



Suicide risk and mortality among patients with cancer

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Despite substantial progress in cancer therapy in recent decades, patients with cancer remain at high suicide risk. Data from individual studies have not been comprehensively quantified and specific risk factors are ill-defined. We assessed suicide mortality risk according to cancer prognosis, stage, time since diagnosis, gender, ethnicity, marital status, year of recruitment and geographic region. We searched EMBASE, MEDLINE, PsycINFO, Web of Science, CINAHL and Google Scholar for relevant articles up to February 2021. We used a random effects model, performed meta-regression meta-analysis and assessed heterogeneity and publication bias using I^2 , funnel plots and Egger's and Begg's tests. We performed a systematic review including 62 studies and 47,035,065 patients. To avoid patient sample overlap, the meta-analysis was performed on 28 studies, involving 22,407,690 patients with cancer. Suicide mortality was significantly increased compared with the general population (standardized mortality ratio = 1.85, 95% confidence interval = 1.55–2.20). Risk was strongly related to cancer prognosis, cancer stage, time since diagnosis and geographic region. Patients with cancer, particularly those with specific risk factors, should be closely monitored for suicidality and need specialized care to reduce short- and long-term risks of suicide.

The Global Burden of Disease Collaboration reported 24.5 million incident cancer cases for 2017, causing 233.5 disability-adjusted life-years and an increasing cancer incidence rate during the last 1.5 decades in 123 of 195 countries¹. For a patient, a diagnosis of cancer is one of the most dramatic and life-changing events, representing a severe psychosocial stressor². Patients with cancer may die by suicide for a number of reasons, including anxiety, pain, loss of perspectives and previous coping strategies, treatment-related adverse events and fatigue³. Suicide is a global public health concern. More than 800,000 people die by suicide each year, with 20 suicidal attempts being carried out for each death by suicide⁴.

Suicidal ideations among patients with cancer may arise through a patient's will for self-autonomy and self-control, but they can also occur in the context of severe depressive symptoms⁵. Whatever the cause, suicides are difficult to handle for next-of-kin and caregivers, who may be affected far beyond the loss of the patient⁶.

The effectiveness of comprehensive psychological, psychiatric and psychotherapeutic management of patients with cancer is underscored by the estimation that every US\$1.00 spent on psychotherapeutic interventions and interventions that strengthen linkages among different health-care providers saves US\$2.50 in the cost of suicides⁷.

Increased suicide rates in patients with cancer compared with the general population have been observed for decades in different populations around the globe^{8–21}. However, only few meta-analyses examined suicide risk among patients with cancer and those studies lacked a comprehensive literature search, generated incomplete findings regarding certain risk groups and/or analyzed only specific cancer entities, and/or presented only incidence rates without comparisons with the general population^{22–27}. The research objectives of the present study were, therefore, to quantify overall suicide mortality in patients with cancer compared with the general population, followed by comprehensive subgroup analyses to identify specific risk factors of particular interest, including cancer prognosis, cancer stage, time since diagnosis, gender, ethnicity, marital status and

geographic region, which have not been performed in a meta-analysis to date. Our aim was to gain a deeper knowledge of risk factors for suicide in patients with cancer to enhance oncological and psychiatric practice, improve the quality of life of patients with a cancer diagnosis and help develop targeted interventions.

Results

Study population. Our database search led to 12,188 records; an additional 5 studies were manually added by the authors. After exclusion of duplicates, 7,565 records were screened by titles and abstracts. A total of 768 of 934 reports did not meet the inclusion criteria and were excluded during full text screening (Fig. 1). In 62 of the remaining 166 cohort studies, results were presented as standardized mortality ratios (SMRs) and were therefore included, yielding a study population of over 47,035,065 patients with cancer, 69,401 of whom died by suicide during at least 107,961,345 person-years of follow-up. Sample sizes of included studies ranged from 8,908 to 8,651,569 patients: 52 studies encompassed both genders, 8 studies were conducted in men only whereas 2 focused on women, for a total sample size of >21,648,774 men and >20,538,111 women. There were 30 studies performed in the USA, 25 in Europe, 1 combined data from both the USA and Europe, 5 were carried out in Asia and 2 were performed in Australia (Supplementary Table 1). Collectively, those studies were at least age adjusted and examined suicide mortality across 35 distinct cancer sites, grouped into 21 cancer entities. All 62 included studies were classified as high quality according to the Newcastle–Ottawa Scale (NOS) (Supplementary Table 2).

Next, we screened the 62 included studies for potential patient overlap, which may occur in studies using the same databases with overlapping recruitment times and tumor entities. As patient overlap may significantly bias the results from meta-analyses²⁸, we further excluded all studies with a potential risk of sample overlap and remained with a core set of 28 independent studies comprising 22,407,690 cancer patients, which were subsequently meta-analyzed. An overview of sample sizes of subgroups included in the present meta-analysis is shown in Supplementary Table 3.

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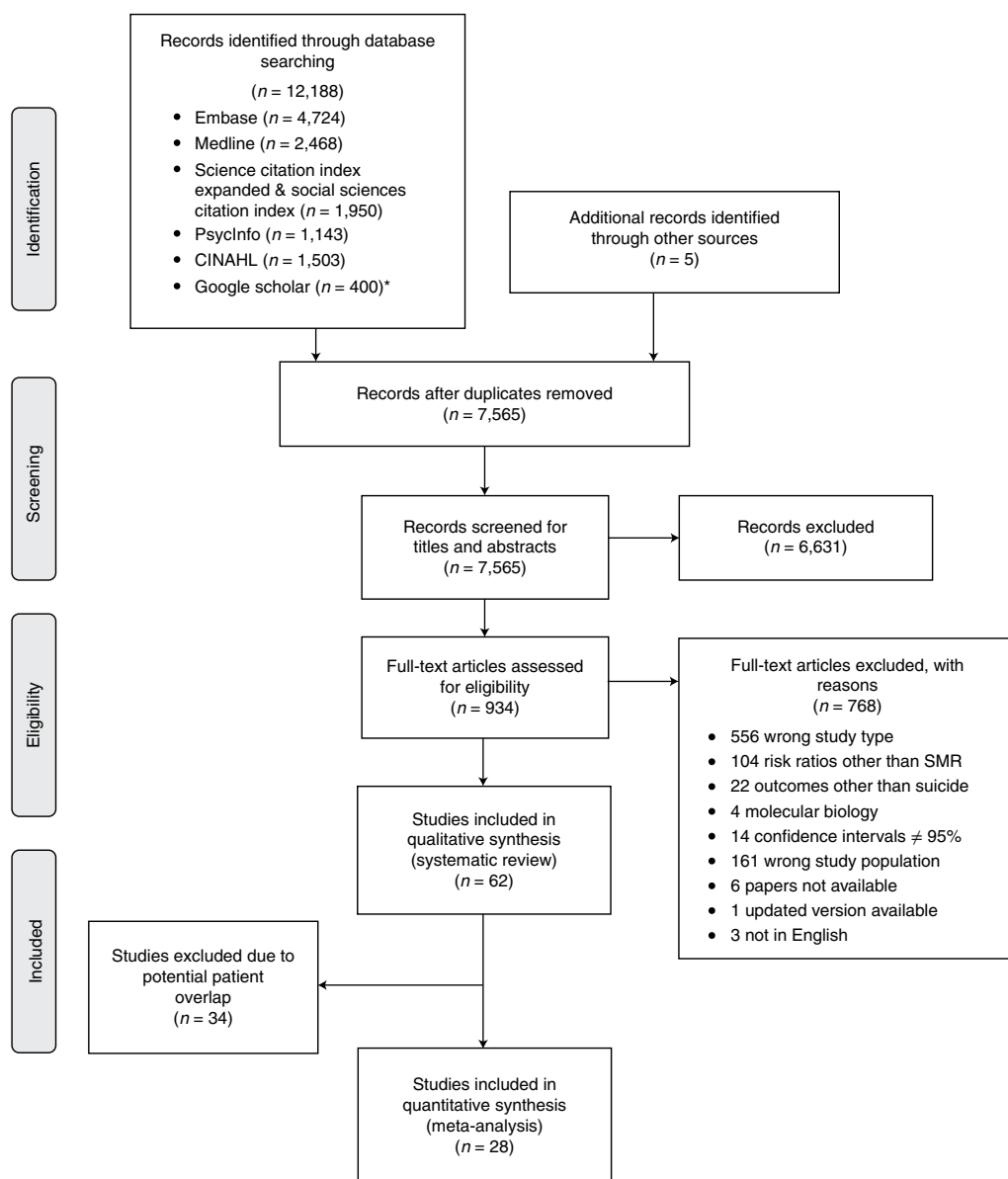


Fig. 1 | PRISMA flow diagram for details on the study selection process of the present meta-analysis and systematic review. n, Number of included studies. *Due to the limitations of the Google Scholar research platform, search results are limited to 400 entries, 200 of which could be exported and were sorted by relevance.

