



HAL
open science

Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: Results from a risk-based assessment of surgical interventions

Jesús de Pedro-Cuesta, Ignacio Mahillo-Fernández, Alberto Rábano, Miguel Calero, Mabel Cruz, Åke Siden, Henning Laursen, Gerhard Falkenhorst, Kåre Mølback

► To cite this version:

Jesús de Pedro-Cuesta, Ignacio Mahillo-Fernández, Alberto Rábano, Miguel Calero, Mabel Cruz, et al.. Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: Results from a risk-based assessment of surgical interventions. *Journal of Neurology, Neurosurgery and Psychiatry*, 2010, 82 (2), pp.204. 10.1136/jnnp.2009.188425 . hal-00557409

HAL Id: hal-00557409

<https://hal.science/hal-00557409>

Submitted on 19 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Title: Nosocomial transmission of sporadic Creutzfeldt-Jakob disease: Results from a risk-based assessment of surgical interventions

Corresponding author:

Name: Jesús de Pedro Cuesta

Postal address: Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Calle Monforte de Lemos 5
28029 MADRID, Spain

E-mail address: jpiedo@isciii.es; Phone +34 918222650; Fax +34 913877815

Authors: Jesús de Pedro-Cuesta,^{1,2} Ignacio Mahillo-Fernández,^{1,2} Alberto Rábano,³ Miguel Calero,^{2,4} Mabel Cruz,⁵ Åke Siden,⁵ Henning Laursen,⁶ Gerhard Falkenhorst,⁷ Kåre Mølbak,⁷ and the EUROSURGYCJD Research Group.[§]

Affiliations:

¹Department of Applied Epidemiology. National Center for Epidemiology.

Carlos III Institute of Health. C/ Sinesio Delgado 6. 28029 Madrid. Spain.

²Consortium for Biomedical Research in Neurodegenerative Diseases (*Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas - CIBERNED*).

³Pathology Unit, Fundación Alcorcón University Teaching Hospital. Avda Budapest, 1 Alcorcón 289220. Spain

⁴Department of Spongiform Encephalopathies. National Microbiology Center. Carlos III Institute of Health. Ctra. Majadahonda-Pozuelo, Km. 2.200. 28220 Majadahonda. Spain

⁵ Department of Clinical Neurosciences, Neurology Division, Karolinska Institutet, SE-141 86 Stockholm, Sweden

⁶Neuropathology Laboratory, 6301. H:S Rigshospitalet, Blegdamsvej, 9. DK-2100, Copenhagen. Denmark.

⁷ Department of Epidemiology, Statens Serum Institut. Artillerivej, 5, DK-2300, Copenhagen. Denmark

[§] Other group members are listed under Acknowledgments

Key words: Creutzfeldt-Jakob disease, epidemiology, etiology, safety, surgery.

Number of words in abstract: 250

Number of words in manuscript (abstract and acknowledgments also excluded): 3445

Number of references: 54

Number of Figures: 3

Number of tables: 5

"All authors declare that the answer to the questions on your competing interest form (<http://bmj.com/cgi/content/full/317/7154/291/DC1>) are all No and therefore have nothing to declare"

"the Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ editions and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence (<http://resources.bmj.com/bmj/authors/checklists-forms/licence-for-publication>)."

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disease characterised by deposition of a pathological isoform of the normal cellular prion protein (PrP^C). CJD exists in various forms, namely, genetic, caused by mutations in the gene encoding PrP^C, acquired (variant and iatrogenic) and sporadic. Most cases are classified as sporadic (sCJD). Twelve case-control studies (1-12) and one meta-analysis (13) have examined surgical transmission of sCJD. The outcomes have been partly diverging due to methodological constraints, including problems in selection of control subjects and in particular exposure assessment (9, 14). Most studies have relied on surrogate informants and medical records for surgical histories, inevitably prone to recall- and selection-bias. A recent register-based case-control study (9), which by design had a less biased assessment of surgical exposures (15), corroborated that a proportion of sCJD may be transmitted by surgery following long incubation periods (20 years or more). However, a limitation shared by all the above mentioned studies could be misclassification bias induced by the use of standard categories of surgical procedures (SP).

Case-control studies focusing on surgical transmission of sCJD have been conducted using convenient anatomic references for classification of surgical interventions (1-8,10-12) or national body-system classifications of SP (9). However, such a standard classification of surgical exposures may lead to misclassification. For example, in many ophthalmic and neurosurgical procedures, surgical instruments are not likely to encounter potentially high-risk infective tissue (16). In a Swedish dataset, only 27% of ophthalmologic SP were included in a risk category in which contact with retina and optic nerve was explicit or likely (17). As neither infectivity, nor cellular prion-protein expression patterns, nor the routes of experimentally transmitted infections fit broad anatomic SP classifications or groups used in prior research, we created a risk-based classification system for surgical exposures (17). Sensitivity analysis corroborated that case-control studies in this field may have been subject to misclassification bias due to the use of SP classifications that were insufficiently specific or sensitive to distinguish between low-risk and high-risk interventions for sCJD transmission (17).

The aim of the present study was to apply the risk-based classification system (17) to determine the association between surgery and sCJD and thereby quantify effects potentially masked in prior case-control studies (1-12).

METHODS

Study design and selection of cases and controls

The study was designed (9) as a case-control study including 167 probable or definite sCJD cases fulfilling established EUROCJD diagnostic criteria (18), with clinical onset during the period 1987-2003, and resident

in Denmark or Sweden. Two sets of randomly selected population controls were included, i.e., 835 matched (MC, 5:1 by gender, year, month of birth, and municipality of residence at death of the corresponding case), and 2,224 unmatched controls (UMC, sampled from the annual, resident, national study populations aged 40 years and over). For latency analysis purposes, three time-windows (TWs) were adopted as described (9). These were based on two operational dates, of death and of clinical onset for cases, and corresponding index dates, denoted index dates 1 and 2 (ID-1 and ID-2), for controls, **Figure 1** (9). Relevant parameters for our design of TWs 1,2 and 3 were onset of surgical procedure registration at hospital discharges in the early 1970s, reported length of latency time in iatrogenic CJD due to dura mater grafts, uncertainties in symptoms onset in sCJD, and the study size.

Exposure ascertainment

The surgical history was obtained from national registers, and assigned, blind to subjects' case or control status, to one of the three TWs, and where required, to all three pooled TWs covering registered hospital stay up to one year before clinical onset or ID-2.

