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*Rafael Tabares Seisdedos y colaboradores**
Departamento de Medicina
Facultad de Medicina de Valencia

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.

Key Words

Comorbidity, Multimorbidity, cancer, CNS disorders, Alzheimer's disease, amyotrophic lateral sclerosis, autism spectrum disorders, Down's syndrome, Huntington's disease, multiple sclerosis, Parkinson's disease, schizophrenia

Abstract

Background*:** There is a lack of scientific consensus about cancer comorbidity in people with CNS disorders. This study assesses the co-occurrence of cancers, overall and by subtype, in patients with CNS disorders, in general and individually, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism spectrum disorders (ASD), Down's syndrome (DS), Huntington's disease (HD), multiple sclerosis (MS), Parkinson's disease (PD) and schizophrenia (SCZ). ***Method: Comprehensive search in PubMed/MEDLINE, SCOPUS and ISI Web of Knowledge of the literature published before March 2013. We identified 51 relevant articles from 2,229 discrete references, 50 of which contained data suitable for quantitative synthesis (577,013 participants). Pooled effect sizes (ES) were calculated using multiple random-effects meta-analyses. Sources of heterogeneity and uncertainty were explored by means of previously defined subgroup and sensitivity analyses, respectively. ***Results:*** The presence of CNS disorders was associated with a reduced co-occurrence of cancer (ES = 0.92; 95% confidence interval [CI] 0.87-0.98; I^2 = 94.5%). A consistently lower overall co-occurrence of cancer was detected in patients with neurodegenerative disorders (0.80; 0.75-0.86; 82.8%), and in those with AD (0.32; 0.22-0.46; 0.0%), PD (0.83; 0.76-0.91; 80.0%), MS (0.91; 0.87-0.95; 30.3%), and HD (0.53; 0.42-0.67; 56.4%). Patients with DS had a higher overall co-occurrence of cancer (1.46; 1.08-1.96; 87.9%). No association was observed between cancer and ALS (0.97; 0.76-1.25; 0.0%) or SCZ (0.98; 0.90-1.07; 96.3%). Patients with PD, MS and SCZ showed (a) higher co-occurrence of some specific cancers (e.g., PD with melanoma, MS with brain cancers and SCZ with breast cancer); and (b) lower co-occurrence of other specific cancers (e.g., lung, prostate and colorectal cancers in PD; lung and prostate cancer in MS; and melanoma and

prostate cancer in SCZ). ***Conclusion:*** Increased and decreased co-occurrence of cancer in patients with CNS disorders represents an opportunity to discover biological and non-biological connections between these complex disorders

Introduction

Multiple health problems are present in almost a quarter of all patients and in more than half of those with a chronic disorder.[1] However, the role of comorbidity (the presence of additional diseases in relation to an index disease) and/or multimorbidity (the presence of two or more diseases) in medical research and practice is relatively unexplored in comparison to that of individual diseases.[1,2] Comorbidity between cancer and disorders of the central nervous system (CNS) has been established by a series of observational studies.[3-5] For example, Down's syndrome (DS) is among the CNS disorders most heavily associated with increased co-occurrence of cancer; specifically, acute leukaemia, testicular cancer and some gastrointestinal cancers.[6] At the same time, emerging evidence points to a lower-than-expected probability of some types of cancer in certain CNS disorders,[3,4,7] an association that we have termed "inverse cancer comorbidity".[6,8] For example, inverse comorbidity of several forms of cancer has been reported in individuals with schizophrenia (SCZ) and Parkinson's disease (PD), specifically colorectal and prostate cancers.[6,9] Establishing the co-occurrence of cancer in individuals with CNS disorders could be a crucial step toward the development of effective strategies of cancer prevention.[10-14] Furthermore, understanding why people with certain CNS disorders are protected against some forms of cancer could be the key to finding novel treatments for both types of conditions.

In this report, we present a comprehensive systematic review and meta-analysis conducted with the aim of consolidating available data regarding the epidemiology of comorbid cancers and CNS disorders. Particular attention has been given to both general and site-specific cancer in patients with Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), autism spectrum disorders (ASD), DS, Huntington's disease (HD), multiple sclerosis (MS), PD and SCZ.

Methods

Comprehensive Literature Search

We systematically reviewed research published up until March 2013 to identify epidemiological studies reporting cancer comorbidity in patients with CNS disorders. We did this by conducting a search of PubMed/MEDLINE, SCOPUS and ISI Web of Knowledge using combinations of key terms distributed into three blocks: "cancer", "CNS disorders" and "epidemiology". Further details of our search strategies are available in the online supplement (see eAppendix Table S1 "Details of search terms used in the bibliographical review").

Eligibility

Studies were selected if they met the following two criteria: i) cohort and/or nested case-control observational study evaluating the association between cancer and CNS disorders; and ii) reporting of an estimate of association (e.g., relative risk, odds ratio, standardised incidence ratio, or hazard ratio) with measures of variation (i.e., confidence intervals). We included epidemiological studies performed in the general population (population-based) and/or in healthcare settings (e.g., hospital-based studies). Hospital records and cancer registers (also known as "data record-linkage") were also considered eligible when accuracy was explicitly ensured (disease diagnosis implies being admitted to hospital at least once; i.e., during a first episode of SCZ). We used the investigator-reported disease definitions according to well-accepted clinical diagnosis criteria (International Classification of Diseases [ICD] and/or Diagnostic and Statistical Manual of Mental Disorders [DSM]). Studies in which a survey or self-reports instrument had been used were excluded.

Study selection

Three reviewers (two medical doctors and one epidemiologist) searched the literature independently and then screened it for potentially eligible studies. Discrepancies were resolved by consensus. The full text of each potentially eligible publication was examined before a final decision was reached about whether or not to include or exclude it in/from the analysis.

Data extraction

Information about the design and participants of each study was extracted as recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (eAppendix Table S2: "PRISMA checklist").[16] Data were extracted from the source documents independently by two investigators (one medical doctor and one epidemiologist). Any discrepancy was resolved by consensus. The following data were extracted from each of the selected studies: author and year of publication; country; follow-up period; sampling framework; study design (prospective or retrospective; cohort or nested case-control); setting (population-based or hospital-based); sample size; patient characteristics (age and sex); CNS disorder; diagnostic criteria (ICD, DSM); and outcome of interest, along with other information, including the disorders studied. We did not have access to individual patient-level data, so the combined effects taken from published reports were used in their place. The methodological quality of the studies was assessed independently by two reviewers using a modified version of the Newcastle-Ottawa scale (NOS) for observational studies[17], which has a value range of 0 to 9. Any discrepancies were evaluated and resolved by a third reviewer.

Data analysis

Overall and cancer site-specific meta-analyses were performed using effect size (ES) measures of cancer comorbidity across individual studies. The results were pooled using the inverse variance method based on the DerSimonian and Laird random-effects model[18] and were classified by CNS disorder and year of study. This model was selected *a priori* to synthesise the epidemiological evidence as it considers both within-study and between-study variation by incorporating the heterogeneity of effects into the overall analysis. Additionally, fixed-effects models were applied when the effects of a certain study were reported according to sex, and also when study included data obtained in more than one region of a country or relating to different outcomes.

