

Review

A systematic review of the association of depression and psychological distress with cancer incidence and mortality risk in people with chronic diseases: evidence primarily from diabetes populations

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CITATION

Lyu M, Li Y. A systematic review of the association of depression and psychological distress with cancer incidence and mortality risk in people with chronic diseases: evidence primarily from diabetes populations. *Psycho-Oncologie*. 2026; 20(10): 5866. <https://doi.org/10.18282/po5866>

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Abstract: Objective: This systematic review examined the association between depression, anxiety, psychological distress, and the risks of cancer incidence and mortality in adults with chronic diseases, to inform integrated chronic disease management. **Methods:** PubMed, Embase, Web of Science, and the Cochrane Library were searched from inception to April 2026. Eligible studies included adults (≥ 18 years) with chronic diseases, or those allowing subgroup extraction for such populations. Exposures of interest were depression, anxiety, or psychological distress assessed before cancer outcomes. Outcomes included overall and site-specific cancer incidence and mortality. Core evidence from chronic disease populations was synthesized separately from supplementary general-population evidence. **Results:** All directly relevant core evidence was confined to diabetes populations. In a Taiwanese cohort, diabetes with comorbid depression was associated with a mildly increased overall cancer incidence (adjusted hazard ratio [HR] = 1.08, 95% confidence interval [CI]: 1.05–1.11). A US National Health Interview Survey–National Death Index (NHIS-NDI) study showed that higher psychological distress in diabetes was linked to increased all-cause mortality (HRs: 1.39–1.98), with cancer mortality showing a similar but non-significant interaction. A United Kingdom (UK) Biobank study reported that comorbid diabetes and depression increased cancer mortality risk (HR = 1.62, 95% CI: 1.35–1.93), potentially exceeding additive effects. Pancreatic cancer evidence suggested new-onset depression, anxiety, and diabetes were associated with increased risk, but mainly driven by treatment initiated within 3 months prediagnosis, indicating reverse causation. Supplementary general-population evidence generally supported associations but cannot substitute for chronic-disease-specific data. **Conclusion:** In chronic disease populations, particularly diabetes, depression and psychological distress may serve as useful prognostic signals, with more consistent evidence for cancer mortality than incidence. Causal effects on incidence remain uncertain due to confounding, behavioral mediation, surveillance bias, and reverse causation. Evidence for other chronic diseases—including cardiovascular disease, chronic obstructive pulmonary disease, chronic pain, and multimorbidity—remains insufficient.

Keywords: chronic disease; depression; psychological distress; cancer incidence; cancer mortality; diabetes

1. Introduction

At present, chronic noncommunicable diseases have become a major source of global disease burden and health resource consumption. With population aging, lifestyle changes, and the continued accumulation of metabolic risk factors, the

prevalence of long-term health problems such as diabetes, cardiovascular disease, chronic respiratory disease, chronic kidney disease, chronic liver disease, and multimorbidity continues to rise [1]. A systematic analysis based on GBD 2021 showed that noncommunicable diseases caused approximately 43.8 million deaths in 2021 and accounted for about 1.73 billion disability-adjusted life-years, indicating that they remain a leading contributor to global mortality and disease burden [1]. These data make clear that chronic diseases affect not only older adults, but also working-age populations, family functioning, and broader social participation. Chronic diseases are usually characterized by long disease courses, high recurrence rates, and multiple complications. Patients often require long-term medication, lifestyle adjustment, and continuous medical follow-up. Their impact is therefore not confined to physical impairment, but is also commonly accompanied by difficulties in psychological adaptation, reduced social functioning, a stronger perceived disease burden, and impaired quality of life [2, 3]. For this reason, chronic disease management is gradually moving beyond the simple control of physiological indicators toward an integrated model that also addresses psychological status, behavioral patterns, and long-term outcomes.

Depression and psychological distress are common but often underestimated problems among people with chronic diseases [4]. According to a study based on GBD 2021, approximately 332.4 million people worldwide were living with depressive disorders in 2021, suggesting that depressive disorders remain a major global public health concern [5]. For patients with chronic diseases, depression and psychological distress are not merely emotional reactions. They are often intertwined with pain, fatigue, functional limitation, treatment burden, financial pressure, uncertainty about illness, and inadequate social support [3]. Systematic reviews have shown that psychiatric comorbidities such as depression and anxiety are relatively common among patients with chronic physical diseases, with a risk substantially higher than that among individuals without chronic physical conditions [4]. This psychological burden becomes even more evident in people with multimorbidity. Compared with individuals without chronic disease or with only one chronic condition, those with multimorbidity have an approximately 2- to 3-fold higher likelihood of developing depression, according to systematic review findings [6]. In chronic disease populations, therefore, psychological symptoms are not only important determinants of quality of life; they may also influence long-term health outcomes through behavioral, physiological, and healthcare utilization pathways [7].

Cancer is another important outcome that cannot be overlooked during long-term follow-up of populations with chronic diseases [8]. According to GLOBOCAN 2022 estimates, there were nearly 20 million new cancer cases and approximately 9.7 million cancer deaths worldwide in 2022, and cancer remains one of the major causes of premature death and life-years lost globally [9]. Chronic diseases and cancer are linked in complex ways. Diabetes, obesity, chronic inflammation, insulin resistance, impaired liver and kidney function, and long-term unhealthy lifestyles may all be associated with increased risks of multiple cancers [10, 11]. These factors suggest that people with chronic diseases may already represent a key population for cancer risk prevention and control. Whether cancer incidence and cancer mortality risks are further altered when depression or psychological distress is also present in this population deserves systematic review and careful evaluation.

From biological and behavioral perspectives, depression and psychological distress may contribute to cancer incidence and mortality risk through multiple pathways. Long-term psychological stress can activate the hypothalamic-pituitary-

adrenal axis and the sympathetic nervous system, leading to abnormal cortisol rhythms, upregulation of inflammatory factors, increased oxidative stress, and altered immune surveillance, all of which may affect tumor initiation and progression [12, 13]. At the same time, depression and psychological distress are often associated with smoking, alcohol consumption, sleep disturbance, physical inactivity, unhealthy diet, obesity, and reduced treatment adherence. These behavioral factors are themselves important risk factors for many cancers [11, 14]. For patients with chronic diseases, psychological distress may weaken disease self-management and may be linked to lower participation in cancer screening, thereby potentially affecting early cancer detection and long-term outcomes [15]. Depression and psychological distress should therefore not be viewed as isolated psychological problems. Rather, they may represent important links connecting chronic disease status, health behaviors, healthcare utilization, and cancer outcomes.