For cases and controls, data on past hospital discharges [diagnoses, SP codes, and dates of admission and discharge] were obtained from the National Hospital Discharge Registers in Sweden and Denmark. Personal identifiers and case-status indication were removed before analyzing the data with respect to exposure to SP. Reported SP codes were identified and categorized according to Swedish, Danish, and Nordic (NOMESCO-NCSP) SP classifications (19–21). Codes describing procedures that were not properly surgical, e.g., delivery, and nonspecific codes, e.g. 'investigative procedures connected with surgery', were omitted. The 5990 remaining SP were categorized into two major groups, namely: 'main surgical procedures'; and 'subsidiary procedures', a heterogeneous category that included minor surgery (punctures, needle aspiration or biopsy, superficial incision), other nonsurgical, potentially invasive procedures, such as transluminal endoscopies (with or without biopsy), and – in a few instances in Denmark– blood transfusion. The selected surgical experience of cases and controls corresponded to 1,445 distinct SP codes and 5,990 SP associated with 3,876 registered discharges during TWs 1-3, i.e., dating 1 or more years before the operational disease onset or ID-2 used in the reported study (9).

SP reclassification by risk-level. A total of 1,445 unrepeated SP codes were decoded and their 5,990 discharge dates were re-classified blindly to individual outcomes according to the reported method (17). The following two attributes were assigned to each SP: a) probable use of non-disposable instruments involved; and b) list of up to four (of the 24 reported) tissue types or anatomical structures with the highest assigned risk level most likely contacted by such instruments (22). In total, 4,813 repeated or not SP codes with different discharge dates were reclassified into six putative categories of CJD-acquisition risk level (16):

High-risk; Diluted-High-risk; Lower-risk; Diluted-Lower-risk; Lowest-risk; No-risk (when deemed to have been conducted with disposable instruments). Furthermore, 1,177 SP were not reclassified, including 865 transluminal endoscopies and 198 minor surgical procedures and blood transfusions. Endoscopies were not reclassified because early registration periods did not discriminate between procedures that were and those that were not associated with invasive procedures such as biopsies.

SP reclassification by tissue/structure. Surgical exposure was defined as tissue/structure-specific by possible contact of non-disposable instruments with up to 4 assigned tissues/structures (17). The abovementioned 4,813 SP generated up to 4 of 24 binary categorical variables for 24 different types of tissue or anatomic structure (22).

Individual exposure assignment by potential entry site. An individual was assigned to one out of three mutually exclusive exposure categories per window (see **Figure 2a** for examples), namely: exposed to tissue/structure under study; exposed to other tissues/structures; and unexposed.

- An individual was assigned as exposed to a specific tissue/structure under study when at least one discharge associated with a SP involving such tissue/structure was found at a date within the limits of a TW.
- An individual was deemed as exposed to a tissue/structure other than that under study, during any given TW, when at least one discharge was associated with a tissue/structure other than that under study. Persons solely exposed to no-risk and not-reclassified SP were included here.
- Finally, unexposed individuals were defined as those who had never been discharged or undergone a discharge associated with any "reclassified" or "not-reclassified" SP during the TW under study.

Individual exposure assignment by putative risk level. Individual levels of exposure were collapsed to five categories, **Figure 2b**. These were: 1) High-risk; 2) Lower-risk; 3) Lowest-risk; 4) No-risk or not-reclassified procedures; and, 5) Unexposed. The hypothetical risk level of surgical exposure assigned to a given individual during a specific TW was the highest SP risk level found to be associated with the hospital discharges registered during that TW. As done in the preceding report, an individual was classified as exposed to a specific risk-category of surgery in a specific TW when at least one discharge associated with at least one code of such surgery had taken place at a date within the limits of the individually designated TW. Multiple exposures to a specific category were determined by the number of surgical discharges with one or more SP codes reclassified in that same category.

Data analysis

We determined the risk of sCJD by presumed risk-level and by contacted tissue/structure. Statistical methods with regard to design of variables, choice of reference groups, latency intervals, multivariate models

and procedures for calculation of 95% confidence intervals (CI) replicates those used in the preceding analysis (9). Conditional logistic regression was used for comparisons with MCs, and logistic regression with adjustment for age, sex, and country of residence at ID-1, for comparisons with UMCs. Exposures during single TWs, 1, 2 and 3, and one combined TW, 1–3, i.e., predating onset/ID-2 by ≥ 1 year, were included in main and complementary analyses. When an association was based on a meaningful number of exposed cases, we explored the presence of a dose-response effect quantifying the linear increase of OR for the number of surgical discharges. We assessed potential confounding by associated tissue/structure types in tissue/structure specific models, by including, as independent variables, the tissue/structure present in at least 25% of the discharges associated with the repeated or unrepeated tissue/structure-specific SP under study. Since only comparisons related to single one-at-a-time hypotheses were planned, we followed Rothman, Greenland and Last, recommendations to refrain from use of conventional procedures for widening the confidence intervals (23).

The study was formally notified to the Danish Data Protection Agency (record No. 2003-41-3104) and approved by the Karolinska Institute Ethics Committee (South; report No. 452/02).

RESULTS

Figure 3 shows, separately for cases and controls, the results of the reclassification of the 5,990 selected SP. Surgery on brain, retina, spinal cord and pituitary gland or dura mater accounted for approximately 2% of reclassified procedures.

In the analyses of risk factors for sCJD, high-risk surgery among cases was almost absent in all TWs, which made statistical inference less meaningful for these SPs, **Table I**. However, Lower-risk surgery carried out more than 20 years before disease-onset or ID-2 was associated with an increased risk of sCJD (OR for MCs (OR_{MC}) 2.81 and an OR for UMCs (OR_{UMC}) of 2.54). Furthermore, there was for lower-risk procedures a dose-response relation with a linear increase by discharge (OR_{MC} 1.34 and OR_{UMC} 1.33). In addition, point estimates of the OR increased by latency period for lower-risk surgery, and those for latencies 10 years or longer decreased moving from high-risk through lower-risk to lowest-risk.

For surgery classified by the tissue/structure involved, results from comparisons with matched and unmatched control groups were fairly similar. Findings for surgery conducted at any time throughout the entire study period, TWs 1-3, were negative, **Table II**, except when instruments contacted retina and optic nerve being in such case associated with an increased risk of sCJD OR_{MC} (95%CI) 5.53 (1.08-28.0) (based on three exposed cases and compared with matched controls only). However, 16 of the 23 remaining comparisons yielded statistically non-significant OR point values above the unit. No significant differences were found at 1-9 years before onset (data not shown). For surgery conducted 10-19 years before onset,

TW-2, **Table III**, point estimates generally exceeded 1, being statistically significantly higher in both comparisons those for surgery in contact with peripheral nerves and, when compared with MCs only, those for surgery on skeletal muscle. Several significant differences were found at TW-1, ≥ 20 years, **Table IV**, for several categories, including surgery involving blood vessels, peritoneum, skeletal muscle, and the group of other tissues.

When complementary subgroup analyses by alternative TWs were conducted, we observed a statistically significant excess risk for lower-risk surgery performed at least 15 years before onset in both comparisons, and for putatively high-risk surgery performed 5-14 years before onset using UMCs (**Table V**). Positive findings similar to those yielded by the core analysis were detected for strata by country, sex, alternative study period, and age at CJD onset, or for definite cases, during both TW-1 and TW-2 (data not shown).

