

Association between antidepressant exposure and prognosis in breast cancer: A systematic review and meta-analysis

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Abstract. To date, the prognostic impact of antidepressant (AD) use on breast cancer (BC) outcomes remains unclear. The present study investigated the relationship between AD exposure and survival outcomes in patients with BC. PubMed, Web of Science, Embase and the Cochrane Library databases were systematically searched from inception to October 2025. The hazard ratio (HR) with its 95% confidence interval (CI) was used as the effect size. The primary outcomes of the present study were overall survival (OS) and BC-specific survival (BCSS). The protocol was registered with the International Prospective Register of Systematic Reviews database (study no. CRD420251232706). In total, nine studies comprising ~90,000 AD-exposed and >300,000 unexposed patients with BC were included. AD-exposed patients had worse OS (HR=1.28; 95% CI, 1.22-1.34; P<0.001) and BCSS (HR=1.16; 95% CI, 1.09-1.25; P<0.001) compared with the control group. In geographical subgroup analyses, AD-exposed patients in Europe demonstrated worse OS (HR=1.27; P<0.001) and BCSS (HR=1.18; P<0.001), and those in Asia had worse BCSS (HR=1.30; P<0.001); by contrast, for North America (P=0.671), no significant difference in BCSS was observed compared with non-exposed patients. By drug class, patients exposed to selective serotonin reuptake inhibitors (SSRIs) had worse OS (HR=1.34; P<0.001) and BCSS (HR=1.21, P<0.001) compared with non-exposed patients. Among individual SSRIs, no significant differences in BCSS were observed for sertraline (P=0.547), paroxetine (P=0.063) or fluoxetine (P=0.647), whereas citalopram exposure (HR=1.29; P<0.001) had worse

BCSS compared with non-exposed patients. Tricyclic ADs demonstrated worse BCSS (HR=1.26; P<0.001) compared with the control group. Regarding exposure timing, both continuous (OS: HR=1.24; P<0.001; BCSS: HR=1.14; P<0.001) and post-diagnosis (OS: HR=1.32; P<0.001; BCSS: HR=1.22; P=0.001) exposure had worse prognosis compared with the control group. In conclusion, observational evidence suggested that AD exposure may be associated with worse BC prognosis, and this association appeared to be influenced by geographical regions and drug classes.

Introduction

Breast cancer (BC) is one of the most prevalent malignancies among women worldwide. In 2022, female BC accounted for >2.3 million novel cases, constituting 11.6% of the global cancer incidence rate and for 6.9% of all cancer-associated mortalities (1).

BC incidence has shifted toward younger populations, with a notable annual increase of 2.5% among women aged 20-29 years (2). It has been reported that ~30.2% of patients with BC experience depression (3). Notably, younger patients with BC are more susceptible to depressive symptoms, such as persistent sadness, fatigue and loss of appetite; a previous study reported that patients with BC aged ≤45 years had a 1.5 times higher risk of screening positive for potential depression compared with those aged >45 years (4). It is well known that depressive and anxious states can impair the quality of life of patients (5,6), which may adversely affect tumor recovery. Therefore, psychological support should be considered for these patients with BC, and for those with severe or persistent psychological distress, adjunctive pharmacotherapy with antidepressant (AD) or anxiolytic may be warranted.

Regarding the association between AD exposure and BC prognosis, a previous cohort study by Baxter *et al* (7) reported an 11% increase in mortality risk among exposed patients compared with the control group. However, other studies (8,9), including those focusing on major AD classes such as selective serotonin reuptake inhibitors (SSRIs) and tricyclic ADs (TCAs), have not identified an association between

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AD exposure and BC prognosis. Another previous study by Suppli *et al* (10) suggested that the observed association might not be attributable to AD *per se*, but rather to the finding that patients with AD exposure had worse adherence to standard BC treatment compared with the control group. Thus, research findings on AD exposure and BC outcomes remain conflicting, and currently no meta-analysis has explored this association, to the best of our knowledge. Therefore, the present study aimed to investigate this association by systematically searching for and reviewing relevant cohort studies and randomized controlled trials (RCTs).

Materials and methods

Study design. The present meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (11). Furthermore, the present study was registered in the International Prospective Register of Systematic Reviews database under (<https://www.crd.york.ac.uk/PROSPERO/>) registration number CRD420251232706.

Search strategy. A systematic literature search was conducted across PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://webofscience.com/>), Embase (<https://www.embase.com/>) and the Cochrane Library databases (<https://www.cochranelibrary.com/>) from inception to October 2025 to identify studies investigating the association between AD exposure and survival outcomes in patients with BC. The search strategy combined Medical Subject Headings terms and free-text keywords using Boolean operators. The detailed search strategy is provided in Table SI. For example, terms for BC (<https://www.ncbi.nlm.nih.gov/mesh/68001943>) included 'breast neoplasms', 'neoplasm, breast' and 'breast cancer'; and terms for AD (<https://www.ncbi.nlm.nih.gov/mesh/68000928>) included 'antidepressive agents', 'antidepressant medication' and 'antidepressant'. To identify additional relevant studies, the reference lists of included publications were manually searched in the aforementioned databases. To ensure comprehensiveness and minimize oversight, all searches were performed independently by two reviewers and any disagreements were resolved through discussion or by consulting a third reviewer. The titles and abstracts were first screened and then the full texts of potentially eligible studies were assessed.