Existing evidence on this topic comes from several key studies with complementary but distinct contributions. A study based on Taiwan's National Health Insurance database found that patients with diabetes and comorbid depression had a mildly increased subsequent risk of cancer [16]. Using NHIS-NDI data, Huang et al. reported that psychological distress was associated with increased mortality risk among patients with diabetes, with cancer mortality showing a similar direction [17]. Prigge et al., using UK Biobank, further showed that comorbid diabetes and depression may have a joint effect on cancer mortality [7]. However, some long-term follow-up studies have not observed a stable association between depressive symptoms and overall cancer incidence. Findings have differed across cancer sites, follow-up periods, and adjustment models [18, 19]. Although these studies provide an important basis for understanding psychological factors and cancer, they do not fully answer questions specific to chronic disease populations. The relationship between depression, psychological distress, and cancer outcomes cannot be simply summarized as a one-way increase in risk. Conclusions may be jointly influenced by study population characteristics, exposure measurement tools, chronic disease type, cancer outcome definitions, follow-up duration, and the degree of confounder control. Moreover, patients with chronic diseases differ from the general population. Many live for long periods with metabolic dysregulation, chronic inflammation, organ dysfunction, polypharmacy, and frequent contact with healthcare systems. Some cancers may also cause fatigue, weight loss, sleep disturbance, pain, and mood changes before clinical diagnosis. This is particularly relevant for occult malignancies such as pancreatic cancer, in which new-onset depression or anxiety before diagnosis may not be a cancer risk factor, but rather part of the early pathological process or a preclinical manifestation of the tumor [20]. Therefore, when systematically evaluating the literature in this field, it is not enough to examine whether a statistical association exists. It is also necessary to determine whether psychological exposure preceded the cancer outcome, whether baseline cancer patients were excluded, whether lag analyses were performed, and whether factors such as smoking, alcohol consumption, body weight, physical activity, chronic disease severity, and cancer screening behavior were adequately adjusted for. Only under these conditions can the true relationship of depression and psychological distress with cancer incidence and mortality be judged more cautiously.

Against this background, this study aimed to systematically review the relationship between depression, psychological distress, related psychological symptoms, and the risks of cancer incidence and cancer mortality in adult populations with chronic diseases. The focus was placed on longitudinal evidence in which psychological

exposure occurred before cancer outcomes. Existing literature was synthesized from the perspectives of chronic disease type, definition of psychological exposure, cancer outcome type, follow-up duration, confounder adjustment, and bias control, with the aim of clarifying which conclusions are currently supported by evidence, what uncertainties remain, and which aspects require further improvement in future research.

2. Materials and methods

2.1. Study design

The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guideline for systematic reviews [21]. The development and presentation of the literature search strategy referred to the PRISMA-S statement [22], and the evidence synthesis process referred to the Synthesis Without Meta-analysis (SWiM) reporting guideline [23], in order to ensure transparency, standardization, and reproducibility. The review was not registered in PROSPERO or another prospective registry. The eligibility criteria and synthesis approach were defined a priori before screening commenced, and no deviations from the initial plan occurred during the review process.

2.2. Study population

Eligible participants were adults aged ≥ 18 years with chronic diseases, mainly including diabetes, cardiovascular disease, hypertension, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, post-stroke status, arthritis, chronic pain, obesity, multimorbidity, and other long-term chronic health conditions. For cancer incidence outcomes, participants should, in principle, have had no cancer diagnosis at baseline. For cancer mortality outcomes, studies were required to clearly document participants' chronic disease status and to confirm subsequent cancer deaths through follow-up, death registries, medical records, or cause-of-death codes in databases. When a study was conducted in the general population but allowed extraction of subgroup results for people with chronic diseases, the corresponding subgroup data were included as core evidence. Studies from which results for chronic disease populations could not be obtained were used only as supplementary background material or as sources for reference tracing, and were not included in the core evidence synthesis.

2.3. Exposures

The exposures of interest were depression, psychological distress, and related psychological symptoms that had existed or been assessed before cancer incidence or cancer death. Exposure status could be determined through clinical diagnosis, medical records, psychiatric treatment records, antidepressant use records, or standardized psychological scales. Common assessment tools included the Patient Health Questionnaire-9, Center for Epidemiologic Studies Depression Scale, Hospital Anxiety and Depression Scale, Beck Depression Inventory, General Health Questionnaire, Kessler Psychological Distress Scale, and Depression Anxiety Stress Scales. For studies using composite indicators of psychological distress, relevant information was extracted according to the definitions used in the original articles. To ensure the temporal sequence between exposure and outcome, psychological exposure had to be assessed before confirmation of cancer incidence, cancer death, or other cancer-related outcomes.

2.4. Outcomes

Cancer incidence was defined as a malignant tumor first diagnosed during

follow-up, including overall cancer incidence and site-specific cancer incidence. Cancer mortality referred to death events in which a malignant tumor was recorded as the underlying or main cause of death. Cancer outcomes could be confirmed through cancer registries, inpatient or outpatient medical records, health insurance databases, pathological diagnosis, death certificates, national death registration systems, or the National Death Index. When a study reported outcomes for specific cancers, such as lung cancer, colorectal cancer, breast cancer, prostate cancer, liver cancer, or pancreatic cancer, the corresponding results were further extracted. All-cause mortality was recorded only as supplementary information and was not regarded as a core outcome of this study.

2.5. Literature search strategy

PubMed/MEDLINE, Embase, Web of Science Core Collection, and the Cochrane Library were systematically searched from database inception to April 2026. The search was conducted on April 15, 2026. The search was limited to English-language publications. No additional filters (e.g., publication type, age group, or study design restrictions) were applied during the database searches to maximize sensitivity. To reduce omissions, the researchers also traced the references of included studies and relevant reviews to identify potential studies not captured by database searches. The PubMed search strategy is presented as an example in **Table 1**. Complete search strategies for Embase, Web of Science, and the Cochrane Library are provided in **Supplementary Table 1**, with search terms adapted according to the subject headings (e.g., Emtree terms for Embase) and syntax of each database. Search strategies for Embase, Web of Science, and the Cochrane Library were adjusted according to the subject headings and syntax of each database. In addition, to improve the sensitivity of searches for diabetes-related studies, a supplementary search strategy was used: ((depress OR "psychological distress" OR "mental distress" OR anxiety) AND (diabetes OR diabetic OR "Diabetes Mellitus") AND (cancer OR neoplasm OR malignancy OR carcinoma) AND (incidence OR risk OR mortality OR death) AND (cohort OR prospective OR retrospective OR longitudinal OR registry)).

Table 1. Search strategy

Database	Search formula
PubMed	((("Depression"[Mesh] OR "Depressive Disorder"[Mesh] OR depress*[Title/Abstract] OR "depressive symptom*[Title/Abstract] OR "psychological distress"[Title/Abstract] OR "mental distress"[Title/Abstract] OR "psychological stress"[Title/Abstract] OR "emotional distress"[Title/Abstract] OR anxiety[Title/Abstract] OR "Anxiety Disorders"[Mesh] OR "K6"[Title/Abstract] OR "K10"[Title/Abstract] OR "PHQ-9"[Title/Abstract] OR "CES-D"[Title/Abstract] OR "HADS"[Title/Abstract] OR "GHQ"[Title/Abstract] OR "BDI"[Title/Abstract]) AND ("Chronic Disease"[Mesh] OR "chronic disease*[Title/Abstract] OR "long-term condition*[Title/Abstract] OR multimorbidity[Title/Abstract] OR comorbid*[Title/Abstract] OR "Diabetes Mellitus"[Mesh] OR diabetes[Title/Abstract] OR hypertension[Title/Abstract] OR "Cardiovascular Diseases"[Mesh] OR "cardiovascular disease*[Title/Abstract] OR "coronary heart disease"[Title/Abstract] OR "heart failure"[Title/Abstract] OR stroke[Title/Abstract] OR "chronic obstructive pulmonary disease"[Title/Abstract] OR COPD[Title/Abstract] OR "chronic kidney disease"[Title/Abstract] OR CKD[Title/Abstract] OR "chronic liver disease"[Title/Abstract] OR arthritis[Title/Abstract] OR "chronic pain"[Title/Abstract] OR obesity[Title/Abstract]) AND ("Neoplasms"[Mesh] OR cancer*[Title/Abstract] OR neoplasm*[Title/Abstract] OR carcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract]) AND ("Incidence"[Mesh] OR incident[Title/Abstract] OR onset[Title/Abstract] OR risk[Title/Abstract] OR mortality[Title/Abstract] OR death[Title/Abstract] OR "Cause of Death"[Mesh]) AND (cohort[Title/Abstract] OR prospective[Title/Abstract] OR retrospective[Title/Abstract] OR longitudinal[Title/Abstract] OR "follow-up"[Title/Abstract] OR "population-based"[Title/Abstract] OR registry[Title/Abstract]))

