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Abstract

Background: Epidemiologic evidence of surgical transmission of sporadic Creutzfeldt-Jakob Disease (sCJD) remains controversial.

Methods: From Danish and Swedish registries we selected 167 definite and probable sCJD cases, with onset during 1987-2003; and 3,059 controls, 835 age-, sex-, and residence-matched, and 2,224 unmatched. Independent of case/control status, ~~Individual~~ surgical histories were obtained ~~-~~from National Hospital Discharge Registries. Surgical procedures were categorized ~~as main, i.e., major surgery, or subsidiary, and~~ by body-system group,~~,~~ assigned to specific time-lag windows prior to onset of sCJD, and compared using logistic regression.

Results: A history of m~~M~~ajor surgery involving all body systems, conducted 20 or more years before clinical sCJD onset, was more common in cases than both ~~displayed a significant association when conducted 20 or more years before clinical sCJD onset and compared to~~ matched (odds ratio (OR) ~~and unmatched controls, with odds ratios (ORs) (95% confidence interval) of~~ 2.44; 95% CI ~~(~~ 1.46-4.07) and unmatched controls (OR ~~and~~ 2.25; 95% CI ~~(~~ 1.48-3.44). This observation was corroborated by a l~~, respectively, and a l~~inear increase in risk per surgical discharge (OR~~,~~ 1.57 (95% CI 1.13-2.18) and OR 1.50 (95% CI 1.18-1.91), respectively). Surgery on a range of body-systems were incriminated, ~~In comparisons with both types of controls, procedures that displayed a statistically significant excess risk were those~~ including operations~~conducted 20 or more years before clinical onset on~~ on peripheral vessels, digestive system and spleen, and female genital organs~~;~~ ~~comparisons with unmatched controls yielded figures of 4.99 (1.37-18.24), 2.72 (1.33-5.57) and 2.17 (1.06-4.45), respectively~~. ~~Heart surgery, mainly coronary, undergone at a <10 year lag, was more frequent in cases, 2.58 (1.07-6.24).~~

Conclusions: Following a long incubation period, a variety of major s~~We provide additional evidence to indicate that s~~urgi~~er~~cal procedures constitute ~~y, acting with long incubation periods, has constituted~~ a risk factor of sCJD, and a considerable number of sCJD cases may be conceived as health-care related, accidentally transmitted disorders.

~~in Sweden and Denmark. The reasons for a potentially increased incidence of sCJD after coronary~~

~~surgery are unclear. Associations may have implications for precautionary measures and surveillance.~~

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare, fatal, neurodegenerative disease with deposition of a pathologic isoform (termed PrPSc) of the normal cellular prion protein (PrPC). CJD exists in various forms, namely, inherited, caused by mutations in the gene encoding PrPC, acquired (variant and iatrogenic), and sporadic. Most cases are classified as sporadic (sCJD), the etiology of which remains unknown [1]. A history of n~~While n~~eurosurgery can be risk factor for CJD. In addition, ~~,~~ a proportion of CJD cases might be transmitted during other major surgical interventions by infectious PrPSc surface-bound to reused instruments, despite repeated cleaning and sterilization [2].

Seven case-control studies [3-10] and one meta-analysis [11] investigated surgical history as a risk factor for sCJD with ~~, but the results proved~~ partially inconsistent results. Several of these epidemiologic studies had important limitations, due to potentially underlying case-selection and/or recall bias [3-10], or ~~asymmetry~~ bias conferred by the ~~through~~ use of clinical controls [3-6], surrogate informants solely for cases [3,4,7,9] and different ~~calendar~~ time intervals for operations [7,9]. Hence, there is a clear call for studies that can overcome these limitations [10]. This need has ~~recently~~ been underscored by additional evidence of blood-related iatrogenic transmission of vCJD [12-15], a human transmissible encephalopathy with a considerable accumulation of PrPSc in lymphoreticular tissues [16], and by evidence from experimental models demonstrating a significant probability of successful transmission among animals exposed to infective tissue by different, surgically relevant routes [17,18]. Experimental work suggests that lower inocula of prion protein correlate with a long incubation period [19], which may indicate that the sCJD incubation period from time of surgery may be long.

The aim of this registry-based case-control study was to identify associations between history of surgery and onset of sCJD in two national populations, i.e., those of Denmark and Sweden. For both cases and controls, information on surgical history was retrieved from national hospital discharge registries, thereby ensuring an unbiased ascertainment of exposures.

METHODS

The study was designed as a case-control study with two control groups: One matched and the other unmatched. We selected two control groups in order to improve the reproducibility of the study, the robustness, and allow for comparison with previous published work which included both matched and unmatched reference groups. ~~In order to ensure unbiased assessment of the history of~~

surgical procedures, the studies were based on existing medical-care registries. The base study population was aged 40 years and over, and resident in the periods 1994 through 2003 in Denmark and 1987 through 2002 in Sweden. Cases of sCJD were identified countrywide, and two sets of randomly chosen population controls, matched and unmatched, were included. After validation of clinical onset and sCJD diagnosis for cases, the time-lag intervals prior to and after onset were defined. Five exposure windows,20 with limits based on biologic knowledge, clinical management, and study size, were adopted using two index dates, and constituted the focus of the whole study, Figure 1. Index date I (IDI) for cases was date of death and, when the death of a case was not registered after follow up (which occurred in two instances), it was date of latest hospital discharge. IDI for matched controls (MC) was the IDI of the corresponding case. IDI for unmatched controls (UMC) was December 31 of annual sampled population. Index date II (IDII) corresponded: to an operational date of symptom onset for cases and the same for corresponding MC; and to IDI minus 159 or 151 days for UMC from study populations pre- and post-December 31, 1996, respectively, since vCJD was first reported in 1996. History of exposure in windows 1-3 was considered highly relevant for CJD transmission and was ascertained from the two National Hospital Discharge Registries, targeting surgery registered at discharge, 365 or more days before the operational time-point of disease onset and IDII.

