SUPPLEMENTARY MATERIAL FOR

Inverse and Direct Cancer Comorbidity in People with Central Nervous System Disorders: a meta-analysis of cancer incidence in 577,013 participants of 50 observational studies.

Table S1: Details of search terms used in bibliographical review.

PubMed/MEDLINE: Cancer-related terms: ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "malignancy"[All Fields]) Selected central nervous system conditions-related terms: ("schizophrenia"[MeSH Terms] OR "multiple sclerosis"[MeSH Terms] OR "alzheimer disease"[MeSH Terms] OR "parkinson disease"[MeSH Terms] OR "down syndrome"[MeSH Terms] OR "down syndrome"[All Fields] OR "autistic disorder"[MeSH Terms] OR "huntington disease"[MeSH Terms] OR "sclerosis"[MeSH Terms]) Epidemiology-related terms: ("incidence"[MeSH Terms] OR "comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "multimorbidity"[All Fields])
SCOPUS: (TITLE-ABS-KEY("neoplasm" OR "cancer" OR "carcinoma" OR "malignancy") AND TITLE-ABS-KEY("schizophrenia" OR "multiple sclerosis" OR "down syndrome" OR "Parkinson disease" OR "Autism" OR "Autistic disorder" OR "Huntington disease" OR "sclerosis") AND TITLE-ABS-KEY("incidence" OR "comorbidity" OR "multimorbidity" OR "standardized incidence ratio")) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar)
ISI Web of Knowledge: Topic=(neoplasm* OR cancer* OR carcinoma* OR malignancy*) AND Topic=(schizophrenia* OR multiple sclerosis* OR down syndrome* OR Parkinson disease* OR Autism* OR Autistic disorder* OR Huntington disease* OR sclerosis*) AND Topic=(incidence* OR comorbidity* OR multimorbidity* OR standardized incidence ratio*) Timespan=1960-2013. Search language=English Lemmatization=On

Table S2: PRISMA Checklist

TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover page¶1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract¶2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Introduction, ¶4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Introduction, ¶5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, ¶5-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, ¶5-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Methods, ¶5-7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, ¶5-7

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, ¶5-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, ¶5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Methods, ¶6 and Annex Table S5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, ¶7 and Annex Table S5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, ¶8-9
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Methods, ¶9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, ¶8-9

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Results, ¶9-10; Figure 1, Annex
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, ¶9-16; Table S5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	table S6

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Results, ¶9-16; Table S5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Results, ¶9-16; Figures 2-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Results, ¶15-16; Tables S7-S11, Figures S1-S3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, ¶16-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, ¶19,20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, ¶20,21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Disclosures

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S3: References for the studies included in the systematic review.

Alzheimer's disease

1. Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC. Alzheimer disease and cancer. Neurology. 2005;64:895-8.
2. Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, Williams MM, Kopan R, Behrens MI, Morris JC. Cancer linked to Alzheimer disease but not vascular dementia. Neurology. 2010;74(2):106-12.
3. Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, Kiel DP, Lu KP, Seshadri S, Wolf PA. Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. BMJ. 2012;344:e1442. doi: 10.1136/bmj.e144

Parkinson's disease

4. Jansson B, Jankovic J. Low cancer rates among patients with Parkinson´s disease. Ann Neurol. 1985;17:505-9.
5. Møller H, Mellemkjaer L, McLaughlin JK, Olsen JH. Occurrence of different cancers in patients with Parkinson's disease. BMJ. 1995;310(6993):1500-1.
6. Minami Y, Yamamoto R, Nishikouri M, Fukao A, Hisamichi S. Mortality and cancer incidence in patients with Parkinson's disease. J Neurol 2000;247: 429e34.
7. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellemkjaer L, Moller H. Atypical cancer patterns in patients with Parkinson's disease. Br J Cancer. 2005;92:201-5.
8. Elbaz A, Peterson BJ, Bower JH, Yang P, Maraganore DM, McDonnell SK. Risk of cancer after the diagnosis of Parkinson's disease: a historical cohort. Mov Disord. 2005;30:719-25.
9. Lo RY, Tanner CM, Van Den Eeden SK, Albers KB, Leimpeter AD, Nelson LM. Comorbid Cancer In Parkinson's Disease. Mov Disord. 2010;25(12):1809-17.
10. Becker C, Brobert GP, Johansson S, Jick SS, Meier CR. Cancer risk in association with Parkinson Disease: A population - based study. Parkinsonism Relat Disord 2010;16(3): 186-90.
11. Fois AF, Wotton CJ, Yeates D, Turner MR, Goldacre MJ. Cancer in patients with motor neuron disease, multiple sclerosis and Parkinson's disease: record linkage studies. J Neurol Neurosurg Psychiatry. 2010;81(2):215-21. **(included in the analyses of multiple sclerosis, Parkinson's disease and amyothrophic lateral sclerosis)**
12. Sun LM, Liang JA, Chang SN, Sung FC, Muo CH, Kao CH. Analysis of Parkinson's disease and subsequent cancer risk in Taiwan: a nationwide population-based cohort study. Neuroepidemiology 2011; 37: 114-9.
13. Rugbjerg K, Friis S, Lassen CF, Ritz B, Olsen JH. Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. Int J Cancer 2012; 131: 1904-11.
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Multiple sclerosis

15. Midgard R, Glattre E, Grønning M, Riise T, Edland A, Nyland H. Multiple sclerosis and cancer in Norway. A retrospective cohort study. Acta Neurol Scand. 1996;93(6):411-5.
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18. Nielsen NM, Rostgaard K, Rasmusen S, Koch-Henriksen N and cols. Cancer risk among patients with multiple sclerosis: A population based register study. Int J Cancer 2006;118(4):979-84.
19. Lebrun C, Debouverie M, Vermersch P, Clavelou P, Rumbach L, de Seze J, Wiertlevski S, Defer G, Gout O, Berthier F, Danzon A. Cancer risk and impact of disease-modifying treatments in patients with multiple sclerosis. Mult Scler. 2008;14(3):399-405.

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2010;81(2):215-21. (**included in the analyses of multiple sclerosis, Parkinson's disease and amyothrophic lateral sclerosis)**]

20. Bahmanyar S, Montgomery SM, Hillert J, Ekbom A, Olsson T. Cancer risk among patients with multiple sclerosis and their parents. Neurology. 2009;72(13):1170-7.
21. Kingwell E, Bajdik C, Phillips N, Zhu F, Oger J, Hashimoto S, Tremlett H. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. Brain. 2012;135(Pt 10):2973-9.
22. Goldacre MJ, Seagroatt V, Yeates D, Acheson ED. Skin cancer in people with multiple sclerosis: a record linkage study. J Epidemiol Community Health. 2004;58(2):142-4. **(only contributed with data for secondary meta-analysis of melanoma)**

Lateral amyotrophic sclerosis

23. Zisfein J, Caroscio JT. No association of amyotrophic lateral sclerosis with cancer. Mt Sinai J Med. 1988 Mar;55(2):159-61.

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Schizophrenia

24. Dupont A, Moller Jensen O, Strömgren E et al. Incidence of cancer in patients diagnosed as schizophrenic in Denmark. In: ten Horn, GHMM, Giel R, Gulbinat W, et al (Eds.). Psychiatric case registries in public health. Amsterdam: Elsevier Science Publishers; 2006. Amsterdam, pp. 229- 239.
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41. Hippisley-Cox J, Vinogradova Y, Coupland C, Parker C. Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. Arch Gen Psychiatry. 2007;64(12):1368-76. **(only contributed with data for secondary meta-analysis of breast cancer, prostate cancer, lung cancer and colorectal cancer)**
42. Barak Y, Levy T, Achiron A, Aizenberg D. Breast cancer in women suffering from serious mental illness. Schizophr Res. 2008 Jul;102(1-3):249-53. **(only contributed with data for secondary meta-analysis of breast cancer)**

Down's syndrome

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Huntington disease

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Autism

51. Lauritsen MB, Mors O, Mortensen PB, Ewald H. Medical disorders among inpatients with autism in Denmark according to ICD-8: a nationwide register-based study. J Autism Dev Disord. 2002;32:115-9.

Table S4: List of excluded referenes and reasons for exclusion.