We went on to explore which specific operations among cases might have contributed to the excess risk. The highest risk, observed for surgery on the retina during the combined TWs 1-3, was based on two surgical discharges after retinal detachment and one involving electrocoagulation of choroidea and retina dating back 9, 12 and 13 years before clinical onset. Surgery during TW-1 with lower but significant risk excess included SP on: blood vessels (n=6, corresponding in all cases to veins); peritoneum (n=15, with 4 and 11 of them being gynaecologic and gastrointestinal, respectively); skeletal muscle (n=23, with 7 and 5 of the SP codes being gynaecologic/obstetric- and bone/orthopaedic-related, respectively); and "other tissues" (n=28, with the majority of these being gynaecologic SP with vaginal approach, e.g., uterus curettage, n=12, and interventions on cervix n=9). Surgery during TW-2 on peripheral nerves among cases (n=4), included two finger and toe phalangeal amputations, one acoustic nerve neurinoma excision, and one pyloroplasty+vagotomy, and 10 of 33 SP under the "skeletal muscle" heading were gynecologic procedures.

DISCUSSION

The key features of the present study design enabled us to address novel aspects of the potential of surgical transmission of CJD (9) The additional introduction of an etiological classification, i.e. unmasking associations hidden by the body-system approach (17, 24), disclosed a number of statistically significant associations, associations of higher magnitude, and new effects with a particular pattern at 10-19 years latency. Limitations, which in part is discussed elsewhere (9) comprises: the low statistical power for some latencies and exposure categories; missing information on interventions undergone prior to registration or as out-patients, and; lack of control of potential confounders such as blood transfusion, overlooked dura mater implants, or hospital hygiene level.

The new SP classification system was built in a tissue/structure classification reported in 2005 (22) combining features of the 1st WHO Classification on Tissue infectivity (24) and of experimental efficiency of prion disease transmission to animals when using different routes of inocula administration (26-29). The plausibility of the risk excess of surgery of retina and peripheral nerves here seen might be supported by studies in experimental scrapie (Sc). PrP^{Sc} injected into the eye travelling via defined neuroanatomical connections has been demonstrated to be able to reach larger brain regions (30,31). In hamsters, PrP^{Sc} spreads along the vagus nerve to the medulla, pons, midbrain, cerebellum and thalamus via neuroanatomic pathways (32). The increasing risk found for SP involving veins, peritoneal cavity, and lymph nodes at longer latencies, fits proposals on prion neuroinvasion and transport, suggesting that prions first replicate and accumulate in the lymphoreticular system (LRS) (see reference 33 for a recent review). In addition, it would appear that risk excess and latency are inversely correlated: 1) for surgery of retina, OR 5.53, at mean 11 years; for surgery of peripheral nerves, OR 4.41, at 10-19 years, and for lower-risk SP OR 2.4, at ≥ 20 years. In summary, our findings might be consistent with proposed biological mechanisms potentially underlying the rapid access to the CNS by direct contact (34), prion uptake through the skin, neuroinvasion from the spleen and spread of prions along peripheral and CNS pathways (33,35).

Compared with other studies, the main contribution of the new methodology may be credibility to consistently positive results from large recent studies covering lifetime surgery and pointing to likewise underlying diluting effects (7,8). In a study with negative results, retina surgery was unfortunately not investigated separately from other ophthalmologic surgery (12). Findings for lower-risk procedures at >20 years would correspond to a similar risk excess before reclassification for main surgical procedures (9). However, the association with coronary surgery seen in TW-3 when using unmatched controls as well as the body system approach has not a corresponding finding here. Since the association of coronary surgery with sCJD has been reported for Alzheimer's disease at similar latency, confounding from vascular risk factors generating both dementia and coronary disease followed by coronary surgery may be proposed as a potential explanation unrelated to prion transmission consistent with absence of findings after reclassification (36).

Unrecorded information potentially determining our results might be length of pathway to the brain, short in the case of retina and acoustic nerve. An overlooked autologous dura mater graft, implanted during the above mentioned acoustic neurinoma intervention was excluded by direct perusal of the surgeon's report, issued in 1977, by an author, HL, who excluded an accidentally transmitted CJD by dura mater implant. Improved cleaning of instruments in recent times may in part explain decreased excess risk with shorter latencies.

Blood transfusion has not been identified as a risk factor for sCJD, however, Riggs et al warn about weaknesses of case-control studies frequently reporting protective effects (37). Inability to adjust for blood transfusion is a limitation of the study, since it has been estimated that blood transfusion is present in 50% of all major surgical interventions (38), blood thus comprises a potential confounder (39). Since it would appear that the excess risk seen here for some tissues, for instance for retina surgery, is difficult to attribute to simultaneous blood transfusion, some of the present results might be consistent with confounded effects of surgical instruments and blood. This view contradicts observations on variant CJD, where transmission by blood has been demonstrated (40-43), but not risk excess for surgery (44). However, differences between sCJD and vCJD or Kuru are so large that inferences should perhaps be inappropriate. Furthermore, the exposures studied might not be independent phenomena representing either a potential entry site for prions or the above mentioned uncontrolled confounding. For example, cohorting of surgical instruments occurs and an instrument used once for e.g. retina surgery has in all likelihood been repeatedly used for retina surgery. It is therefore possible that our findings could in part be explained by infectivity determined by tissue remnants adhered to instruments (not controlled for here) rather than by the putative entry site (i.e., tissue contacted). Consequently, the 18% (9) to 35% (7) proportion of sCJD which has been suggested might be causally related to surgery, while in theory consistent with observations from animal models, would be difficult to ascribe to a single biological mechanism based on our data.

The results might be surprising since identified iatrogenic events related to surgery appear to be very rare. Surveillance since 1993 by 11 countries at the EURO-CJD consortium includes data on more than 6000 sCJD cases (<http://www.eurocjd.ed.ac.uk/genetic.htm>). The number of iatrogenic cases related to surgery are 53 assigned to dura mater, 2 to corneal implants and nil to neurosurgery. However, routine surveillance data will usually not recognise surgical risk exposures for iatrogenic CJD other than grafts. Reasons to explain this might be: 1) the overwhelming difference in annual cohort size, i.e. >100,000 surgical in-patients per million in Sweden 2004 (<http://192.137.163.40/epcfs/index.asp?modul=ope>), versus approximately 200 dura mater grafts per million in the 1990s in Japan (45); 2) the comparatively large attrition by low survival of neurosurgical and dura mater grafted cohorts (45-47); 3) surveillance encompasses the end of the iCJD epidemic (48); 4) large differences in duration of incubation periods, mean 11 years for iCJD by dura mater reduce differences in cumulative risk (48); 5) similar genetic susceptibility might be a strong determinant of surgical risk linked or not to grafts, and is shared by iCJD and sCJD as shown by homozygosity at codon 129 (48,49) but can be interpreted in different ways. CJD surveillance captures epidemiologically compelling evidences required for correct CJD diagnosis; the OR for exposure to cadaveric dura mater for CDJ in Japan (50) was 32.5 95%CI (2.6 – infinity). Our three cases with history of retina surgery were first discharged with

CJD diagnosis from three different hospitals, at different years, in two countries, and most probably diagnosed by different clinicians. Views for iCJD from surveillance and results of this study are perhaps not so difficult to reconcile when biology, diagnosis, epidemiology and public-health practice (51) are simultaneously considered.