Overall analysis. Our overall analysis revealed an 85% increased suicide mortality rate among patients with cancer compared with the general population (SMR=1.85, 95% confidence interval (CI)=1.55–2.20), with considerable heterogeneity among studies (percentage of variation across studies that is due to heterogeneity rather than chance (I^2)=99.37%, P value for heterogeneity < 0.0001) (Fig. 2). We therefore performed stratified analyses to detect potential causes of heterogeneity.

Cancer prognosis, stage and time since diagnosis. First, we grouped cancers according to 5-year relative survival, defined as good prognosis (5-year survival rates >90%), intermediate prognosis (5-year survival rates 50–90%) and poor prognosis (5-year survival rates <50%)^{29–31}. Suicide mortality differed markedly according to cancer prognosis (P value for difference < 0.001) (Figs. 3 and 4). Specifically, suicide mortality was low (SMR = 1.50, 95% CI = 1.12–2.00) with high heterogeneity between studies

(I^2 = 98.97%; P value for heterogeneity < 0.0001) for cancers known to have a good prognosis, including thyroid cancer, nonmetastatic melanoma and nonmelanoma skin cancer, prostate cancer and testicular cancer. Suicide mortality was intermediate (SMR = 1.98, 95% CI = 1.56–2.51) with high heterogeneity between studies (I^2 = 98.99%; P value for heterogeneity < 0.0001) for cancers known to have a moderate prognosis, including cancers of the breast, female genital system, colon and rectum, urinary system including kidney and bladder, leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma and cancers of the connective tissue. Suicide mortality was high (SMR = 3.53, 95% CI = 2.75–4.53) with high heterogeneity between studies (I^2 = 98.80%; P value for heterogeneity < 0.0001) for cancers known to have a poor prognosis, including cancers of the liver and biliary system, stomach, head and neck, central nervous system, pancreas and esophagus, and mesothelioma. Risk estimates for each cancer site are shown in Extended Data Fig. 1.

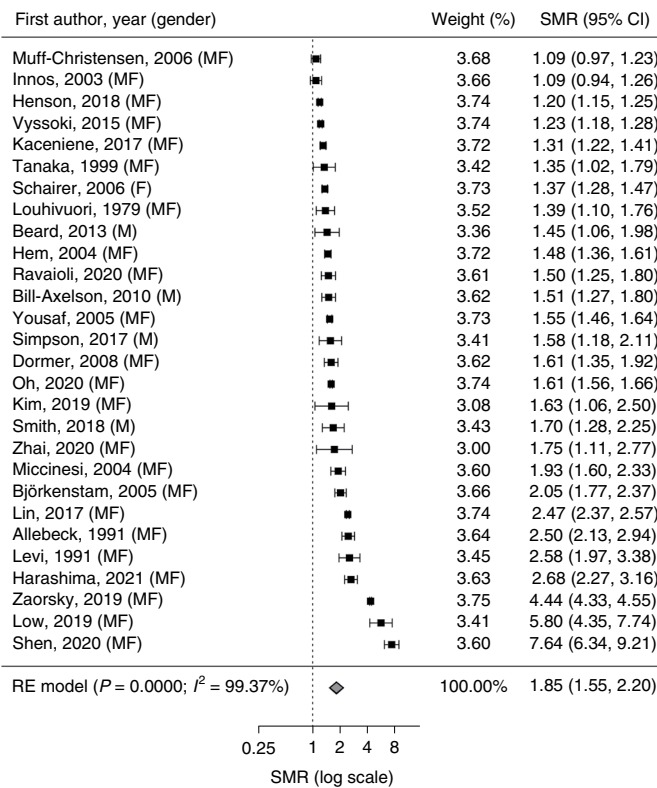


Fig. 2 | Forest plot of random effect meta-analysis including 28 cohort studies of suicide in patients with cancer compared with the general population. Studies are listed by magnitude of risk estimate and weighted by their contribution to the summary risk estimate ($I^2 = 99.37\%$, P value of heterogeneity < 0.0001). F, women only; M, men only; MF, men and women combined; RE, risk estimate. Squares depict SMR point estimates and error bars their corresponding 95% CIs.

A statistically significant difference in suicide mortality was also observed between cancer stages (P value for difference < 0.001 ; Fig. 4). Specifically, suicide mortality was low (SMR = 1.50, 95% CI = 1.16–1.94) with high heterogeneity between studies ($I^2 = 98.99\%$; P value for heterogeneity < 0.0001) for cancers of an earlier stage, defined as ‘carcinoma in situ’, ‘localized’, ‘regional’, ‘early’, ‘M0’, ‘stage I’, ‘stage II’ or ‘stage III’. Suicide mortality was high (SMR = 3.12, 95% CI = 2.22–4.38) with high heterogeneity between studies ($I^2 = 97.04\%$; P value for heterogeneity < 0.0001) for cancers of a late stage, defined as ‘distant’, ‘advanced’, ‘late’ or ‘M1’.

We proceeded to explore further potential sources of heterogeneity (Fig. 4). Suicide mortality was higher within the first year of cancer diagnosis than ≥ 1 year after diagnosis (P value for difference < 0.001), with high heterogeneity between studies ($I^2 = 99.12\%$; P value for heterogeneity < 0.0001). Multiple meta-regression revealed that data for cancers with poor prognosis were redundant to suicide mortality within the first year after diagnosis, with poor cancer prognosis being the dominant variable.

Geographic region, marital status, gender, year of recruitment and ethnicity. Suicide mortality among patients with cancer was higher in the USA than in Europe, Asia or Australia when compared with the respective general population (P value for difference = 0.01; $I^2 = 99.33\%$; P value for heterogeneity < 0.0001). Suicide mortality was also higher in unmarried patients with cancer compared with patients living in a marriage, but the results did not reach statistical significance (P value for difference = 0.41; $I^2 = 99.57\%$; P value for heterogeneity < 0.0001). By comparison, suicide mortality did

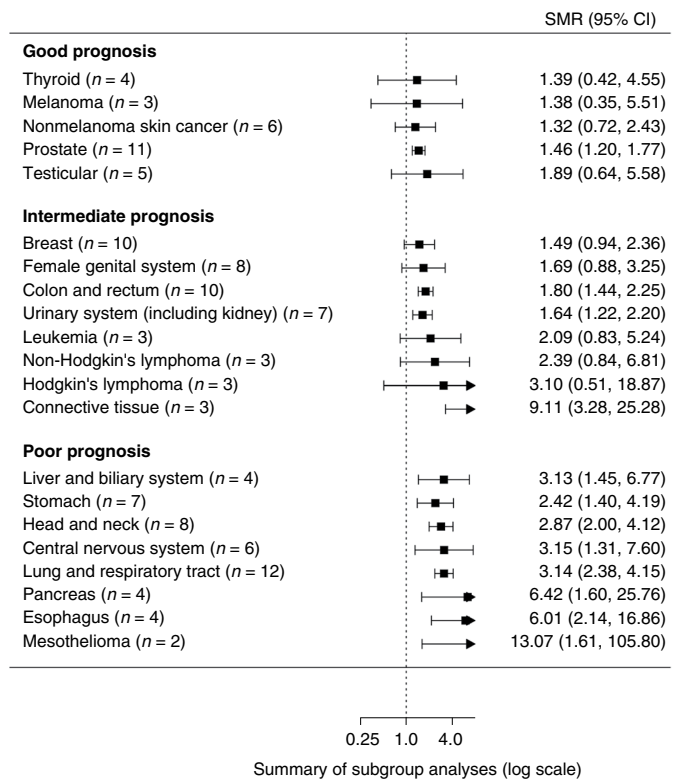


Fig. 3 | Summary Forest plot of cancer sites, by prognosis. Good prognosis was defined as a 5-year survival rate $> 90\%$; intermediate prognosis was defined as a 5-year survival rate of 50–90%; poor prognosis was defined as a 5-year survival rate $< 50\%$ ($I^2 = 98.97\%$, P value heterogeneity < 0.0001). Cancer sites with $n = 1$ were not included in the analysis. Squares depict SMR point estimates and error bars their corresponding 95% CIs.

not significantly vary by gender (P value for difference = 0.41), year of recruitment (P value for difference = 0.58) or ethnicity (P value for difference = 0.99), with African-Americans showing a slightly decreased suicide mortality rate compared with other ethnic groups (Table 1).

The risk factors are also summarized by grade of suicide mortality (low, intermediate and high) as depicted in Table 2.