Case- and control-selection

Cases were selected from 212 possible cases in Sweden (population 9 million) and 78 in Denmark (population 5 million) who had either been reported to National Surveillance Units prior to 2004 with suspected or diagnosed prion disorder, or identified from the respective National Hospital Discharge -and Cause-of-Death registers, with diagnoses at death or at hospital discharge coded as per International Classification of Diseases, 9th Revision (ICD-9) 046.1 and 331.5 or International Classification of Diseases, 10th Revision (ICD-10) A81.0 for the period 1984-2002 in Sweden, and ICD-10 A81.0 or F021 from January 1, 1994 in Denmark. Diagnoses of probable or definite sCJD, and dates of clinical onset and death were validated for 168 of the above-mentioned 290 potential cases which fulfilled reported diagnostic criteria [20]. To this end, CJD-surveillance personnel or board-certified neurologists used information from surveillance units, and death or medical records from selected pathologists, hospital departments, and caring institutions where the death certificate had been issued. The life status of cases was verified in 2003 using national population registries and

direct contacts, with two Swedish and one Danish probable sCJD cases being alive at the end of case-finding. ~~The diagnostic criteria were strictly applied. Only 1 of 55 probable sCJD cases was excluded from study.~~ Information on 113 definite and 54 probable sCJD cases under study is given in Table 1. Mean disease duration [range] was 154 days [3, 963].

~~Two~~ The ~~sets of~~ controls were randomly sampled from national population registries. A total of ~~as follows: A)~~ 835 matched controls were ~~were selected from the annual resident population~~ sampled ~~matched~~ 5:1 to each case, matched by sex, year and month of birth, and municipality of residence of case, either 1) at 31 December ~~31~~ of year of case death, or, 2) for a few cases with unregistered deaths at time of control selection, at 31 December ~~31~~ of year of clinical onset reported to surveillance or date of latest hospital discharge. For the unmatched controls, ~~B)~~ 2,224 individuals ~~population controls~~ were sampled from the general population aged 40 years and over, and resident at 1 January ~~1~~ of a given year: 1) in the case of Sweden for the period 1987-2002, with a probability of 20/million; and, 2) in the case of Denmark in two steps, namely, first with a probability of 30/million, from registered residents in Denmark for the period 1994-2003, and second, by random allocation to year after verification of life status, by death not registered at population registry at December 31.

Definition of periods of exposure (time-lags)

After validation of clinical onset and sCJD diagnosis for cases, the time-lag intervals prior to and after onset were defined. Five exposure windows [21], based *a priori* on biologic knowledge, clinical management, and study size, were adopted using two index dates, Figure 1. Index date I (IDI) for cases was date of death and, when the death of a case was not registered after follow up, the date of latest hospital discharge (two cases only). IDI for matched controls (MC) was defined as the IDI of the corresponding case. IDI for unmatched controls (UMC) was defined as 31 December of annual sampled population. Index date II (IDII) corresponded to an operational date of symptom onset for cases and the same for corresponding MC; and to IDI minus 159 or 151 days for UMC from study populations pre- and post- 31 December 1996, respectively, since vCJD was first reported in 1996.

Surgical interventions, individual exposure assignment and data analysis

For cases and controls, ~~coded~~ data on past hospital discharges (diagnoses and surgical procedures and ~~registered at hospital discharge at any time, plus~~ dates of admission and discharge) were obtained from the National Hospital Discharge Registers in Sweden and Denmark by authors ÅS and KM. After removal of the person numbers, these data were then sent to Madrid for analysis.

Here, authors JPC and IM, duly blinded to case-control status, proceeded to edit and list 7,165 surgical procedure (SP) codes, and identify their rubrics from diverse versions of Swedish, Danish and Nordic (NOMESCO-NCSP) classifications of surgical procedures. [22-24]. A total of 577 codes, deemed to be irrelevant as invasive exposure, were omitted from further analysis. These corresponded to codes with unidentified rubrics, codes related to Chapters X, Y and Z of NCSP 1.7 "Investigative procedures connected with surgery", "Procurement of organs for transplantation" and "General qualifiers", other similar procedures from national classifications, and procedures that were not properly surgical, such as delivery, etc..

The selected surgical experience of cases and controls, correspondedinged to 1,445 distinct SP codes associatedrelated towith 3,876 registered discharges during windows 1-3 (Figure 1). , was categorized as follows: bBlind to individual outcomes, JPC and IM classified these SPs by body-system groupchapter, using the original classifications [22-24], yet sometimes reallocating or collapsing groups when it became necessary to generate more homogeneous or broader categories. Two major exposure categories were considered and defined in the legend to Figure 2, namely: 1) "main surgical procedures" , a category that, for our purposes, was indiscriminately denoted as "major surgery" fragmented into 15 body-system groups, and 2) "subsidiary procedures" . The latter is a heterogeneous category that includes blood transfusion, an infrequent code at discharge, minor surgery, and other non-surgical, potentially invasive procedures, such as transluminal endoscopies, with or without biopsy.