References	Reason
1. Acqui M, Caroli E, Di Stefano D, Ferrante L. Cerebral ependymoma in a patient with multiple sclerosis case report and critical review of the literature. Surg Neurol. 2008;70:414-20.	1
2. Adityanjee A, Khurana V, Caldito G, For C. Is schizophrenia a protective factor against cancer? Schizophr Res. 2006;81:supl:175.	1
3. Albert SM. Neurodegenerative disease and cancer: a critical role for melanoma? Neuroepidemiology. 2010;35:305-6.	1
4. Almeida L, Neves M, Cardoso E, Melo A. Chronic myeloid leukaemia in two multiple sclerosis patients on interferon beta-1a. J Clin Pharm Ther. 2009;34:125-7.	2
5. Ananth J, Burnstein M. Cancer: less common in psychiatric patients? Psychosomatics. 1977;18(2):44-6.	1
6. Arico M, Ziino O, Valsecchi MG, et al. Acute lymphoblastic leukemia and Down syndrome: presenting features and treatment outcome in the experience of the Italian Association of Pediatric Hematology and Oncology (AIEOP). Cancer. 2008;113:515-21.	1
7. Baade PD, Fritschi L, Freedman DM. Mortality due to amyotrophic lateral sclerosis and Parkinson's disease among melanoma patients. Neuroepidemiology. 2007;28:16-20.	3
8. Baek KH, Zaslavsky A, Lynch RC, et al. Down's syndrome suppression of tumour growth and the role of the calcineurin inhibitor DSCR1. Nature 2009;459:1126-30.	4
9. Blatt J, Deal AM, Mesibov G. Autism in children and adolescents with cancer. Pediatr Blood Cancer. 2010;54:144-7.	2
10. Barbeau A, Roy M, Cloutier T. Smoking, cancer and parkinson´s disease. Ann Neurol 1986;20(1):105-6.	1
11. Behrens MI, Lendon C, Roe CM. A common biological mechanism in cancer and Alzheimer's disease? Curr Alzheimer Res. 2009;6(3):196-204.	1
12. Bennett DA, Leurgans S. Is there a link between cancer and Alzheimer disease? Neurology. 2010;74(2):100-1.	1
13. Bergamaschi R, Montomoli C. Melanoma in multiple sclerosis treated with natalizumab: causal association or coincidence? Mult Scler. 2009;15:1532-3.	2
14. Bernard SM, Cartwright RA, Darwin CM, Richards ID, Roberts B, O'Brien C, Bird CC. A possible epidemiological association between multiple sclerosis and lymphoma/leukaemia. Br J Haematol. 1987;65(1):122-3.	2
15. Bertoni JM, Arlette JP, Fernandez HH, et al. Increased melanoma risk in Parkinson disease: a prospective clinicopathological study. Arch Neurol. 2010;67:347-52.	3
16. Bjørge T, Cnattingius S, Engeland A, Tretli S, Lie RT, Lukanova A. Fetal Down syndrome and the risk of maternal breast cancer. Epidemiology. 2009;20:584-9	2
17. Boice J, Linet M. Chernobyl, childhood cancer, and chromosome 21. BMJ. 1994;309:139-40.	4
18. Braun DL, Green MD, Rausen AR, et al. Down's syndrome and testicular cancer: a possible association. Am J Pediatr Hematol Oncol. 1985;7:208-11.	2
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2008;117:323-36.	
23. Catts VS, Catts SV. Apoptosis and schizophrenia: is the tumour suppressor gene, p53, a candidate susceptibility gene? Schizophr Res. 2000;41:405-15.	**4**
24. Chiò A, Cucatto A, Calvo A, Terreni AA, Magnani C, Schiffer D. Amyotrophic lateral sclerosis among the migrant population to Piemonte, northwestern Italy. J Neurol. 1999;246:175-80.	**4**
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26. Confavreux C, Saddier P, Grimaud J, Moreau T, Adeleine P, Aimard G. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology. 1996;46:1607-12.	**2**
27. Constantinescu R, Romer M, Kieburtz K; DATATOP Investigators of the Parkinson Study Group. Malignant melanoma in early Parkinson's disease: the DATATOP trial. Mov Disord. 2007;22:720-2	**2**
28. Creutzig U, Ritter J, Vormoor J, Ludwig WD and cols. Myelodysplasia and acute myelogenous leukemia in Down´s síndrome. A report of 40 children of the AML-BFM Study Group. Leukemia 1996; 10:1677-86.	**2**
29. D'Amelio M, Ragonese P, Morgante L, et al. Tumor diagnosis preceding Parkinson's disease: a case-control study. Mov Disord. 2004;19:807-11.	**2**
30. Dalton SO, Laursen TM, Mellemkjaer L, Johansen C, Mortensen PB. Risk for cancer in parents of patients with schizophrenia. Am J Psychiatry. 2004; 161:903-8.	**6**
31. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T. A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. Cancer Epidemiol Biomarkers Prev. 2007;16:1260-5.	**2**
32. Elbaz A, Peterson BJ, Yang P. Nonfatal cancer preceding Parkinson´s Disease: A Case- Control Study. Epidemiology. 2002;13:157-64	**2**
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34. Fiala KH, Whetteckey J, Manyam BV. Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? Parkinsonism Relat Disord. 2003;9:321-7.	**1**
35. Fong CT, Brodeur GM. Down's syndrome and leukemia: epidemiology, genetics, cytogenetics and mechanisms of leukemogenesis. Cancer Genet Cytogenet. 1987;28(1):55-76.	**1**
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39. Foster HD, Hoffer A. Schizophrenia and cancer: the adrenochrome balanced morphism. Med Hypotheses. 2004;62(3):415-9.	**4**
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Cancer Causes Control 2003;14:847-57.	
42. Gaikwad A, Rye CL, Devidas M, Heerema NA, Carroll AJ, Izraeli S, Plon SE, Basso G, Pession A, Rabin KR. Prevalence and clinical correlates of JAK2 mutations in Down syndrome acute lymphoblastic leukaemia. Br J Haematol. 2009;144(6):930-2.	**4**
43. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. Neurology. 2009;73:1286-91.	**6**
44. Garber K. Parkinson's disease and cancer: the unexplored connection. J Natl Cancer Inst. 2010;102(6):371-4.	**1**
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46. Grant WB. Smoking, Parkinson's disease, and melanoma. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2517-8.	**1**
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50. Hasle H. Pattern of malignant disorders in individuals with Down's syndrome. Lancet Oncol. 2001;2(7):429-36.	**1**
51. Hermon C, Alberman E, Beral V, Swerdlow AJ. Mortality and cancer incidence in persons with Down's syndrome, their parents and siblings. Ann Hum Genet. 2001;65:167-76.	**3**
52. Herrero Hernández E. Pigmentation genes link Parkinson's disease to melanoma, opening a window on both etiologies. Med Hypotheses. 2009;72:280-4.	**4**
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Reasons for exclusion: 1. Review/commentary; 2. Study design (e.g. cross-sectional, case-control, randomised control trial); 3. Incidence data not reported and/or not available with sufficient detail; 4. Not a relevant topic; 5. Duplicate study; 6. Study population (e.g. patient relatives, Veterans, Institutionalized patients, etc.)

Table S5: Selected characteristics of the epidemiological studies included in the systematic review.

Author, year of publication	Cancer co-morbidity of interest	Study design, country	Follow-up period (mean, years)	Endpoint measure	No. of subjects with CNS	No. of subjects with cancer	Age (mean or range) Female (%)	Data source CNS and cancer definitions	Confounders/ effect modifiers controlled for
Roe et al, 2005	Alzheimer's disease	Prospective cohort, USA (1 community: Washington University Alzheimer's Disease Research Center)	1992-(-) (dementias: 3.2)	HR	AD: 395	Incident cases: 50	75 64	Hospital-based Clinical Dementia Rating, clinical interview/examination	Yes (age, sex, education)
Roe et al, 2010	Alzheimer's disease	Prospective cohort, USA (4 communities)	1989-1999 (dementias: 5.4; cancers: 8.3)	HR	AD only: 244	Incident cases: 376	78 60	Population-based MMSE, clinical interview/examination; ICD-9	Yes (age, sex, education, income, smoking, obesity, etc.)
Driver et al, 2012	Alzheimer's disease	Prospective cohort and nested case-control, USA (1 community: Framingham Heart Study)	1986-1990 (10)	HR	Possible AD: 256; Probable AD: 221	Incident cases: 247	68-96 62	Population-based MMSE, clinical interview/examination; ICD-O	Yes (age, sex, smoking, body mass index)
Jansson and Jankovic, 1985	Parkinson's disease	Prospective cohort, USA (1 clinic center)	1978-1984 (8.6)	RR	PD: 406	Incident cases: 6	58 40	Hospital-based, clinical records	Yes (age, sex, smoking)
Møller et al, 1999	Parkinson's disease	Retrospective cohort, Denmark (nationwide)	1977-1989 (4.6)	RR	PD: 7,046	Incident cases: 554	- 51	Hospital-based, clinical records	Yes (age, calendar period)

Minami et al, 2000	Parkinson's disease	Retrospective cohort, Japan (1 community, Miyagi)	1984–1992 (8)	SIR	PD: 228	Incident cases: 15	66 58	Population-based NA	Yes (age)
Olsen at al, 2005	Parkinson's disease	Retrospective cohort, Denmark (nationwide)	1977–1998 (5)	SIR	PD: 14,088	Incident cases: 1,282	73 49	Population-based ICD-8, ICD-10	Yes (age, sex)
Elbaz et al, 2005	Parkinson's disease	Retrospective cohort and nested case-control, USA (1 community)	1976–1995 (8)	RR	PD: 196	Incident cases: 71	72 48	Population-based H-ICDA	Yes (age, sex, smoking)
Lo et al, 2010	Parkinson's disease	Retrospective cohort and nested case-control, USA (Kaiser Permanente Northern California)	1994–1995/ 2000–2003	RR, OR adjusted	PD: 692	Incident cases: 56	66 37	Population-based NA	Yes (age, sex, smoking, alcohol, etc.)
Becker et al, 2010	Parkinson's disease	Retrospective cohort and nested case-control, UK (GPRD database)	1994–2005 (–)	IRR, OR adjusted	PD: 2,993	Incident cases: 466	NA	Population-based OXMIS coding	Yes (age, sex, general practice, diagnosis date, smoking, etc.)
Fois et al, 2010	Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis	Retrospective cohort, UK (1 community: Oxford)	1963–1999 (PD: 3.2; MS: 6.9; ALS: 3.1)	RR	PD: 4,355 MS: 4,295 ALS: 1,429	Incident cases: 219 (PD); 222 (MS); 62 (ALS)	– 51 (PD); 65 (MS); 41 (ALS)	Hospital-based NA (in full-text)	Yes (age, sex, time period in single calendar years and district of residence)

Sun et al, 2011	Parkinson's disease	Retrospective cohort, Taiwan (nationwide)	1996–2008 (–)	HR	PD: 4,957	Incident cases: –	63 48	Population-based ICD-9	Yes (age, sex, urbanization, occupation, co-morbidities)
Rugbjerg et al, 2012	Parkinson's disease	Retrospective cohort, Denmark (nationwide)	1977–2006 (5.7)	SIR	PD: 20,343	Incident cases: 2,218	73	Population-based ICD-8, ICD-9, ICD-10	Yes (age, sex, calendar period)
Bertoni et al, 2010	Parkinson's disease (only melanoma)	Prospective cohort, USA and Canada (31 centers)	2003 (–)	RR	PD: 2,106	Prevalent cases: 68 Incident cases: 24	69 32	Population-based NA	Yes (age, sex)
Midgard et al, 1996	Multiple sclerosis	Retrospective cohort, Norway (3 communities)	1953–1992 (18.4)	SIR	MS: 1,271	Incident cases: 73	30 58	Population-based ICD-7	Yes (age, sex, county, main industries in the place of residency)
Sumelahti et al, 2004	Multiple sclerosis	Retrospective cohort, Finland (3 healthcare districts)	1964–1993 (35)	SIR	MS: 1,597	Incident cases: 85	36 66	Hospital-based Poser criteria, ICD-10	Yes (age, sex, period)
Achiron et al, 2005	Multiple sclerosis	Prospective cohort, Israel (1 center)	1960–2003 (–)	SIR	MS: 1,338	Incident cases: 48	– 67	Hospital-based Poser criteria, ICD-9	Yes (age, sex, immodulatory therapy)
Nielsen et al, 2006	Multiple sclerosis	Retrospective cohort, Denmark (nationwide)	1949–2003 (13)	SIR	MS: 11,817	Incident cases: 1,037	– 61	Population-based Poser criteria, ICD-7, ICD-O	Yes (age, sex, parity, age at delivery of first child, time since MS diagnosis)
Lebrun et al, 2006	Multiple sclerosis	Prospective cohort, France (9 centers)	1995–2006 (11)	SIR	MS: 7,418	Incident cases: 136	38 70	Hospital-based Poser criteria, McDonald criteria, ICD-O3	Yes (age, treatments)

Bahmanyar et al, 2009	Multiple sclerosis	Retrospective cohort, Sweden (nationwide)	1969–2005 (35)	HR	MS: 20,276	Incident cases: 2,139	– 65	Population-based ICD-7	Yes (age, sex, region of residence, and socioeconomic index)
Kingwell et al, 2012	Multiple sclerosis	Retrospective cohort, Canada (4 centers in the region of British Columbia)	1980–2004 (–)	SIR	MS: 6,917	Incident cases: 502	31 72	Population-based Poser criteria, –	Yes (age, sex, calendar year)
Goldacre et al, 2004	Multiple sclerosis (only skin cancers including melanoma)	Retrospective cohort, UK (1 community: Oxford)	1963–1999 (11)	RR	MS: 5,004	Incident cases: 10 (skin cancers); 4 (melanoma)	46 –	Hospital-based ICD-7, ICD-8, ICD-9, ICD-10	Yes (age, sex, district of residence, and calendar year of first admission)
Zisfein and Caroscio, 1988	Amyotrophic lateral sclerosis	Retrospective cohort , USA (1 center, Mont Sinai Hospital, New York)	– (2.5)	–	ALS: 347	Incident cases: 5	57 –	Hospital-based –	No
Dupont et al, 1986	Schizophrenia	Retrospective cohort, Denmark (nationwide)	1957–1980	SIR	Schizophrenia: 6,152	Incident cases: –	– –	Population-based	No