The potential applicability of results in prevention is complex. Cautiousness might be recommended for planning of surgical interventions for patients where CJD diagnosis has been considered, and for decontamination and quarantining of such surgical instruments, avoiding reuse during the interval CJD diagnosis has not been excluded. Established instrument-quarantining, -tracking, -cleaning, and prion-disinfection policies, which generally target infrequent procedures, such as neurosurgery and ophthalmologic, spine and ear surgery (38, 52), are based on decontamination of remnants and applied to surgical activity defined by type of surgeon, i.e., by body-system group. Current sterilization procedures undertaken in hospitals for delicate instrumentation are insufficient to ensure total removal of infectious prion protein, and carriers of infective prions are difficult to detect (52,53). Extension of such measures, after appropriate assessment, to instruments contacting or potentially contacting veins, female genital organs, peritoneal cavity, peripheral nerves and muscle could be a priority. In addition, new decontamination procedures (54) may have a wider-than-expected field of application.

To sum up, these results suggest that surgery constitutes a risk factor for sCJD, acting with long incubation periods, and less frequently with shorter latencies when the central- or peripheral nervous system as well as skeletal muscle are implicated. In addition, results are in concordance with animal models of experimental prion transmission through various routes of inoculation that may mimic accidentally transmitted CJD, and might have implications for prevention of CJD spread in medical settings.

Acknowledgments

The EUROSURGYCJD group members are grateful: to Prof. Maurizio Pocchiari, Italy, for contributing to this proposal in respect of the biological plausibility of surgical transmission of prion disorders, to Pascual Sanchez-Juan, Spain, for criticism; and to Margareta Löfdahl (Swedish CJD Surveillance Unit), Curt-Lennar Spetz, Leif Forsberg (Socialstyrelsen) and Lars Caderius (Population Statistics), Sweden, for their help with data-collection. Funding was obtained from The Research Commission EU, Concerted Action QLRG3-CT-2002-81223, NEUROPRION, and the Spanish RECSP C03-09, CIEN C03-06 and CIBERNED networks. Ethical evaluation was cleared Dnr 452/02 by KI Forskningsetikkommittee Syd on December 2, 2002. Jesús de Pedro-Cuesta has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Preliminary results were presented at the EUROOCJD/NEUROOCJD Public Health EU Meeting, held in Paris on December 5, 2006.

EUROSURGYCJD group members. Danish team: Gerhard FALKENHORST, Henning LAURSEN, Kåre MØLBAK. Finnish team: Jussi KOVANEN. Swedish team: Mabel CRUZ, Åke SIDEN. Spanish team: Javier ALMAZÁN, María J. BLEDA, Miguel CALERO, Ignacio MAHILLO, Pablo MARTÍNEZ-MARTÍN, Jesús de PEDRO-CUESTA (coordinator), Alberto RÁBANO.

References

1. Kondo K, Kuroiwa Y. A case-control study of Creutzfeldt-Jakob disease: association with physical injuries. *Ann Neurol* 1982;11:377-81.
2. Davanipour Z, Alter M, Sobel E, et al. Creutzfeldt-Jakob disease: possible medical risk factors. *Neurology* 1985;35:1483-6.
3. Harries-Jones R, Knight RSG, Will RG, et al. Creutzfeldt-Jakob disease in England and Wales, 1980-1984: a case-control study of potential risk factors. *J Neurol Neurosurg Psychiatry* 1988;51:1113-9.
4. van Duijn CM, Delasnerie-Lauprêtre N, Masullo C, et al: Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993-95. *Lancet* 1998;351:1081-1085.
5. Zerr I, Brandel J-P, Masullo C, et al.: European surveillance on Creutzfeldt-Jakob disease: a case-control study for medical risk factors. *J Clin Epidemiol* 2000 ;53:747-754.
6. Collins S, Law MG, Fletcher A, et al. Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:69.
7. Ward HJT, Everington D, Croes EA, et al: Sporadic Creutzfeldt-Jakob disease and surgery: a case-control study using community controls. *Neurology* 2002;59:543-548.
8. Ward HJ, Everington D, Cousens SN, et al. Risk factors for sporadic Creutzfeldt-Jakob disease. *Ann Neurol* 2008;63:347-54.
9. Mahillo-Fernandez I, de Pedro-Cuesta J, Bleda MJ, et al: Surgery and risk of sporadic Creutzfeldt-Jakob disease in Denmark and Sweden: registry-based case-control studies. *Neuroepidemiology* 2008;31:229–240.
10. Riegger J, Stoeck K, Amsler L, et al. A case-control study of sporadic Creutzfeldt-Jakob disease in Switzerland: analysis of potential risk factors with regard to an increased CJD incidence in the years 2001-2004. *BMC Public Health* 2009, 9:18 January 14. Publication ahead of print. doi:10.1186/1471-2458-9-18.
11. Hamaguchi T, Noguchi-Sinohara E, Nozaki I, et al. Medical procedures and risk for sporadic Creutzfeldt-Jakob disease, Japan, 1999-2008. *Emerg Infect Dis* 2009;15:265-71.
12. S-Juan P, Ward HJ, De Silva R, Knight R, Will RG. Ophthalmic surgery and Creutzfeldt-Jakob disease. *Br J Ophthalmol*. 2004;88:446-9.
13. Wientjens DPWM, Davanipour Z, Hofman A, et al. Risk factors for Creutzfeldt-Jakob disease: a reanalysis of case-control studies. *Neurology* 1996;46:1287-1291
14. Barash JA, Johnson BT, Gregorio I. Is surgery a risk factor for Creutzfeldt-Jakob disease? Outcome variation by control choice and exposure assessments. *Infect Control Hosp Epidemiol*. 2008;29:212-8