The earliest limit of individuals' time window 1 was open-ended. This corresponded to early national discharge registry coverage, which was fairly comprehensive in Denmark in 1974 and had been progressive in Sweden since 1973, reaching 78% of the somatic care hospital population by 1977 (www.sos.se/epc; www.scb.se/databaser). The earliest-in-life registered surgical discharge of a case occurred at age 23 years in 1979.

An individual was classified as exposed to a specific type of surgery/procedure under study defined by body-system group or wider categories, during a specific window, when at least one discharge associated with at least one code of such surgery/procedure had taken place at a date within the limits of the designated window; surgical history in other windows was disregarded. In core analyses, unexposed individuals during a specific window were those who underwent no kind of main surgical or subsidiary procedure during the window under study. In practice, this was obtained by

~~creating a single, three level, exposure-variable for each model, i.e. categorical regression with 3-nominal-level scaling of independent variable.~~ The independent effect of "main surgical" and "subsidiary" procedures was quantified in complementary analyses by introducing the two exposure variables -binary in this case- in the same model; the unexposed groups of individuals for each variable were different. Multiple exposures were defined by number of surgical discharges. ~~, which in practice meant that those with one or more codes for main surgical procedures in windows with significant findings were computed.~~

Conditional logistic regression was used for comparisons with MC, and logistic regression -with adjustment for age, sex, and country of residence at IDI- for comparisons with UMC. Only exposures during time windows 1-3, i.e., predating IDII by one or more years, were considered relevant for the present study and included in the analyses.

The study~~project~~ was notified to the Danish Data~~-~~ Protection Agency (record no. 2003-41-3104) and approved by the Karolinska Institute's Ethical Committee (South), report 452/02.

RESULTS

Mean age [range] at clinical onset or IDII was 67 years [40, 88] for cases, 67 years [40, 88] for MC and 60 years [40, 99] for UMC. The annual number of cases was higher in Sweden than in Denmark (which has a smaller background population). Due to the sampling procedures, ~~and~~ Denmark had more unmatched~~that of population~~ controls ~~was higher i~~than ~~n Denmark~~Sweden, Table 1. ~~Duration of registered residence in Sweden from January 1, 1969 to clinical onset or IDII accounted for 100%, 99%, and 96% of lifetime intervals during the same period for cases, MC, and UMC, respectively.~~

Twenty or more years prior to disease onset, cases had an increased risk of major surgery versus both MC, odds ratio (OR) 2.44 (95% confidence interval (CI) 1.46-4.07), and UMC, OR 2.25 (95% CI 1.48-3.44), Table 2, with significant dose-response effects. There was also a tendency towards increased risk of major surgery in the time period of 10 to 19 years prior to disease onset, but no indication of excess risk in the period of 1 to 9 years prior to disease onset, Table 2.

We conducted subgroup analyses by country, study period, gender, age of onset, and case classification, Table 3. ~~In complementary analyses for window 1, Table 3, a~~A statistically significant excess risk for main surgical procedures carried out at least 20 years before onset of sCJD was present in most of these analyses, and the point estimates remained stable.~~at least one comparison~~

~~for definite/probable CJD with respect to both countries, both study intervals, both sexes, and age <68 at onset/IDII, where mean age at first registered surgical discharge was lowest, i.e., 34 years, compared to 52 years for age >=68 years at onset/IDII.~~

Table 4 shows results ~~of available comparisons~~ for specific body-systems, as well as ~~in the case of surgery 20 or more years before clinical onset, and~~ statistically significant findings for procedures carried out in other ~~other~~time-windows. The number of procedures available for study in window 1 varied substantially between groups, and statistically significant excess risk, sometimes based on sparse data, was registered for gastrointestinal surgery, gynecologic surgery (compared with~~to~~ matched controls only), surgery of peripheral vessels and lymphatic system, and thorax surgery. The most frequent surgical procedures undergone by cases, for which excess risk was observed, were distributed as follows: of 14 gastrointestinal procedures, three were appendectomy, three explorative laparotomy, and two hemorrhoidectomy; of 26 gynecologic procedures, ten were uterus curettage and nine were cervix conization, excision or curettage; and of six vascular procedures, all were varicose venous surgery. In addition, in comparisons with UMC, we observed an excess number of operations on heart and major thoracic vessels predating clinical onset by one or more years, 2.61 (1.08-6.31), and at a 1- to 9-year time lag, 2.61 (1.07-6.24) in cases. Five of the seven cases exposed to heart surgery were definite sCJD or had undergone a coronary anastomosis or by-pass.

Finally, we undertook c~~C~~omplementary analyses for alternative windows, 1-4, 5-14 and >=15 years predating onset/IDII, Table 5, confirmed most prior significant findings. In these analyses, however, the excess risk of gynecologic and cardiac surgery, and -on controlling for the effect of main surgical procedures- that of subsidiary procedures, became statistically nonsignificant.

When major surgery, other than cardiac, was analyzed, there was an increase in risk with time lag after operation for MC and UMC, namely OR 1.06 (95% CI 1.02-1.09) and OR 1.05 (95% CI 1.02-1.08) per latency year, respectively.

We examined spatial patterns for major surgery which took place 20 or more years before onset and for which statistically significant excess risk was observed. Each of the 28 patients concerned had been discharged after such surgery from different hospitals, except for two who were admitted to the same clinic over a 13-month period and developed sCJD 23 and 21 years later, respectively.