Gulbinat et al, 1992	Schizophrenia	Retrospective cohort , USA (Hawaii), Japan (Nagasaki) and Denmark (Aarhus),	1972–1980 (USA, Hawaii) (–) 1960–1978 (Nagasaki, Japan) (–) 1957–1980 (Denmark)	RR	Schizophrenia: 6,977 (Hawaii, USA); 3,107 (Nagasaki, Japan), 6,152 (Denmark)	Incident cases: 59, 44, 792	– 40, 45	Population-based DSM-III-R, ICD-8	Yes (age, sex)
Lawrence et al, 2000	Schizophrenia	Retrospective cohort, Australia (1 community)	1982–1995 (–)	RR	Schizophrenia: –	Incident cases: 496	NA	Population-based ICD-8, ICD-9	Yes (age, sex)
Lichtermann et al, 2001	Schizophrenia	Retrospective cohort, Finland (nationwide)	1971–1996 (16)	SIR	Schizophrenia: 26,996	Incident cases: 724	– 42	Population-based DSM-III-R, ICD-8, ICD-9	Yes (sex)
Barak et al, 2005	Schizophrenia	Retrospective cohort, Israel (1 medical center)	1993–2003	SIR	Schizophrenia: 3,226	Incident cases: 120	49 39	Hospital-based DSM-IV, ICD-C	Yes (age, sex)
Grinshpoon et al, 2005	Schizophrenia	Retrospective cohort, Israel (nationwide)	1962–2001 (–)	SIR	Schizophrenia: 33,372	Incident cases: 1,504	– –	Population-based ICD-9, ICD-03	Yes (sex, place of birth)
Dalton et al, 2005	Schizophrenia	Retrospective cohort, Denmark (nationwide)	1969–1993 (–)	SIR	Schizophrenia (hospitalised patients): 22,766	Incident cases: 1,394	38 43	Population-based ICD-7, ICD-8	Yes (age, sex, calendar year)
Goldacre et al, 2005	Schizophrenia	Retrospective cohort, UK (1 community: Oxford)	1963–1999 (13)	RR	Schizophrenia (hospitalised patients): 9,649	Incident cases: 486	40 –	Hospital-based ICD-9	Yes (age, sex, calendar year)

Chou et al, 2011	Schizophrenia	Retrospective nested case-control, Taiwan (nationwide)	1999–2008 (9)	HR	Schizophrenia: 59,257	Incident cases: 1,145	40 44	Population-based ICD-9-CM	Yes (age, sex), income, CCIS)
Lin et al, 2011	Schizophrenia	Retrospective cohort, Taiwan (nationwide)	1997–2009 (7)	SIR	Schizophrenia: 71,317	Incident cases: 1,129	37 47	Population-based ICD-9	Yes (age, sex)
Ji et al, 2012	Schizophrenia	Retrospective cohort, Sweden (nationwide)	1965–2008	SIR	Schizophrenia: 59,233	Incident cases: 6,137	38, 47 46	Population-based ICD-7, ICD-8, ICD-9, ICD-10	Yes (age, sex, calendar year, socioeconomic status, residential area and comorbidity)
McGinty et al, 2012	Schizophrenia	Retrospective cohort, USA (1 community, Maryland Medicaid beneficiaries)	1994–2004 (–)	SIR	Schizophrenia: 2,315	Incident cases: 155	41 48	Population-based, administrative claims ICD-9	Yes (race, sex)
Kisely et al, 2013	Schizophrenia	Retrospective cohort, Australia (Wester Australia region)	1988–2007 (–)	RR	Schizophrenia: –	Incident cases: 275	– –	Population-based ICD-9, ICD-10, ICD-O	Yes (age, sex)
Crump et al, 2013	Schizophrenia	Prospective cohort, Sweden (nationwide)	2003–2009 (–)	HR	Schizophrenia: 8,277	Incident cases: 487	– 42	Population-based ICD-10	Yes (age, sociodemographic factors, substance use disorders)
Lin et al, 2013	Schizophrenia	Retrospective cohort, Taiwan (nationwide)	1995–2007 (7.6)	SIR	Schizophrenia: 102,202	Incident cases: 1,738	– 45	Population-based ICD-9	Yes (age, sex)

Osborn et al, 2013	Schizophrenia	Retrospective cohort, UK (THIN database)	1990–2008 (–)	IRR	Schizophrenia: 6,845	Incident cases: –	43 49	Population-based –	Yes (age, sex, deprivation, smoking, BMI)
Dalton et al, 2003	Schizophrenia (only breast cancer)	Retrospective cohort, Denmark (nationwide)	1970–1997 (–)	RR	Schizophrenia: 7,541	Incident cases: 74	– 100	Population-based ICD-7, ICD-8, ICD-10	Yes (age, calendar period, age at birth of first child, number of children)
Hippisley-Cox et al, 2007	Schizophrenia (only breast, prostate, lung and colorectal cancers)	Retrospective nested case-control, UK (QRESEARCH database)	1995–2005	OR	Schizophrenia: 710	Incident cases: 139	67 60	Population-based –	Yes (age, sex, smoking, BMI, etc.)
Barak et al, 2008	Schizophrenia (only breast cancer)	Retrospective cohort, Israel (1 center)	1960–2005 (–)	SIR	Schizophrenia: 2,011	Incident cases (breast cancer): 51	– 100	Hospital-based DSM-IV, ICD-9	No
Hasle et al, 2000	Down's syndrome	Retrospective cohort, Denmark	1968–1995 (–)	SIR	Down's syndrome: 2,814	Incident cases: 60	– 45	Population-based ICD-7	Yes (age, sex, period)
Boker et al, 2001	Down's syndrome	Retrospective cohort, Israel (nationwide)	1948–1995 (–)	SIR	Down's syndrome: 2,635	Incident cases: 24 (both registry and institution groups combined)	– –	Population-based ICD-9	Yes (age, sex, place of birth, year-specific national cancer incidence rates)
Goldacre et al, 2004	Down's syndrome	Retrospective cohort, UK (1 community: Oxford)	1963–1999 (10)	RR	Down's syndrome: 1,453	Incident cases: 26	13 –	Hospital-based –	Yes (age, sex, calendar year)

Patja et al, 2006	Down's syndrome	Retrospective cohort, Finland (nationwide)	1978–2002 (18)	SIR	Down's syndrome: 3,581	Incident cases: 22	– 47	Population-based ICD-8	Yes (age, sex, calendar year)
Sullivan et al, 2007	Down's syndrome	Retrospective cohort, Australia (1 region)	1953–2002 (–)	SIR	Down's syndrome: 1,298	Incident cases: 21	20–25 –	Population-based ICD-10	Yes (age, sex)
Bjørge et al, 2008	Down's syndrome	Retrospective cohort, Norway and Sweden (nationwide)	1967–2004 (Norway) 1973–2004 (Sweden)	SIR	Down's syndrome: 2,108 (Norway); 3,201 (Sweden)	Incident cases: 51 (Norway), 71 (Sweden)	– –	Population-based ICD-8, ICD-9, ICD-10	Yes (age, country region)
Sørensen et al, 1999	Huntington disease	Retrospective nested case-control, Denmark (nationwide)	1943–1993 (16)	SIR	Huntingtion disease: 694	Incident cases: 55	– –	Population-based ICD-7	Yes (age, sex, calendar year)
Ji et al, 2012	Huntington disease	Retrospective cohort, Sweden (nationwide)	1969–2008 (–)	SIR	Huntington disease: 1,510	Incident cases: 91	54 51	Population-based ICD-7, ICD-8, ICD-9, ICD-10	Yes (age, sex, socioeconomic status,calendar year, region of residence)
Laurtisen et al, 2002	Autism	Retrospective nested case-control, Denmark (nationwide)	1978–1993 (–)	OR	Autism: 244	Incident cases: 1 (brain cancer)	– –	Population-based ICD-8	Yes (age, sex)

Table S6 : Methodological Quality Assessment of Observational Studies Based on the Newcastle-Ottawa (NOS) scale.

Author, year of publication	Cancer co-morbidity of interest	Selection		Comparability		Outcome		Total score
		Representativeness of CNS cases/cohort	Identification of Cancer	Controlled for age	Controlled for co-morbidities	Follow-up length (e.g. > 5y)	Adequacy follow-up	
Roe et al, 2005	Alzheimer's disease			*				**1**
Roe et al, 2010	Alzheimer's disease			*		*	*	**3**
Driver et al, 2012	Alzheimer's disease	*	*	*		*	*	**5**
Jansson and Jankovic, 1985	Parkinson's disease			*	*			**2**
Møller et al, 1999	Parkinson's disease	*		*			*	**2**
Minami et al, 2000	Parkinson's disease	*	*	*		*	*	**4**
Olsen at al, 2005	Parkinson's disease	*	*	*			*	**4**
Elbaz et al, 2005	Parkinson's disease	*	*	*		*	*	**5**
Lo et al, 2010	Parkinson's disease		*	*		*		**3**
Becker et al, 2010	Parkinson's disease			*	*			**2**
Fois et al, 2010	Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis		*	*				**2**
Sun et al, 2011	Parkinson's disease	*		*	*	*		**4**
Rugbjerg et al, 2012	Parkinson's disease	*	*	*		*		**4**
Bertoni et al, 2010	Parkinson's disease (only melanoma)	*	*				*	**3**
Midgard et al, 1996	Multiple sclerosis	*	*	*		*	*	**5**
Sumelahti et al, 2004	Multiple sclerosis	*	*	*		*	*	**5**
Achiron et al, 2005	Multiple sclerosis	*	*	*			*	**4**
Nielsen et al, 2006	Multiple sclerosis	*	*	*		*	*	**5**
Lebrun et al, 2006	Multiple sclerosis	*	*	*		*	*	**5**
Bahmanyar et al, 2009	Multiple sclerosis	*	*	*		*	*	**5**
Kingwell et al, 2012	Multiple sclerosis	*	*	*		*	*	**5**
Goldacre et al, 2004	Multiple sclerosis (only skin cancers including melanoma)	*		*		*		**3**
Zisfein and Caroscio, 1988	Amyotrophic lateral sclerosis	*						**1**