2.6. Inclusion and exclusion criteria

The inclusion criteria were as follows: the study population consisted of adult patients with chronic diseases, or subgroup results for chronic disease populations could be extracted; the exposure was depression, psychological distress, mental distress, or related psychological symptoms; psychological exposure was assessed before confirmation of cancer incidence or cancer mortality; outcomes included overall cancer incidence, site-specific cancer incidence, cancer mortality, or site-specific cancer mortality; the study design was a prospective cohort study, retrospective cohort study, nested case-control study, or registry-based longitudinal observational study; and the study reported association results between psychological exposure and cancer outcomes, including HR, Risk Ratio (RR), Odds Ratio (OR), Standardized Incidence Ratio (SIR), Standardized Mortality Ratio (SMR), incidence rate, mortality rate, or other data that allowed assessment of the direction and magnitude of the association. The exclusion criteria were reviews, meta-analyses, umbrella reviews, conference abstracts, commentaries, editorials, case reports, or case series; cross-sectional studies in which the temporal sequence between psychological exposure and cancer outcome could not be determined; studies in which the population was not a chronic disease population and subgroup results for chronic disease populations could not be extracted; studies that did not report cancer incidence, cancer mortality, or site-specific cancer outcomes; and studies in which psychological exposure occurred after cancer diagnosis and the main topic was psychological status and prognosis among patients with cancer.

2.7. Literature screening

All retrieved records were imported into EndNote for management, and duplicates were removed through software-assisted processing combined with manual checking. Literature screening was independently performed by two researchers; if consensus still could not be reached, a third researcher made the final decision. The literature screening process was presented using a PRISMA flow diagram.

2.8. Data extraction

A predesigned data extraction form was used to collect information from the included studies. Data extraction was independently completed by two researchers and then cross-checked. Extracted information included first author, publication year, country or region, study design, data source, sample size, age, sex distribution, chronic disease type, diagnostic basis for chronic disease, baseline cancer status, definition of depression or psychological distress, assessment tool, scale cutoff, timing of exposure assessment, definition of the control group, cancer outcome type, method of outcome confirmation, follow-up duration, statistical analysis method, confounder adjustment, main effect estimates and 95% confidence intervals, subgroup analysis results, sensitivity analysis results, authors' main conclusions, and study limitations. If the same study reported multiple statistical models, the model with more adequate confounder adjustment and without obvious overadjustment for potential mediators was preferentially extracted. Other model results were also recorded to help assess the stability of the findings.

2.9. Risk of bias assessment

Potential sources of bias were assessed with reference to the Risk Of Bias In Non-randomized Studies of Exposure effects (ROBINS-E) tool for non-randomized studies of exposure effects [24]. A study-level risk-of-bias table was constructed, with judgments recorded for the following domains: bias due to confounding, bias in the

selection of participants, bias in exposure classification, bias due to co-exposures or interventions, bias due to missing data, bias in outcome measurement, and bias in the selection of reported results.

2.10. Evidence synthesis

The researchers first grouped the literature according to cancer outcome type, including studies on cancer incidence risk, cancer mortality risk, and site-specific cancer incidence or mortality. Results were then compared according to chronic disease type, psychological exposure type, and study design. A narrative synthesis approach was used because meta-analysis was not feasible due to substantial heterogeneity across studies in populations (different chronic diseases), exposures (depression diagnoses vs. various distress scales with different cutoffs), outcomes (overall vs. site-specific cancer, incidence vs. mortality), effect estimates (HRs, ORs, with varying adjustment sets), and chronic disease categories. Pooling these heterogeneous estimates would have produced a statistically unstable and potentially misleading summary estimate. During evidence synthesis, particular attention was paid to effect direction, effect size, confidence interval width, sample size, number of cancer events, follow-up duration, exposure measurement method, outcome confirmation method, adequacy of confounder adjustment, and risk of bias assessment results. For studies with consistent effect directions but different levels of statistical significance, differences in statistical power, exposure misclassification, follow-up duration, and adjustment factors were further examined. For studies with inconsistent effect directions, possible explanations were explored in terms of chronic disease type, psychological exposure definition, cancer site, exclusion of baseline cancer, adjustment for health behaviors, and implementation of lag analyses. A certainty-of-evidence assessment was performed for the three main conclusions, using a structured approach adapted from GRADE but presented narratively due to the heterogeneity noted above.

2.11. Handling of reverse causality and confounding factors

Because some cancers may cause fatigue, weight loss, sleep disturbance, pain, and psychological symptoms before clinical diagnosis, reverse causation may exist between depression or psychological distress and cancer incidence. Therefore, in interpreting the results, particular attention was paid to whether each study excluded patients with previous cancer at baseline, whether individuals who developed cancer or died during early follow-up were excluded, whether lag analyses were performed, and whether smoking, alcohol consumption, body mass index (BMI), physical activity, diet, chronic disease severity, complication burden, medication use, cancer screening behavior, and healthcare utilization were adjusted for.

3. Results

3.1. Literature search and screening results

Database searches identified 397 records (PubMed: 112; Embase: 148; Web of Science: 119; Cochrane Library: 18). After duplicate removal, 287 remained. After title and abstract screening, 258 records were excluded because they did not meet the population, exposure, or outcome criteria. Twenty-nine full-text articles were then assessed, and 17 articles were excluded for reasons including: no extractable data for chronic disease populations (n=9), exposure assessed after cancer diagnosis (n=4), cross-sectional design with unclear temporality (n=2), and duplicate publication (n=2). Finally, 12 studies were included for narrative synthesis, including 4 studies as core

evidence from chronic disease populations and 8 studies as supplementary evidence from general populations or as methodological explanatory evidence (**Figure 1**).