DISCUSSION

Overall, the present study indicates that a considerable proportion of sCJD may constitute a healthcare-related disorder, accidentally transmitted during surgery. While this has been suggested before [7-10], the present study is unique because of the unbiased assessment of exposure histories for decades before disease onset, randomly chosen controls, and strict lag time measurement. Lack of surgical history data prior to the establishment of National Hospital Discharge Registries in the early 1970s and low statistical power preclude assessment of early-in-life surgery or specific infrequent procedures. The main findings were supported by analyses including both matched and unmatched controls. The unmatched controls were not essential for the study, but it was reassuring to learn that a similar study could be undertaken in another setting where it was impossible to sample matched controls as referent group. ~~Moreover, diverse potential sources of bias may affect interpretation of findings at different latencies.~~

The validity of these results could be affected by s~~S~~election bias ~~might be present~~ if CJD detection rates were higher among surgical patients subjected to follow-up by surgeons aware of possible complications of surgery, such as those expected from shunt-based hydrocephalus treatment. ~~, and were more likely to act in the short term.~~ Since most associations were only seen for long latency periods (i.e., 20 years or more prior to onset of CJD), such a mechanism does not seem to be conceivable. One exception, however, might be the case of coronary surgery, but ~~which~~ would require the presence of considerable CJD underascertainment at baseline.

Another source of selection bias may be attributed to s~~S~~elective sCJD underascertainment~~, whether~~ at date of diagnosis or due to ~~our casefinding~~case finding~~, might have introduced selection bias~~. sCJD cases, ~~-~~clinically indistinguisable from other dementia types and identified simply because of a more aggressive diagnostic approach, may have resulted from~~:~~ increased awareness on the part of clinicians prior to 1996~~,~~; the availability of the CSF 14-3-3 test since 1998~~;~~, and/or an increasing post-mortem confirmation ratio. The expected result would be a change~~n increase~~ in the sensitivity and accuracy of sCJD diagnoses, thereby reducing underascertainment and increasing incidence. The confirmed proportion of definite+probable sCJD cases increased from 68% in the 1970-199825 period to 100% thereafter, http://www.smittskyddsinstitutet.se/statistik/creutzfeldt-jakobs-sjukdom-cjd/ and http://www.eurocjd.ed.ac.uk/sporadicneuro.htm. However, i~~I~~n Sweden, sCJD incidence for 1970-1998 [25] was similar to that reported during active surveillance ~~(same data sources)~~. This may

suggest that sCJD with atypical EEC in Sweden -and probably in Denmark too- was captured by post-mortem studies on demented patients. Accordingly, the present data indicate~~suggest~~ that sCJD ascertainment was stable and that sCJD underascertainment, whether or not selective, was low, both before and after introduction of 14-3-3 tests and active surveillance. Consequently, our low study accrual rate for the period 1987-1998 might best be attributed to difficulties in finding hospital records to which sCJD diagnostic criteria could be applied, and would thus be unrelated to underascertainment or surgical history. Moreover, since long-term associations post-surgery were more evident after 1998 and in subjects aged <68 at onset, among whom ascertainment would be expected to be highest, it would appear that such associations should not be attributed to selective underascertainment.

Due to unregistered use of duramater grafts in surgery, differential misclassification of outcome, including a number of iatrogenic cases misdiagnosed as sCJD, might appear as a possible phenomenon which was overlooked as a result of surgical records not being examined. In Sweden, inspection of medical records revealed the presence of one case of iatrogenic CJD that died in 2002 as a consequence of an aneurism, was registered at discharge as CJD, and was subsequently removed from the study. While dura mater grafts may, in theory, have been used in gynecologic surgery for urinary incontinence and in other surgery, the lack of reported iatrogenic CJD in Sweden [25], and the shorter incubation periods described for iatrogenic CJD [26] suggest that overlooked heterologous dura mater grafts do not underlie excess risk of sCJD for individuals exposed to specific groups of surgical interventions.

Surveillance bias, i.e., overascertainment of sCJD among 54 probable sCJD cases, basically consisting of notifications of non-CJD dementia, false-positive to 14-3-3 test and without post-mortem confirmation, cannot be ruled out. Is it possible then that surveillance bias in the form of a small number of cases of CJD buried within a large number of dementia patients could explain the results of coronary surgery?~~.~~ We feel that this interpretation should be rejected, since only two~~2~~ of the seven~~7~~ cases were probable sCJD with short disease durations, and of these, one showed onset as having been in 1990, at a time before surveillance had officially started.

The geographically-based referral system for surgery in both countries, with free and equal access to healthcare, SP registration prior to sCJD diagnosis, and similar expected-versus-registered times of residence, should have minimized differential misclassification of exposure. Non-differential

misclassification of exposure to surgery, potentially resulting from our window design [27], errors in person numbers, or coding of SP, should be low. Moreover, since their additional effect is dilution, i.e., OR towards the unit [28], associations should be higher than those observed. Owing to the design, recall bias can be ruled out.

Confounders are overlooked causes of CJD associated with surgery, not implicated in the same causal chain. Intra- or post-operative blood or blood-component transfusion and skin incision is a potential confounder which we did not control for. Neither surgery undergone in the 1970s nor body-system groups with highest excess risk appears to be especially correlated with considerable loss of blood, blood transfusion or size of surgical incision. Confounding by calendar-time variation in surgical indication or policy was controlled for by year-to-year entry on study.

At all events, the highest estimates in the earliest time window fit the notion that they are the direct effects of surgery [20,27]. The long latency required for the process of neuroinvasion acting post-surgery [29] fits well with causal associations with long latency. However, a confounding effect of main surgical procedures would account for the excess sCJD risk for subsidiary procedures in period 1 suggested by the complementary analysis.