Sensitivity analyses using all 62 eligible studies. In a sensitivity analysis, we meta-analyzed all 62 eligible studies from our systematic review comprising 47,035,065 patients with cancer. Despite the risk of sample overlap, particularly between Surveillance, Epidemiology, and End Results (SEER) studies, the results were not substantially different from our main analysis (SMR = 1.94, 95% CI = 1.72–2.18 in the analysis based on 62 studies versus SMR = 1.85, 95% CI = 1.55–2.20 based on 28 studies; Fig. 2 and Extended Data Fig. 2). Similar observations were made for the respective subgroup analyses (Figs. 3 and 4, and Extended Data Figs. 3 and 4).

Assessment of publication bias. A funnel plot showed minor asymmetry around the pooled SMR using all 62 eligible studies regardless of potential sample overlap (Extended Data Fig. 5). However, Begg's correlation and Egger's regression tests indicated no evidence for publication bias (P value for Begg's test = 0.42; P value for Egger's test = 0.4239).

Discussion

Our comprehensive meta-analysis of 28 nonoverlapping studies from 62 high-quality cohort studies revealed that patients with cancer have an almost twofold increased risk of dying by suicide

compared with the general population. In addition, we identified certain patient groups at particularly elevated risk of suicide mortality (summarized in Table 2). Specifically, patients with cancers known to have a poor prognosis and patients with cancer during the initial year after diagnosis showed an approximately 3.5- and 3-fold increased suicide mortality, respectively, compared with the general population. We also found marked geographic variation in suicide mortality, with cancer patients in the USA exhibiting the highest rate of suicide mortality and a 1.5-fold greater suicide mortality than patients with cancer in Europe. In contrast, suicide rates in the general population show no significant differences between European countries and the USA (Extended Data Fig. 6).

Six previous meta-analyses focused on suicide mortality in patients with any type of cancer^{22–27}. An increased overall risk for suicide mortality in patients with cancer compared with the general population was consistently observed in those studies. However, previous meta-analyses lacked comprehensiveness and differed in their sample sizes and statistical power, including only 22 (ref. ²³), 19 (ref. ²²), 36 (ref. ²⁴), 5 (ref. ²⁵), 12 (ref. ²⁶) and 5 (ref. ²⁷) studies, whereas our systematic review was based on 62 studies, of which 28 were meta-analyzed. We evaluated previous systematic reviews and meta-analyses^{22–27} using the PRISMA and ROBIS tools³² and were unable to definitively assess which specific factors explained our larger sample size, although our assessment showed that previous meta-analyses failed to adequately report on their literature search methods or did not encompass a comprehensive range of databases. Furthermore, our study covered more time, which led to the inclusion of at least four additional studies compared with the most recent previous study²⁴.

Previous meta-analyses also differed from our study in terms of the depth of analyses on risk factors for suicide. Although Harris and Barraclough²⁵ reported suicide in cancer patients without considering population subgroups, Ravaoli et al.²² mainly explored overall mortality, gender differences and time since diagnosis, with more detailed analyses limited to their north Italian cohort; Amiri et al.²³ focused on three continents, different cancer sites and gender. Brunckhorst et al.²⁶ and Guo et al.²⁷ limited their analyses to prostate and bladder cancer, respectively. Du et al.²⁴ explored subgroups defined by gender, age, geographic region, time since diagnosis, cancer stage, cancer type and marital status. However, Du et al.²⁴ did not sufficiently account for sample overlap, with potentially biased estimates. Brunckhorst et al.²⁶ reported mostly incidence rates without risk estimate comparisons to the general population. In contrast, our meta-analysis went beyond those analyses, including more databases for the literature search, calculating missing SMRs where data were available and performing additional analyses as well as meta-regression, interaction and sensitivity analyses and—for the first time in a meta-analysis—showing a clear relationship of cancer prognosis to suicide rates among the largest ever reported independent set of patients with cancer (Supplementary Table 4).

The association between cancer prognosis and high suicide mortality may reflect causality by advanced tumor stage and grade resulting in more severe adverse effects on the quality of life of patients with cancer³. The prospect of aggressive cancer therapy, hopelessness due to a life-changing or fatal cancer diagnosis or even existential angst could further increase suicidal thoughts and actions in patients with cancer. Suicide as an act of ultimate self-autonomy and control over one's life may also account for some cases of suicide.

Time since diagnosis was an additional important risk factor for suicide mortality. Patients who survived the first year after diagnosis had a significantly lower risk of suicide mortality, although they still showed an increased risk compared with the general population. Our meta-regression analyses on cancer prognosis and time since diagnosis identified poor cancer prognosis as the crucial variable for suicide mortality in patients with cancer. Previous

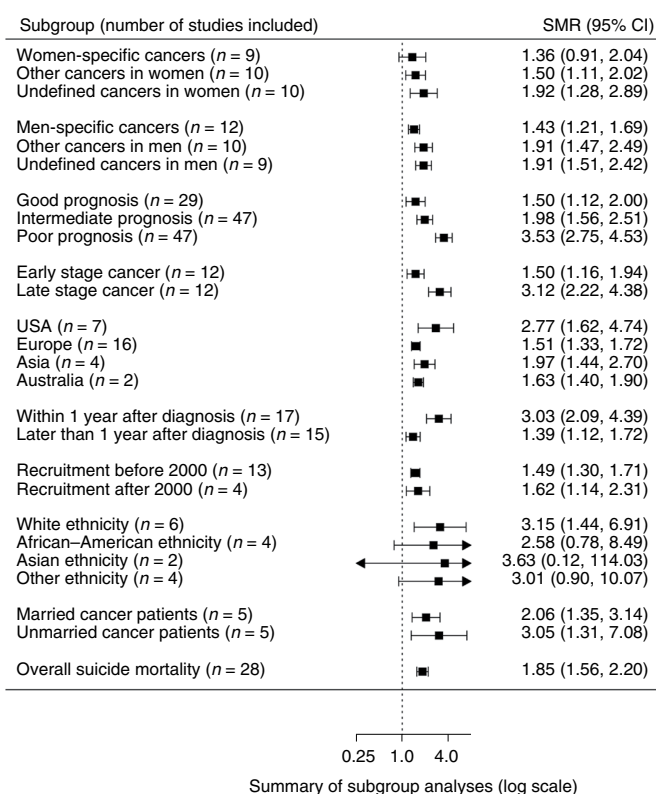


Fig. 4 | Summary Forest plot of subgroup analyses of suicide in patients with cancer. Squares depict SMR point estimates and error bars their corresponding 95% CIs.

studies that identified the first year after diagnosis as being associated with increased suicide rates did not consider the competing effect of cancer prognosis^{9,20,33–35}. Apart from the distress caused by a cancer diagnosis itself, which on its own is a potential risk factor for suicidal behavior, the high mortality rate within the first year after diagnosis could additionally be explained by risk factors that are similar to those for cancer prognosis, for example, cancer stage or the plethora of social and personal consequences of any life-changing event. In 80% of suicides, recent life-changing events have been reported³⁶. Poor cancer prognosis and cancer stage may add to the distress experienced by a newly diagnosed patient with cancer, particularly during the first year after diagnosis. Therefore, the psychological consequences caused by a cancer diagnosis and the primary treatment itself should be closely monitored in the initial year after diagnosis³⁷. Considerable heterogeneity was observed among studies reporting on subgroups according to time since diagnosis. In line with previous studies, the first year after diagnosis was the most crucial and statistically relevant time cut-point for suicide mortality, even though prostate cancer patients can exhibit risk of suicidal death for up to 15 years after diagnosis compared with the general population³⁸.