Inclusion and exclusion criteria. Study eligibility was determined based on the following framework: Population, Intervention, Comparison, Outcomes and Study Design (12). The inclusion criteria were as follows: i) The study population comprised of patients with BC; ii) the exposure group involved patients who received any class of AD; iii) the control group consisted of patients not exposed to AD; iv) the study reported patient survival outcomes, specifically with overall survival (OS) or BC-specific survival (BCSS); v) the study design was a cohort study or an RCT; and vi) the article was published in English. Studies were excluded if any of the following criteria applied: i) Data were unavailable or could not be extracted; ii) full-text articles were not accessible; and iii) the study was a duplicate publication or an updated version of an already included study.

Data extraction. A standardized data extraction form was used to collate the following information from each included study: Authors, publication year, country, study design, sample size, participant characteristics (for example, mean age), follow-up duration, type of AD, exposure definition, exposure assessment, adjusted covariates and prognostic data (13). For studies reporting BCSS, the present study verified that the outcome was consistently defined as BC-specific mortality based on the underlying cause of mortality. Data extraction was performed independently by two reviewers. Any discrepancies between the reviewers were resolved through consensus or by consulting a third reviewer.

Risk of bias and quality assessments. The methodological quality of the included studies was appraised using design-specific tools. For the RCTs, the Cochrane Risk of Bias tool (ROB 1; version 5.1.0) was used (14). The Cochrane Risk of Bias tool evaluated the risk of bias across six domains: Selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases (such as baseline imbalance, funding bias or early trial termination). Each domain was judged as 'low risk', 'high risk' or having an 'unclear risk' of bias. For cohort studies, the Newcastle-Ottawa Scale (NOS) was utilized, rating the studies on selection (0-4 points), comparability (0-2 points) and outcome ascertainment (0-3 points) (15). The total score ranged from 0 to 9, with higher scores reflecting improved methodological quality and a lower risk of bias. Two reviewers independently conducted these assessments and any disagreements that arose were resolved through discussion with a third reviewer.

Statistical analysis. In the present meta-analysis, all statistical analyses were performed using Stata software (version 12.0; StataCorp LP). The association between AD exposure and BC prognosis was evaluated by pooling hazard ratios (HR) with 95% confidence intervals (CIs). An HR>1 indicated that AD exposure was associated with worse prognosis; by contrast, an HR <1 suggested that AD exposure was associated with improved prognosis. Heterogeneity across studies was evaluated using the I^2 statistic, with an I^2 value >50% denoting notable heterogeneity and an I^2 value ≤50% denoting low heterogeneity. Due to the potential sources of heterogeneity (for example, ethnicity, tumor stage and type or frequency of AD exposure), a random-effects model was used for the present meta-analysis to improve the robustness of the statistical results. To investigate the sources of heterogeneity, subgroup analyses were performed based on pre-specified factors including AD type and timing of exposure associated with cancer diagnosis. The potential for publication bias was examined using Egger's test (16). Sensitivity analyses were performed using the leave-one-out approach, in which each included study was sequentially omitted to evaluate whether any single study markedly influenced the pooled estimates (17). All P-values were two-sided and P<0.05 was considered to indicate a statistically significant difference.

Results

Study search results. The initial systematic search across four databases yielded 13,661 records. After removing duplicates,