15. Ward H, Knight R. Surgery and Risk of Sporadic Creutzfeldt-Jakob Disease. *Neuroepidemiology* 2008;31:241–242.
16. CJD UK Incidents Panel. Management of possible exposure to CJD through medical procedures: a consultation paper. Department of Health Publications, London, 2001. pp 11-27
17. de Pedro-Cuesta J, Bleda M.J, Rábano A, et al. Classification of surgical procedures for epidemiologic assessment of sporadic Creutzfeldt-Jakob Disease transmission by surgery. *Eur J Epidemiology*, 2006; 21:595-604.
18. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000;55:811-815.
19. Klassifikation av operationer, 6:e upplagan. Socialstyrelsen. Norstedts T. Stockholm 1993.
20. Operations og Behandlings-Klassifikation, 3 udgave. Sundhedsstyrelsen, Copenhagen. Munksgaard. 1988.
21. Nordic Medico Statistical Committee N. NOMESCO classification of surgical procedures. Copenhagen, NOTEX, 2003.
22. Rábano A., de Pedro-Cuesta J., Mølbak K, et al. Tissue classification for the epidemiologic assessment of surgical transmission of sporadic Creutzfeldt-Jakob disease. A proposal on hypothetical risk levels. *BMC Public Health* 2005;5:9.
23. Modern Epidemiology KJ Rothman, S Greenland and TL Last, 3rd ed. Lippincott Williams & Wilkins. Philadelphia, PA. USA. 2008. pp 234-237
24. Dosemeci M, Wacholder S, Lubin JH. Does non-differential misclassification of exposure always bias a true effect toward the null value?. *Am J Epidemiol* 1990;132:746-748
25. Health Technology and Pharmaceuticals Cluster W. WHO Guidelines on Transmissible Spongiform Encephalopathies I relation to biological and pharmaceutical products. WHO/BCT/QSD/03.01, 1-26, 2003.
26. Kimberlin RH, Walker CA: Pathogenesis of scrapie (strain 263K) in hamsters infected intracerebrally, intraperitoneally or intraocularly. *J Gen Virol* 1986, 67:255-263.
27. Race R, Oldstone M, Chesebro B: Entry versus blockade of brain infection following oral or intraperitoneal scrapie administration: role of prion protein expression in peripheral nerves and spleen. *J Virol* 2000, 74:828-833.
28. Bradley R: Animal prion diseases. In *Prion diseases* Edited by: Collinge J and Palmer MS. Oxford, Oxford University Press; 1997.

29. Scott JR, Foster JD, Fraser H: Conjunctival instillation of scrapie in mice can produce disease. *Vet Microbiol* 1993, 34:305-309.
30. Fraser, H. Neuronal spread of scrapie agent and targeting of lesions within the retino-tectal pathway. *Nature* 1982, 295, 149–150.
31. Brandner, S. *et al.* Normal host prion protein (Pr^{PC}) is required for scrapie spread within the CNS. *Proc. Natl Acad. Sci. USA* 1996;93:13148–13151.
32. Beekes, M., McBride, P. A. & Baldauf, E. Cerebral targeting indicates vagal spread of infection in hamsters fed with scrapie. *J. Gen. Virol.* 1998;79: 601–607.
33. Aguzzi A, Calella M. Prions: Protein aggregation and infectious diseases. *Physiol Rev* 2009;89:1105-1152.
34. Bartz JC, Dejoia C, Tucker T, et al. Extraneural prion neuroinvasion without lymphoreticular system infection. *J Virol* 2005;79:11858–11863.
35. Kimberlin RH, Hall SM, Walker CA. Pathogenesis of mouse scrapie. Evidence for direct neural spread of infection to the CNS after injection of sciatic nerve. *J Neurol Sci.* 1983;61:315-25.
36. Knopman DS, Petersen RC, Cha RH, et al. Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer disease. *Neurology.* 2005,11;65(7):986-90
37. Riggs JE, Moudgil SS, Hobbs GR. Creutzfeldt-Jakob disease and blood transfusions: a meta-analysis of case-control studies. *Mil Med* 2001;166:1057-1058.
38. Garske T, Ward HT, Clarke P, et al. Factors determining the potential for onward transmission of variant Creutzfeldt-Jakob disease via surgical instruments. *J R Dsoc. Interface* 2006;3:757-766.
39. Brown P. Creutzfeldt-Jakob disease: reflections on the risk from blood product therapy. *Haemophillia.* 2007;13 Suppl 5:33-40.
40. Llewelyn CA, Hewitt PE, Knight RS, et al. Possible transmission of variant Creutzfeldt-Jakob disease by blood transfusion. *Lancet.* 2004;363:417-21.
41. Peden AH, Head MW, Ritchie DL, et al. Preclinical vCJD after blood transfusion in a codon 129 heterozygous patient. *Lancet,* 2004;364:527-9.
42. Collinge J. Molecular neurology of prion disease. *J Neurol Neurosurg Psychiatry* 2005;76: 906–19.
43. Wroe SJ, Pal S, Siddique D, et al. Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report. *Lancet* 2006;368:2061–67.
44. Ward HJ, Everington D, Cousens SN, et al. Risk factors for variant Creutzfeldt-Jakob disease: a case-control study. *Ann Neurol.* 2006;59:111-20.

45. Nakamura Y, Aso E, Yanagawa H. Relative risk of Creutzfeldt-Jakob disease with cadaveric dura transplantation in Japan. *Neurology* 1999;53:218-220.
46. Martinez-Lage JF, Poza M, Brown P, et al. Enfermedad de Creutzfeldt-Jakob en Neurocirugía: una revisión de riesgos y medidas de prevención. *Neurocirugía* 1997;8:284-293
47. Bird SM, Merrall EL, Ward HJ, Will RG. Survival and re-operation rates after neurosurgical procedures in Scotland: implications for targeted surveillance of sub-clinical variant Creutzfeldt-Jakob disease. *Neuroepidemiology*. 2009;33:1-11.
48. Brown P, Brandel JP, Preese M, Sato T. Iatrogenic Creutzfeldt-Jakob disease. The waning of an era. *Neurology* 2006;67:389-393.
49. Kovács GG, Puopolo M, Ladogana A, et al.. Genetic prion disease: the EUROCJD experience. *Hum Genet* 2005;118:166-174
50. Nakamura Y, Oki I, Tanihara S et al. A case-control study of Creutzfeldt-Jakob disease in Japan: transplantation of cadaveric dura mater was a risk factor. *J Epidemiol*, 2000;10:399-402.
51. Lenglet A, Hernández Pezzi G. Comparison of the European Union Disease Surveillance Networks' websites. *Euro Surveill*. 2006;11(5):pii=625.
52. Yan, Z., Stitz, L., Heeg, P., et al. Infectivity of prion protein bound to stainless steel wires: a model for testing decontamination procedures for transmissible spongiform encephalopathies. *Infect. Control Hosp. Epidemiol*. 2004; 25; 280–283.
53. Baxter RL, Baxter HC, Campbell GA, et al. Quantitative analysis of residual protein contamination on reprocessed surgical instruments. *J Hosp Infect*. 2006;63:439-44.
54. Lemmer K, Mielke M, Kratzel C, et al. Decontamination of surgical instruments from prions. II. In vivo findings with a model system for testing the removal of scrapie infectivity from steel surfaces. *J Gen Virol*. 2008;89:348-58

FIGURE LEGENDS

Figure 1. Schematic illustration of the study design and methodological procedure for life-time-interval definition of the registered surgical history of cases and controls. Time windows included in the present study were those covering surgical history >1 year prior to clinical onset of cases or index-date-2 of controls, namely, windows 1, 2 and 3. Modified from ref 9, where details of individuals life-time references are given.

Figure 2. **a** Example of individual categories of exposure by tissue/structure under study when focusing on *retina, optic nerve*, at a specific window, for three different individuals. **b** SP risk categories after reclassification, and corresponding individual categories of exposure to surgery.