Heterogeneity was assessed using Cochran's Q and I-squared (I^2) statistics.[19-21] Subgroup analyses were performed by taking into consideration the nature of the CNS disorder. For instance, AD, PD, MS, ALS and HD are a result of neurodegenerative processes, (fundamentally protein folding and aggregation dysfunction), while SCZ and DS are both neurodevelopmental and neurodegenerative processes, and ASD are neurodevelopmental conditions. Potential sources of heterogeneity were explored via alternative subgroup analyses for selected covariates related to the nature of the data, study design, methodological quality, and other factors. A sensitivity analysis was also conducted to examine the possible influence of single studies by excluding possible outlier (extreme) observations. Identification of outlier studies was not based on any previously established statistical criterion, but rather on visual inspection of forest plots of the data of all the selected studies.

Publication bias was assessed using the funnel plot method. As a rule, tests for funnel plot asymmetry were employed when the meta-analyses included at least 10 studies (observations), as the power of the tests is too low to distinguish chance from real asymmetry when the number of studies is low. [22]

All the analyses were performed using STATA 12 (StataCorp, College Station, TX, USA).

Results

Study Selection and their main characteristics

Electronic database searches yielded 2,229 references. Exclusion of irrelevant references and/or duplicates left 204 potential full-text articles. Fifty-one articles[3,7,23-71] (with a total of 577,013 participants) fulfilled our inclusion criteria (**Figure 1**) and were included in the qualitative data synthesis. All except one[71] provided data for quantitative synthesis. The full lists of included and excluded references are provided

in the online supplement (eAppendix: Table S3 "References of the studies included in the systematic review" and Table S4 "List of excluded references").

The characteristics of the epidemiological studies analysed are summarised in eAppendix Table S5. Forty-three cohort studies were included, of which 8 had a prospective design and 35 had a retrospective design, and 8 were nested case-control studies. Three reports[7,23,24] contained data on cancer comorbidity in patients with AD, 11 in PD,[25-35] 9 in MS,[32,36-43] 2 in ALS,[32,44] 19 in SCZ,[45-63] 6 in DS,[3,64-68] 2 in HD,[69,70] and one in ASD.[71] Patient data were collected from population-based registries in 38 of the studies, of which 13 were hospital-based. The number of participants in each study ranged from 196 to 102,202. Three (5·9%) studies were published in the 1980's, 4 (7.8%) in the 1990's and 44 (86.3%) after 2000. Twenty-three studies were based in Nordic countries (11 in Denmark, 7 in Sweden, 3 in Finland and 2 in Norway), 13 in North America (11 in the United States and 2 in Canada), 9 in East Asia (7 in Taiwan and 2 in Japan), 8 in Western European countries (7 in the United Kingdom and 1 in France), 5 in the Middle East (all of them in Israel), and 4 in Oceania (all of them in Australia). The methodological quality of the reports, measured by the NOS scale, ranged from 1 to 5 points, with a median of 4 (eAppendix: Table S6 "Methodological quality assessment of observational studies based on the Newcastle-Ottawa (NOS) scale").

The main qualitative findings of the multiple meta-analyses are summarised in **Table 1**.

Overall and Site-Specific Cancers in Patients with CNS disorders

Figure 2 shows estimates of cancer comorbidity in individuals with CNS disorders (Pooled effect sizes [ES] with a corresponding 95% confidence interval [CI]) from each study and, where appropriate, pooled across studies. The analyses were stratified by CNS disorder.

Overall, there was a significant inverse association between CNS disorders and cancer (ES=0.92;95%CI=0.87-0.98;I^2=94.5%), with substantial between-study heterogeneity (Q statistic *P value*<0.01). In the case of the subgroup of CNS disorders whose main underlying process is neurodegeneration, the potential protective effect was more pronounced (ES=0.80;95%CI=0.75-0.86;I^2=82.8%), with substantial between-study heterogeneity being demonstrated once again (Q statistic *P*<0.01) (see eAppendix Figure S1). Specifically, inverse comorbidities were detected for colorectal cancer (ES=0.73;95%CI=0.57-0.94;I^2=59.1%), lung cancer (ES=0.55;95%CI=0.37-0.82;I^2=84.6%) and prostate cancer (ES=0.75;95%CI=0.68-0.82;I^2=0.0%), while a direct comorbidity was shown between brain cancer (ES=1.31;95%CI=1.12-1.53;I^2=0.0%) and neurodegenerative disorders (**Figure 3**).

Alzheimer's Disease

Three studies[7,23,24] of a total of 895 AD patients pointed to a markedly lower co-occurrence of cancer in general in these individuals (ES=0.32;95%CI=0.22-0.46;I^2=0.0%), with no apparent between-study heterogeneity (Q statistic *P*=0.761) (**Figure 2**). However, no data were available to explore the association between AD and specific cancers.

Parkinson's Disease

Analysis of ten studies[25-34] of 55,304 PD patients revealed a significantly reduced co-occurrence of cancer in general in these individuals (ES=0.83;95%CI=0.76-0.91;I^2=80.0%), with substantial between-study heterogeneity (Q statistic *P*<0.01) (**Figure 2**).

Cancer-specific comorbidity in these PD patients is shown in **Figure 4**. Co-occurence of lung cancer (ES=0.44;95%CI=0.35-0.55;I^2=60.7%), prostate cancer (ES=0.75;95%CI=0.68-0.83;I^2=0.0%) and colorectal cancer (ES=0.81;95%CI=0.71-0.91;I^2=45.5%) was significantly lower in this patient group. On the other hand, co-occurrence of melanoma (ES=1.65;95%CI=1.39-1.96;I^2=0.0%) was highly significant, and that of brain cancer (ES=1.21;95%CI=0.95-1.52;I^2=0.0%) and breast cancer (ES=1.12; 95%CI=0.94-1.35;I^2=48.7%) showed only a slightly higher trend toward significance.

Multiple Sclerosis

Eight studies[32,36-42] of 54,929 patients with MS reflected a reduced incidence of cancer in general (ES=0.91;95%CI=0.87-0.95;I^2=30.3%), with low between-study heterogeneity (Q statistic *P*=0.19) (**Figure 2**). Cancer-specific comorbidity in these patients is presented in **Figure 5**. A significantly higher co-occurrence of brain cancers was detected in this group (ES=1.39;95%CI=1.13-1.71;I^2=17.7%). In contrast, lung cancer (ES=0.72;95%CI=0.62-0.84;I^2=26.7%), prostate cancer (ES=0.74;95%CI=0.59-0.94;I^2=41.2%) and melanoma (ES=0.86;95%CI=0.73-1.03;I^2=0.0%) were less common, though not significantly so in the case of melanoma. The co-occurrence of colorectal cancer was lower, but not statistically significant (ES=0.83;95%CI=0.57-1.20;I^2=70.3%). No association with breast cancer was apparent (ES=1.02;95%CI=0.88-1.18;I^2=66.5%).