The association with coronary surgery is open to ~~difficult to~~ explain~~ation~~. A twofold ~~or more biased~~ increase in sCJD incidence several years after surgery is difficult to attribute to complete elimination of what, as has been shown above, is an unlikely 50% underascertainment among patients, because of their contact with healthcare. Instability due to small numbers might not be found to be a sufficiently convincing, isolated explanation. Interestingly, ~~, since~~ cognitive impairment and brain emboli following coronary artery bypass grafting have been reported [30] If one were to speculate, the partly biased association might be a combined effect of three factors acting with increasing delays, namely: 1) indication of coronary surgery, perhaps due to symptoms associated with or attributed to coronary pathology, in patients with undiagnosed sCJD; 2) embolus disclosing subclinical CJD by shortening the disease course; and 3) infective brain embolus or contaminated instruments acting on the myocardial nerves of healthy persons, generating CJD after almost a decade.

~~Our diluted,~~The negative results for all body-system surgery predating >1-year onset are consistent with positive results for life-time surgical history [7,9,10]. Like us, one study reports dose-response effects [7]. Hence, in accordance with the above mentioned [7,9,10] and other reports suggesting that some surgery, e.g., cataract surgery [31,32], might be performed as a consequence

of early sCJD manifestations, it would appear that surgery may constitute: 1) a risk factor of sCJD with a considerable time lag; and, 2) for coronary surgery specifically, a risk indicator with yet unknown causal links.

What then are the potential implications for public health? Based on period-specific odds ratios of 1.44 (10 to 19 years) and 2.44 (≥ 20 years), and 22% and 19% exposed, unrepeated cases for each window, the population attributable proportion was estimated to be 18%. This figure may constitute a considerable underestimation of the effect of life-time surgical history on sCJD incidence for several reasons. First of all, results suggest that the lower the age at surgery, the higher the risk. Due to the design, surgical history at ages ≥23 years in Sweden was underregistered, and surgery among cases at ages below 23 years was not captured by registries. Since a positive lifetime surgical history was recorded from 1980 onwards in 58% and 59% of vCJD cases and controls in the UK, with median ages of 26 and 33 years [33], the figure of 35% proposed by Ward et al [9] would appear to be a conservative estimate of the sCJD-population attributable risk due to lifetime surgery for Denmark and Sweden. While negative results have been reported for clustered surgical chains [34], studies supporting the hypothesis of a frequent surgical transmission of sCJD might be: a French cluster of multi-operated cases [35]; the high sCJD incidence in regions with high incidence of genetic TSE, potentially acting as a focus for point source epidemics, such as in the Spanish Basque Country [36] (http://www.isciii.es/htdocs/pdf/DatosRegistroCreutzfeldJacob.ppt) ; and occasional increases in CJD incidence in countries where iatrogenia has been mentioned as a possible cause [37].

~~CONCLUSIONS~~

To conclude, w~~W~~e provide additional evidence to indicate that surgery, acting with long incubation periods, has constituted a risk factor for sCJD in Sweden and Denmark. ~~The reasons for a possibly increased incidence of sCJD after coronary surgery are unclear.~~ The associations may have implications for precautionary measures and surveillance.

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Table I. Cases and controls included in study[a,b]

Population study year or year of clinical onset	Cases					Number of controls		
	Number of sCJD cases				Average age in years at clinical onset		Unmatched	
	All	Definite/probable	Male / female	Swedish/Danish		Matched	All	Swedish/Danish
1987	3	1/2	3/0	3/0	59	15	79	79/0
1988	4	2/2	2/2	4/0	68	20	80	80/0
1989	6	2/4	4/2	6/0	67	30	80	80/0
1990	6	4/2	5/1	6/0	59	30	81	81/0
1991	3	1/2	2/1	3/0	61	15	82	82/0
1992	4	3/1	2/2	4/0	66	20	83	83/0
1993	6	4/2	1/5	6/0	70	30	83	83/0
1994	13	5/8	6/7	9/4	70	65	179	84/95
1995	8	4/4	5/3	7/1	70	40	171	84/87
1996	7	4/3	1/6	2/5	68	35	172	85/87
1997	19	17/2	7/12	11/8	63	95	172	85/87
1998	16	12/4	7/9	11/5	68	80	178	86/92
1999	17	13/4	10/7	11/6	66	85	176	86/90
2000	14	12/2	4/10	10/4	69	70	172	87/85
2001	17	12/5	9/8	11/6	68	85	180	87/93
2002	14	12/2	6/8	4/10	65	70	183	88/95
2003	10	5/5	4/6	0/10	68	50	73	0/73
All	167	113/54	78/89	108/59	67	835	2,224	1,340/884

a Surveillance diagnostic criteria for definite or probable sCJD were used. Definite cases were neuropathologically/immunochemically confirmed. Probable sCJD fulfilled reported21 clinical criteria (rapidly progressive dementia and specific symptoms) and laboratory criteria (typical EEG or positive 14-3-3 protein test in CSF+duration <2 years), http://www.cjd.ed.ac.uk/criteria.htm.

b At end of casefinding, all definite sCJD cases were included; one probable sCJD case was excluded from study due to unclear onset within limits of study period.

Table 2. Number of cases and controls, and associations for main surgical and subsidiary procedures for specific periods predating onset or IDII, with selected, period-specific control of time of residence.