Figure 3. Percentage distributions of 5,990 selected SP codes associated with surgical discharges during TWs 1-3, either classified by body-system, or reclassified by hypothetical transmission risk level (n=5990) or contacted tissue/structure (n=4813). Three SP categories yielding zero values (trigeminal ganglia, olfactory mucosa and cerebrospinal fluid), are not represented. Added percentages by tissue or anatomic structure exceed 100%.

Table I. Associations for surgery by risk level for specific periods predating onset or ID-2. OR for comparisons with UMC was adjusted by age, sex and country.

Time window	Subject	Putative risk categories after reclassification								
		Unexposed ¹	<i>High-risk</i>		<i>Lower-risk</i>		<i>Lowest-risk</i>		<i>No-risk or not reclassified</i>	
		n (%)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Time window 1 (≥ 20 years)	Cases	134 (80.2)	0 (0.0)		25 (15.0)		7 (4.2)		1 (0.6)	
	MC	745 (89.2)	0 (0.0)	–	58 (6.9)	2.81 (1.62 – 4.88) ²	29 (3.5)	1.70 (0.71 – 4.04)	3 (0.4)	2.09 (0.18 – 23.8)
	UMC	1,985 (89.3)	1 (0.0)	–	162 (7.3)	2.54 (1.59 – 4.06) ³	66 (3.0)	1.67 (0.72 – 3.86)	10 (0.4)	1.35 (0.14 – 12.9)
Time window 2 (10 - 19 years)	Cases	110 (65.9)	2 (1.2)		44 (26.3)		10 (6.0)		1 (0.6)	
	MC	603 (72.2)	6 (0.7)	1.72 (0.34 – 8.59)	167 (20.0)	1.49 (1.00 – 2.22)	48 (5.7)	1.16 (0.59 – 2.28)	11 (1.3)	0.51 (0.07 – 3.96)
	UMC	1,569 (70.5)	10 (0.4)	2.53 (0.57 – 11.3)	474 (21.3)	1.45 (0.99 – 2.12)	128 (5.8)	1.20 (0.61 – 2.38)	43 (1.9)	0.30 (0.04 – 2.24)
Time window 3 (1 - 9 years)	Cases	116 (69.5)	2 (1.2)		33 (19.8)		9 (5.4)		7 (4.2)	
	MC	565 (67.7)	8 (1.0)	1.22 (0.26 – 5.77)	192 (23.0)	0.84 (0.55 – 1.29)	42 (5.0)	1.04 (0.50 – 2.18)	28 (3.4)	1.22 (0.50 – 2.94)
	UMC	1,526 (68.6)	16 (0.7)	1.41 (0.33 – 6.10)	513 (23.1)	0.74 (0.49 – 1.11)	115 (5.2)	0.96 (0.47 – 1.96)	54 (2.4)	1.59 (0.69 – 3.66)
All time TWs (≥ 1 year)	Cases	72 (43.1)	4 (2.4)		81 (48.5)		7 (4.2)		3 (1.8)	
	MC	399 (47.8)	13 (1.6)	1.67 (0.50 – 6.51)	333 (39.9)	1.35 (0.96 – 1.91)	68 (8.1)	0.57 (0.25 – 1.30)	22 (2.6)	0.76 (0.21 – 2.74)
	UMC	1,056 (47.5)	27 (1.2)	1.94 (0.67 – 5.58)	907 (40.8)	1.28 (0.91 – 1.79)	184 (8.3)	0.56 (0.25 – 1.24)	50 (2.2)	0.76 (0.23 – 2.54)

¹ Reference category. No registered surgery.

² Linear increase per discharge: OR = 1.34, 95% CI = 1.07 – 1.69

³ Linear increase per discharge: OR = 1.33, 95% CI = 1.09 – 1.61

Table II. Associations for surgery by tissue/structure contacted 1 or more years before onset or ID-2. OR for comparisons with UMC was adjusted by age, sex and country.

Tissue/structure	Subject	Unexposed ¹	Tissue/structure under study		Other surgery ²
		n (%)	n (%)	OR (95% CI)	n (%)
Retina, optic nerve	Case	72(43.1)	3(1.8)		92(55.1)
	MC	399(47.8)	3(0.4)	5.53 (1.10-27.79)	433(51.9)
	UMC	1056(47.5)	14(0.6)	2.96 (0.66-9.62)	1154(51.9)
Spinal ganglia	Case	72(43.1)	1(0.6)		94(56.3)
	MC	399(47.8)	3(0.4)	1.77 (0.18-17.04)	433(51.9)
	UMC	1056(47.5)	8(0.4)	1.66 (0.09-9.74)	1160(52.2)
Dura mater	Case	72(43.1)	1(0.6)		94(56.3)
	MC	399(47.8)	10(1.2)	0.53 (0.07-4.27)	426(51.0)
	UMC	1056(47.5)	11(0.5)	1.19 (0.06-6.49)	1157(52.0)
Peripheral nerves	Case	72(43.1)	5(3.0)		90(53.9)
	MC	399(47.8)	13(1.6)	2.10 (0.74-6.00)	423(50.7)
	UMC	1056(47.5)	39(1.8)	1.76 (0.58-4.31)	1129(50.8)
Lymph nodes	Case	72(43.1)	9(5.4)		86(51.5)
	MC	399(47.8)	52(6.2)	0.97 (0.46-2.07)	384(46.0)
	UMC	1056(47.5)	122(5.5)	0.92 (0.41-1.81)	1046(47.0)
Tonsil	Case	72(43.1)	1(0.6)		94(56.3)
	MC	399(47.8)	8(1.0)	0.69 (0.09-5.60)	428(51.3)
	UMC	1056(47.5)	21(0.9)	0.99 (0.05-4.97)	1147(51.6)
Kidney	Case	72(43.1)	1(0.6)		94(56.3)
	MC	399(47.8)	6(0.7)	0.92 (0.11-7.72)	430(51.5)
	UMC	1056(47.5)	5(0.2)	2.58 (0.13-16.92)	1163(52.3)
Blood vessels	Case	72(43.1)	15(9.0)		80(47.9)
	MC	399(47.8)	56(6.7)	1.51 (0.80-2.85)	380(45.5)
	UMC	1056(47.5)	109(4.9)	1.66 (0.88-2.97)	1059(47.6)
Anterior olphthalmic	Case	72(43.1)	7(4.2)		88(52.7)
	MC	399(47.8)	19(2.3)	2.10 (0.83-5.32)	417(49.9)
	UMC	1056(47.5)	52(2.3)	1.60 (0.63-3.55)	1116(50.2)
Skeletal muscle	Case	72(43.1)	63(37.7)		32(19.2)
	MC	399(47.8)	257(30.8)	1.38 (0.94-2.02)	179(21.4)
	UMC	1056(47.5)	714(32.1)	1.33 (0.92-1.91)	454(20.4)
Peritoneum	Case	72(43.1)	34(20.4)		61(36.5)
	MC	399(47.8)	136(16.3)	1.44 (0.89-2.33)	300(35.9)
	UMC	1056(47.5)	389(17.5)	1.32 (0.85-2.04)	779(35.0)
Subcutaneous	Case	72(43.1)	6(3.6)		89(53.3)
	MC	399(47.8)	26(3.1)	1.28 (0.51-3.24)	410(49.1)
	UMC	1056(47.5)	88(4.0)	0.89 (0.33-1.96)	1080(48.6)
Other tissues	Case	72(43.1)	43(25.7)		52(31.1)
	MC	399(47.8)	198(23.7)	1.22 (0.79-1.88)	238(28.5)
	UMC	1056(47.5)	533(24.0)	1.17 (0.78-1.74)	635(28.6)

¹ Reference category. No registered surgery.