Amyotrophic Lateral Sclerosis

Two studies[32,44] of 4,836 participants revealed no association between ALS and overall cancer co-occurrence (ES=0.97;95%CI=0.76-1.25;I^2=0.0%), with no evidence of between-study heterogeneity (Q statistic *P*=0.85) (**Figure 2**). No data were available to explore the relation between this disorder and specific cancers.

Schizophrenia

Sixteen studies[45-60] of 427,843 patients with SCZ showed no association between SCZ and cancer in general (ES=0.98;95%CI=0.90-1.07;I^2=96.3%), with substantial between-study heterogeneity (Q statistic *P*<0.01) (**Figure 2**).

Cancer-specific comorbidity in patients with SCZ is shown in **Figure 6**. Co-occurrence of breast cancer was significantly higher (ES=1.25;95%CI=1.10-1.42;I^2=89.7%), while that of prostate cancer (ES=0.55;95%CI=0.45-0.67;I^2=60.4%) and melanoma (ES=0.72;95%CI=0.62-0.83;I^2=0.6%) was significantly lower. No association was found between SCZ and brain cancer (ES=1.00;95%CI=0.76-1.31;I^2=78.4%), colorectal cancer (ES=0.95;95%CI=0.80-1.13;I^2=86.6%) or lung cancer (ES=0.92;95%CI=0.72-1.17;I^2=94.6%).

Down's Syndrome

Six studies[3,64-68] of 17,090 DS patients revealed a significantly increased overall co-occurrence of cancer in these individuals (ES=1.46;95%CI=1.08-1.96;I^2=87.9%), with substantial between-study heterogeneity (Q statistic *P*<0.01) (**Figure 2**).

Cancer-specific comorbidity in patients with DS is shown in **Figure 7**. Interestingly, both leukaemia (ES=17.41;95%CI=10.69-28.34;I^2=86·2%) and testicular cancer (ES=4.53;95%CI=2.51-8.18;I^2=20.1%) were significantly more frequent in this group. Co-occurrence of colorectal cancer (ES=1.37; 95% CI=0.60-3.11; I^2=0.0%) was numerically higher but not significantly so, and that of brain cancer was unaltered (ES=0.72;95%CI=0.11-4.65;I^2=0.0%).

Huntington's Disease

Two studies[69,70] of 2,204 patients with HD showed a highly significant reduction in the overall incidence of cancer (ES=0.53;95%CI=0.42-0.67;I^2=56.4%), with moderate between-study heterogeneity (Q statistic *P*=0.13) (**Figure 2**). Significantly lower rates of several specific cancers were evident, particularly breast cancer (ES=0.59;95%CI=0.38-0.90;I^2=0.0%), gastrointestinal cancers including colorectal cancer (ES=0.53;95%CI=0.37-0.76;I^2=0.0%), lung cancer (ES=0.50;95%CI=0.26-0.96;I^2=0.0%), and malignancies of haemopoietic and lymphoid tissue (ES=0.36;95%CI=0.15-0.85;I^2=0.0%) (**Figure 8**).

Autism Spectrum Disorders

Our search also included studies on cancer incidence in patients with ASD, but we found only one article[71] that fulfilled the inclusion criteria. Overall cancer incidence was not reported in the study in question, but a significantly higher co-occurrence of malignant neoplasm of the brain was observed in these patients.

Sensitivity and Subgroup Analyses

Overall summary estimates after excluding extreme outliers[25,28,40,56,65,66] remained consistent across the CNS disorders studied (see eAppendix Figure S2 "Cancer comorbidity in patients with CNS disorders. Sensitivity analysis"). The results of the subgroup analyses of sources of heterogeneity are provided in the online supplement (see eAppendix Tables S7-S11), where it can be seen that they did not make any noticeable difference to the above analyses. No publication bias was evident on visual inspection of the funnel plots (see eAppendix Figure S3).

Discussion

The results of our analyses show that, in general, individuals with CNS disorders are at a lower co-occurrence of developing cancer compared to those without CNS disorders (a relative risk reduction of 8%). A similar but more pronounced reduction of cancer co-occurrence was identified in patients with neurodegenerative disorders (20%). A more detailed inspection of the data revealed that the incidence of cancer in individuals with AD (68%), HD (47%), PD (17%) and MS (9%) was even lower, suggesting a global anti-cancer effect in neurodegenerative disorders. When the relationship between individual types of cancer and specific CNS disorders were explored the results proved more complex. For example, in patients with PD or MS the incidence of lung and prostate cancer was lower, while melanomas were more common among the former group (PD) and brain cancer was more common among the latter (MS). Patients with SCZ were less likely to develop prostate cancer and melanoma but more likely to suffer breast cancer. The available data did not allow the relationship between AD and specific cancers to be explored. However, there were data available to show that HD and DS are located at opposite poles of the cancer-CNS disorder comorbidity continuum; the former at the *inverse cancer comorbidity pole*, associated with a lower co-occurrence of developing any of the cancers considered, and the latter at the *direct cancer comorbidity pole*, associated with a higher co-occurrence of many types of cancer studied.

Our findings have important implications for both medical research and health care. In relation to medical research, they may represent a step towards understanding why some people with CNS disorders are relatively vulnerable to or protected against certain cancers. For example, it is possible that the higher co-occurrence of breast cancer and melanoma in patients with SCZ and PD, respectively, is associated with diverse and non-mutually exclusive factors related to behaviour (including illness behaviour) [72], environment and health care. In particular, these could include: (a) clinical factors (e.g. smoking and alcohol consumption, or the impaired fertility characteristic of female patients with SCZ); (b) medication side-effects (e.g. hyperprolactinaemia associated with antipsychotic drugs); (c) unhealthy lifestyle (e.g. obesity, physical inactivity, inadequate sun exposure/low vitamin D concentrations);

(d) poor access to optimal health care (e.g. absence of cancer screening, underdiagnosis and undertreatment); and (e) socioeconomic status (e.g. limited access to vaccines for infections related with cancer and other preventive strategies).