Our analysis revealed that geographic region is an important risk factor for suicide mortality in patients with cancer. Specifically, US cancer patients showed the most pronounced relative suicide mortality increase worldwide, with a significant difference to European cancer patients. Whereas most European countries have universal health care with easy access for a broad majority of the population, the USA is the only industrialized nation without a universal health-care system. According to the US Centers for Disease Control and Prevention (CDC), an estimated 49.9 million Americans (16.3% of the population) were uninsured in 2010, with an even higher rate of underinsurance³⁹. Lacking universal health care, cancer therapy

Table 1 | Summary table of meta-regression tests

Co-variable	SMR	95% CI	P value	q value
Women	1.59	1.27-1.97	0.41	0.53
Other cancers in women	1.50	1.11-2.02	-	
Women-specific cancers	1.36	0.91-2.04	0.75	
Undefined cancers in women	1.92	1.28-2.89	0.20	
Men	1.74	1.52-2.00	0.17	0.31
Other cancers in men	1.91	1.47-2.49	-	
Men-specific cancers	1.43	1.21-1.69	0.11	
Undefined cancers in men	1.91	1.51-2.42	0.98	
Prognosis	2.31	1.97-2.70	<0.001	<0.001
Good prognosis	1.50	1.12-2.00	-	
Intermediate prognosis	1.98	1.56-2.51	0.15	
Poor prognosis	3.53	2.75-4.53	<0.001	
Time since diagnosis	2.09	1.62-2.70	<0.001	0.001
Later than 1 year	1.39	1.12-1.72	-	
Within 1 year	3.03	2.09-4.39	<0.001	
Cancer stage	2.14	1.66-2.76	<0.001	0.002
Early stage	1.50	1.16-1.94	-	
Late stage	3.12	2.22-4.38	<0.001	
Geographic region	1.83	1.54-2.17	0.01	0.03
Europe	1.51	1.33-1.72	-	
USA	2.77	1.62-4.74	0.001	
Asia	1.97	1.44-2.70	0.27	
Australia	1.63	1.40-1.90	0.79	
Year of recruitment	1.52	1.33-1.73	0.58	0.66
Before 2000	1.49	1.30-1.71	-	
After 2000	1.62	1.14-2.31	0.58	
Marital status	2.54	1.59-4.03	0.41	0.53
Not married	3.05	1.31-7.08	-	
Married	2.06	1.35-3.14	0.41	
Ethnicity	3.03	1.72-5.36	0.99	0.99
White	3.15	1.44-6.91	-	
African-American	2.58	0.78-8.49	0.81	
Asian	3.63	0.12-114.03	0.88	
Other	3.01	0.90-10.07	0.96	

Results are presented for the overall test as well as the comparison of each category compared with the reference category (depicted by a dash '-'). Variables with statistical significance are presented as emboldened. P value is the summary effect of each subgroup in the meta-analysis; the q value is the false discovery rate-adjusted P value of the overall test corrected for multiple testing.

Table 2 | Summary table of risk factors by grade of suicide mortality

Risk factor	Low risk	Intermediate risk	High risk
Prognosis	Good	Intermediate	Poor
Cancer stage	-	Early	Late
Time after diagnosis	Later than 1 year	-	Within 1 year
Men	Men-specific cancers	Other cancers in men	-
Women	Women-specific cancers	Other cancers in women	-
Geographic region	-	Europe, Australia, Asia	USA (all ethnicities)

Risk factors were stratified according to their SMR. As low risk, an SMR ≤ 1.50 was defined, risk factors with SMR 1.51-1.99 were included as intermediate and high risk was defined as SMR ≥ 2.00 . No data were available for risk categories marked by a dash '-'.

represents an enormous financial burden for US citizens and their families, causing bankruptcy or forcing patients to abandon their cancer care altogether⁴⁰. Poverty and deprivation are additional risk factors for suicide⁴¹. Other explanations for increased risk of suicide among US cancer patients compared with the general US population may include cultural differences such as a strong belief in self-autonomy⁴² or easy access to firearms. In the USA in 2018, 24,432 of 48,344 suicides were carried out by firearms⁴³. This represents a tenfold increased rate compared with European countries, for example, Italy and Germany⁴⁴. In the USA, cancer patients show an increased odds ratio (OR) of 1.35 (95% CI=1.17–1.56) of dying by suicide by firearms compared with the general population⁴⁵.

In a further subgroup analysis based on studies from the USA, African-Americans showed a slightly decreased risk of suicide after a cancer diagnosis compared with whites, Asians and other ethnic groups. Possible reasons for this observation are misclassification of suicides⁴⁶ in African-Americans, strong religious beliefs, family bonds and communalism observed in African-Americans^{46–48}. The only European study analyzing suicides in different ethnic groups⁸ showed increased suicide mortality in patients with cancer only for whites, whereas Asians, Africans and other ethnicities all showed a lower or not significantly increased suicide mortality.

We found suggestively higher suicide risks among men than among women with cancer, but these results did not reach statistical significance. Our results in cancer patients do not mirror the higher suicide rates among men than women observed in the general population²⁴ because the increased baseline risk for suicide among men in the general population was accounted for by our SMR calculation. The statistically nonsignificant tendency toward lower suicide risks observed in women with cancer may be due to greater resilience and stronger social and psychological support in women than in men with cancer⁴⁹.

We observed an influence of marital status on suicide mortality in patients with cancer. Married patients with cancer showed lower suicide mortality than unmarried patients with cancer, that is, single, widowed or separated patients. As being married is known to prevent suicide in general⁵⁰, fundamental additional resilience deriving from a marriage partner and friend could be a strong pillar in coping with a cancer diagnosis. Due to a lack of data in the primary studies, we were unable to evaluate suicide risk among patients with cancer in a domestic relationship but not married.

The present study is the largest and most comprehensive meta-analysis on suicide mortality in patients with cancer to date. With 22,407,690 independent patients with cancer from a total of at least 47,035,065 patient records, subgroup analyses were amply powered to detect relationships in patient groups at particular risk. Therefore, our study has numerous relevant clinical implications for the treatment of patients with cancer. The observed heterogeneity across subgroups resulted from the various cancer sites examined, potential differences in documenting cases of cancers and deaths across national registries, and a certain degree of divergence in analytic strategies across the primary studies.

We were unable to address suicidal ideations, suicide attempts, psychiatric comorbidities, depressive symptoms, psychotherapeutic care and the influence of pharmacological antidepressant therapy as additional outcomes because only one of the included studies focused on suicidal thoughts and attempts³³, with the addition of only one study taking into account the influence of prediagnosis psychiatric care on suicide mortality in patients with cancer⁵¹. Although individual primary studies (for example, Smalylet et al.⁵²) identified age as additional possible risk factor for suicide in patients with cancer, we were unable to perform a summary analysis of age because of the large overlap of age categories between studies.

We were not able to evaluate physician-assisted death compared with suicidal death. Among the countries with specific data on suicide mortality in our meta-analysis, Switzerland and Australia

were the only countries with legalized physician-assisted death (Switzerland since 2012, Australia since 2017). For Switzerland, only one primary study was available (Levi et al.¹⁵). The most recent primary study in Australia⁵³ was conducted with patients recruited until 2007, before the change in legislation.

Depending on privacy restrictions and classification criteria of different national mortality databases, misreporting of suicides as cause of death cannot be excluded. The level of adjustment for confounders was not homogeneous across studies because some studies controlled for age and gender only, whereas other studies additionally adjusted for marital status and ethnicity.

Due to limited availability of data from low-income countries, the present study is primarily generalizable to high-income countries. Creating a global literature base including low- and middle-income countries would help improve future analyses and allow a more comprehensive assessment of suicide among cancer patients.

Despite immense progress in cancer therapy and prognosis in the past decades, suicide remains an important cause of death in patients with cancer. Access to professional medical care and follow-up should therefore represent an integral component of any cancer therapy. Recognizing and attenuating the adverse psychological impact of a cancer diagnosis may not only reduce suicide rates but also improve overall quality of life. The identification of patients at particular risk for suicide could increase the awareness of caregivers on this topic, which may lead to increased screening for suicidality and earlier involvement of specialized care. Completed suicides are usually preceded by suicidal thoughts or attempts. Future studies should focus on identifying risk factors for anxiety and depression preceding suicide to help develop suicide prevention strategies in patients with cancer. Intervention studies could quantify the effect of psychotherapy on the prevention of suicide in patients with cancer, including subgroup analyses by marital status, prognosis, cancer stage and comorbidities. A particular focus should be given to the role of psychiatric disorders such as depression preceding and following a cancer diagnosis. Future research should also focus on suicide compared with assisted death and should address suicide rates for different cancer sites, treatment options and end-of-treatment situations. Furthermore, studies need to determine the cause of suicide among patients with cancer, that is, to distinguish between the wish for self-autonomy and severe depression. Also, the role and efficacy of pharmacological antidepressant treatment among patients with cancer with depressive symptoms have not been well studied, particularly in elderly patients^{54,55}.

Screening for suicide, especially among patients with cancers with intermediate or high risk of suicide mortality, requires even quicker review and follow-up than for other symptoms of depression or anxiety, and should also be available in centers with low resource levels devoted to screening and biopsychosocial care⁵⁶. Whereas a question on suicide is not included in the Distress Thermometer, a landmark tool for measuring the biopsychosocial impact of cancer and its treatment, and in other common measures to assess symptoms of anxiety and depression, such as the Hospital Anxiety and Depression Scale, few questionnaires screen for suicidality, as, for example, the Patient Health Questionnaire 9 (ref. ⁵⁷). There are important challenges in screening for suicide in a routine clinical encounter, including the still existing stigmatization around mental health and particularly suicide⁵⁸ or the fear that reporting of suicidal ideation and planned self-harm could result in involuntary commitment of an individual. Suicidal attempts represent the most important risk factor for suicidal death. In up to 66% of patients dying by suicide, an antecedent communication of their intent could be observed⁵⁹ and up to 45% of deaths by suicide were preceded by contacts with mental health and primary care providers⁶⁰. The initial assessment of the acute danger of suicide is of particular importance⁶¹. Previous studies have shown that talking openly about suicidal thoughts and ideations reduces pressure and suicide

risks among affected patients⁶². Therefore, screening tools should be accompanied by personal interviews and early involvement of specialized care.