Period	Surgery under study	Subject	No registered surgery [a]	Surgery under study		Other surgery [b]
			No. (%)	No. (%)	OR (95% CI)	No. (%)
Period 1 >=20 years	Main surgical procedures	Case	134 (80.2)	32 (19.2)		1 (0.6)
		MC	745 (89.2)	89 (10.7)	2.44[c] (1.46 – 4.07)	1 (0.1)
		UMC	1,985 (89.3)	230 (10.3)	2.25[d] (1.48 – 3.44)	9 (0.4)
	Subsidiary procedures	Case	134 (80.2)	3 (1.8)		30 (18.0)
		MC	745 (89.2)	13 (1.6)	1.64 (0.43 – 6.42)	77 (9.2)
		UMC	1,985 (89.3)	34 (1.5)	1.25 (0.36 – 4.36)	205 (9.2)
Period 2 10 – 19 years	Main surgical procedures	Case	110 (65.9)	57 (34.1)		0 (0.0)
		MC	603 (72.2)	223 (26.7)	1.44 (1.01 – 2.04)	9 (1.1)
		UMC	1,569 (70.5)	623 (28.0)	1.40 (0.99 – 1.98)	32 (1.4)
	Subsidiary procedures	Case	110 (65.9)	11 (6.6)		46 (27.5)
		MC	603 (72.2)	50 (6.0)	1.24 (0.64 – 2.38)	182 (21.8)
		UMC	1,569 (70.5)	148 (6.7)	1.11 (0.57 – 2.17)	507 (22.8)
Period 3 1 – 9 years	Main surgical procedures	Case	116 (69.5)	46 (27.5)		5 (3.0)
		MC	565 (67.7)	245 (29.3)	0.92 (0.62 – 1.34)	25 (3.0)
		UMC	1,526 (68.6)	645 (29.0)	0.83 (0.58 – 1.18)	53 (2.4)
	Subsidiary procedures	Case	116 (69.5)	13 (7.8)		38 (22.8)
		MC	565 (67.7)	70 (8.4)	0.90 (0.48 – 1.70)	200 (24.0)
		UMC	1,526 (68.6)	177 (8.0)	0.88 (0.48 – 1.64)	521 (23.4)
All periods >=1 year	Main surgical procedures	Case	72 (43.1)	94 (56.3)		1 (0.6)
		MC	399 (47.8)	418 (50.1)	1.25 (0.89 – 1.76)	18 (2.2)
		UMC	1,056 (47.5)	1,127 (50.7)	1.19 (0.86 – 1.65)	41 (1.8)
	Subsidiary procedures	Case	72 (43.1)	23 (13.8)		72 (43.1)
		MC	399 (47.8)	118 (14.1)	1.09 (0.64 – 1.84)	318 (38.1)
		UMC	1,056 (47.5)	316 (14.2)	1.03 (0.62 – 1.70)	852 (38.3)

MC: matched control ; UMC: unmatched control

[a] Reference category

[b] Procedures, either main surgical or subsidiary, other than surgery under study.

[c] OR 2.09 95%CI (1.17 - 3.73) for one discharge and OR 3.37 95%CI (1.52 - 7.45) for two or more discharges

[d] Linear increase per discharge OR 1.57 95%CI (1.13 - 2.18)

[e] 2.01 (1.23 - 3.31) for one discharge and 2.90 (1.40 - 7.76) for two or more discharges

[f] Linear increase per discharge OR 1.50 95%CI (1.18 – 1.91)

Table 3. Results of complementary analyses. Number of cases and controls, and associations for specific country of residence, study period, sex, age at onset or IDII, and for *definite* sCJD

			No registered surgery [a]	Surgery under study		Other surgery [b]
Alternative design	Surgery under study	Subject	No. (%)	No. (%)	OR (95% CI)	No. (%)
Period 1 >=20 years						
Residence at death-IDI in Sweden	Main surgical procedures	Case	90 (83.3)	18 (16.7)		0 (0.0)
		MC	494 (91.5)	45 (8.3)	2.65 (1.31 – 5.38)	1 (0.2)
		UMC	1,207 (90.1)	131 (9.8)	1.97 (1.13 – 3.43)	2 (0.1)
Residence at death-IDI in Denmark	Main surgical procedures	Case	44 (74.6)	14 (23.7)		1 (1.7)
		MC	251 (85.1)	44 (14.9)	2.34 (1.11 – 4.92)	0 (0.0)
		UMC	778 (88.0)	99 (11.2)	2.72 (1.39 – 5.31)	7 (0.8)
Study period 1987 - 1998	Main surgical procedures	Case	158 (94.6)	9 (5.4)		0 (0.0)
		MC	816 (97.7)	18 (2.2)	3.35 (1.31 – 8.54)	1 (0.1)
		UMC	2,153 (96.8)	67 (3.0)	1.74 (0.84 – 3-58)	4 (0.2)
Study period 1999 - 2003	Main surgical procedures	Case	143 (85.6)	23 (13.8)		1 (0.6)
		MC	764 (91.5)	71 (8.5)	2.25 (1.22 – 4.15)	0 (0.0)
		UMC	2,056 (92.4)	163 (7.3)	2.27 (1.40 – 3.67)	5 (0.2)
Men	Main surgical procedures	Case	67 (85.9)	11 (14.1)		0 (0.0)
		MC	367 (94.1)	23 (5.9)	2.81 (1.21 – 6.51)	0 (0.0)
		UMC	999 (92.8)	71 (6.6)	2.34 (1.17 – 4.69)	6 (0.6)
Women	Main surgical procedures	Case	67 (75.3)	21 (23.6)		1 (1.1)
		MC	378 (84.9)	66 (14.8)	2.22 (1.18 – 4.18)	1 (0.2)
		UMC	986 (85.9)	159 (13.9)	2.22 (1.30 – 3.79)	3 (0.3)
Age <68 at onset or IDII	Main surgical procedures	Case[c]	62 (76.5)	18 (22.2)		1 (1.2)
		MC	362 (89.4)	43 (10.6)	3.36 (1.78 – 6.33)	0 (0.0)
		UMC	1,362 (89.0)	165 (10.8)	2.71 (1.55 – 4.75)	4 (0.3)
Age >=68 at onset or IDII	Main surgical procedures	Case[d]	72 (83.7)	14 (16.3)		0 (0.0)
		MC	383 (89.1)	46 (10.7)	1.85 (0.81 – 4.21)	1 (0.2)
		UMC	623 (89.9)	65 (9.4)	1.85 (0.98 – 3.52)	5 (0.7)
Definite sCJD cases	Main surgical procedures	Case	88 (77.9)	24 (21.2)	2.46 (1.37 – 4.41)	1 (0.9)
		MC	498 (88.1)	66 (11.7)	2.56 (1.58 – 4.14)	1 (0.2)
		UMC	1,985 (89.3)	230 (10.3)		9 (0.4)