Biological factors may also play a role in the comorbidity demonstrated by our meta-analysis.[6,9] Indeed, several molecular and genetic mechanisms have been proposed to explain the relationship between cancer and AD,[73] including alterations of the PIN1 (peptidyl-prolyl *cis-tras* isomerase NIMAinteracting 1) and tumour suppressor protein p53 (TP53) signalling pathways, the role of γ-secretase complex, the trade-off effect of *APOE4,* and the role of microRNAs (miR-9 and miR-29 families), which function as endogenous silencers of many genes and which may be tumour suppressors. The inverse association between some cancers and SCZ could be due to the expression of specific tumour-suppressor genes (e.g., *TP53* and *XRCC4*) that are downregulated in certain cancers (prostate and colorectal, respectively) and upregulated in SCZ. In this way, it is biologically plausible that genes upregulated in SCZ (and other CNS disorders) significantly enrich genes downregulated in cancer, and, conversely, that genes downregulated in schizophrenia significantly enrich genes upregulated in cancer.[6,9] Other biological explanations for the inverse and direct cancer comorbidity in PD[74], MS[75], DS[76] and HD[70] can be found in the literature. Specifically, it has been proposed that advanced paternal age (a known risk factor for neurodevelopmental disorders), may be differentially associated with de novo mutations in genes that (a) impact on cell proliferation in spermatogonial cells, and (b) are associated with cancer pathways.[77]

The findings of our meta-analysis also suggest the implication of common genetic, molecular and/or cellular mechanisms in neurodegeneration and carcinogenesis in a two-way street scenario (i.e., low neural proliferation and early neuronal death *versus* high neural proliferation and resistance to neuronal death, respectively). Furthermore, the lower incidence of cancer comorbidity in people with neurodegenerative disorders could be explained by the brain's ability to modulate tumour initiation and/or progression or metastasis, which may have a knock-on effect elsewhere in the body. [78] We have recently proposed that communication between the immune and nervous systems is a component of tumour-CNS crosstalk and intrinsic to the cancer-CNS disorder relationship. For example, an imbalance of autoimmunity and anti-tumour immunity produced by dendritic cells is a potential main player of this interplay.[73] A deeper understanding of the mechanisms that protect against cancer could be of invaluable help in determining cancer and CNS disorder pathways and developing novel treatments for both sets of conditions.

In relation to health care, our findings may help to draw up clinical practice guidelines aimed at minimizing the impact of comorbidity and secondary and tertiary prevention programmes for some types of cancer. Such strategies should include control of

tobacco/alcohol use and sun exposure, changes in lifestyle (promotion of regular physical activity and healthier diet), screening programmes (e.g., for melanoma and breast cancer in patients with PD and SCZ, respectively), and prevention and control of malignant viral infections (e.g., hepatitis B and C virus, carcinogenic human papilloma virus, human herpes virus 8, and human T-cell leukemia virus). Implementation of these strategies and action plans will require the designing (where none exist) and reinforcing of health care services at national and regional levels to give priority to long-term non-communicable diseases including comorbid chronic cancers and CNS disorders. Integrated programmes of healthcare for comorbid patients and the coordination of services on different levels (intersectoral approach) are vital. In this context, specific prevention and control programmes should be integrated into health policy and clinical practice guidelines in the areas of oncology and CNS disorders.[14,79,80]

Although this study is the largest systematic effort to date to quantitatively synthesize data regarding cancer comorbidity in a range of CNS disorders, our meta-analysis is undermined somewhat by limitations inherent in the original observational studies, which should be borne in mind when interpreting the results. As in other meta-analyses, given the lack of data in each study, we did not make adjustments for smoking habit, family history or additional confounders (e.g., body mass index, physical activity, alcohol consumption). Therefore, it is of utmost importance to replicate our findings in further analyses of individual-level data that allow for adjustment for potential key determinants of cancer incidence. Moreover, meta-analyses have intrinsic methodological limitations[81] related to including studies with different designs and diverse patient populations, diverse settings and treatment strategies. For example, the present analysis has been applied to a series of studies in which substantial variations of effect sizes underlie the observations reported (e.g., heterogeneity), particularly in terms of the population, setting, diagnostic criteria and methods applied. Although robust estimates were obtained in most of the analyses, it is worth noting that the number of studies and sample sizes limited the power of some of the comparisons. Therefore, the absence of statistically significant evidence of a comorbid effect of some specific cancers should not be confused with evidence of the absence of a true effect for an evaluated comorbity. In addition, the subgroup and sensitivity analyses may have suffered from multiple testing. Nevertheless, despite these shortcomings, we believe that our core findings are internally valid and general enough to establish strong hypotheses for large and low-bias studies in the future.

In conclusion, the present findings provide up-to-date epidemiological evidence that patients with neurodegenerative disorders display a significantly decreased co-occurrence of cancer in general. PD, MS and SCZ are associated with both increased and decreased co-occurrence of a range of cancers, while DS is characterised by a higher incidence of all the types of cancer studied. These associations have important

implications for medical research, healthcare policy and clinical practice. Perhaps most importantly, inverse and direct cancer comorbidity in patients with CNS disorders represents an opportunity to discover biological and non-biological connections between complex disorders, thus helping to understand why some people are relatively vulnerable or resistant to certain cancers. Finally, our findings call for further research into the epidemiology of cancer comorbidity and complex disorders with the aim of creating effective strategies to meet and overcome the challenge of comorbidity in the population as a whole.[82]

Conflicts of interest: We declare that we have no conflicts of interest.

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TABLES

Table 1: Summary of the meta-analysis findings regarding cancer comorbidities in CNS disorders.

	Increased co-occurrence of cancer	**Decreased co-occurrence of cancer**	**No effect/neutral co-occurrence of cancer**
Alzheimer's disease		**Overall cancer**	
Parkinson's disease	**Melanoma;** Brain cancers*; breast cancer*	**Overall cancer** **Lung cancer; prostate cancer; colorectal cancer**	
Multiple sclerosis	**Brain cancer**	**Overall cancer** **Lung cancer; prostate cancer;** colorectal cancer*; melanoma*	**Breast cancer**
Amyotrophic lateral sclerosis			**Overall cancer**
Schizophrenia	**Breast cancer**	**Prostate cancer; melanoma;** lung cancer*	**Overall cancer, Brain cancer, Colorectal cancer**
Down's syndrome	**Overall cancer** **Leukaemia; testicular cancer;** colorectal cancer*	Brain cancer*; Breast cancer*; Non-Hodgkin's lymphoma*; Lung cancer*	
Huntington's disease		**Overall cancer** **Breast cancer; gastrointestinal cancers, including colorectal; lung cancer; malignancies of the haemopoietic and lymphoid tissues**	

Conditions in **bold** indicate statistically significant results obtained in the meta-analyses (p values < 0.05).
*Conditions for which non-statistically significant results were obtained, but where a trend towards an effect size was identified (i.e., increased or decreased co-occurrence of cancer).

FIGURES

Figure 1: Flow diagram of study selection process.