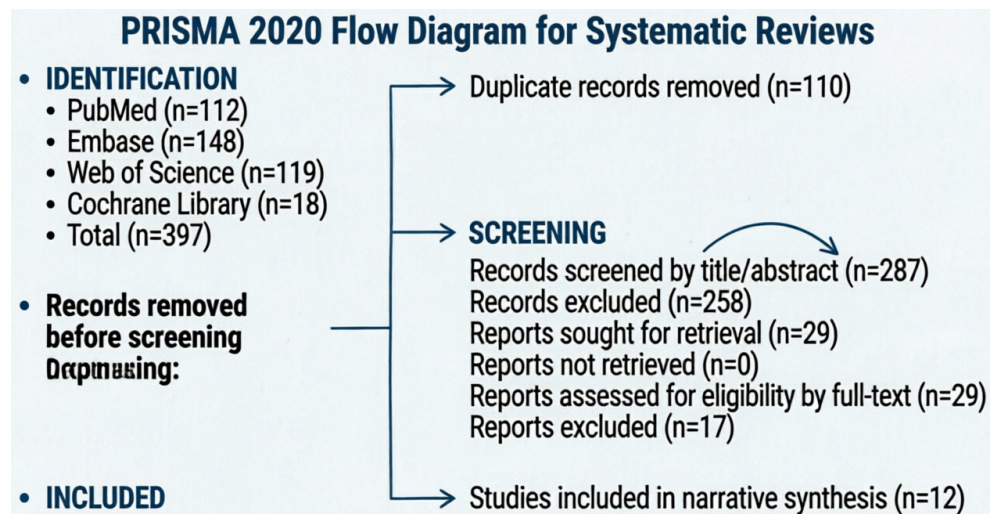


Figure 1. PRISMA flow diagram of the literature screening process.

3.2. General characteristics of included studies

The available literature shows that studies directly addressing “the association between depression or psychological distress and the risks of cancer incidence and mortality in populations with chronic diseases” remain limited. Core evidence is mainly concentrated in patients with diabetes. Diabetes-related studies included a study based on Taiwan’s National Health Insurance database, a prospective cohort study using the US NHIS-NDI data, a UK Biobank prospective cohort study, and a Finnish registry-based study. In contrast, direct evidence for populations with cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, chronic pain, and multimorbidity was clearly insufficient. Most relevant articles came from general population cohorts and could only be used as supplementary evidence or as a basis for discussion (**Table 2**).

Table 2. Basic characteristics of included studies

Author / Year	Country or region	Data source	Study design	Study population / Sample size	Chronic disease or population type	Main exposure	Main outcome	Evidence positioning
Shi-Heng et al., 2023 [16]	Taiwan, China	Taiwan National Health Insurance Database	Population-based matched cohort study	85,489 patients with diabetes and depression; 427,445 diabetic controls without depression	Diabetes	Depression	Overall cancer incidence and site-specific cancer incidence	Core evidence
Huang et al., 2021 [17]	United States	NHIS 1997–2013, linked to the National Death Index	Prospective cohort study	485,864 adults, including 39,576 patients with diabetes	Diabetes/ non-diabetes comparison	K6 psychological distress	All-cause mortality, cardiovascular mortality, cancer mortality	Core evidence

Continuation Table:

Author / Year	Country or region	Data source	Study design	Study population / Sample size	Chronic disease or population type	Main exposure	Main outcome	Evidence positioning
Prigge et al., 2022 [7]	United Kingdom	UK Biobank	Prospective cohort study	499,830 participants	Diabetes, depression, and their comorbidity	Depression, diabetes	All-cause mortality, cancer mortality, circulatory disease mortality, other-cause mortality	Core evidence
Li et al., 2023 [20]	Finland	Finnish registry databases and the Finnish Cancer Registry	Registry-based case-control study and survival analysis	6,492 patients with pancreatic cancer; 32,460 matched controls	Diabetes; depression and anxiety also assessed	Depression, anxiety, diabetes	Pancreatic cancer incidence, treatment, and survival	Core evidence (site-specific/ reverse causality)
Lee and Singh, 2021 [25]	United States	NHIS-NDI 1997–2014	Prospective cohort study	513,012 adults	General population	Serious psychological distress	Cancer mortality	Supplementary evidence
Batty et al., 2017 [26]	United Kingdom	16 prospective cohorts	Individual participant data pooled analysis	163,363 participants without cancer at baseline	General population	GHQ-12 psychological distress	Overall and site-specific cancer mortality	Supplementary evidence
Russ et al., 2012 [27]	United Kingdom	10 prospective cohorts	Individual participant data pooled analysis	Large-scale general population cohorts	General population	GHQ-12 psychological distress	All-cause mortality, cardiovascular mortality, cancer mortality, external-cause mortality	Supplementary evidence
Hamer et al., 2009 [28]	United Kingdom	Community sample linked to cancer registry and mortality data	Prospective cohort study	15,453 participants, including 295 with a history of cancer	General population, including subgroup with previous cancer	GHQ-12 psychological distress	Cancer mortality, lung cancer mortality	Supplementary/ methodological evidence
Archer et al., 2015 [29]	United Kingdom	Whitehall II Study	Prospective cohort study	Participants in the Whitehall II cohort	General population	Depressive symptoms	Overall cancer incidence	Supplementary evidence
Trudel-Fitzgerald et al., 2022 [30]	United States	Nurses' Health Study	Prospective cohort study	42,913 women; 1,009 lung cancer cases	General female population	Depressive symptoms/ depression status	Lung cancer incidence	Supplementary evidence

Continuation Table:

Author / Year	Country or region	Data source	Study design	Study population / Sample size	Chronic disease or population type	Main exposure	Main outcome	Evidence positioning
Xia et al., 2022 [31]	China	Chinese adult cohort data	Prospective cohort study	8,151 adults	General population	Self-reported depression	All-cause mortality, cardiovascular mortality, cancer mortality	Supplementary evidence
Mössinger et al., 2023 [32]	Germany	Disease Analyzer database	Retrospective cohort study	235,404 patients	General clinical population	Depression diagnosis	Subsequent cancer diagnosis	Supplementary evidence

NOTE: General Health Questionnaire-12(GHQ-12)

3.3. Depression and cancer incidence risk among patients with diabetes

Regarding cancer incidence, the most direct evidence came from a matched cohort study by Shi-Heng et al[16]. based on Taiwan's National Health Insurance database. The study included 85,489 patients with diabetes and comorbid depression and 427,445 diabetic controls without depression. The results indicated a mild but statistically significant increase in overall cancer incidence risk among patients with diabetes and depression, with an adjusted HR of 1.08 and a 95% CI of 1.05–1.11. Further analyses linked depression to increased risks of oropharyngeal cancer, esophageal cancer, liver cancer, gynecologic cancers, prostate cancer, kidney cancer, and hematologic malignancies. The cancer incidence rate was higher among patients with recurrent major depressive disorder than among those with dysthymia or unspecified depressive disorder, suggesting that the severity of depression may influence cancer risk. In addition, the association was more evident among younger patients with diabetes, whereas no significant relationship was observed between adherence to antidepressant treatment and cancer risk. These findings suggest that depression may be associated with increased cancer incidence risk among patients with diabetes, although the effect size is small and may vary by cancer site, age, and depression severity (**Table 3**).

Table 3. Core study results in chronic disease populations

Author/Year	Chronic disease background	Exposure definition	Outcome type	Main results	Interpretation
Shi-Heng et al., 2023 [17]	Diabetes	Depression identified through health insurance diagnostic records; comparison between patients with diabetes and depression and those with diabetes but without depression	Overall cancer incidence and site-specific cancer incidence	Patients with diabetes and depression had an increased risk of overall cancer incidence, with an adjusted HR of 1.08 and a 95% CI of 1.05–1.11. Increased risks were observed for oropharyngeal cancer, esophageal cancer, liver cancer, gynecological tumors, prostate cancer, kidney cancer, and hematological malignancies. Patients with recurrent major depression had a higher cancer incidence.	Depression was associated with a slight increase in subsequent cancer incidence among patients with diabetes, but the effect size was small, and differences were observed by cancer site and depression severity.