In conclusion, the current meta-analysis with systematic review identified an increased suicide mortality among patients with cancer compared with the general population. In addition, specific risk factors for suicide were determined, including cancer prognosis, cancer stage, time since cancer diagnosis and geographic region. These findings strongly imply the need for close medical observation strategies during clinical follow-up. Future research should focus on improving the quality of life of patients being given a cancer diagnosis, identifying early signs of suicide intentions and reducing short- and long-term risk of suicide not only for patients but also for communities and society as a whole.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-022-01745-y>.

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Methods

The present study was registered in PROSPERO (ID: CRD42021265254).

Search strategy, selection criteria and data extraction. We carried out a systematic literature search of English language articles on completed suicides in patients with cancer published from inception to February 2021 in Embase (Ovid), MEDLINE (Ovid), PsycInfo (EBSCOhost), Science Citation Index Expanded & Social Sciences Citation Index (Web of Science), CINAHL (EBSCOhost) and Google Scholar (Supplementary Table 5). We also screened the reference lists of included articles for additional studies. Our search strategy followed the recommendations of the Peer Review of Electronic Search Strategies (PRESS)⁶³, the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)⁶⁴ and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines⁶⁵. A PRISMA-S checklist is presented in Supplementary Table 6 (ref. ⁶⁶).

Cancer was defined according to the *International Classification of Disease* (ICD)-10 (ref. ⁶⁷) codes C00–C97 and suicide was defined according to the ICD-10 codes X60–X84 (intentional self-harm) and Y87.0 (sequelae of intentional self-harm). We disregarded ICD-10 codes representing undetermined or nonclassifiable violent deaths. We included observational studies of patients with any diagnosis of cancer and noncancer individuals as a control group that analyzed death by suicide as the outcome, with suicide rates and published observed numbers of deaths or an SMR as risk estimate and corresponding 95% CIs. We did not include studies that presented ORs or hazard ratios because these risk estimates are typically compared with study-specific internal control groups and not with the general population. Studies in languages other than English were excluded to avoid translation bias. Cross-sectional studies were excluded due to their low validity and their lack of follow-up time after cancer diagnosis. Exclusion criteria of studies screened for full text are listed in Fig. 1. One case–control study²¹ met our inclusion criteria but was excluded to avoid bias by study-type heterogeneity. Where available, risk estimates were calculated using data from the primary studies.

The study selection process was performed independently by two authors (M.H. and L.H.) and disagreements were resolved by a third researcher (C.S.). The workflow and reasons for excluding articles are shown in the PRISMA-Flowchart (Fig. 1).

We extracted data about the first author, year of publication, study population size, number of suicide cases, geographic region, length of follow-up, tumor type, adjustment factors and SMRs and their CIs. If several models were reported, the most comprehensively adjusted model was used. If analyses were provided for both men and women, we considered genders separately. Study quality was assessed using the NOS⁶⁸. Studies assigned seven or more points were classified as high-quality studies, whereas studies assigned fewer than seven points were considered to be moderate- to low-quality studies. More details about the methods are reported in the [Supplementary Appendix](#).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Data in the published article (and its [Supplementary Information](#)) have been presented where possible in aggregated form. Data from primary studies are publicly available within the databases listed in [Supplementary Information](#). The datasets generated and/or analyzed during the current study are available from C.S. (by mail at Corinna.Seliger-Behme@med.uni-heidelberg.de) upon reasonable request as part of a scientific collaboration with adherence to standards of good scientific practice, although restrictions may apply due to privacy reasons and ongoing research projects. Data sharing will require a Materials Transfer Agreement (MTA) and is limited to noncommercial use. Requests will be answered within 4 weeks.

Code availability

All codes were adapted using R software, v.4.0.2 and v.4.1.1. Data sheets were created using Microsoft Excel v.16.57. The codes that support the findings of this study are available from the corresponding author (C.S.) (by mail at Corinna.Seliger-Behme@med.uni-heidelberg.de) upon reasonable request as part of a scientific collaboration with adherence to standards of good scientific practice, although restrictions may apply due to privacy reasons and ongoing research projects. Data sharing will require an MTA and is limited to noncommercial use. Requests will be answered within 4 weeks.

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Author contributions

M.H. was responsible for conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, visualization and writing (original draft and writing, review and editing). L.H. was responsible for conceptualization, data curation, investigation, resources and writing (review and editing). H.J. was responsible for conceptualization, data curation, formal analysis, investigation, methodology, resources, software, supervision, validation, visualization and writing (review and editing). P.K. was responsible for conceptualization and writing (review and editing). H.K. performed conceptualization, investigation, resources and writing (review and editing). M.L. was responsible for conceptualization, methodology, supervision and writing (review and editing). C.S. performed conceptualization, investigation, methodology, resources, project administration, supervision, validation and writing (review and editing).

Competing interests

The authors declare no competing interests.

Additional information

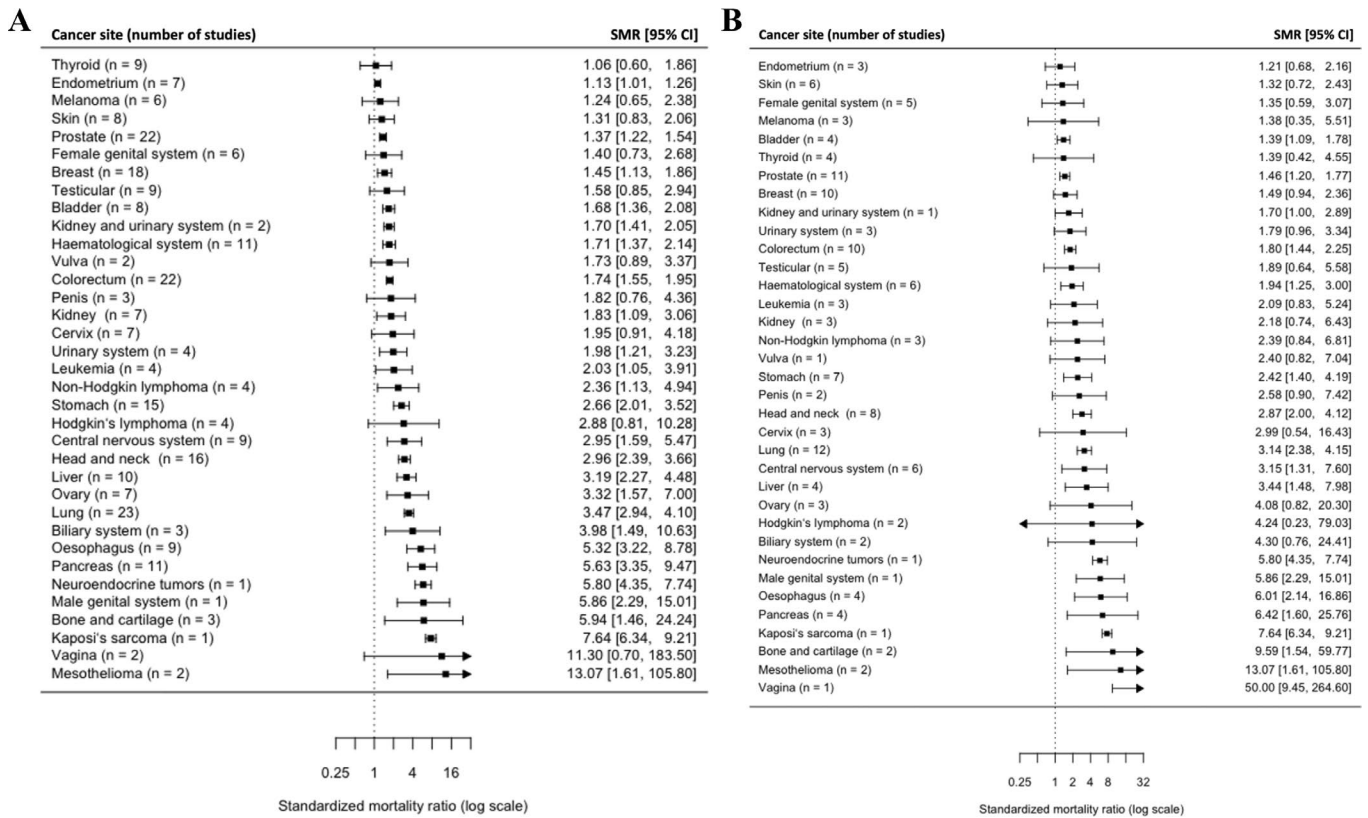
Extended data are available for this paper at <https://doi.org/10.1038/s41591-022-01745-y>.