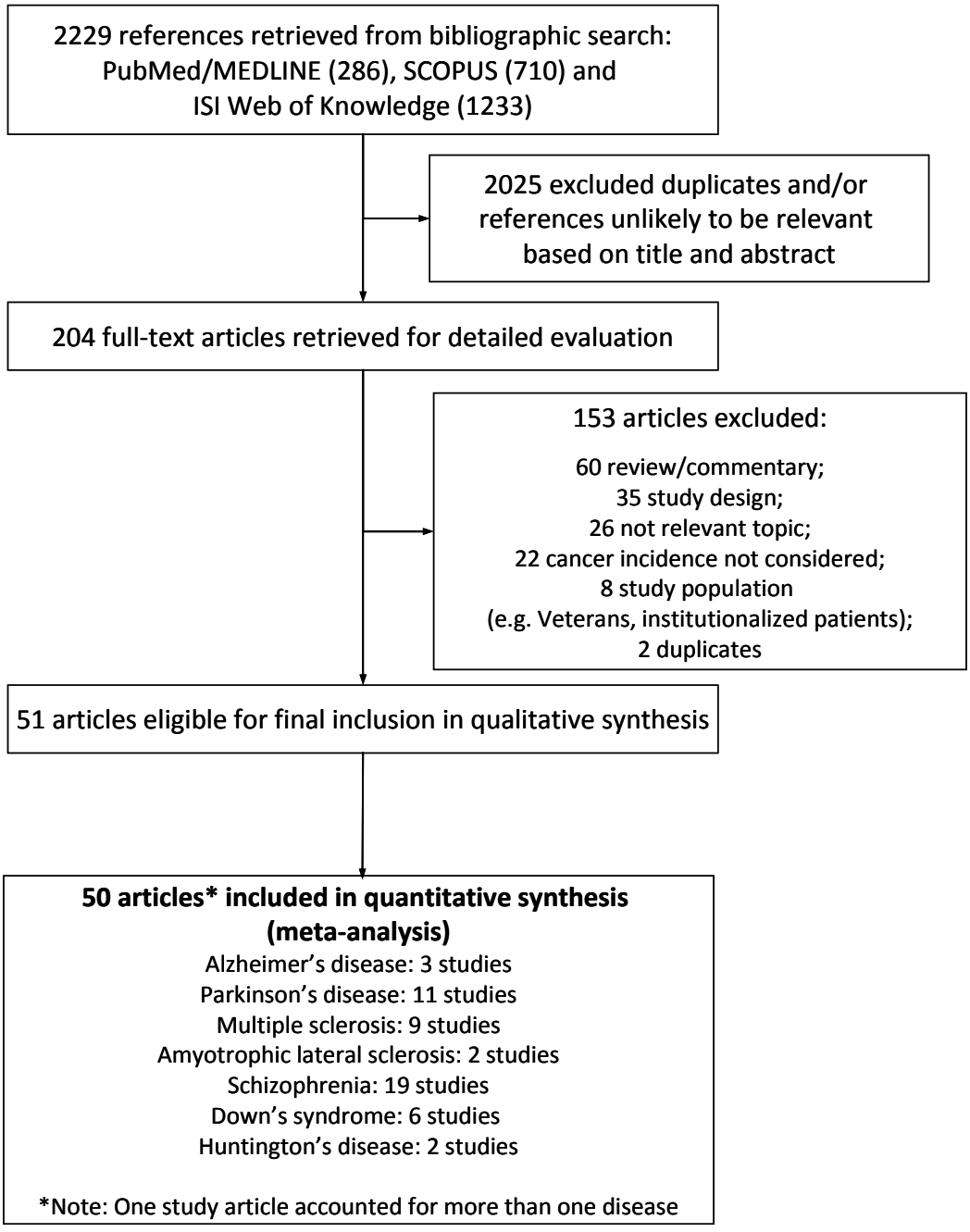
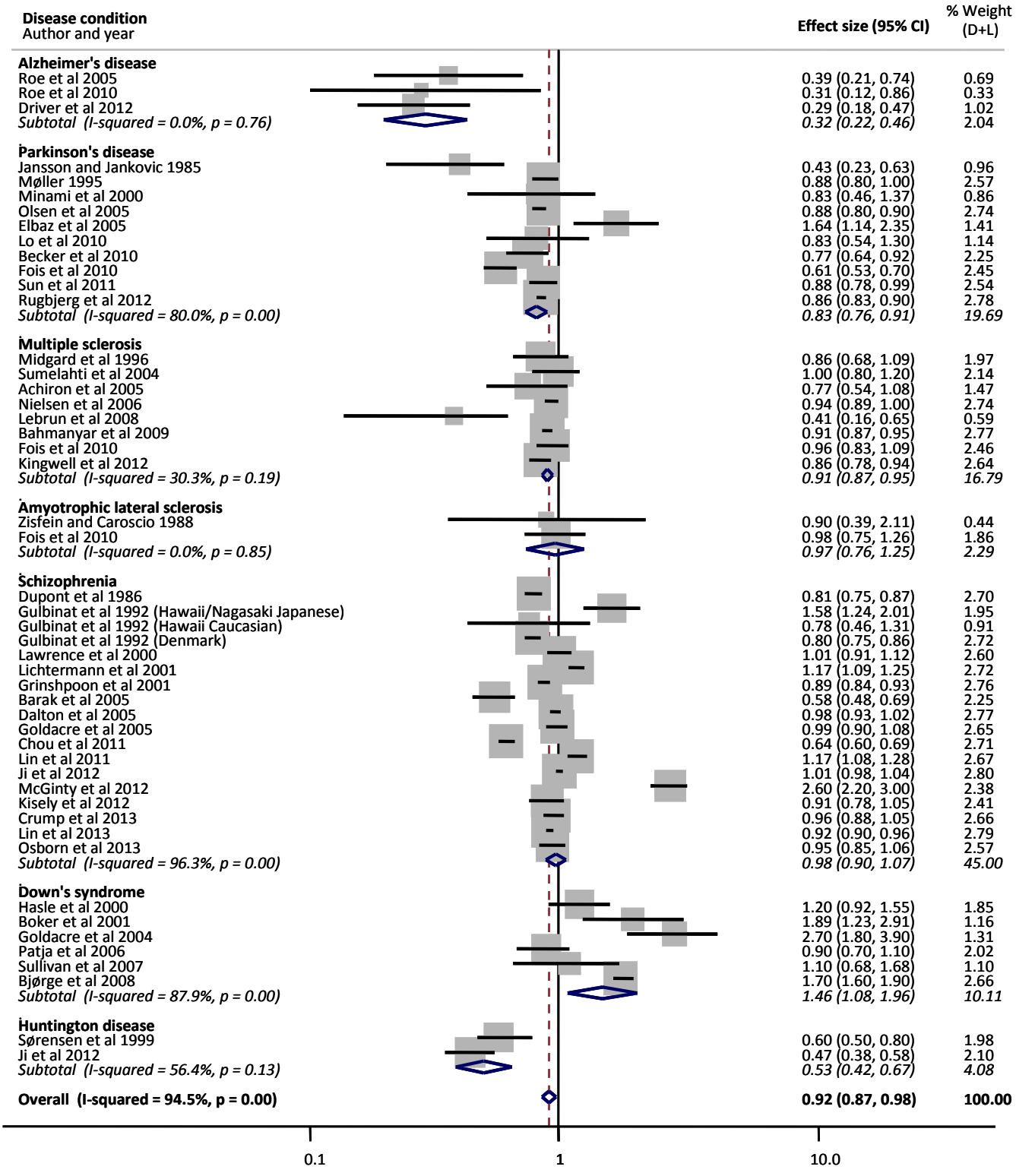
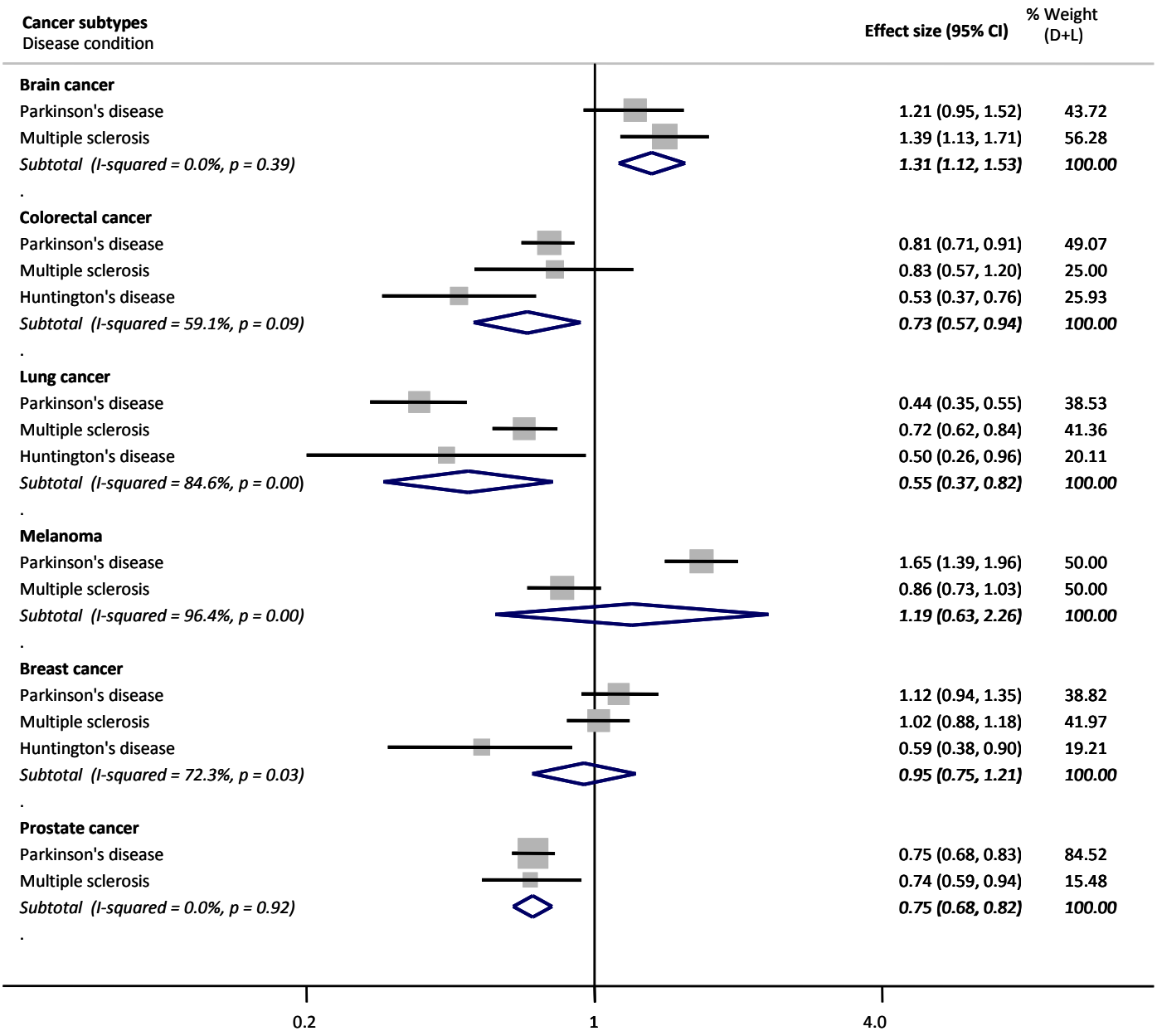