Dupont et al, 1986	Schizophrenia	*				*		**2**
Gulbinat et al, 1992	Schizophrenia	*	*	*		*	*	**5**
Lawrence et al, 2000	Schizophrenia	*	*	*			*	**4**
Lichtermann et al, 2001	Schizophrenia		*	*		*	*	**4**
Barak et al, 2005	Schizophrenia	*	*	*				**3**
Grinshpoon et al, 2005	Schizophrenia	*	*	*		*	*	**5**
Dalton et al, 2005	Schizophrenia	*	*	*		*	*	**5**
Goldacre et al, 2005	Schizophrenia			*		*		**2**
Chou et al, 2011	Schizophrenia	*	*	*		*	*	**5**
Lin et al, 2011	Schizophrenia		*	*		*		**3**
Ji et al, 2012	Schizophrenia		*	*		*	*	**4**
McGinty et al, 2012	Schizophrenia		*	*				**2**
Kisely et al, 2013	Schizophrenia	*	*	*				**3**
Crump et al, 2013	Schizophrenia	*	*	*	*			**4**
Lin et al, 2013	Schizophrenia	*	*	*		*		**4**
Osborn et al, 2013	Schizophrenia			*	*			**2**
Dalton et al, 2013	Schizophrenia (only breast cancer)	*	*	*				**3**
Hippisley-Cox et al, 2007	Schizophrenia (only breast, prostate, lung and colorectal cancers)			*	*			**2**
Barak et al, 2008	Schizophrenia (only breast cancer)	*	*	*			*	**4**
Hasle et al, 2000	Down’s syndrome	*	*	*		*	*	**5**
Boker et al, 2001	Down’s syndrome	*	*	*		*	*	**5**
Goldacre et al, 2004	Down’s syndrome			*		*		**2**
Patja et al, 2006	Down’s syndrome		*	*		*	*	**5**
Sullivan et al, 2007	Down’s syndrome		*	*		*	*	**4**
Bjørge et al, 2008	Down’s syndrome	*	*	*		*	*	**5**
Sørensen et al, 1999	Huntington disease	*	*	*		*	*	**5**
Ji et al, 2012	Huntington disease	*	*	*		*	*	**5**
Laurtisen et al, 2002	Autism			*				**1**

Table S7: Cancer comorbidity in patients with Parkinson's disease: subgroup meta-analysis and heterogeneity analysis

Characteristics	Observations (N)	Random effects, ES (95% CI)	I^2	P value
Base case	**10**	**0.83 (0.75-0.91)**	**90.5%**	**<0.01**
Sex				
Men	7	0.81 (0.71-0.93)	72.4%	<0.01
Women	7	0.94 (0.89-0.99)	3.2%	0.40
Origin of sample				
Population-based	7	0.88 (0.82-0.94)	57.4%	0.03
Hospital-based	3	0.65 (0.47-0.92)	90.5%	<0.01
Geographic location				
North America	3	0.85 (0.40-1.81)	89.2%	<0.01
Europe	4	0.81 (0.73-0.89)	84.0%	<0.01
Middle East	-	-	-	-
North East Asia	2	0.88 (0.78-0.99)	80.0%	0.84
Other	-	-	-	-
Coverage				
Nationwide	5	0.86 (0.84-0.89)	0.0%	0.71
Subregional/Local	5	0.79 (0.51-1.22)	86.5%	<0.01
Sample size				
< 1000 subjects	4	0.85 (0.48-1.50)	84.1%	<0.01
> 1000 subjects	6	0.82 (0.75-0.89)	80.3%	<0.01
Latitude				
> 50 °	5	0.81 (0.73-0.89)	84.0%	<0.01
< 50 °	5	0.89 (0.61-1.23)	79.1%	<0.01
Study design				
Cohort	7	0.81 (0.74-0.89)	80.8%	<0.01
Nested case-control	3	1.00 (0.62-1.63)	85.2%	<0.01
Follow-up				
Prospective	1	0.43 (0.26-0.71)	-	-
Retrospective	9	0.84 (0.77-0.92)	78.9%	<0.01
Effect size				
SIR				
Other (e.g. RR, HR)				
Adjustment for confounders (other than age and sex)				
Yes	7	0.81 (0.69-0.95)	86.1%	<0.01
No	3	0.88 (0.83-0.93)	0.0%	0.98
Publication year				
1980-1989	1	0.43 (0.23-0.63)	-	-
1990-1999	1	0.88 (0.80-0.98)	-	-
2000-2009	3	1.06 (0.69-1.63)	82.1%	<0.01
2010-to date	5	0.78 (0.68-0.90)	82.7%	<0.01

ES = effect size. SIR = Standardized Incidence Ratio. RR = Relative Risk. HR = Hazard Ratio.

Table S8: Cancer comorbidity in patients with Multiple Sclerosis: subgroup meta-analysis and heterogeneity analysis

Characteristics	Observations (N)	Random effects, ES (95% CI)	I^2	P value
Base case	**8**	**0.91 (0.87-0.95)**	**30.3%**	**0.19**
Sex				
Men	7	0.79 (0.66-0.93)	78.3%	<0.01
Women	7	0.87 (0.77-0.99)	83.5%	<0.01
Origin of sample				
Population-based	4	0.91 (0.88-0.94)	0.0%	0.42
Hospital-based	4	0.88 (0.71-1.07)	57.6%	0.07
Geographic location				
North America	1	0.86 (0.78-0.94)	-	-
Europe	6	0.92 (0.88-0.97)	30.4%	<0.01
Middle East	1	0.77 (0.54-1.09)	-	-
North East Asia	-	-	-	-
Other	-	-	-	-
Coverage				
Nationwide	3	0.92 (0.89-0.95)	0.0%	0.58
Subregional/Local	5	0.89 (0.78-1.00)	52.0%	0.08
Sample size				
< 1000 subjects	-	-	-	-
> 1000 subjects	8	0.91 (0.87-0.95)	30.3%	0.19
Latitude				
> 50 °	6	0.92 (0.89-0.95)	0.0%	0.54
< 50 °	2	0.61 (0.33-1.10)	59.9%	0.11
Study design				
Cohort	8	0.91 (0.87-0.95)	30.3%	0.19
Nested case-control	-	-	-	-
Follow-up				
Prospective	2	0.61 (0.33-1.10)	59.9%	0.11
Retrospective	6	0.92 (0.89-0.95)	0.0%	0.54
Effect size				
SIR	5	0.89 (0.80-0.99)	56.7%	0.05
Other (e.g. RR, HR)	3	0.91 (0.88-0.95)	0.0%	0.67
Adjustment for confounders (other than age and sex)				
Yes	7	0.91 (0.89-0.94)	0.0%	0.54
No	1	0.41 (0.20-0.83)	-	-
Publication year				
1980-1989	-	-	-	-
1990-1999	1	0.86 (0.68-1.09)	-	-
2000-2009	5	0.92 (0.86-0.98)	46.9%	0.11
2010-to date	2	0.90 (0.81-1.00)	41.3%	0.19

ES = effect size. SIR = Standardized Incidence Ratio. RR = Relative Risk. HR = Hazard Ratio.

Table S9: Cancer comorbidity in patients with Schizophrenia: subgroup meta-analysis and heterogeneity analysis

Characteristics	Observations (N)	Random effects, ES (95% CI)	I²	P value
Base case	**18**	**0.98 (0.90-1.07)**	**96.3%**	**<0.01**
Sex				
Men	15	0.87 (0.77-0.99)	95.9%	<0.01
Women	15	1.11 (1.01-1.22)	94.0%	<0.01
Origin of sample				
Population-based	16	1.01 (0.92-1.10)	96.5%	<0.01
Hospital-based	2	0.76 (0.45-1.29)	96.2%	<0.01
Geographic location				
North America	2	1.46 (0.45-4.75)	94.7%	<0.01
Europe	8	0.95 (0.88-1.03)	92.2%	<0.01
Middle East	2	0.72 (0.48-1.10)	95.0%	<0.01
North East Asia	4	1.00 (0.77-1.30)	98.0%	<0.01
Other	2	0.97 (0.88-1.07)	21.3%	0.26
Coverage				
Nationwide	10	0.94 (0.86-1.02)	96.0%	<0.01
Subregional/Local	8	1.05 (0.80-1.37)	97.0%	<0.01
Sample size				
< 1000 subjects	-	-	-	-
> 1000 subjects	18	0.98 (0.90-1.07)	96.3%	<0.01
Latitude				
> 50 °	8	0.95 (0.88-1.03)	92.2%	<0.01
< 50 °	10	1.01 (0.85-1.20)	97.5%	<0.01
Study design				
Cohort	17	1.01 (0.93-1.09)	95.2%	<0.01
Nested case-control	1	0.64 (0.60-0.69)	-	-
Follow-up				
Prospective	1	0.96 (0.88-1.05)	-	-
Retrospective	17	0.98 (0.90-1.07)	96.5%	<0.01
Effect size				
SIR	9	1.03 (0.92-1.15)	97.2%	<0.01
Other (e.g. RR, HR)	9	0.93 (0.80-1.07)	93.6%	<0.01
Adjustment for confounders (other than age and sex)				
Yes	6	0.91 (0.80-1.04)	96.5%	<0.01
No	12	1.02 (0.90-1.16)	96.6%	<0.01
Publication year				
1980-1989	1	0.81 (0.75-0.87)	-	-
1990-1999	3	1.01 (0.60-1.68)	92.9%	<0.01
2000-2009	6	0.94 (0.83-1.05)	93.0%	<0.01
2010-to date	8	1.04 (0.90-1.21)	96.3%	<0.01

ES = effect size. SIR = Standardized Incidence Ratio. RR = Relative Risk. HR = Hazard Ratio.

Table S10: Cancer comorbidity in patients with Down's syndrome: subgroup meta-analysis and heterogeneity analysis

Characteristics	Observations (N)	Random effects, ES (95% CI)	I^2	P value
Base case	**6**	**1.46 (1.08-1.96)**	**87.9%**	**<0.01**
Sex				
Men	3	1.18 (0.75-1.86)	68.6%	0.04
Women	3	0.92 (0.71-1.19)	0.0%	0.57
Origin of sample				
Population-based	5	1.30 (0.96-1.78)	88.0%	<0.01
Hospital-based	1	2.70 (1.83-3.97)	-	-
Geographic location				
North America	-	-	-	-
Europe	4	1.46 (1.00-2.14)	92.1%	<0.01
Middle East	1	1.89 (1.23-2.91)	-	-
North East Asia	-	-	-	-
Other	1		-	-
Coverage				
Nationwide	4	1.35 (0.95-1.91)	90.4%	<0.01
Subregional/Local	2	1.74 (0.72-4.19)	88.6%	<0.01
Sample size				
< 1000 subjects	-	-	-	-
> 1000 subjects	6	1.46 (1.08-1.96)	87.9%	<0.01
Latitude				
> 50 °	4	1.46 (1.00-2.14)	92.1%	<0.01
< 50 °	2	1.45 (0.85-2.46)	65.4%	0.09
Study design				
Cohort	6	1.46 (1.08-1.96)	87.9%	<0.01
Nested case-control	-	-	-	-
Follow-up				
Prospective	-	-	-	-
Retrospective	6	1.46 (1.08-1.96)	87.9%	<0.01
Effect size				
SIR	5	1.30 (0.96-1.78)	88.0%	<0.01
Other (e.g. RR, HR)	1	2.70 (1.83-3.97)	-	-
Adjustment for confounders (other than age and sex)				
Yes	4	1.50 (0.94-2.38)	88.9%	<0.01
No	2	1.45 (0.96-2.19)	70.9%	0.06
Publication year				
1980-1989	-	-	-	-
1990-1999	-	-	-	-
2000-2009	6	1.46 (1.08-1.96)	87.9%	<0.01
2010-to date	-	-	-	-

ES = effect size. SIR = Standardized Incidence Ratio. RR = Relative Risk. HR = Hazard Ratio.