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41591-022-01745-y>.

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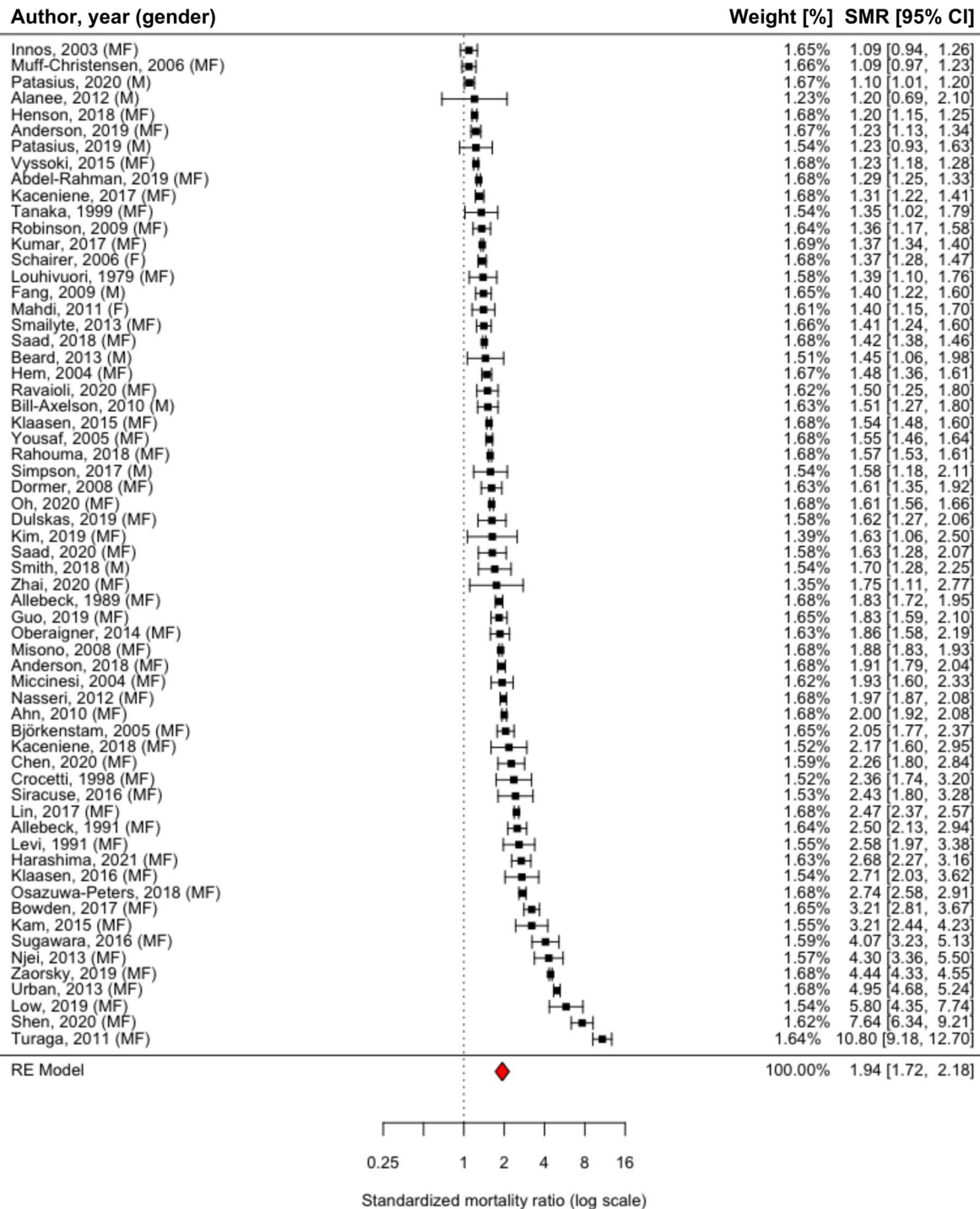
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Extended Data Fig. 1 | Forest plot of individual cancer sites of all studies included in the (A) systematic review and (B) meta-analysis, by magnitude of risk estimate. $I_{SR}^2 = 98.86\%$ and $I_{MA}^2 = 99.03\%$, P -heterogeneity < 0.0001 . Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; I_{SR}^2 , I^2 -statistic for systematic review; I_{MA}^2 , I^2 -statistic for meta-analysis. Squares depict SMR point estimates and error bars their corresponding 95% confidence intervals.

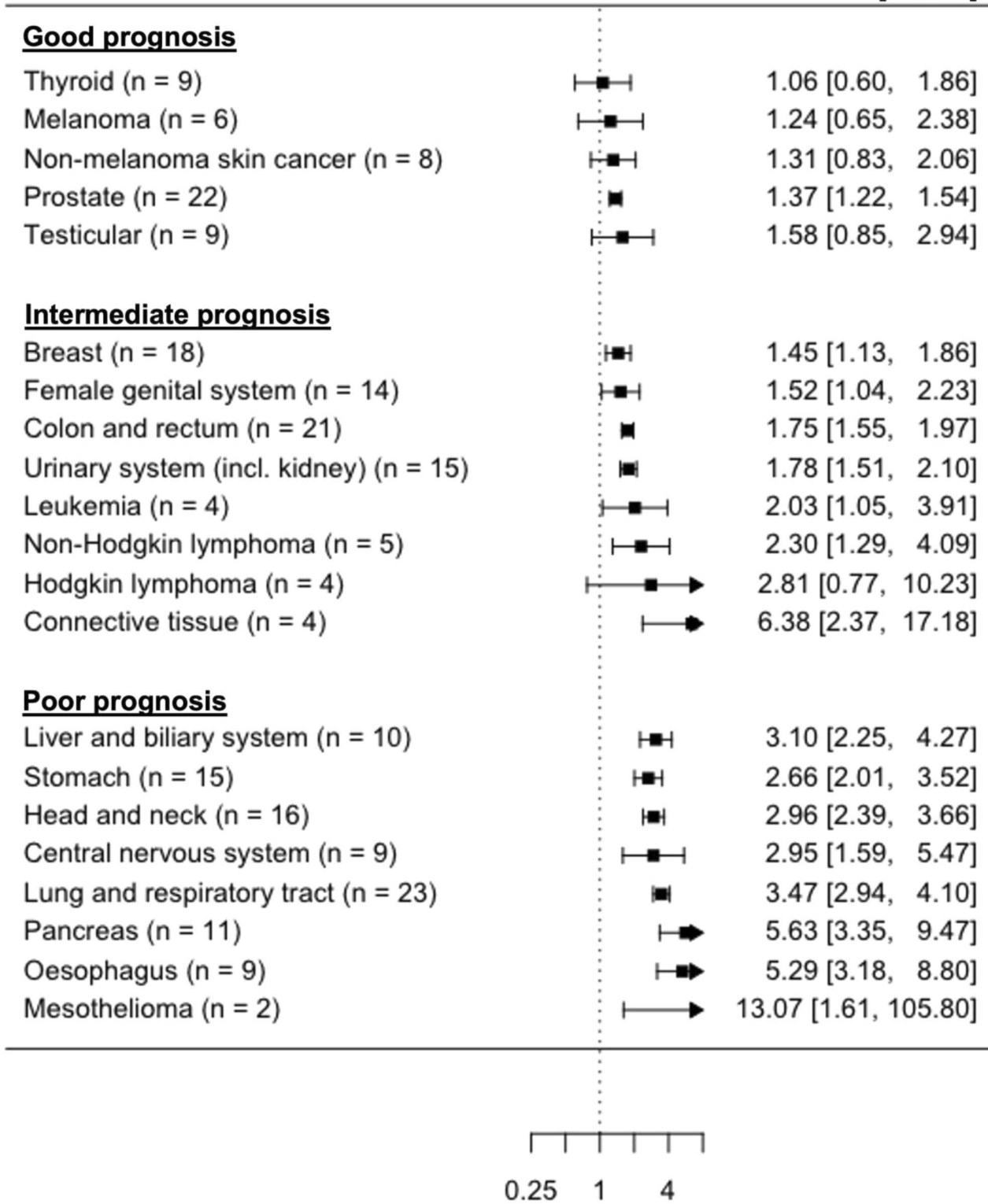
Overall suicide mortality in cancer patients compared to the general population



Extended Data Fig. 2 | Forest plot of random effects meta-analysis including 62 cohort studies of suicide in cancer patients extracted from all databases. Studies are listed by magnitude of risk estimate and weighted by their contribution to the summary risk estimate. $I^2 = 99.55\%$, P -heterogeneity < 0.0001 . Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; MF, men and women combined; M, men only; F, women only; RE, risk estimate. Squares depict SMR point estimates and error bars their corresponding 95% confidence intervals.