Continuation Table:

Author/Year	Chronic disease background	Exposure definition	Outcome type	Main results	Interpretation
Huang et al., 2021 [16]	Diabetes/ non-diabetes comparison	Psychological distress assessed using the K6 scale and categorized as none, mild, moderate, or severe	All-cause mortality, cardiovascular mortality, cancer mortality	Among patients with diabetes, the risk of all-cause mortality increased as the level of psychological distress rose. For all-cause mortality, compared with non-diabetic individuals without distress, diabetic patients with none, mild, moderate, and severe distress had HRs of 1.39, 1.59, 1.90, and 1.98, respectively. Cancer mortality showed a similar direction, but the interaction between diabetes and psychological distress for cancer mortality did not reach statistical significance.	This study supports an association between psychological distress and all-cause mortality risk among patients with diabetes. The HRs listed above refer to all-cause mortality and should not be described as HRs for cancer mortality. Cancer mortality findings are suggestive but not statistically robust for interaction.
Prigge et al., 2022 [7]	Diabetes, depression, and their comorbidity	Diabetes and depression identified through self-reported diagnosis, prescription records, and hospital records	All-cause mortality, cancer mortality, circulatory disease mortality, other-cause mortality	Compared with individuals without diabetes or depression, those with both diabetes and depression had an HR of 2.16 for all-cause mortality, with a 95% CI of 1.94–2.42; an HR of 1.62 for cancer mortality, with a 95% CI of 1.35–1.93; an HR of 2.22 for circulatory disease mortality, with a 95% CI of 1.80–2.73; and an HR of 3.60 for other-cause mortality, with a 95% CI of 2.93–4.42.	Comorbid diabetes and depression may have a joint effect on cancer mortality and overall mortality. This is core evidence for the cancer mortality section of the present review.
Li et al., 2023 [20]	Diabetes; depression and anxiety also involved	Prescription drug purchase records used to identify depression, anxiety, and diabetes, with exposures classified as long-term, recent, or new-onset	Pancreatic cancer incidence	Long-term anxiety: OR=1.13, 95% CI: 1.04–1.22; long-term diabetes: OR=1.72, 95% CI: 1.55–1.90; new-onset depression: OR=1.52, 95% CI: 1.31–1.75; new-onset anxiety: OR=1.76, 95% CI: 1.50–2.07; new-onset diabetes: OR=3.92, 95% CI: 3.44–4.48. The effects of new-onset exposures were mainly driven by individuals who began treatment within 3 months before diagnosis.	New-onset depression, anxiety, and diabetes were associated with increased pancreatic cancer risk, but these associations more likely reflected preclinical manifestations or reverse causality.

3.4. Psychological distress and cancer mortality risk among patients with diabetes

Regarding cancer mortality, important evidence was provided by Huang et al.[17], who used data from the 1997–2013 NHIS linked to the National Death Index. The study included 485,864 US adults, including 39,576 patients with diabetes. Psychological distress was assessed using the K6 scale, and mortality outcomes included all-cause mortality, cardiovascular disease mortality, and cancer mortality. Psychological distress was associated with increased risks of all-

cause mortality, cardiovascular mortality, and cancer mortality, with higher risk levels observed among patients with diabetes. Critically, the frequently cited HRs of 1.39, 1.59, 1.90, and 1.98 in this study refer to all-cause mortality, not cancer mortality. Using individuals without diabetes and without psychological distress as the reference group, patients with diabetes already had an increased all-cause mortality risk even in the absence of psychological distress. As psychological distress increased, the all-cause mortality HR among patients with diabetes rose from 1.39 to 1.98. Cancer mortality followed a direction similar to all-cause and cardiovascular mortality, but the interaction between diabetes and psychological distress for cancer mortality did not reach statistical significance. Therefore, this study supports the importance of psychological distress in mortality risk assessment among patients with diabetes, while the interaction effect on cancer mortality should still be interpreted cautiously (**Table 3**).

3.5. Joint effect of diabetes and depression comorbidity on cancer mortality

The prospective cohort study by Prigge et al[7], based on UK Biobank further suggested that comorbid diabetes and depression may have a joint effect on cause-specific mortality, particularly cancer mortality. The study included 499,830 participants with a median follow-up of 6.8 years. Participants were divided into four groups according to the presence or absence of diabetes and depression at baseline. Compared with individuals without diabetes or depression, those with both diabetes and depression had the highest mortality risk. The HR was 2.16 for all-cause mortality, with a 95% CI of 1.94–2.42; 1.62 for cancer mortality, with a 95% CI of 1.35–1.93; 2.22 for circulatory disease mortality, with a 95% CI of 1.80–2.73; and 3.60 for other-cause mortality, with a 95% CI of 2.93–4.42. The study also reported that the risks of all-cause mortality, cancer mortality, and other-cause mortality among individuals with both diabetes and depression exceeded the sum of the independent effects of diabetes and depression, suggesting that the comorbid state may exert a risk effect beyond simple additivity (**Table 3**).

3.6. Site-specific cancer results and reverse causality

Li et al.[20] found long-term anxiety, long-term diabetes, new-onset depression, new-onset anxiety, and new-onset diabetes were all associated with increased pancreatic cancer risk. The OR was 1.52 for new-onset depression, with a 95% CI of 1.31–1.75; 1.76 for new-onset anxiety, with a 95% CI of 1.50–2.07; and 3.92 for new-onset diabetes, with a 95% CI of 3.44–4.48. However, the study further noted that the effects of new-onset conditions were mainly driven by cases in which treatment was initiated within 3 months before cancer diagnosis. This suggests that new-onset depression, anxiety, or diabetes may more often reflect preclinical manifestations of pancreatic cancer rather than true etiological factors. This finding indicates that, when evaluating the relationship between psychological exposure and cancer incidence, it is essential to distinguish long-standing psychological symptoms from short-term new-onset symptoms before cancer diagnosis.

For lung cancer, the Nurses' Health Study reported an association between depressive symptoms and lung cancer incidence among women. Compared with women with low or no depressive symptoms, those with the highest level of depressive symptoms still had an increased risk of lung cancer in the fully adjusted model, with an HR of 1.25 and a 95% CI of 1.04–1.51. Mediation analysis showed that smoking pack-years explained approximately 38% of the overall association. This suggests that the relationship between depression and lung cancer risk may be

at least partly mediated through smoking behavior. It also indicates that, in studies of chronic disease populations, health behaviors such as smoking, alcohol consumption, physical activity, and obesity must be considered as key confounders or mediators (Table 3).

3.7. Supplementary evidence from general populations

General population studies generally support an association between psychological distress and increased cancer mortality risk, but this evidence cannot directly substitute for evidence from chronic disease populations and is presented here as contextual support rather than as core evidence. Lee and Singh[25] analyzed 513,012 US adults using NHIS-NDI data and found that individuals with serious psychological distress had an increased risk of cancer mortality. In the fully adjusted model, cancer mortality risk increased by 33%, with an HR of 1.33 and a 95% CI of 1.21–1.46. Batty et al.[26] pooled 16 prospective cohorts including 163,363 participants without cancer at baseline and found that psychological distress was associated with increased mortality risks for some site-specific cancers. Russ et al.[27] performed an individual participant data pooled analysis of 10 prospective cohorts and found a dose-response relationship between psychological distress and all-cause mortality, while cancer mortality risk increased mainly at higher levels of psychological distress. These studies suggest that psychological distress may be related to cancer mortality. However, because the study populations were mainly drawn from the general population, the findings should be used in this review as external comparisons and background support rather than as sources of core conclusions (Table 4).