Figure 2: Cancer comorbidity in patients with CNS disorders.



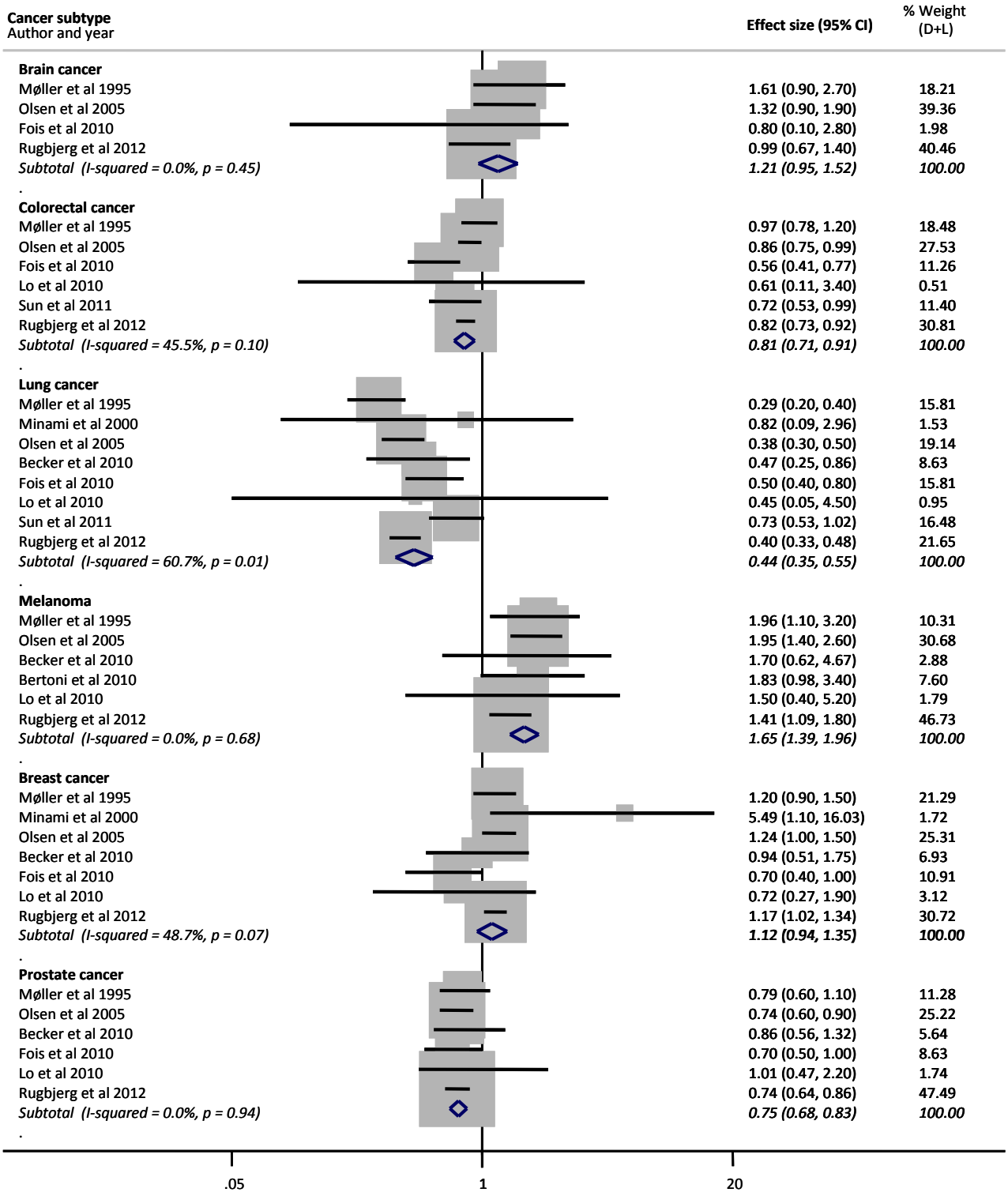
Weights correspond to random-effects (DerSimonian and Laird) model.