Table S11: Cancer comorbidity in patients with CNS disorders: subgroup meta-analysis and heterogeneity analysis

Characteristics	Observations (N)	Random effects, ES (95% CI)	I^2	P value
Base case	**49**	**0.92 (0.87-0.98)**	**94.5%**	**<0.01**
Sex				
Men	32	0.85 (0.78-0.93)	92.8%	<0.01
Women	32	1.01 (0.94-1.08)	91.8%	<0.01
Origin of sample				
Population-based	36	0.95 (0.89-1.02)	95.4%	<0.01
Hospital-based	13	0.82 (0.69-0.98)	88.9%	<0.01
Geographic location				
North America	10	0.74 (0.46-1.19)	95.8%	<0.01
Europe	26	0.92 (0.86-0.99)	94.4%	<0.01
Middle East	4	0.89 (0.64-1.24)	90.9%	<0.01
North East Asia	6	0.96 (0.78-1.18)	96.7%	<0.01
Other	3	0.98 (0.90-1.07)	0.0%	0.46
Coverage				
Nationwide	25	0.92 (0.86-0.99)	93.4%	<0.01
Subregional/Local	24	0.89 (0.76-1.03)	95.5%	<0.01
Sample size				
< 1000 subjects	9	0.61 (0.42-0.90)	82.7%	<0.01
> 1000 subjects	40	0.95 (0.90-1.02)	95.2%	<0.01
Latitude				
> 50 °	26	0.92 (0.86-0.99)	94.8%	<0.01
< 50 °	23	0.90 (0.78-1.02)	94.4%	<0.01
Study design				
Cohort	43	0.95 (0.90-1.01)	94.1%	<0.01
Nested case-control	6	0.71 (0.54-0.92)	87.7%	<0.01
Follow-up				
Prospective	7	0.49 (0.32-0.76)	87.4%	<0.01
Retrospective	42	0.96 (0.90-1.02)	95.0%	<0.01
Effect size				
SIR	24	0.96 (0.89-1.05)	96.0%	<0.01
Other (e.g. RR, HR)	25	0.88 (0.80-0.96)	90.1%	<0.01
Adjustment for confounders (other than age and sex)				
Yes	30	0.87 (0.81-0.93)	91.8%	<0.01
No	19	1.01 (0.90-0.98)	96.5%	<0.01
Publication year				
1980-1989	3	0.68 (0.43-1.06)	66.8%	0.05
1990-1999	6	0.88 (0.73-1.06)	86.4%	<0.01
2000-2009	21	1.02 (0.92-1.12)	93.7%	<0.01
2010-to date	19	0.87 (0.79-0.96)	96.1%	<0.01

ES = effect size. SIR = Standardized Incidence Ratio. RR = Relative Risk. HR = Hazard Ratio.

Figure S1: Subgroup meta-analysis. Cancer comorbidity in patients with neurodegenerative disorders and neurodevelopmental disorders.

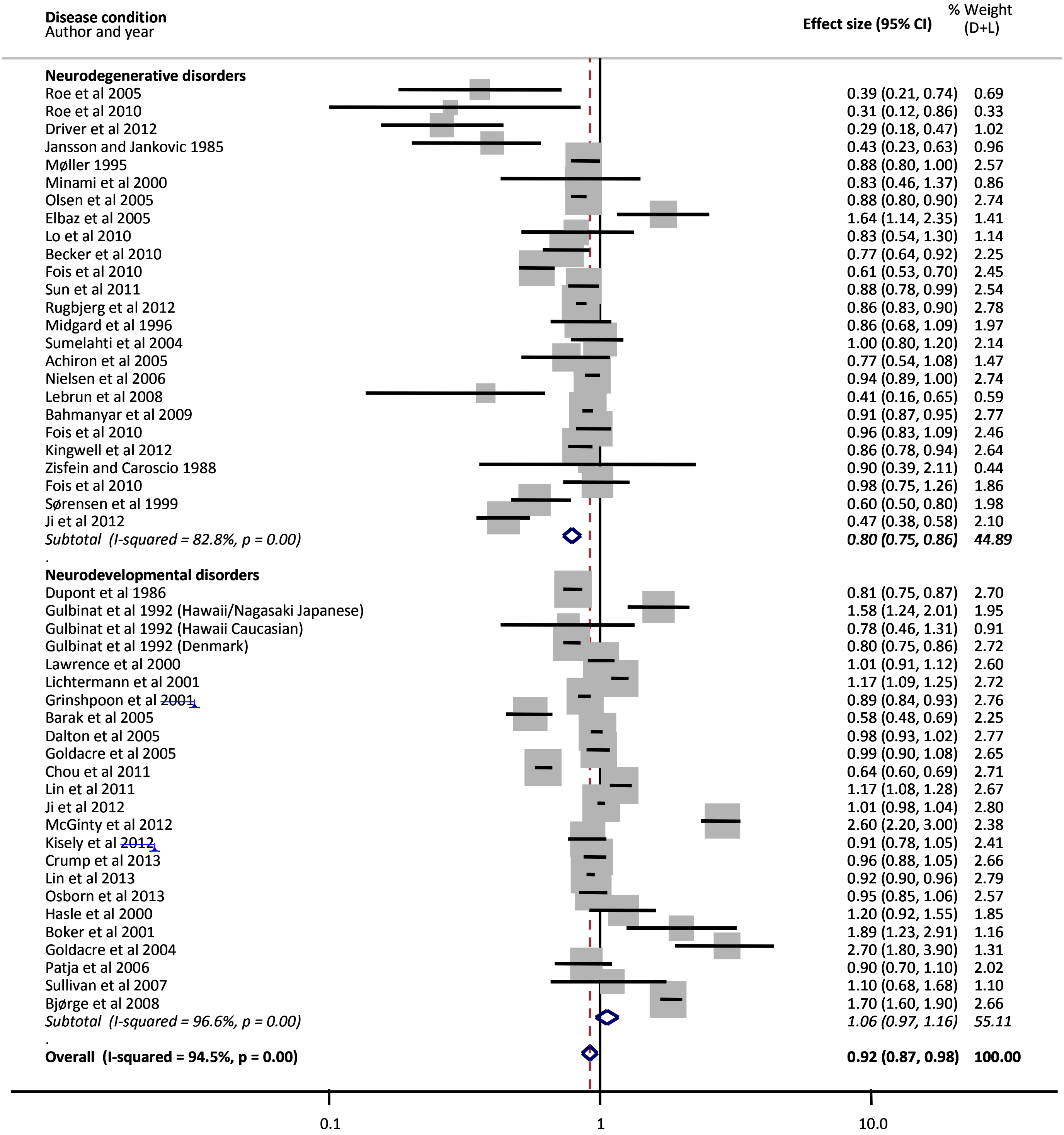


Figure S2: Cancer comorbidity in patients with CNS disorders. Sensitivity analysis.

Disease condition Author and year	Effect size (95% CI)	% Weight (D+L)
Alzheimer's disease		
Roe et al 2005	0.39 (0.21, 0.74)	0.61
Roe et al 2010	0.31 (0.12, 0.86)	0.29
Driver et al 2012	0.29 (0.18, 0.47)	0.94
Subtotal (I-squared = 0.0%, p = 0.76)	*0.32 (0.22, 0.46)*	*1.84*
.		
Parkinson's disease		
Jansson and Jankovic 1985	0.43 (0.23, 0.63)	0.88
Møller 1995	0.88 (0.80, 1.00)	2.78
Minami et al 2000	0.83 (0.46, 1.37)	0.78
Olsen et al 2005	0.88 (0.80, 0.90)	3.02
Lo et al 2010	0.83 (0.54, 1.30)	1.06
Becker et al 2010	0.77 (0.64, 0.92)	2.35
Fois et al 2010	0.61 (0.53, 0.70)	2.62
Sun et al 2011	0.88 (0.78, 0.99)	2.74
Rugbjerg et al 2012	0.86 (0.83, 0.90)	3.08
Subtotal (I-squared = 75.3%, p = 0.00)	*0.81 (0.74, 0.88)*	*19.31*
.		
Multiple sclerosis		
Midgard et al 1996	0.86 (0.68, 1.09)	2.00
Sumelahti et al 2004	1.00 (0.80, 1.20)	2.21
Achiron et al 2005	0.77 (0.54, 1.08)	1.41
Nielsen et al 2006	0.94 (0.89, 1.00)	3.03
Bahmanyar et al 2009	0.91 (0.87, 0.95)	3.07
Fois et al 2010	0.96 (0.83, 1.09)	2.64
Kingwell et al 2012	0.86 (0.78, 0.94)	2.88
Subtotal (I-squared = 0.0%, p = 0.54)	*0.92 (0.89, 0.94)*	*17.24*
.		
Amyotrophic lateral sclerosis		
Zisfein and Caroscio 1988	0.90 (0.39, 2.11)	0.38
Fois et al 2010	0.98 (0.75, 1.26)	1.86
Subtotal (I-squared = 0.0%, p = 0.85)	*0.97 (0.76, 1.25)*	*2.24*
.		
Schizophrenia		
Dupont et al 1986	0.81 (0.75, 0.87)	2.97
Gulbinat et al 1992 (Hawaii/Nagasaki Japanese)	1.58 (1.24, 2.01)	1.97
Gulbinat et al 1992 (Hawaii Caucasian)	0.78 (0.46, 1.31)	0.83
Gulbinat et al 1992 (Denmark)	0.80 (0.75, 0.86)	2.99
Lawrence et al 2000	1.01 (0.91, 1.12)	2.82
Lichtermann et al 2001	1.17 (1.09, 1.25)	2.99
Grinshpoon et al 2001	0.89 (0.84, 0.93)	3.05
Barak et al 2005	0.58 (0.48, 0.69)	2.35
Dalton et al 2005	0.98 (0.93, 1.02)	3.06
Goldacre et al 2005	0.99 (0.90, 1.08)	2.89
Chou et al 2011	0.64 (0.60, 0.69)	2.98
Lin et al 2011	1.17 (1.08, 1.28)	2.92
Ji et al 2012	1.01 (0.98, 1.04)	3.10
Kisely et al 2012	0.91 (0.78, 1.05)	2.56
Crump et al 2013	0.96 (0.88, 1.05)	2.90
Lin et al 2013	0.92 (0.90, 0.96)	3.10
Osborn et al 2013	0.95 (0.85, 1.06)	2.79
Subtotal (I-squared = 94.6%, p = 0.00)	*0.93 (0.86, 1.00)*	*46.26*
.		
Down's syndrome		
Hasle et al 2000	1.20 (0.92, 1.55)	1.85
Boker et al 2001	1.89 (1.23, 2.91)	1.09
Patja et al 2006	0.90 (0.70, 1.10)	2.06
Sullivan et al 2007	1.10 (0.68, 1.68)	1.02
Bjørge et al 2008	1.70 (1.60, 1.90)	2.91
Subtotal (I-squared = 88.0%, p = 0.00)	*1.30 (0.96, 1.78)*	*8.94*
.		
Huntington disease		
Sørensen et al 1999	0.60 (0.50, 0.80)	2.01
Ji et al 2012	0.47 (0.38, 0.58)	2.16
Subtotal (I-squared = 56.4%, p = 0.13)	*0.53 (0.42, 0.67)*	*4.16*
.		
Overall (I-squared = 93.4%, p = 0.00)	**0.89 (0.84, 0.94)**	**100.00**