Table 4. Supplementary evidence from general populations

Author / Year	Population source	Exposure	Cancer-related outcome	Main results	Role in the present review
Lee and Singh, 2021 [25]	General adults from the US NHIS-NDI	Serious psychological distress	Cancer mortality	Individuals with serious psychological distress had an increased risk of cancer mortality; fully adjusted HR=1.33, 95% CI: 1.21–1.46.	Supports an association between psychological distress and increased cancer mortality risk, but cannot replace evidence from chronic disease populations.
Batty et al., 2017 [26]	16 UK prospective cohorts, participants without cancer at baseline	GHQ-12 psychological distress	Overall cancer mortality and site-specific cancer mortality	High psychological distress was associated with increased risks of overall cancer mortality and some site-specific cancer deaths, including colorectal cancer, prostate cancer, pancreatic cancer, esophageal cancer, and leukemia.	Indicates that the association between psychological distress and cancer mortality may differ by cancer site.
Russ et al., 2012 [27]	10 UK prospective cohorts	GHQ-12 psychological distress	All-cause mortality, cardiovascular mortality, cancer mortality	Psychological distress showed a dose-response relationship with all-cause mortality. Cancer mortality risk increased mainly at higher levels of psychological distress, by approximately 41%.	Supports a graded association between psychological distress severity and mortality risk.

Continuation Table:

Author / Year	Population source	Exposure	Cancer-related outcome	Main results	Role in the present review
Hamer et al., 2009 [28]	UK community sample, including participants with a history of cancer	GHQ-12 psychological distress	Cancer mortality, lung cancer mortality	GHQ-12 ≥ 4 was associated with increased cancer mortality among participants with a history of cancer, with an adjusted HR of 1.97 and a 95% CI of 1.05–3.71. Among those without a history of cancer, no clear association was observed with overall cancer mortality. The age- and sex-adjusted HR for lung cancer mortality was 2.04, but the association was attenuated after multivariable adjustment.	Suggests that prior cancer history and factors such as smoking may influence interpretation of the association.
Archer et al., 2015 [29]	Whitehall II cohort	Chronic depressive symptoms and new-onset depressive symptoms	Overall cancer incidence	Chronic depressive symptoms did not increase the risk of overall cancer incidence, with an HR of 1.03 and a 95% CI of 0.71–1.49. New-onset depressive symptoms were associated with increased cancer incidence during the first 9 years of follow-up, with an HR of 1.89 and a 95% CI of 1.23–2.90.	Shows that long-term exposure and new-onset symptoms should be interpreted separately, supporting the discussion of reverse causality.
Trudel-Fitzgerald et al., 2022 [30]	Nurses' Health Study female cohort	Depressive symptoms/depression status	Lung cancer incidence	Severe depressive symptoms were associated with increased lung cancer risk, with a fully adjusted HR of 1.25 and a 95% CI of 1.04–1.51. Smoking pack-years explained approximately 38% of the overall association.	Indicates that health behaviors such as smoking may mediate the association between depression and lung cancer risk.
Xia et al., 2022 [31]	Chinese adult cohort	Self-reported depression	All-cause mortality, cardiovascular mortality, cancer mortality	Moderate-to-severe/severe depression was associated with increased cancer mortality risk, with an HR of 7.21 and a 95% CI of 2.00–25.99.	Provides supplementary evidence from a Chinese population, but the confidence interval was wide and interpretation should be cautious.
Mössinger et al., 2023 [32]	German Disease Analyzer database	Depression diagnosis	Subsequent cancer diagnosis	The proportion of subsequent cancer diagnosis was 4.9% among patients with depression and 4.1% among those without depression, corresponding to an approximately 18% increase in overall cancer diagnosis risk.	Suggests an association between depression and subsequent cancer diagnosis, but the result may be affected by medical visit frequency and diagnostic surveillance bias.

3.8. Inconsistency in the relationship between depression and cancer incidence

The current evidence on the relationship between depression and cancer incidence risk is not entirely consistent. During 17.4 years of follow-up, the Whitehall II [29] study found that chronic depressive symptoms did not increase the risk of overall cancer incidence, with an HR of 1.03 and a 95% CI of 0.71–1.49. In contrast, new-onset depressive symptoms were associated with an increased risk of cancer incidence within the first 9 years of follow-up, with an HR of 1.89 and a 95% CI of 1.23–2.90. The authors considered that this finding might be related to reverse causation. A study based on the German Disease Analyzer database found that the subsequent cancer diagnosis rate was 4.9% among patients with depression, higher than the 4.1% among those without depression, corresponding to an approximately 18% increase in overall cancer diagnosis risk. Nevertheless, that study was a retrospective clinical database study and may have been affected by healthcare-seeking frequency, diagnostic surveillance, and insufficient control of lifestyle factors. Overall, the evidence linking depression to cancer incidence is weaker than that linking depression to cancer mortality, and is more susceptible to the influence of cancer site, exposure time window, reverse causation, and health behavior factors (Table 4).

3.9. Results of narrative synthesis

Taken together, the existing literature suggests that depression and psychological distress may be associated with cancer-related outcomes in populations with chronic diseases, with the most concentrated evidence found among patients with diabetes. When patients with diabetes have comorbid depression, the subsequent risk of overall cancer incidence is mildly increased. When diabetes coexists with psychological distress or depression, both cancer mortality risk and overall mortality risk tend to increase. Compared with cancer incidence, evidence related to cancer mortality is more consistent, particularly regarding the joint effect of diabetes and depression on cancer mortality risk. Site-specific cancer studies further indicate that findings for pancreatic cancer and lung cancer should be interpreted in light of reverse causation and health behavior mediation. Overall, the current evidence more strongly supports viewing depression and psychological distress as important signals in long-term prognosis and cancer mortality risk assessment among patients with chronic diseases, rather than simply interpreting them as independent etiological factors for cancer incidence (Table 5).

Table 5. Narrative evidence synthesis

Evidence topic	Main references	Direction of results	Certainty of evidence	Integrated conclusion
Depression and cancer incidence among patients with diabetes	Shi-Heng et al., [17]	Positive association	Low to moderate	When patients with diabetes also have depression, the subsequent risk of overall cancer incidence is slightly increased, with more pronounced risks for some site-specific cancers.
Diabetes with psychological distress and cancer mortality	Huang et al., [16]	Positive trend	Low	Higher psychological distress among people with diabetes is associated with increased mortality risk. Cancer mortality shows a similar direction, but evidence for an interaction effect remains insufficient.

