sex		
Female	1.1	Reference
Male	1.3	1.2 (<0.0001)
Race		
Black	0.6	Reference
White	1.3	2.2 (<0.0001)
Other	0.7	1.2 (0.030)
Region		
Midwest	1.3	Reference
South	1.1	0.8 (<0.0001)
Northeast	1.3	1.0 (0.234)
West	1.2	0.9 (0.006)
Total	1.2	

[a] Sources: US national multiple cause-of-death data, National Prion Disease Pathology Surveillance Center data.
[b] Rates are expressed per 1,000,000 persons and are age-adjusted for sex, race, region, and total.

black population and greater number of cases but lower age-adjusted incidence in women have been reported previously.[1] The higher incidence seen among older age groups was expected given the median death age for CJD cases.[1] Towards the end of the surveillance period (2014), the oldest members of the generation born right after World War II (the Baby Boomer generation) turned 68[10]; more CJD cases are likely to be reported annually in the coming years as this large generation continues to age. Increasing trends in incidence seen in the earlier years of the surveillance period most likely reflect improvements in case detection and disease awareness.

Extremely young patients, those <30 years, were very rare, and most (80%) could be attributed to exogenous factors or the presence of a genetic mutation. Given this rarity and the subset that have served as important initial signals for controllable outbreaks, the continued identification and full workup of cases in patients aged <30 years is recommended. Such ongoing surveillance is crucial to detecting potential zoonotic transmission of CWD; as with the vCJD outbreak, an observed change in the epidemiology of human prion disease (e.g., identification of very young patients or an increase in cases among patients most likely exposed to the agent) could indicate zoonotic transmission. Continued surveillance is also prudent to monitor the expected increase in US cases of CJD as the population ages and to facilitate detection of any concomitant increase in possible iatrogenic disease.

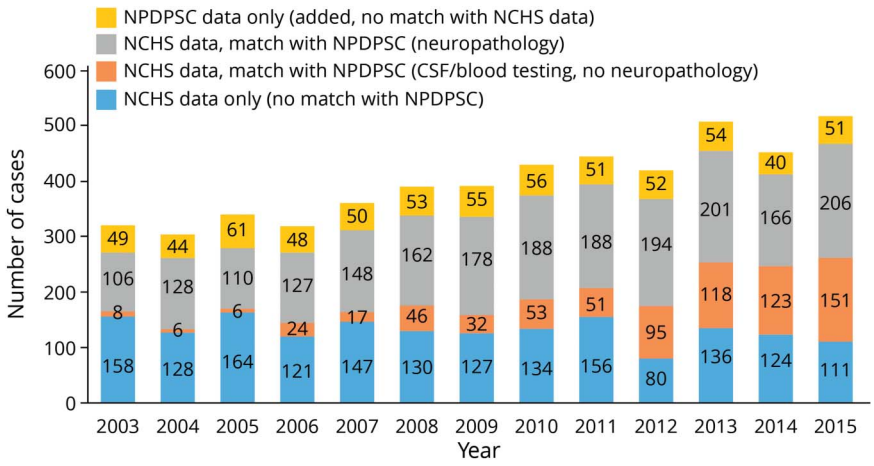
Acknowledgment

The authors thank Arialdi M. Minino, MPH, of the National Center for Health Statistics for sharing the relevant US national multiple cause-of-death data and providing expert advice regarding its use.

Study funding

Work performed by Dr. Brian Appleby and Janis Blevins (National Prion Disease Pathology Surveillance Center) is supported in part by a grant from the Centers for Disease Control and Prevention (CCU 515004).

Figure 2 Prion disease cases by year, United States, 2003–2015



NCHS = National Center for Health Statistics; NPDPSC = National Prion Disease Pathology Surveillance Center.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* November 16, 2018. Accepted in final form July 9, 2019.

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Name	Location	Role	Contribution
Ryan A. Maddox, PhD	Centers for Disease Control and Prevention	Author	Coordinated surveillance activities; cleaned, matched, and interpreted data; drafted manuscript; incorporated author feedback
Marissa K. Person, MSPH	Centers for Disease Control and Prevention	Author	Acquired and analyzed data, revised manuscript with emphasis on methodology
Janis E. Blevins	National Prion Disease Pathology Surveillance Center	Author	Acquired and interpreted data, reviewed manuscript
Joseph Y. Abrams, PhD	Centers for Disease Control and Prevention	Author	Interpreted data, revised manuscript for intellectual content
Brian S. Appleby, MD	National Prion Disease Pathology Surveillance Center	Author	Oversaw specimen testing and dissemination of data, interpreted data, revised manuscript for intellectual content

Appendix *(continued)*

Name	Location	Role	Contribution
Lawrence B. Schonberger, MD	Centers for Disease Control and Prevention	Author	Oversaw surveillance activities, interpreted data, revised manuscript for intellectual content
Ermias D. Belay, MD	Centers for Disease Control and Prevention	Author	Oversaw surveillance activities, interpreted data, revised manuscript for intellectual content

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