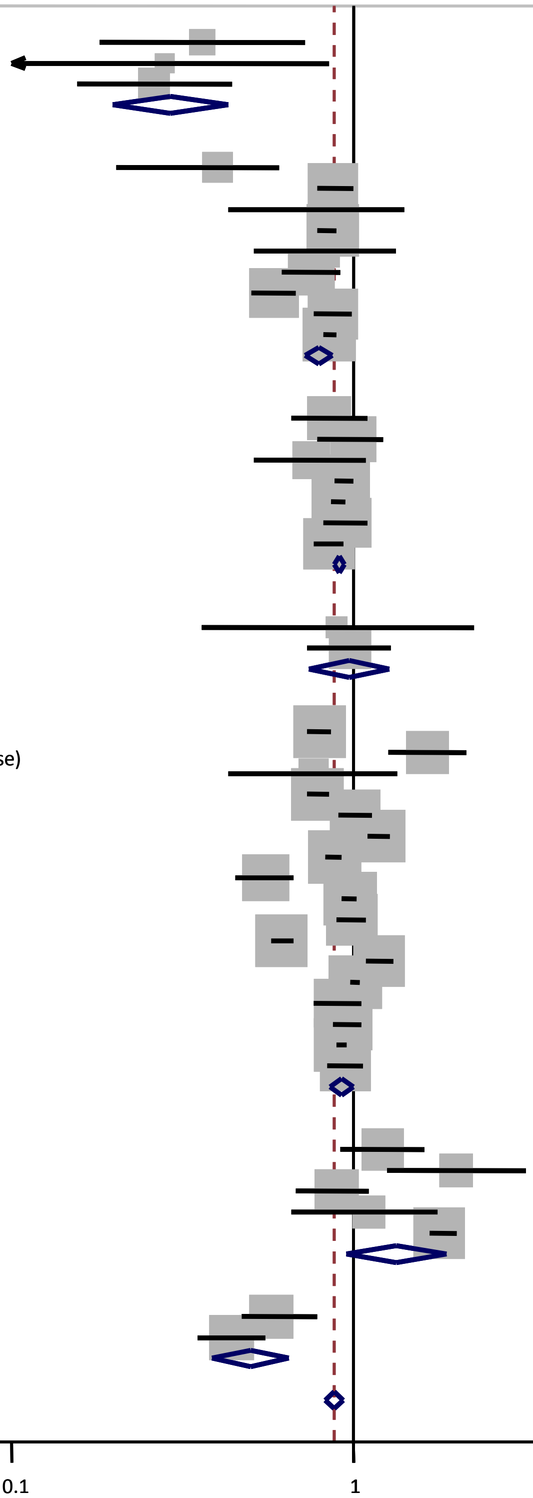
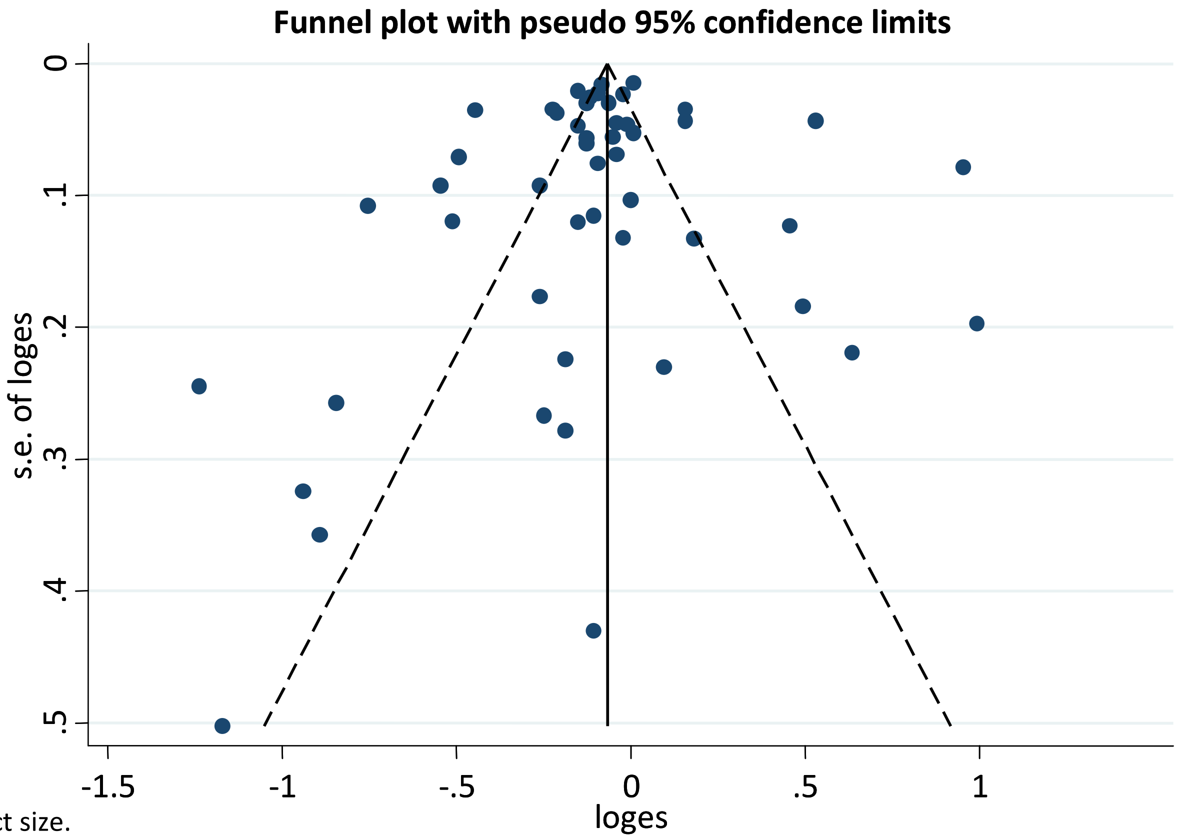


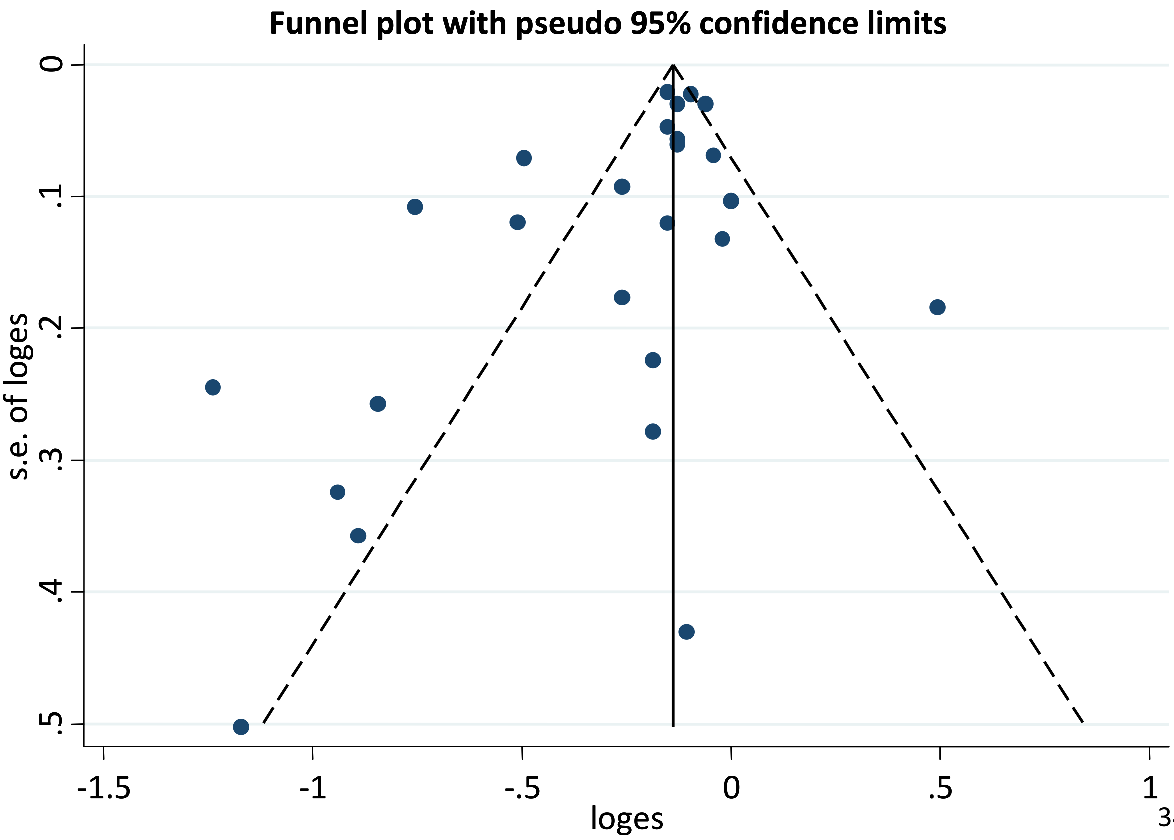
Figure S3: Funnel plots for detecting bias in meta-analyses.

A) Overall cancer comorbidity in patients with CNS disorders.