² Reclassified procedures involving tissues/structures different from that on study only.

Table III. Associations for surgery by tissue/structure contacted 10 - 19 years before onset or ID-2. OR for comparisons with UMC was adjusted by age, sex and country.

Tissue/structure	Subject	Unexposed ¹	Tissue/structure under study		Other surgery ²
		n (%)	n (%)	OR (95% CI)	n (%)
Retina, optic nerve	Case	110 (65.9)	2 (1.2)		55 (32.9)
	MC	603 (72.2)	1 (0.1)	10.7 (0.91 – 124.9)	231 (27.7)
	UMC	1,569 (70.5)	6 (0.3)	3.97 (0.83 – 18.9)	649 (29.2)
Peripheral nerves	Case	110 (65.9)	4 (2.4)		53 (31.7)
	MC	603 (72.2)	5 (0.6)	4.41 (1.17 – 16.6)	227 (27.2)
	UMC	1,569 (70.5)	16 (0.7)	3.83 (1.24 – 11.8)	639 (28.7)
Lymph nodes	Case	110 (65.9)	6 (3.6)		51 (30.5)
	MC	603 (72.2)	18 (2.2)	1.87 (0.72 – 4.86)	214 (25.6)
	UMC	1,569 (70.5)	43 (1.9)	1.82 (0.77 – 4.27)	612 (27.5)
Kidney	Case	110 (65.9)	1 (0.6)		56 (33.5)
	MC	603 (72.2)	3 (0.4)	1.88 (0.19 – 18.5)	229 (27.4)
	UMC	1,569 (70.5)	0 (0.0)		655 (29.5)
Blood vessels	Case	110 (65.9)	5 (3.0)		52 (31.1)
	MC	603 (72.2)	24 (2.9)	1.19 (0.44 – 3.23)	208 (24.9)
	UMC	1,569 (70.5)	50 (2.2)	1.40 (0.55 – 3.58)	605 (27.2)
Anterior ocular	Case	110 (65.9)	3 (1.8)		54 (32.3)
	MC	603 (72.2)	6 (0.7)	2.74 (0.67 – 11.2)	226 (27.1)
	UMC	1,569 (70.5)	15 (0.7)	2.57 (0.70 – 9.42)	640 (28.8)
Skeletal muscle	Case	110 (65.9)	34 (20.4)		23 (13.8)
	MC	603 (72.2)	122 (14.6)	1.58 (1.01 – 2.48)	110 (13.2)
	UMC	1,569 (70.5)	385 (17.3)	1.41 (0.92 – 2.15)	270 (12.1)
Peritoneum	Case	110 (65.9)	19 (11.4)		38 (22.8)
	MC	603 (72.2)	67 (8.0)	1.62 (0.91 – 2.89)	165 (19.8)
	UMC	1,569 (70.5)	190 (8.5)	1.65 (0.97 – 2.79)	465 (20.9)
Subcutaneous	Case	110 (65.9)	4 (2.4)		53 (31.7)
	MC	603 (72.2)	13 (1.6)	1.73 (0.50 – 5.96)	219 (26.2)
	UMC	1,569 (70.5)	35 (1.6)	1.64 (0.57 – 4.70)	620 (27.9)
Other tissues	Case	110 (65.9)	22 (13.2)		35 (21.0)
	MC	603 (72.2)	101 (12.1)	1.22 (0.72 – 2.06)	131 (15.7)
	UMC	1,569 (70.5)	286 (12.9)	1.20 (0.74 – 1.96)	369 (16.6)

¹ Reference category. No registered surgery.

² Reclassified procedures involving tissues/structures different from that on study only. Shown for clarity.

Table IV. Associations for surgery by tissue/structure contacted, 20 or more years before onset or ID-2. OR for comparisons with UMC was adjusted by age, sex and country.

Time window	Tissue/structure	Subject	Unexposed ¹	Tissue/structure under study		Other surgery ²
			n (%)	n (%)	OR (95% CI)	n (%)
Time window 1 (≥20 years)	Peripheral nerves	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	1 (0.1)	6.27 (0.50 – 78.1)	89 (10.7)
		UMC	1,985 (89.3)	7 (0.3)	2.12 (0.20 – 21.9)	232 (10.4)
	Lymph nodes	Case	134 (80.2)	2 (1.2)		31 (18.6)
		MC	745 (89.2)	6 (0.7)	2.18 (0.46 – 10.4)	84 (10.1)
		UMC	1,985 (89.3)	9 (0.4)	2.83 (0.62 – 12.9)	230 (10.3)
	Tonsil	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)	4 (0.2)	6.46 (0.72 – 58.3)	235 (10.6)
	Blood vessels	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)	10 (0.4)	4.15 (1.12 – 15.5)	229 (10.3)
	Skeletal muscle	Case	134 (80.2)	14 (8.4)		19 (11.4)
		MC	745 (89.2)	46 (5.5)	2.04 (1.06 – 3.92)	44 (5.3)
		UMC	1,985 (89.3)	125 (5.6)	1.87 (1.03 – 3.38)	114 (5.1)
	Peritoneum	Case	134 (80.2)	11 (6.6)		22 (13.2)
		MC	745 (89.2)	32 (3.8)	2.38 (1.14 – 4.96)	58 (6.9)
		UMC	1,985 (89.3)	66 (3.0)	2.48 (1.26 – 4.88)	173 (7.8)
	Subcutaneous	Case	134 (80.2)	1 (0.6)		32 (19.2)
		MC	745 (89.2)	3 (0.4)	1.98 (0.19 – 20.6)	87 (10.4)
		UMC	1,985 (89.3)	14 (0.6)	1.06 (0.12 – 9.19)	225 (10.1)
	Other tissues	Case	134 (80.2)	16 (9.6)		17 (10.2)
		MC	745 (89.2)	50 (6.0)	2.26 (1.14 – 4.47)	40 (4.8)
		UMC	1,985 (89.3)	109 (4.9)	2.24 (1.25 – 4.04)	130 (5.8)

¹ Reference category. No registered surgery.