MC: matched control

UMC: unmatched control

[a] Reference category

[b] Procedures, either main surgical or subsidiary, other than surgery under study.

[c] Age at first surgical discharge, mean 34.0 years, SD 7.2 years

[d] Age at first surgical discharge, mean 51.5 years, SD 4.2 years

Table 4. Number of cases and controls, and associations for surgery by body-system group at discharge, 20 or more years before onset or IDII, and statistically significant findings for other windows

			No registered surgery [a]	Body-system group under study		Other surgery [b]
Period	Body-system group	Subject	No. (%)	No. (%)	OR (95% CI)	No. (%)
Period 1 >=20 years	Endocrine system	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	0 (0.0)	–	90 (10.8)
		UMC	1,985 (89.3)	6 (0.3)	3.06 (0.40 – 23.6)	233 (10.5)
	Ear, nose and larynx	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	4 (0.5)	1.92 (0.29 – 12.8)	86 (10.3)
		UMC	1,985 (89.3)	12 (0.5)	1.23 (0.14 – 11.0)	227 (10.2)
	Teeth, jaws, mouth and pharynx	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	2 (0.2)	3.59 (0.39 – 32.8)	88 (10.5)
		UMC	1,985 (89.3)	6 (0.3)	3.40 (0.34 – 33.6)	233 (10.5)
	Chest wall, pleura, lung and other thoracic surgery	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	0 (0.0)	–	90 (10.8)
		UMC	1,985 (89.3)	1 (0.0)	29.3 (1.83 – 470)	238 (10.7)
	Digestive system and spleen	Case	134 (80.2)	10 (6.0)		23 (13.8)
		MC	745 (89.2)	25 (3.0)	2.59 (1.16 – 5.78)	65 (7.8)
		UMC	1,985 (89.3)	56 (2.5)	2.72 (1.33 – 5.57)	183 (8.2)
	Urinary system, Male genital organs and other surgery	Case	134 (80.2)	2 (1.2)		31 (18.6)
		MC	745 (89.2)	5 (0.6)	2.49 (0.48 – 13.0)	85 (10.2)
		UMC	1,985 (89.3)	15 (0.5)	1.71 (0.35 – 8.38)	224 (10.1)
	Female genital organs [c]	Case	67 (75.3)	11 (12.4)		11 (12.4)
		MC	378 (84.9)	41 (9.2)	1.89 (0.88 – 4.08)	26 (5.8)
		UMC	986 (85.9)	74 (6.4)	2.17 (1.06 – 4.45)	88 (7.7)
	Obstetric procedures	Case	134 (80.2)	2 (1.2)		31 (18.6)
		MC	745 (89.2)	7 (0.8)	2.99 (0.50 – 17.9)	83 (9.9)
		UMC	1,985 (89.3)	45 (2.0)	1.19 (0.28 – 5.08)	194 (8.7)
	Musculoskeletal system	Case	134 (80.2)	5 (3.0)		28 (16.8)
		MC	745 (89.2)	12 (1.4)	2.49 (0.81 – 7.67)	78 (9.3)
		UMC	1,985 (89.3)	40 (1.8)	2.12 (0.78 – 5.75)	199 (8.9)
	Peripheral nerves and lymphatic system	Case	134 (80.2)	3 (1.8)		30 (18.0)
		MC	745 (89.2)	4 (0.5)	4.54 (1.01 – 20.3)	86 (10.3)
		UMC	1,985 (89.3)	9 (0.4)	4.99 (1.37 – 18.2)	230 (10.3)
	Skin	Case	72 (43.1)	3 (1.8)		30 (18.0)
		MC	399 (47.8)	6 (0.7)	3.02 (0.66 – 13.9)	84 (10.1)
		UMC	1,056 (47.5)	16 (0.7)	3.83 (0.97 – 15.0)	223 (10.0)
Period 3 1 – 9 years	Heart and major thoracic vessels	Case	116 (69.5)	7 (4.2)		44 (26.3)
		MC	565 (67.7)	17 (2.0)	2.03 (0.85 – 4.89)	253 (30.3)
		UMC	1,526 (68.6)	25 (1.1)	2.58 (1.07 – 6.24)	673 (30.3)
Period 1-3 All periods	Heart and major thoracic vessels	Case	72 (43.1)	7 (4.2)		88 (52.7)
		MC	399 (47.8)	20 (2.4)	2.00 (0.83 – 4.81)	416 (49.8)

	UMC	1,056 (47.5)	28 (1.3)	2.61 (1.08 – 6.32)	1,140 (51.3

MC: matched control UMC: unmatched controls

[a] Reference category ; [b] Other main surgical or subsidiary procedures, other than body-system group under study.