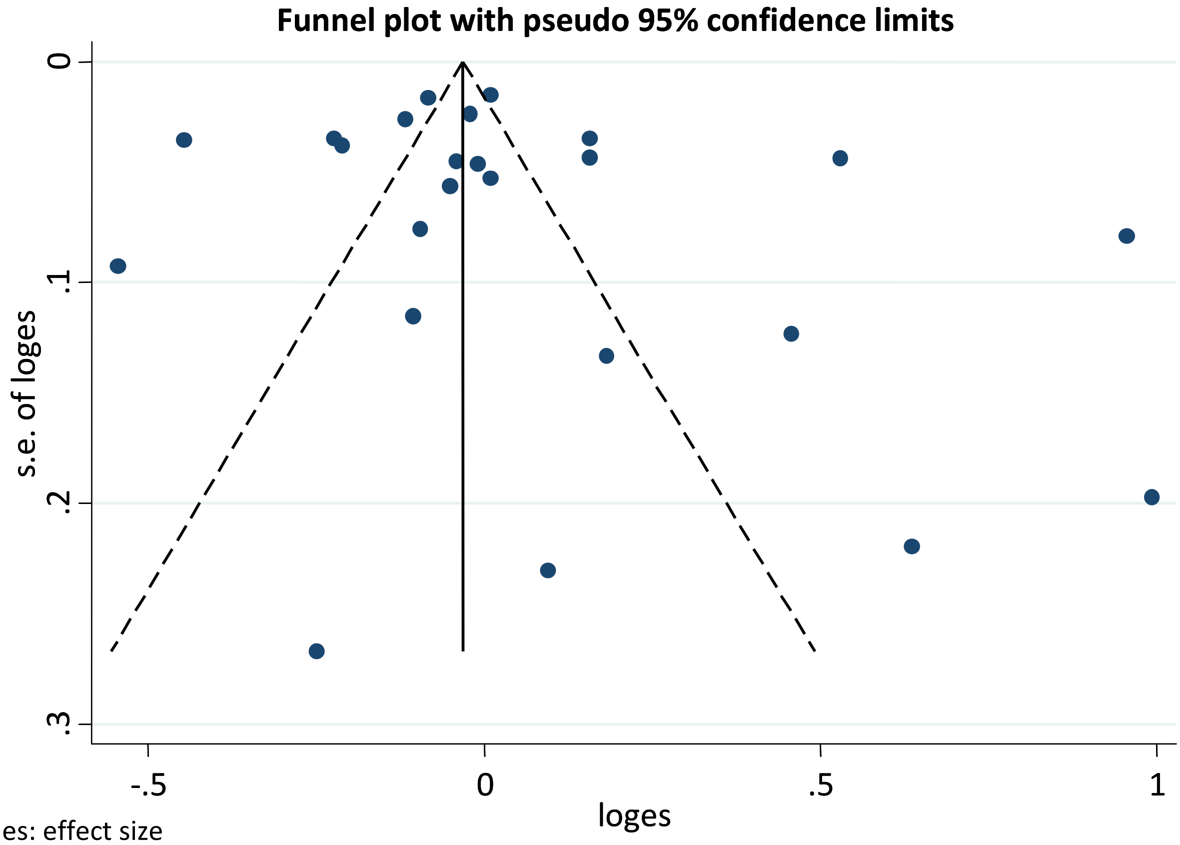


es: effect size.

B) Overall cancer comorbidity in patients with neurodegenerative disorders.

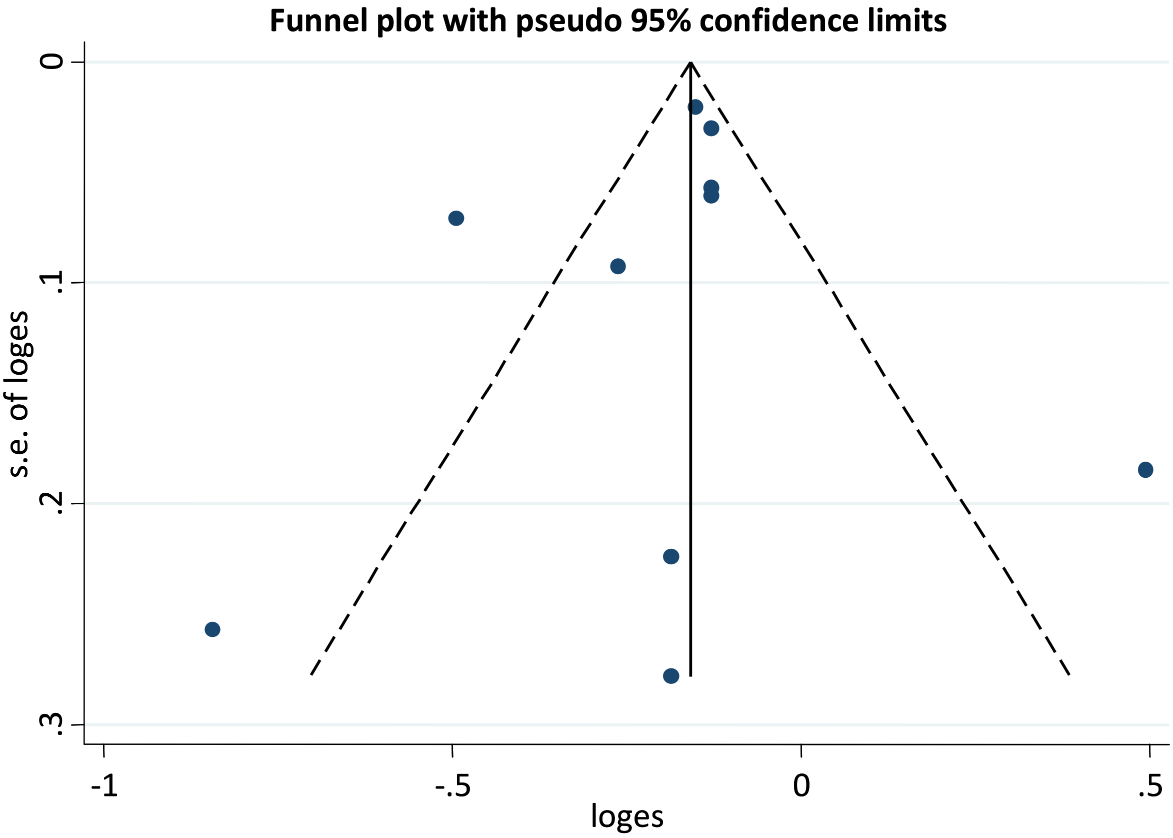


C) Overall cancer comorbidity in patients with neurodevelopmental disorders.

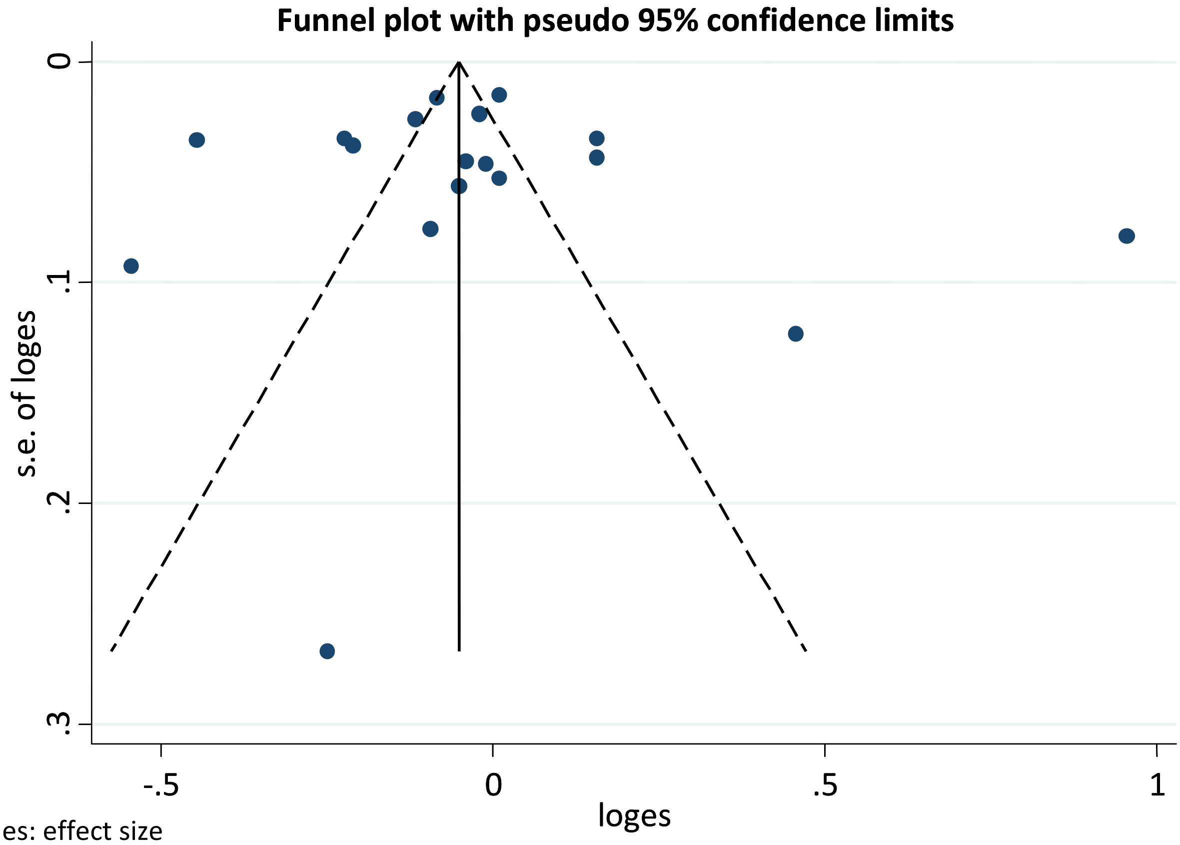


es: effect size

D) Overall cancer comorbidity in patients with Parkinson's disease.

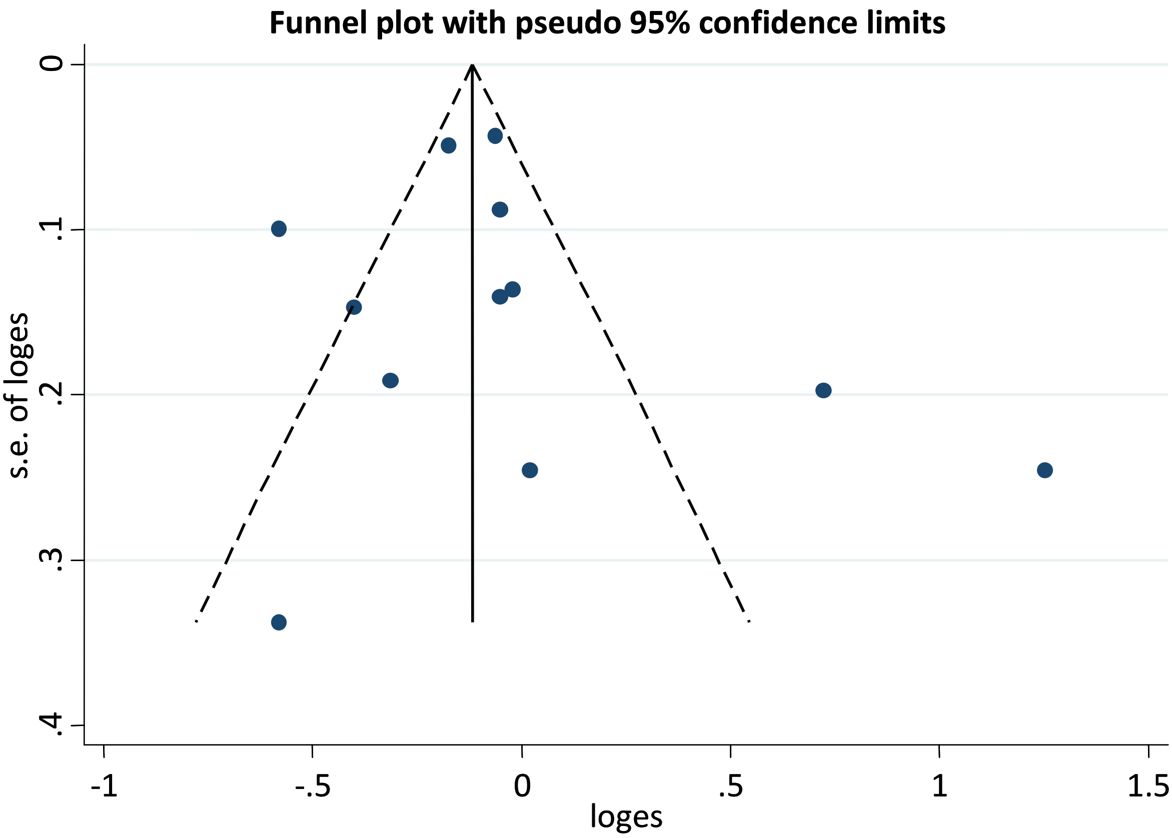


E) Overall cancer comorbidity in patients with schizophrenia.