Figure 3: Cancer-specific comorbidity in patients with neurodegenerative disorders.



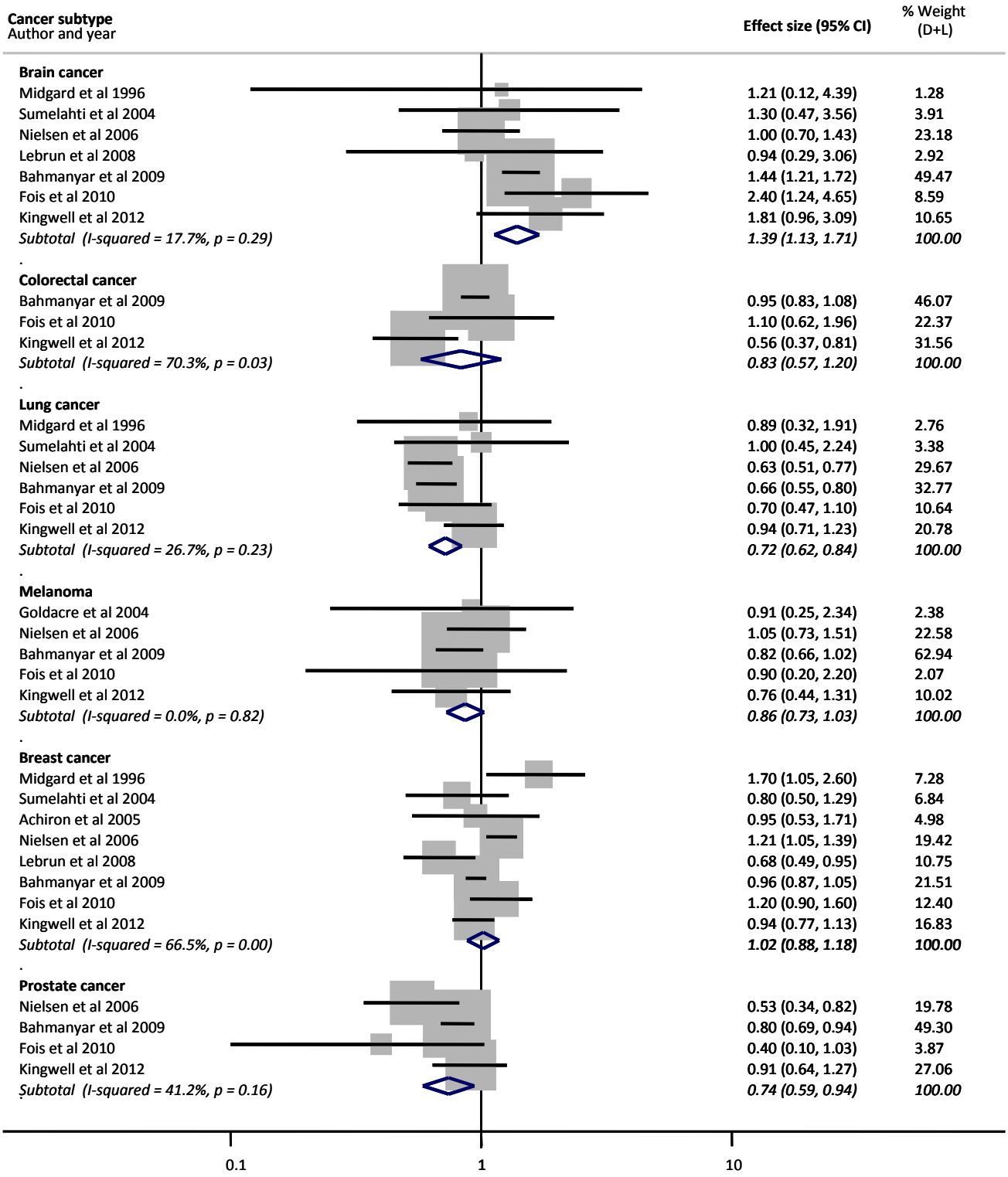
Note: The breast cancer analysis was limited to women and the prostate cancer analysis was limited to men. Weights correspond to random-effects (DerSimonian and Laird) model.

Figure 4: Cancer-specific comorbidity in patients with Parkinson's disease.