Continuation Table:

Evidence topic	Main references	Direction of results	Certainty of evidence	Integrated conclusion
Diabetes with depression and cancer mortality	Prigge et al., [7]	Positive association, with a possible joint effect	Moderate	Patients with both diabetes and depression have an increased risk of cancer mortality, and the risk may exceed the sum of the separate effects of diabetes and depression.
New-onset depression, anxiety, diabetes, and pancreatic cancer	Li et al. [20]	Positive association, but reverse causality may be substantial	Low	New-onset psychological symptoms and new-onset diabetes are associated with increased pancreatic cancer risk, but they more likely reflect preclinical manifestations of cancer.
Depressive symptoms and lung cancer incidence	Trudel-Fitzgerald et al. [30]	Positive association, partly explained by smoking	Low to moderate	The association between depression and lung cancer risk needs to be interpreted in relation to health behaviors such as smoking.
Psychological distress and cancer mortality in general populations	Lee and Singh, [25]; Batty et al., [26]; Russ et al., [27]	Mostly positive associations	Low to moderate	General population studies support an association between psychological distress and increased cancer mortality, but they cannot directly replace evidence from chronic disease populations.
Depression and overall cancer incidence	Archer et al., [29]; Mössinger et al., [32]	Inconsistent	Very low to low	The association between depression and cancer incidence is less stable than that between depression and cancer mortality. Long-term exposure, new-onset symptoms, and diagnostic bias need to be distinguished.
Overall evidence gap	All included studies	Evidence concentrated in diabetes; insufficient evidence for other chronic diseases	Limited generalizability	Direct evidence from chronic disease populations other than diabetes is insufficient and represents a major direction for future research.

3.10. Risk of bias assessment results

The overall risk of bias in the included studies mainly arose from insufficient control of confounding factors, differences in exposure classification, lack of information on cancer screening and healthcare utilization, and inadequate handling of reverse causation. Diabetes-related studies generally clarified the temporal sequence between exposure and outcome, but some did not fully control for disease severity, health behaviors, and screening behavior. In supplementary studies from general populations, baseline cancer history, handling of early follow-up events, and single-time psychological exposure measurement were the main limitations (Table 6).

Table 6. Study-level risk-of-bias assessment (ROBINS-E domains) for core studies

Study	Confounding	Participant selection	Exposure classification	Co-exposures/ interventions	Missing data	Outcome measurement	Selective reporting	Overall
Shi-Heng et al., 2023 [17]	Serious	Low	Serious	Low	Low	Low	Low	Serious

Continuation Table:

Study	Confounding	Participant selection	Exposure classification	Co-exposures/ interventions	Missing data	Outcome measurement	Selective reporting	Overall
Huang et al., 2021 [16]	Serious	Low	Low	Low	Low	Low	Low	Serious
Prigge et al., 2022 [7]	Serious	Serious	Low	Low	Low	Low	Low	Serious
Li et al., 2023 [20]	Serious	Low	Low	Low	Low	Low	Low	Serious

Domain definitions: Confounding—inadequate control for health behaviors, disease severity, cancer screening; Participant selection—UK Biobank healthy volunteer bias; Exposure classification—use of diagnostic records may miss undiagnosed cases; Missing data—generally low due to registry linkage.

4. Discussion

This systematic review summarized the relationship between depression, psychological distress, related psychological symptoms, and the risks of cancer incidence and cancer mortality in adult populations with chronic diseases. Overall, the existing evidence suggests that depression and psychological distress may be associated with adverse cancer-related outcomes among patients with chronic diseases, but this association is neither a simple linear relationship nor direct evidence of causality. Relatively direct evidence is mainly concentrated in patients with diabetes, especially regarding the association between diabetes with comorbid depression and subsequent cancer incidence, as well as the association between diabetes with psychological distress or depression and cancer mortality. By contrast, relevant studies in populations with cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, chronic pain, and multimorbidity remain clearly insufficient, indicating a substantial disease-type bias in the current evidence base. From the perspective of outcomes, evidence linking depression and psychological distress with cancer mortality is relatively more consistent, whereas the relationship with cancer incidence is more easily influenced by cancer site, exposure duration, health behaviors, chronic disease severity, healthcare utilization, and reverse causation.

A key distinction in this review is the separation of core evidence (from chronic disease populations—all of which were diabetes populations) from supplementary evidence (from general population studies used for contextual comparison). The relationship between depression and cancer incidence risk among patients with diabetes represents one of the more direct lines of evidence in this review. Nevertheless, considering the large number of patients with diabetes and the large sample size and long follow-up duration of this study, this mild increase in risk still has some public health significance. Notably, the study also observed that depression was associated with increased risks of several cancer sites, including oropharyngeal cancer, esophageal cancer, liver cancer, gynecologic cancers, prostate cancer, kidney cancer, and hematologic malignancies. In addition, cancer incidence was higher among individuals with recurrent major depressive disorder than among those with dysthymia or unspecified depressive disorder. These findings suggest that the relationship between depression and cancer incidence may not be homogeneous, but may instead be jointly influenced by cancer site, depression severity, disease course, and patient age. Compared with cancer incidence, the relationship between

depression or psychological distress and cancer mortality appears more consistent. The UK Biobank study found that individuals with both diabetes and depression had significantly increased risks of all-cause mortality, cancer mortality, circulatory disease mortality, and other-cause mortality; the HR for cancer mortality was 1.62, with a 95% CI of 1.35–1.93 [7]. More importantly, the study suggested that the cancer mortality risk among individuals with comorbid diabetes and depression exceeded the sum of the independent effects of diabetes and depression, indicating a possible joint effect. This finding has clear clinical relevance. Diabetes itself is associated with insulin resistance, chronic low-grade inflammation, obesity, metabolic dysregulation, and multiple complications, while depression may further weaken self-management, reduce treatment adherence, and impair the maintenance of healthy behaviors. When these two conditions overlap, patients may not only face a higher overall mortality risk, but may also be disadvantaged in cancer diagnosis, treatment uptake, and prognosis improvement.

The study by Huang et al. based on NHIS-NDI data further supports an association between psychological distress and increased mortality risk among patients with diabetes [16]. This study used the K6 scale to assess psychological distress and compared all-cause, cardiovascular, and cancer mortality risks between populations with and without diabetes. Patients with diabetes had a higher all-cause mortality risk than individuals without diabetes and without psychological distress, even when the patients themselves had no psychological distress. As psychological distress increased, all-cause mortality risk among patients with diabetes increased further. It should be emphasized that the frequently cited HRs of 1.39, 1.59, 1.90, and 1.98 in this study refer to all-cause mortality, not cancer mortality. Therefore, the interpretation of this study should remain precise: it shows an increasing trend in mortality risk when diabetes and psychological distress coexist, and cancer mortality also follows a similar direction, but the interaction between diabetes and psychological distress for cancer mortality did not reach statistical significance. In other words, this study reinforces the value of psychological distress as a mortality risk signal among patients with chronic diseases, but it is not sufficient on its own to prove a definite interaction effect on cancer mortality.

Regarding the distinction between long-term and new-onset depression, the Whitehall II study provides useful evidence. Chronic depressive symptoms did not increase overall cancer incidence risk, with an HR of 1.03 and a 95% CI of 0.71–1.49; however, new-onset depressive symptoms were associated with increased cancer incidence risk within the first 9 years of follow-up, with an HR of 1.89 and a 95% CI of 1.23–2.90 [29]. This difference suggests that long-standing stable psychological exposure and newly developed psychological symptoms before cancer diagnosis may have different implications, with the latter more likely to be influenced by underlying cancer or preclinical pathological changes. This distinction between long-term and new-onset depression should be considered in future studies and clinical practice.

