Article

The Case For Including Neuroprotective Factors in Sporadic Creutzfeldt-Jakob Questionnaires

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The Case for Including Neuroprotective Factors in Sporadic Creutzfeldt-Jakob Questionnaires

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Abstract: Background: Demonstrate a theoretical and empirical justification for including potentially protective factors in Sporadic Creutzfeldt-Jakob case-controlled studies alongside the almost exclusively studied risk-enhancing factors. Methods: Synthesize existing sCJD and Alzheimer's disease (AD) research to suggest the plausibility of shared neuroprotective factors. A fixed effects longitudinal analysis of 26 countries across 10 time periods examines whether factors identified to protect against AD are associated with population-level sCJD incidence rates. Results: Increased consumption of beans and nuts, both of which are thought to protect against AD risk, is associated with lower population level sCJD incidence. Conclusion: This study suggests that factors that protect against other neurodegenerative diseases might offer protection from sCJD. The low marginal burden of including protective factors in sCJD questionnaires offers a chance to better understand sCJD at little additional cost.

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Introduction (1)

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare degenerative prion disease that is inevitably fatal (Chen & Dong, 2016). Though rare, sCJD is the most common form of prion disease with a worldwide incidence ratio of approximately one per million (Sitammagari & Masood, 2022). The randomness and rarity with which sCJD strikes make etiological inquiry especially difficult. No clear cause has been identified, and researchers have cast a wide net to identify possible risk factors. Though incredibly useful, identifying potential risk factors is only one side of the coin, and identifying potentially protective factors may yield additional benefits. In this paper, I review currently postulated risk factors for sCJD and draw on sCJD's similarities with Alzheimer's Disease (AD) to provide a theoretical basis for including potential protective factors in case-controlled sCJD studies. Finally, I conduct a multi-country longitudinal regression that suggests at least some AD protective factors might protect against sCJD risk as well.

Current literature indicates that an abnormal protein designated PrPSc is the infectious pathogen responsible for human prion diseases, but the mechanism by which this sporadic disease manifests is not yet understood (Safar, 2012). One theory advocates a spontaneous somatic mutation in the PRNP gene (Prusiner, 2001). A second theory holds that PrPSc-like isoforms may be present and bound to heat shock proteins even in normal brains, but that this protective measure fails with aging (Safar et al., 2005; Yuan et al., 2006). It has also been posited that low-level exposure to a common external factor can be to blame for at least some cases of sCJD (Linsell et al., 2004).

Although the specific trigger or activation factor for sCJD is not known, onset typically occurs at a median age of 68 with a standard deviation of approximately 9 years (Feng et al., 2021; Tam et al., 2022) making age a well-known risk factor (*CDC*, 2022). Likewise, numerous studies have shown an over-representation of 129M/M homozygotes (Kobayashi et al., 2015; Mitrová et al., 2005) in sCJD cases compared to controls, and genetic susceptibility has been known for decades (Deslys et al., 1994).

Though the disease is sporadic, the well-documented risk factors of age and 129M/M homozygosity make it clear that each individual's risk of being affected is not uniformly random and that there are at least some factors that make the initiation of this sporadic process more or less likely. Though elusive, uncovering additional risk factors could help develop a more thorough understanding of sCJD and provide a basis for risk-modifying behaviors.

Potential sCJD Risks (1.1)

To uncover potential risk factors, researchers have investigated the link between sCJD and surgery (Hamaguchi et al., 2009; van Duijn et al., 1998; Ward et al., 2002, 2008), ocular tonometry (Davanipour et al., 2014b), profession (Hermann et al., n.d.), physical injuries (Kondo & Kuroiwa, 1982), living with pets (Harries-Jones et al., 1988), and dementia in relatives (Harries-Jones et al., 1988). While factors such as needing surgery or dental work are scarcely modifiable, several interesting studies have examined a possible link between sCJD and highly modifiable dietary factors.

Even before the vCJD epidemic of the late 80s to 90s, Davanipour et al. (1985) found that increased consumption of roast pork, ham, hot dogs, roast lamb, pork chops, smoked pork, scrapple, rare meat, and raw oysters/clams, liver, and organs was greater among sCJD patients than case controls. The relationship between diet and sCJD was further described by the UK's National CJD Surveillance Unit report that found patients were more likely than controls to have ever eaten lamb or beef, venison, veal, sweetbreads (organ meat), or brains (1996). In a confirmatory case-control study using primarily data from pre-vCJD publicity, Davanipour et al. (2014a) found that consumption of hot dogs, sausage, pepperoni, kielbasa, "other" canned meat, poultry liver, any stomach/intestine, beef stomach/intestine, any organ tissue, and beef organ tissue was individually associated with increased sCJD risk.