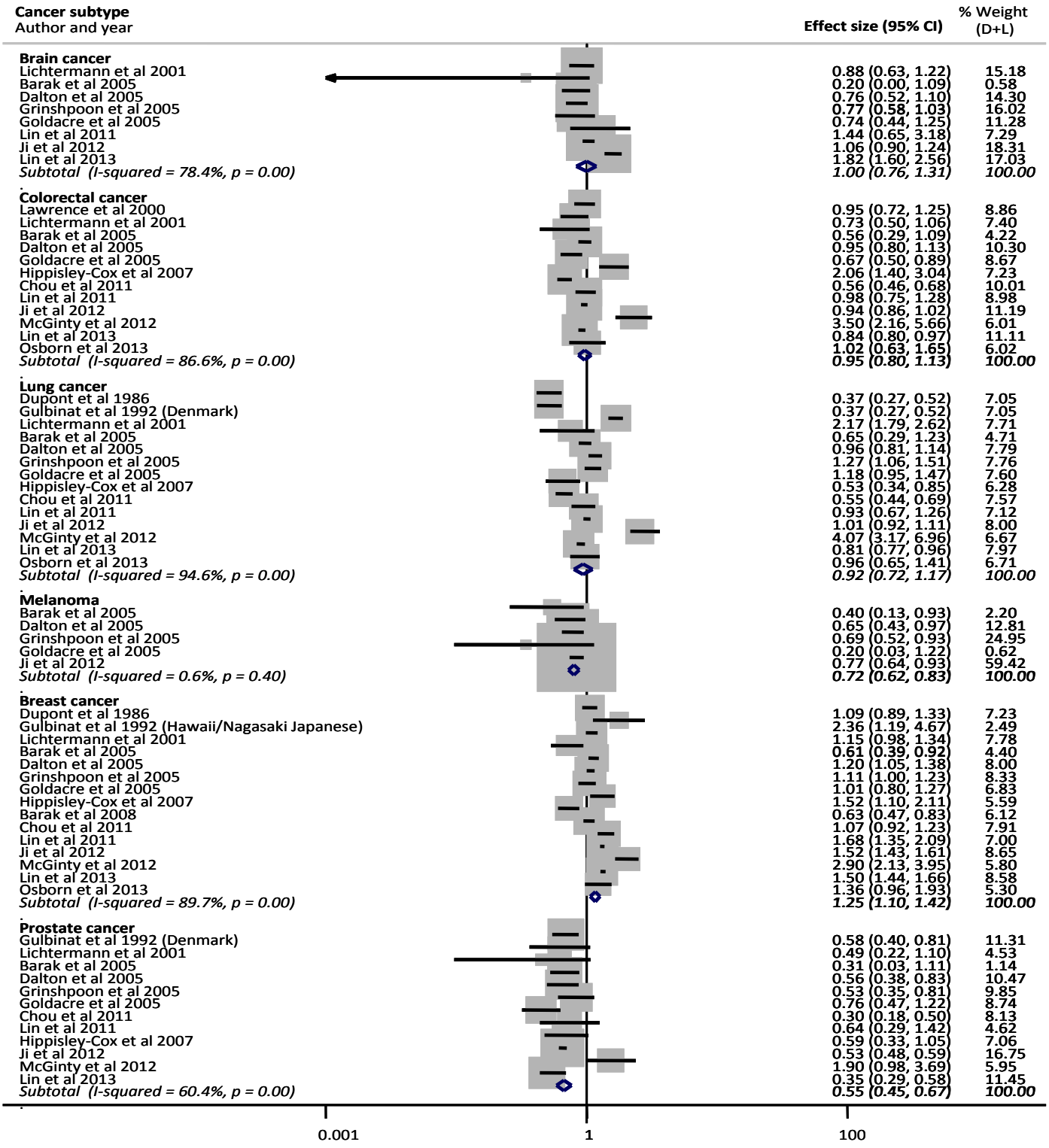
Note: The breast cancer analysis was limited to women and the prostate cancer analysis was limited to men. Weights correspond to random-effects (DerSimonian and Laird) model.

Figure 5: Cancer-specific comorbidity in patients with multiple sclerosis.



Note: The breast cancer analysis was limited to women and the prostate cancer analysis was limited to men. Weights correspond to random-effects (DerSimonian and Laird) model.

Figure 6: Cancer-specific comorbidity in patients with schizophrenia



Note: The breast cancer analysis was limited to women and the prostate cancer analysis was limited to men. Weights correspond to random-effects (DerSimonian and Laird) model.

Figure 7: Cancer-specific comorbidity in patients with Down's syndrome

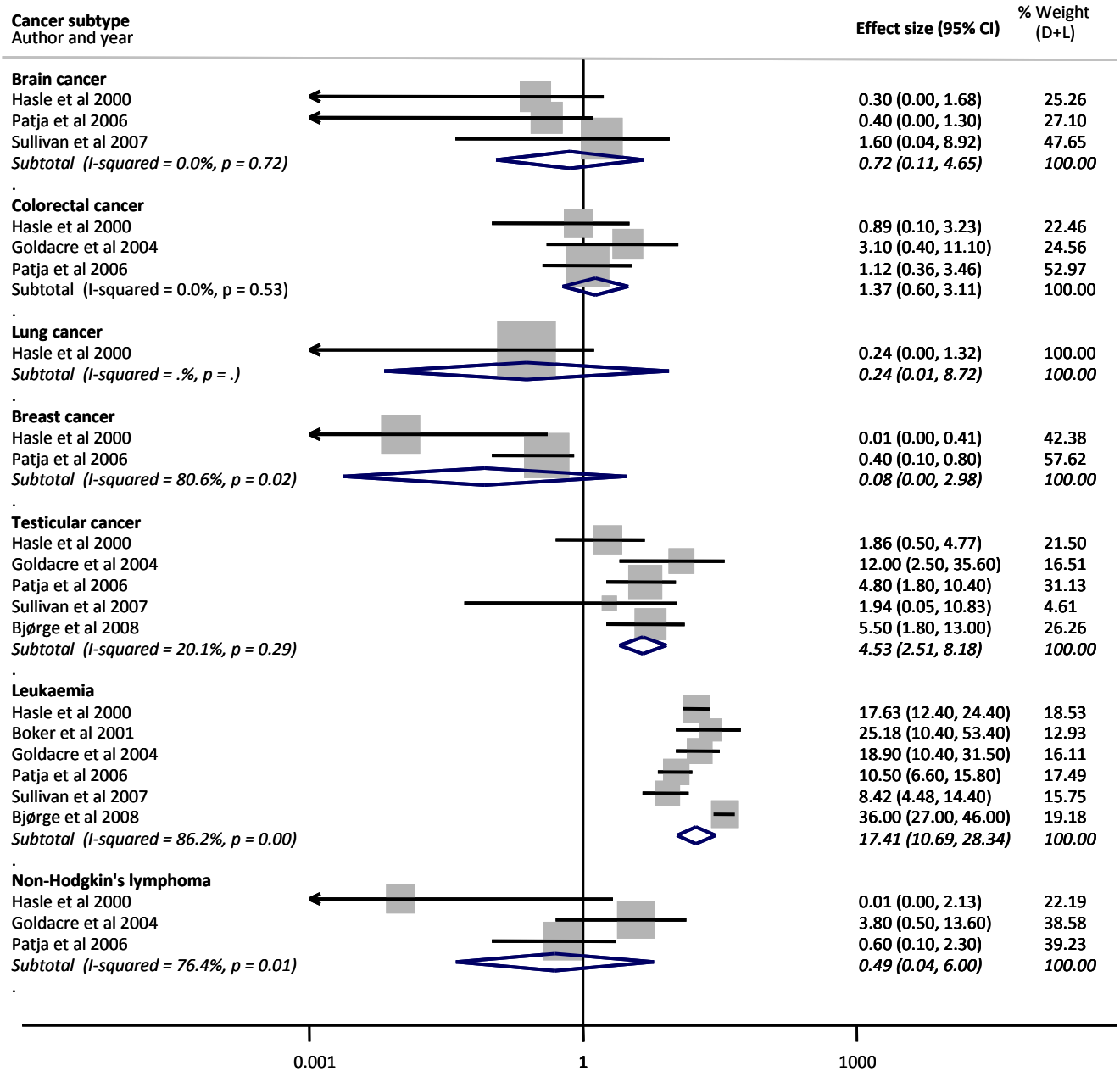


Figure 8: Cancer-specific comorbidity in patients with Huntington's disease