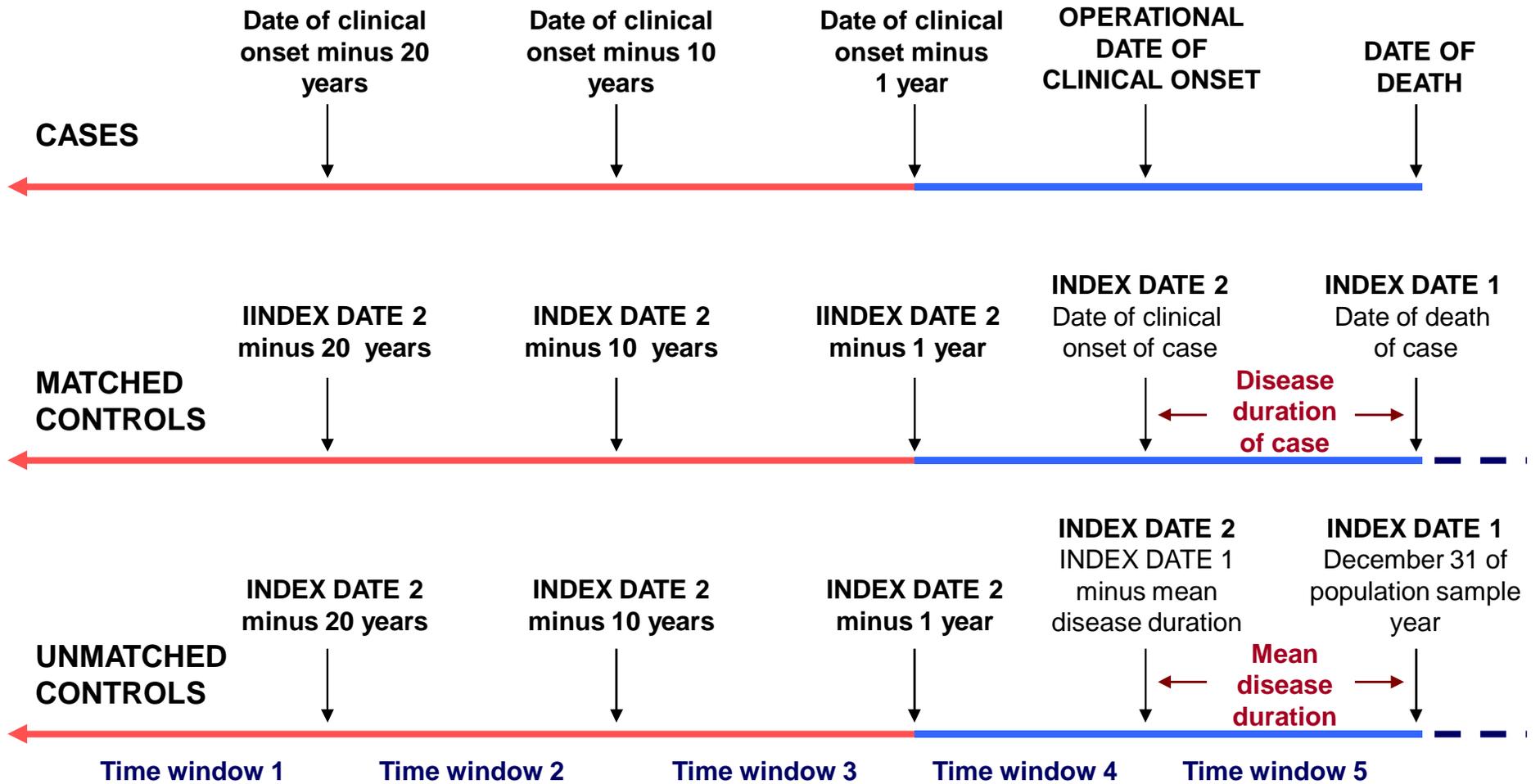
² Reclassified procedures involving tissues/structures different from that on study only. Shown for clarity.

Table V. Complementary analyses by risk level. OR for comparisons with UMC was adjusted by age, sex and country.

Time window	Subject	Unexposed ¹ n (%)	Putative risk categories after reclassification							
			<i>High-risk</i>		<i>Lower-risk</i>		<i>Lowest-risk</i>		<i>No-risk or not reclassified</i>	
			n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)
Time window 1 (≥ 15 years)	Cases	114 (68.3)	0 (0.0)		47 (28.1)		5 (3.0)		1 (0.6)	
	MC	642 (76.9)	2 (0.2)	–	132 (15.8)	2.13 (1.39 – 3.25)	52 (6.2)	0.59 (0.22 – 1.55)	7 (0.8)	0.84 (0.10 – 6.72)
	UMC	1,703 (76.6)	6 (0.3)	–	378 (17.0)	2.05 (1.42 – 2.96)	117 (5.3)	0.67 (0.26 – 1.72)	20 (0.9)	0.80 (0.10 – 6.62)
Time window 2 (5 – 14 years)	Cases	117 (70.1)	3 (1.8)		34 (20.4)		7 (4.2)		6 (3.6)	
	MC	571 (68.4)	8 (1.0)	1.85 (0.49 – 6.96)	188 (22.5)	0.88 (0.59 – 1.33)	48 (5.7)	0.71 (0.31 – 1.61)	20 (2.4)	1.47 (0.57 – 3.79)
	UMC	1,512 (68.0)	11 (0.5)	3.43 (1.01 – 11.6)	531 (23.9)	0.83 (0.56 – 1.24)	123 (5.5)	0.76 (0.34 – 1.68)	47 (2.1)	1.57 (0.64 – 3.85)
Time window 3 (1 – 4 years)	Cases	136 (81.4)	1 (0.6)		22 (13.2)		7 (4.2)		1 (0.6)	
	MC	692 (82.9)	3 (0.4)	1.68 (0.17 – 16.3)	104 (12.5)	1.07 (0.66 – 1.76)	21 (2.5)	1.70 (0.72 – 4.01)	15 (1.8)	0.32 (0.05 – 1.84)
	UMC	1,831 (82.3)	12 (0.5)	0.89 (0.12 – 6.67)	281 (12.6)	0.89 (0.55 – 1.43)	59 (2.7)	1.46 (0.65 – 3.26)	41 (1.8)	0.29 (0.04 – 2.07)

¹ Reference category. No registered surgery.

SURGERY POTENTIALLY INVOLVED IN DISEASE ACQUISITION



(a)

Individual	Surgical procedure	Assigned involved tissues	Category of individual exposure for study of “retina, optic nerve”
Individual 1	CKD75*	Retina, optic nerve Anterior ophthalmic	
	7311**	Other tissues	Exposed to retina, optic nerve
Individual 2	43000***	Skeletal muscle Peritoneum	
	91010****	Not reclassified	Exposed to “Other surgery”
Individual 3	Not registered	-	Unexposed

* Retinotomy

** Conisation of cervix uteri

*** Appendicectomy

**** Gastroscopy

(b)

Risk categories for
surgical procedures

Risk categories of
individual exposure