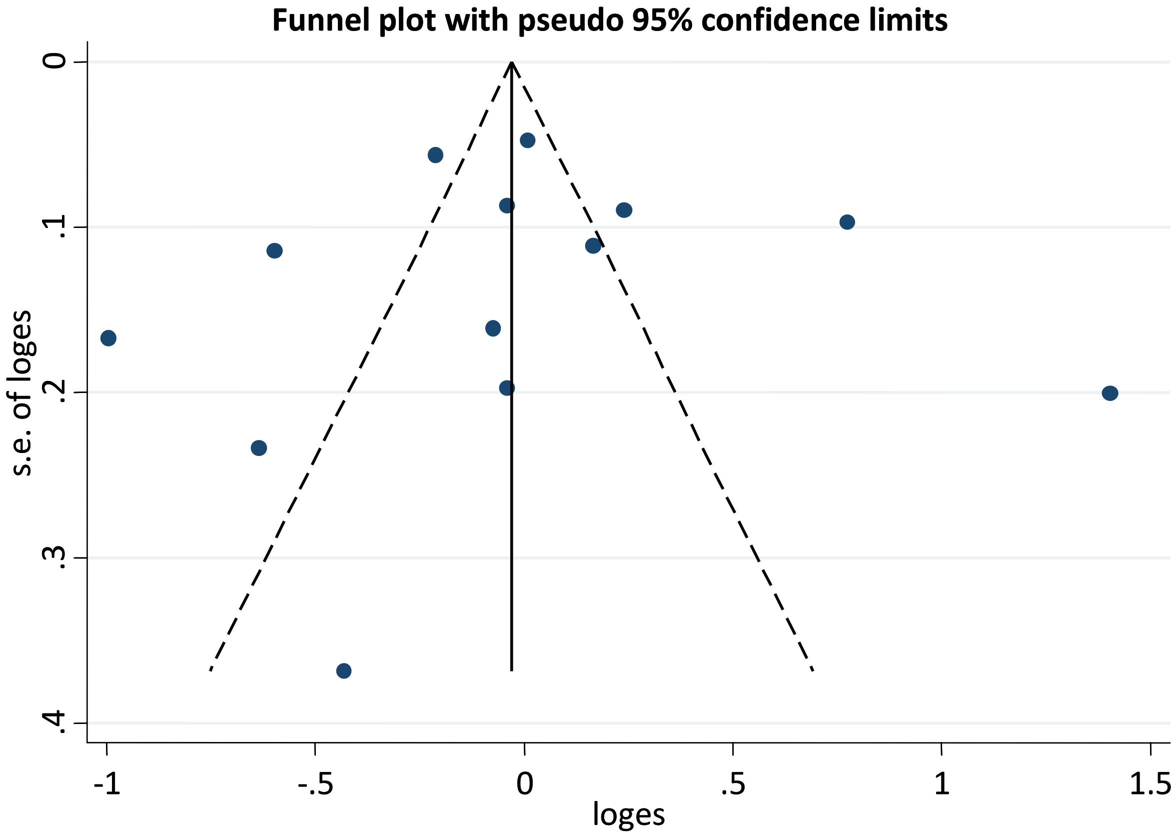


es: effect size

F) Colorectal cancer comorbidity in patients with schizophrenia.

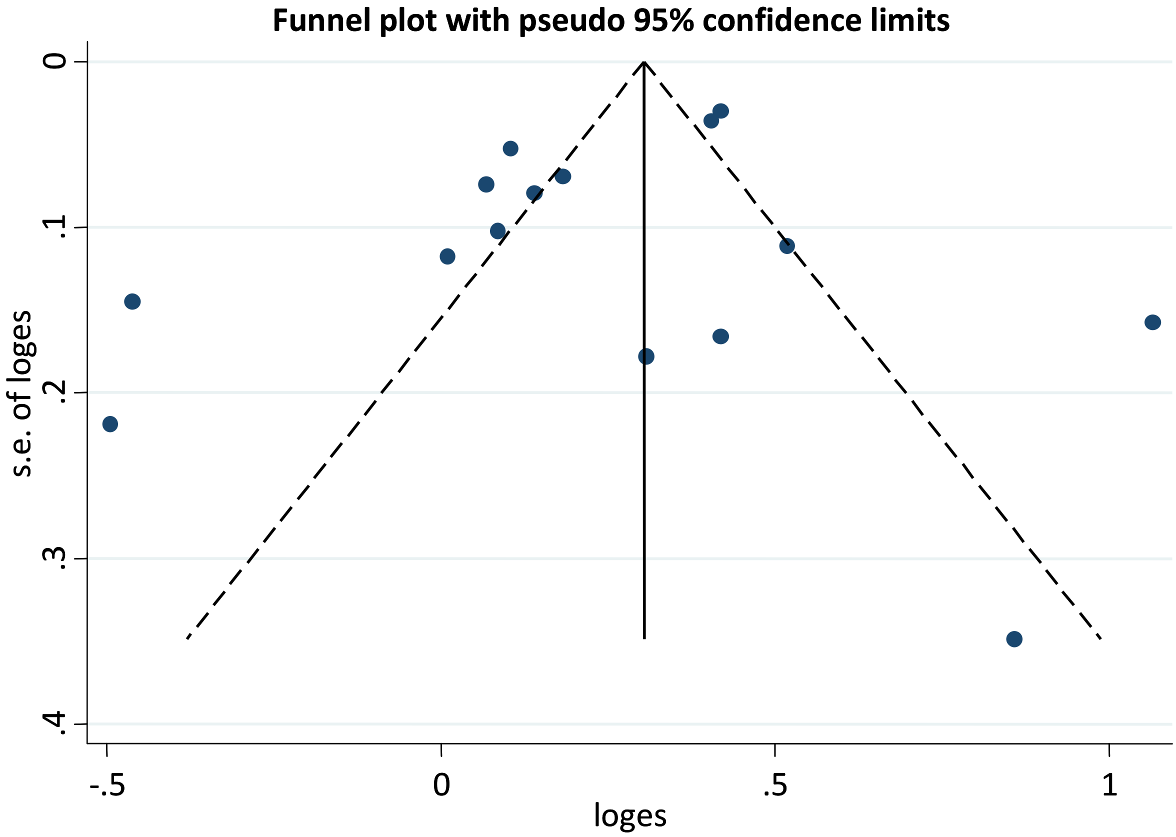


G) Lung cancer comorbidity in patients with schizophrenia.

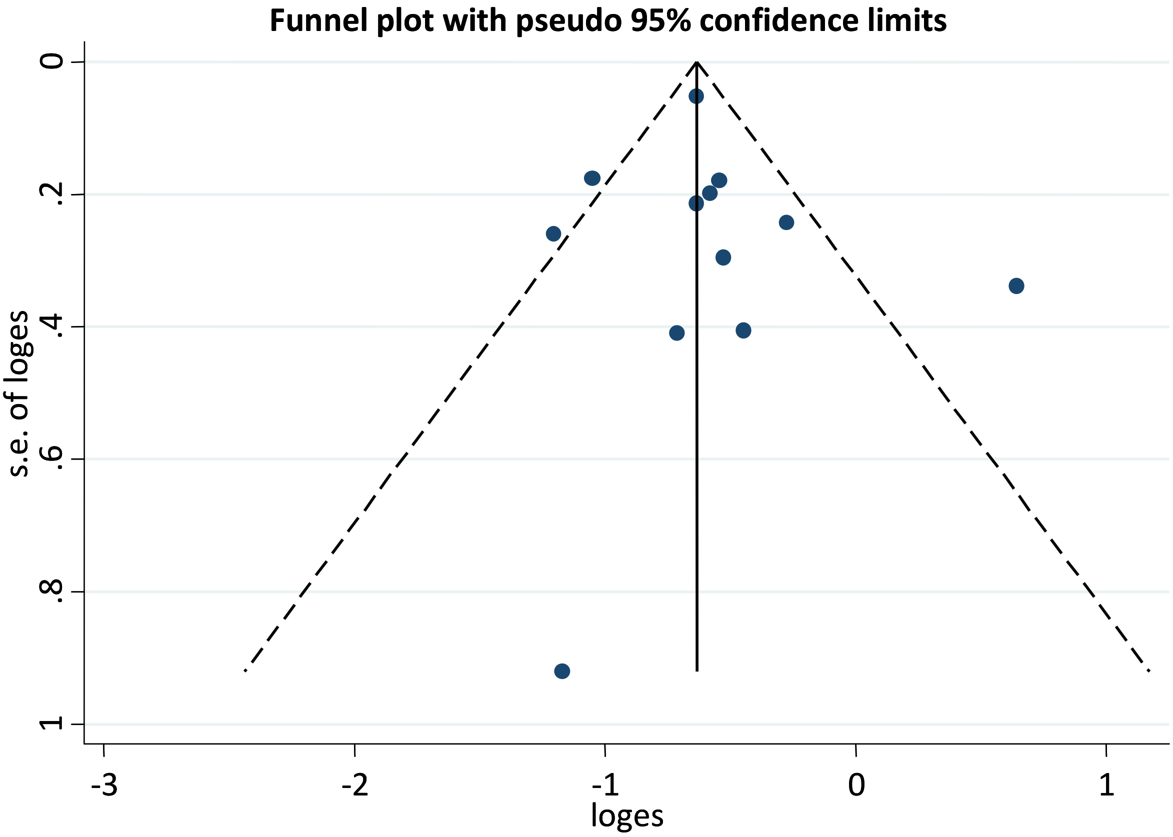


es: effect size

H) Breast cancer comorbidity in patients with schizophrenia.



l) Prostate cancer comorbidity in patients with schizophrenia.



es: effect size