The clear distinction that the aforementioned studies make, both in terms of timing as well as diagnostic criteria, between vCJD and sCJD is vital because it implies that certain foods, particularly meats, not only act as transmission vehicles for the variant form of CJD but that dietary factors may impact the susceptibility to the non-infectious, sporadic form of the disease as well. Though these studies demonstrated dietary risk factors, an exciting corollary is the possibility of yet unknown protective dietary factors.

Similarities with Alzheimer's (1.2)

Asuni (2015) stated that the common theme in the pathogenesis between AD and prion disorders indicates that analogous degenerative processes are likely at play. Extending this statement implies that research into other forms of dementia might not only present a potential rationale for an association between diet and sCJD but a possible short list of dietary factors worthy of inclusion in sCJD questionnaires. A brief overview of the similarities between sCJD and AD, in which 90% of cases also occur sporadically, (Bekris et al., 2010) is provided to support this theory.

Debatin et all, (2008) note that Alzheimer's disease (AD) and prion diseases such as sporadic Creutzfeldt-Jakob disease (sCJD) share common features concerning their molecular pathogenesis and neuropathological presentation. This observation is strengthened when considering that AD and sCJD "have many common features impinging on the metabolism of neuronal membrane proteins" (Aguzzi & Haass, 2003) and that Alzheimer's disease is a consequence of protein misfolding, aggregation, and spread (Carlson & Prusiner, 2021). Given that Alzheimer's exhibits at least some of the misfolded prion protein properties,(Jaunmuktane & Brandner, 2020) it is plausible that factors that increase or decrease AD risk might play a role in sCJD risk as well.

Assuming that the disease pathogenesis between AD and sCJD is comparable enough that there is at least some crossover between risk factors, sCJD researchers might benefit from including AD protective factors in future sCJD studies. While many lifestyle factors such as physical activity (Iso-Markku et al., 2022) and social/cognitive leisure activities (Su et al., 2022) have been found to protect against AD, the finding of a dietary risk for AD (Duplantier & Gardner, 2021) presents the ideal vehicle for exploring possible empirical support of a theoretical carryover of AD protective factors to

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sCJD research as dietary data is freely available from reputable sources at no cost and requires no clinical intervention. If a dietary carryover is identified, then other AD protective factors which require more detailed investigative methods could be studied in the future.

Materials and Methods (2)

To support the theory that AD-protective foods may also protect against sCJD, I present a fixed-effects panel data regression analysis that compares the AD-protective foods identified by Duplantier & Gardner, (2021) against population-level sCJD rates.

To ensure the validity of sCJD incidence data and minimize the effect of differential reporting, all data regarding sCJD cases were collected from the Creutzfeldt-Jakob Disease International Surveillance Network. Dietary data were collected from the United Nations FAOSTAT database (*FAOSTAT*, n.d.), and the median age was gathered from the United Nations (*World Population Prospects - Population Division - United Nations*, n.d.) database. Python's Pandas library was used to merge data from all sources into a consolidated panel which was subsequently analyzed using the gretl 2022C econometrics package.

Results (3)

As expected from the literature review, a higher median age demonstrated a significant (p~.004) positive association with sCJD incidence. The neuroprotective effects of nuts (p~.002) demonstrated in other dementia research were reflected in this study alongside the borderline (p~.094) protective effect of bean consumption. Fish showed no significant effect.

Table I. Key Regression Values.

	Coefficient	Std. Error	t-ratio	p-value	
Constant	−4.088	2.1328	−1.917	0.0668	*
Fish	0.001	0.0203	0.0556	0.9561	
Age	0.175	0.0576	3.0290	0.0056	***
Nuts	−0.224	0.0554	−4.043	0.0004	***
Beans	−0.433	0.2490	−1.740	0.0941	*
Calories	−0.0002	0.0007	−0.2430	0.8100	

It should be noted that the fixed effects model used in this analysis treats each country in the study as its own control to minimize the impact that omitted time-invariant factors have on the analysis. In other words, the model can yield valid results even if a country under/over reports its sCJD rate compared to other countries, so long as this deviation in reporting is chronic and consistent within that country. Sudden spikes in reporting, however, would pose a problem and are discussed later. Likewise, the fixed effects model accounts for genetic heterogeneity among countries so long as there is no major genetic drift during the study. Given the short duration of the study, intergenerational genetic drift is unlikely and genetic equilibrium is assumed.

Discussion (4)

The similarity between AD and sCJD, combined with the finding that two factors that protect against AD also appear to protect against sCJD risk, highlights the similarity between these two sporadic diseases and offers a rational justification for including potential protective factors in future sCJD case-controlled studies.