Cancer group (number of studies)

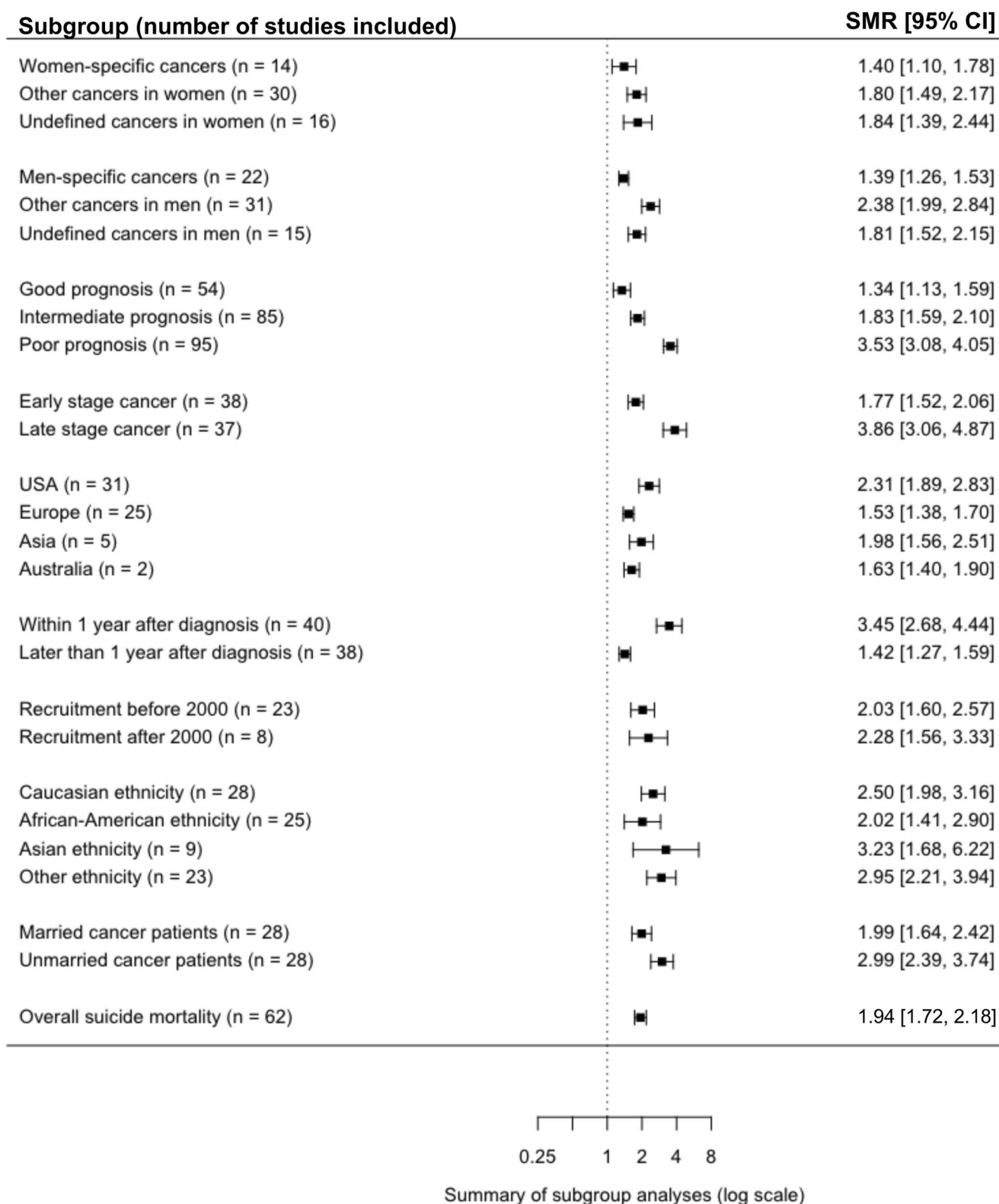
SMR [95% CI]



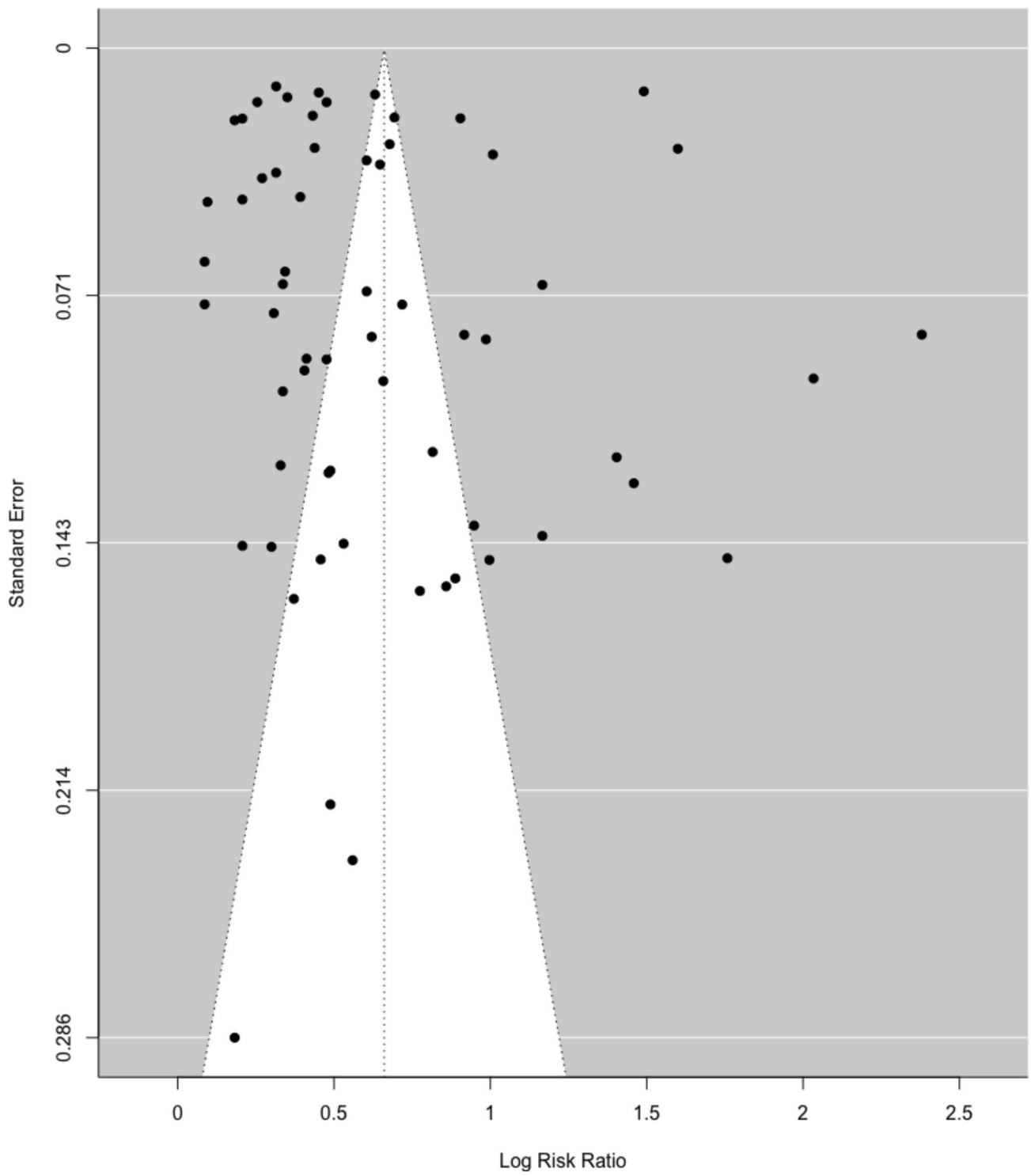
Summary of subgroup analyses (log scale)

Extended Data Fig. 3 | See next page for caption.

Extended Data Fig. 3 | Summary forest plot of cancer sites, by prognosis based on 62 studies. Good prognosis was defined as a 5-year survival rate of >90%; medium prognosis was defined as a 5-year survival rate of 50–90%; poor prognosis was defined as a 5-year survival rate of <50%. $I^2=99.00\%$, $P\text{-heterogeneity}<0.0001$. Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; n, number of studies included in the analysis; cancer sites with $n=1$ were not included in the analysis.