Mechanistically, depression and psychological distress may affect cancer-related outcomes through several interwoven pathways. Long-term psychological stress can activate the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system, inducing disrupted cortisol rhythms, elevated inflammatory cytokines, increased oxidative stress, and impaired immune surveillance, all of which may create an unfavorable internal environment for tumor initiation and progression [12, 13, 33]. For patients with chronic metabolic diseases such as diabetes, inflammation, insulin resistance, and metabolic abnormalities already exist, and depression or psychological

distress may further amplify these pathological processes [34]. At the behavioral level, psychological distress often coexists with smoking, alcohol consumption, physical inactivity, sleep disturbance, unhealthy diet, obesity, and reduced treatment adherence. The Nurses' Health Study found that severe depressive symptoms were associated with an increased risk of lung cancer among women, while smoking pack-years explained approximately 38% of the overall association [30]. This finding suggests that the relationship between depression and cancer is not necessarily driven entirely by psychological status itself; health behaviors may play an important mediating role. Differences in healthcare utilization and disease management may also be involved. Patients with chronic diseases require long-term follow-up, medication, and lifestyle management. Depression or psychological distress may reduce their ability to attend regular follow-up, take medication on time, control body weight, maintain physical activity, and participate in cancer screening. If poor psychological status leads patients to delay medical visits or reduce screening participation, cancer may be detected at a later stage, thereby affecting mortality risk. Conversely, some patients with depression may have more frequent contact with the healthcare system, which could increase the likelihood of cancer diagnosis and lead to surveillance bias. A study based on the German Disease Analyzer database found that patients with depression had a higher subsequent cancer diagnosis rate than those without depression, but because this was a retrospective clinical database study, the influence of healthcare-seeking frequency and diagnostic opportunity could not be fully excluded [32]. Therefore, future studies assessing cancer incidence risk should, whenever possible, incorporate variables such as healthcare utilization, cancer screening behavior, and the quality of chronic disease management.

In addition, some cancers may already cause fatigue, sleep disturbance, appetite loss, weight loss, pain, and mood changes before clinical diagnosis. These symptoms may be recognized by patients or physicians as depression, or captured by psychological scales as psychological distress [35]. Therefore, reverse causation is a key issue that must be considered when interpreting the relationship between depression, psychological distress, and cancer incidence. As noted above, the Whitehall II study clearly showed that new-onset depressive symptoms, rather than chronic depressive symptoms, were associated with increased cancer incidence in the short term [29]. In the present review, pancreatic cancer-related evidence further supports this interpretation. For clinical practice, the significance of this finding is not limited to causal interpretation. When patients with chronic diseases develop recent-onset depression, anxiety, weight loss, or abnormal glucose metabolism, especially when these are accompanied by unexplained physical symptoms, clinicians should remain alert to the possibility of an underlying malignancy.

Finally, although general population studies were included for comparison, their findings cannot fully replace evidence from chronic disease populations and are presented separately in this review. For example, NHIS-NDI data showed that individuals with serious psychological distress had an increased risk of cancer mortality, with a fully adjusted HR of 1.33 and a 95% CI of 1.21–1.46 [25]. Batty et al. pooled 16 prospective cohort studies and found that psychological distress was associated with increased risks of overall cancer mortality and some site-specific cancer mortality [26]. The individual participant data pooled analysis by Russ et al. also showed a dose-response relationship between psychological distress and all-cause mortality, while cancer mortality risk increased mainly at higher levels of psychological distress [27]. These studies suggest that there may be a relatively

general association between psychological distress and cancer mortality. However, because most study populations were drawn from the general population, the findings cannot be directly extrapolated to patients with chronic diseases. Patients with chronic diseases have a higher complication burden, more complex treatment processes, and more frequent healthcare contact, and their risk patterns therefore need to be evaluated independently.

Future research directions. First, prospective cohort studies specifically designed for chronic disease populations beyond diabetes—such as cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, chronic pain, and multimorbidity—are urgently needed. Second, studies should use repeated psychological measurements whenever possible to distinguish long-term persistent depression, recurrent depression, and short-term new-onset psychological symptoms, particularly before cancer diagnosis. Third, adequate adjustment for smoking, alcohol consumption, BMI, physical activity, diet, chronic disease severity, medication use, cancer screening participation, and healthcare utilization should be standard. Fourth, lag analyses or exclusion of early cancer events should be routinely performed to reduce reverse causation bias. Fifth, future studies should analyze specific cancer sites rather than focusing solely on overall cancer incidence, as different cancers likely have different relationships with psychological factors. Finally, the prospective cohort incident-tumor biobank method (PCIBM), which enables investigation of longitudinal long-term factors, biomarkers, and clinical outcomes, has been proposed as a promising approach to gain significant scientific advances in understanding the temporal dynamics of cancer development in relation to long-term risk factors [36].

Limitations: This review has several limitations that should be acknowledged. First and most importantly, direct evidence for chronic disease populations other than diabetes is clearly insufficient. The mechanisms linking different chronic diseases to cancer risk are not the same. For example, chronic obstructive pulmonary disease is closely related to smoking and lung cancer, chronic liver disease has a direct relationship with liver cancer development, patients with chronic kidney disease may be affected by immune, inflammatory, and dialysis-related factors, and patients with cardiovascular disease often have obesity, metabolic abnormalities, and polypharmacy. If conclusions for all chronic disease populations are inferred only from diabetes studies, the findings may be overgeneralized. Second, existing studies differ considerably in how depression and psychological distress are defined, including diagnostic codes, prescription records, self-reported diagnosis, K6, GHQ-12, MHI-5, and other approaches, making exposure misclassification difficult to avoid. Third, the degree of adjustment for health behaviors, chronic disease severity, cancer screening, healthcare utilization, and socioeconomic status varies across studies, reducing comparability between results. Fourth, the search was limited to English-language publications, which may have introduced language bias by excluding relevant non-English studies. Fifth, the risk of bias assessment revealed that confounding control was a major concern across all core studies (rated as "serious" for confounding in all studies), and UK Biobank-based studies are subject to healthy volunteer bias (rated as "serious" for participant selection).

5. Conclusion

The most defensible conclusion from this systematic review is that depression and psychological distress may be useful prognostic or risk-signal variables in

chronic disease care, particularly in diabetes. The association with cancer mortality appears more consistent than that with cancer incidence. However, causal effects on cancer incidence remain uncertain and vulnerable to confounding, health-behaviour mediation, surveillance bias, and reverse causation. The direct evidence base is heavily concentrated in diabetes, while evidence for other chronic disease populations—including cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, chronic pain, and multimorbidity—remains insufficient. Findings should not be interpreted as applying equally to all chronic disease populations. In clinical practice, greater attention should be paid to psychological status assessment among patients with chronic diseases, and psychological screening, lifestyle intervention, chronic disease management, and cancer risk prevention and control should be integrated to improve long-term prognosis.

Supplementary materials: Complete search strategies for Embase, Web of Science, and the Cochrane Library are provided in **Supplementary Table 1**.

Author contributions: Conceptualization, LM and YL; methodology, LM; software, LM; validation, YL; formal analysis; investigation, LM; resources, LM and YL; data curation, LM; writing—original draft preparation, LM; writing—review and editing, YL; visualization, LM; supervision, LM; project administration, LM; funding acquisition, LM and YL. All authors have read and agreed to the published version of the manuscript.

Funding: None.

Ethical approval: Not applicable.

Informed consent statement: Not applicable.

Data availability statement: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: The authors declare no conflict of interest.

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