[c] Analysis restricted to women

Table 5. Results of complementary analyses. Number of cases and controls, and associations for alternative latency time windows.

			No registered surgery [a]	Surgery under study		Other surgery [b]
Alternative design	Surgery under study	Subject	No. (%)	No. (%)	OR (95% CI)	No. (%)
Period 1 >=15 years						
Separate models[c]	Main surgical procedures	Case	114 (68.3)	52 (31.1)		1 (0.6)
		MC	642 (76.9)	188 (22.5)	1.68 (1.11 – 2.54)	5 (0.6)
		UMC	1,702 (76.5)	508 (22.8)	1.66 (1.17 – 2.36)	14 (0.6)
	Subsidiary procedures	Case	114 (68.3)	12 (7.2)		41 (24.6)
		MC	642 (76.9)	35 (4.2)	2.14 (1.08 – 4.22)	158 (18.9)
		UMC	1,702 (76.5)	95 (4.3)	2.13 (1.09 – 4.17)	427 (19.2)
	Chest wall, pleura, lung and other thoracic surgery	Case	114 (68.3)	3 (1.8)		50 (29.9)
		MC	642 (76.9)	1 (0.1)	16.6 (1.6 – 172.6)	192 (23.0)
		UMC	1,702 (76.5)	4 (0.2)	12.2 (2.52 – 58.6)	518 (23.3)
	Digestive system and spleen	Case	114 (68.3)	16 (9.6)		37 (22.2)
		MC	642 (76.9)	55 (6.6)	1.78 (0.92 – 3.44)	138 (16.5)
		UMC	1,702 (76.5)	120 (5.4)	2.20 (1.26 – 3.84)	402 (18.1)
	Musculoskeletal system	Case	114 (68.3)	12 (7.2)		41 (24.6)
		MC	642 (76.9)	30 (3.6)	2.33 (1.17 – 4.66)	163 (19.5)
		UMC	1,702 (76.5)	103 (4.6)	1.75 (0.92 – 3.33)	419 (18.8)
	Peripheral vessels and lymphatic system	Case	114 (68.3)	7 (4.2)		46 (27.5)
		MC	642 (76.9)	14 (1.7)	3.10 (1.23 – 7.84)	179 (21.4)
		UMC	1,702 (76.5)	35 (1.6)	2.82 (1.23 – 6.43)	487 (21.9)
Same model [d]	Main surgical procedures	Case	115 (68.9)	52 (31.1)		
		MC	647 (77.5)	188 (22.5)	1.59 (1.03 – 2.46)	
		UMC	1,716 (77.2)	508 (22.8)	1.56 (1.07 – 2.27)	
	Subsidiary procedures	Case	155 (92.8)	12 (7.2)		
		MC	800 (95.8)	35 (4.2)	1.44 (0.73 – 2.84)	
		UMC	2,129 (95.7)	95 (4.3)	1.43 (0.71 – 2.89)	
Period 3 1 to 4 years						
	Heart and major[c] thoracic vessels	Case	136 (81.4)	5 (3.0)		26 (15.6)
		MC	692 (82.9)	10 (1.2)	2.50 (0.85 – 7.34)	133 (15.9)
		UMC	1,831 (82.3)	17 (0.8)	2.81 (0.97 – 8.11)	376 (16.9)

MC: matched control; UMC: unmatched control

[a] Unexposed. In model with two exposure variables,[d] unexposed groups differ and may include individuals who underwent some surgery.

[b] Procedures, either main surgical or subsidiary, other than surgery under study.

[c] Separate regression models with only one, 3-nominal-level, independent variable for surgical exposure.

[d] One regression model, with two, 2-level variables, independent variables for surgical exposures.

Figure 1. Schematic illustration of study design and methodologic details.

a) Annual (calendar year X) national study population with: 1) selected cases by onset; 2) matched controls, and 3) selected population controls.

b) Time windows included in the present study were those covering surgical history >1 year prior to clinical onset/index date II (IDII), namely, windows 1, 2 and 3, the results for which are reported here. Surgical history during or immediately preceding clinical course (windows 4 and 5) was analyzed separately (data not shown).

Figure 2. Percentage distribution of 5990 codes (regardless of repetition) for surgical procedures and blood transfusion, 341 for cases and 5649 for controls, associated with registered discharges predating operational date of clinical onset or IDII by one or more years. These were categorized into two major types of invasive or potentially invasive procedures for study purposes. SPs denoted as "main surgical procedures" correspond to fifteen NCSP 1.724 body-system groups, Chapters A-Q http://www.nordclass.uu.se/verksam/Ncsp1_7.pdf, and those present in other SP classifications [22,23] fitting the anatomic concept, after exclusion of body-system specific subgroups explicitly denoted as minor surgical procedures and transluminal endoscopies. "Subsidiary procedures" include three well defined groups, namely: 1) "minor surgery", as specifically defined in NCSP 1.7 Chapter T (punctures, needle aspiration, superficial incision and needle biopsy), which included procedures with diagnostic or therapeutic purposes, or both, classified as "Minor surgery" in body-system subchapters in national SP classifications [22,23]; 2) transluminal endoscopies listed in NCSP 1.7 Chapter U and national SP classifications[22,23]; and, 3) codes for blood transfusion.