Extended Data Fig. 4 | Summary forest plot of subgroup analyses of suicide in patients with cancer based on 62 studies. Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; n, number of studies included in the analysis.



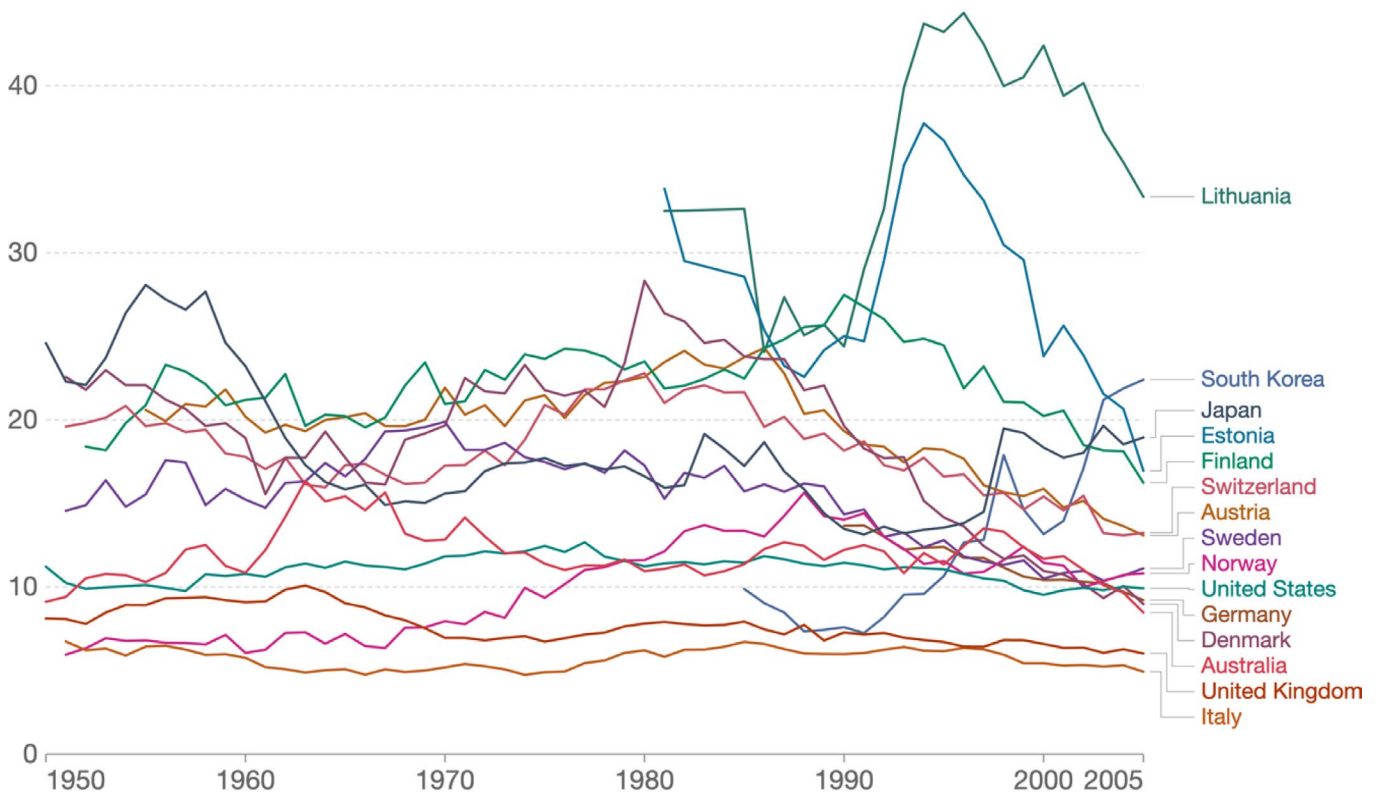
Extended Data Fig. 5 | See next page for caption.

Extended Data Fig. 5 | Funnel plot of random effects meta-analysis including 62 risk estimates of suicide in cancer patients. Two-sided P-value for Begg's test = 0.42; Two-sided P-value for Egger's test = 0.4239.



Suicide rates by country, 1950 to 2005

Suicides per 100,000 people per year. The rate is adjusted for the changing age structure of the population.



Source: World Health Organization (2005)

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Extended Data Fig. 6 | Suicide rates in the general population of countries included in the present meta-analysis, except Taiwan (data not available). Data presented by country, from 1950 to 2005.

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Policy information about [cell lines](#)

Cell line source(s)	<i>State the source of each cell line used.</i>
Authentication	<i>Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.</i>
Mycoplasma contamination	<i>Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.</i>
Commonly misidentified lines (See ICLAC register)	<i>Name any commonly misidentified cell lines used in the study and provide a rationale for their use.</i>

Palaeontology and Archaeology

Specimen provenance	<i>Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.</i>
Specimen deposition	<i>Indicate where the specimens have been deposited to permit free access by other researchers.</i>
Dating methods	<i>If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.</i>
<input type="checkbox"/> Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	<i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research

Laboratory animals	<i>For laboratory animals, report species, strain, sex and age OR state that the study did not involve laboratory animals.</i>
Wild animals	<i>Provide details on animals observed in or captured in the field; report species, sex and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.</i>
Field-collected samples	<i>For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.</i>
Ethics oversight	<i>Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.</i>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	<i>Describe the covariate-relevant population characteristics of the human research participants (e.g. age, gender, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."</i>
Recruitment	<i>Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.</i>
Ethics oversight	<i>Identify the organization(s) that approved the study protocol.</i>

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	<i>Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.</i>
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Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

- | No | Yes | |
|--------------------------|--------------------------|----------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> | Public health |
| <input type="checkbox"/> | <input type="checkbox"/> | National security |
| <input type="checkbox"/> | <input type="checkbox"/> | Crops and/or livestock |
| <input type="checkbox"/> | <input type="checkbox"/> | Ecosystems |
| <input type="checkbox"/> | <input type="checkbox"/> | Any other significant area |

Experiments of concern

Does the work involve any of these experiments of concern:

- | No | Yes | |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | Demonstrate how to render a vaccine ineffective |
| <input type="checkbox"/> | <input type="checkbox"/> | Confer resistance to therapeutically useful antibiotics or antiviral agents |
| <input type="checkbox"/> | <input type="checkbox"/> | Enhance the virulence of a pathogen or render a nonpathogen virulent |
| <input type="checkbox"/> | <input type="checkbox"/> | Increase transmissibility of a pathogen |
| <input type="checkbox"/> | <input type="checkbox"/> | Alter the host range of a pathogen |
| <input type="checkbox"/> | <input type="checkbox"/> | Enable evasion of diagnostic/detection modalities |
| <input type="checkbox"/> | <input type="checkbox"/> | Enable the weaponization of a biological agent or toxin |
| <input type="checkbox"/> | <input type="checkbox"/> | Any other potentially harmful combination of experiments and agents |

ChIP-seq

Data deposition

- Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

*May remain private before publication.**For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session

*(e.g. [UCSC](#))**Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

Flow Cytometry

Plots

Confirm that:

- The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- All plots are contour plots with outliers or pseudocolor plots.
- A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.

Instrument

Identify the instrument used for data collection, specifying make and model number.

Software

Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.

Cell population abundance

Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.

Gating strategy

Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.

- Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type

Indicate task or resting state; event-related or block design.

Design specifications

Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.

Behavioral performance measures

State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).

Acquisition

Imaging type(s)

Specify: functional, structural, diffusion, perfusion.

Field strength

Specify in Tesla

Sequence & imaging parameters

Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.

Area of acquisition

State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.

Diffusion MRI

 Used Not used

Preprocessing

Preprocessing software

Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).

Normalization

If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.

Normalization template

Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g.

Normalization template	<i>original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.</i>
Noise and artifact removal	<i>Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).</i>
Volume censoring	<i>Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.</i>

Statistical modeling & inference

Model type and settings	<i>Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).</i>
Effect(s) tested	<i>Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.</i>
Specify type of analysis:	<input type="checkbox"/> Whole brain <input type="checkbox"/> ROI-based <input type="checkbox"/> Both
Statistic type for inference (See Eklund et al. 2016)	<i>Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.</i>
Correction	<i>Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).</i>

Models & analysis

n/a | Involved in the study

- Functional and/or effective connectivity
 Graph analysis
 Multivariate modeling or predictive analysis

Functional and/or effective connectivity	<i>Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).</i>
Graph analysis	<i>Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).</i>
Multivariate modeling and predictive analysis	<i>Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.</i>