The thesis of this paper is not that sCJD is a dietary disease or that diet can prevent sCJD, but rather that there is sufficient similarity between sCJD and AD that possible protective factors should be included in sCJD studies as they are in almost all other forms of dementia research. If researchers hypothesize that certain factors such as living with pets, getting surgery, or consuming certain foods increase the risk of sCJD, a logical corollary is that some yet unknown factors may likewise decrease

risk. Factors found to be protective in other fields of dementia research are natural candidates for initial consideration.

The significant amount of time needed to identify sCJD cases and appropriate controls also presents an economic argument for including protective factors in sCJD questionaries. Davanipour et al., (2014a) required approximately 30 hours of work for each control included in the study. With so much time being spent on identifying sCJD cases and controls, maximizing the information gleaned from each study is paramount. Compared to the massive time required to identify participants, the inclusion of a few questions regarding potential protective factors contributes little to the cost or time burden of the study but may provide additional insight.

The protective questions should prove no more invasive or difficult to answer for the patient's family than the long-established practice of asking about surgical history or meat consumption. While each sCJD researcher is encouraged to draw on their expertise to decide what potentially protective factors to include in their questionaries, this study suggests that dietary factors which protect against AD might be a good starting point. If initial research indicates that AD-protective foods also show a potentially preventative effect on sCJD, then subsequent inquiry can further develop this relationship by making a more detailed inquiry of food groups as well as other AD-protective habits such as exercise and social engagement that might influence sCJD risk.

Limitations (4.1)

In common with all population-based, non-intervention studies, this research should not be intended to imply a causal relationship between any variables. Given that sCJD cases have historically been under-reported, the potential for differential reporting to influence results is a possible limitation. The panel data fixed effects regression used in this study can accommodate under or over-reporting so long as this over/under-reporting does not suddenly change through increased/decreased surveillance efforts.

Though massive shifts in surveillance are possible, it is unlikely given that all the data in this study was specifically gathered after Europe-wide TSE reporting was instituted in 1999 (*EuroCJD*, n.d.) and after the vCJD epidemic had already increased surveillance efforts.

The inclusion of countries with relatively small populations also presented a limitation in terms of outliers in the regression analysis. Though the average incidence among small countries regresses to the mean across a multi-year time frame, the sporadic distribution of sCJD cases in small countries means that there are years in which not a single case is reported and in other years, it appears that there is a sudden spike in cases as a compensatory higher rate of cases are reported. In this case, the random nature of the disease may cause a country with a very small population to show a doubling or halving of disease incidence from one year to the next even when explanatory variables show little change.

It should be noted that such “small countries” constituted a relatively minor portion of the total cases and that preserving the unaltered quality of the data was judged to be more important than dropping countries to produce a more pristine model. To confirm the limited impact of such “small countries” a follow-up regression was conducted in which any country that reported zero sCJD cases at any point during the study period was removed from the model altogether. The secondary model with 22 countries instead of 26 substantiated the direction and magnitude of relationships among variables in the first study, but the p-value for bean consumption (.136) in the follow-up study was greater than the p-value of (.094) in the primary analysis making it non-significant at any commonly accepted cutoff.

Lastly, data aggregation at the FAOSTAT level made testing all of the AD-protective foods in Duplantier & Gardner’s (2021)’s meta-analysis impossible as FAOSTAT doesn't report a “whole grain” category. Simply aggregating other grain categories is insufficient because they may or may not be consumed whole. For this reason, the category of whole grains was dropped from the study leaving nut, fish, and bean consumption as the three dietary explanatory variables.

Conclusion (5)

Sporadic Creutzfeldt-Jakob disease is a rapidly progressive, invariably fatal neurodegenerative disease with a worldwide incidence of approximately one per million. The rarity of this disease makes etiological inquiry difficult, and few risk factors have yet to be identified.

In this study, I present a multi-country, ecological analysis that indicates that the neuroprotective effect of nut and bean consumption against AD also appears to be protective against population-level sCJD rates. As with all non-interventional, population-based studies, this study should not be construed as "proving" that certain foods protect against sCJD risk. Rather, these findings suggest that some factors which reduce the risk of AD might also reduce sCJD risk. Studies that solely focus on hypothesized risk-increasing factors leave half the equation off the table, and including a few questions regarding potentially protective factors may yield great additional insight with little additional cost or time commitment to the study. Though there are potentially innumerable factors that could decrease/increase sCJD risk, this literature review, and the findings of the multi-country analysis, suggest that including factors that have been demonstrated to reduce AD risk would be a logical starting point for inclusion in sCJD research.

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