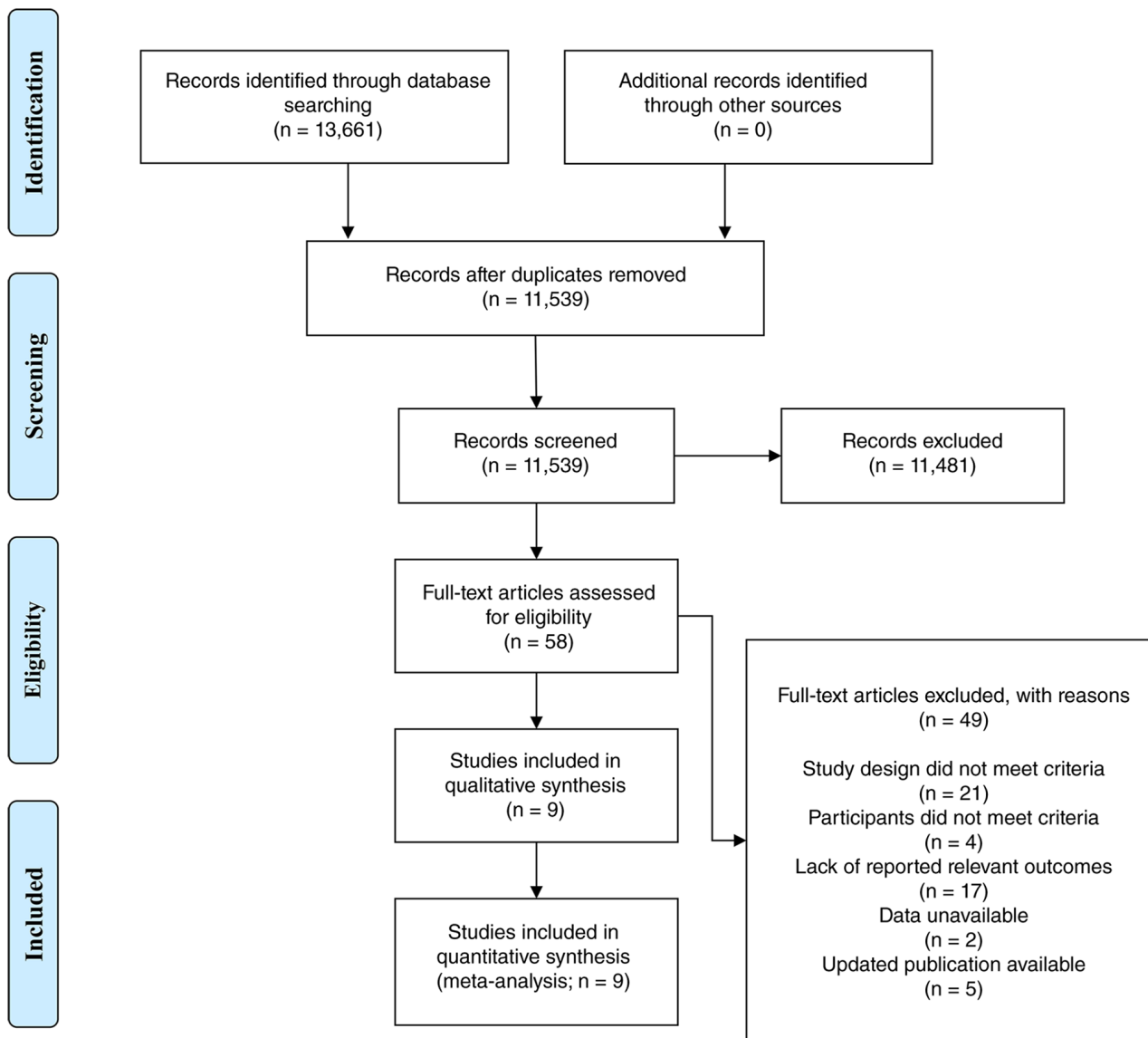


Figure 1. Flowchart representing details of the study selection.

11,539 unique records remained. Following screening of titles and abstracts, 11,481 records were excluded, leaving 58 studies for full-text review. Upon detailed assessment, 49 studies were excluded for the following reasons: Used an ineligible study design (n=21), enrolled a population that did not meet the inclusion criteria of the present study (n=4), lacked reporting on relevant outcomes (n=17), had unavailable or non-extractable data (n=2) and were identified as duplicate or updated publications (n=5). This process resulted in the inclusion of nine studies (7-10,18-22), as detailed in Fig. 1.

Study characteristics. The nine included studies, published between 2007 and 2025, were conducted across eight countries: United States (n=2), Australia, Northern Ireland, Israel, South Korea, United Kingdom, France and Denmark (each n=1). The total sample size consisted of ~90,000 patients in the AD-exposed group and >300,000 patients in the control group. The types of AD exposure varied, including any AD as well as specific agents such as SSRIs, TCAs,

sertraline, venlafaxine and mianserin. Regarding exposure definition, six studies involved post-diagnosis use and six studies involved continuous use, as three studies (8,19,21) reported both exposure definitions. Notably, patients with pre-diagnosis use who were included without specification of post-diagnosis were classified into the continuous use group. The primary outcomes of interest in the present study were OS and BCSS. A summary of these study characteristics is presented in Table I. Additional information, such as cohort names and dates of BC diagnosis, are provided in Table SII.

Quality assessment and risk of bias. Among the nine included studies, one study was an RCT. The methodological quality of this RCT was appraised using The Cochrane Risk of Bias tool, and it was judged to be at an overall low risk of bias. The remaining eight studies were cohort designs, which were assessed using the NOS. The NOS scores for these cohort studies ranged from 6 to 8, indicating moderate to high methodological quality. The detailed ratings for all studies are provided in Tables SIII and SIV.

Table I. Characteristics of all the studies included in the present meta-analysis.

First author, year	Country	No. of AD-exposed patients	No. of unexposed patients	AD type	Exposure definition	Outcomes reported	(Refs.)
Stockler <i>et al</i> , 2007	Australia	32	157	Sertraline	Sertraline; 50 mg daily	OS	(18)
Baxter, <i>et al</i> , 2025	Northern Ireland	4,358	9,488	Any AD	Filled AD prescription within 12 months before breast cancer diagnosis	OS and BCSS	(7)
Fischer <i>et al</i> , 2022	Israel	1,048	3,143	SSRIs	Use of SSRIs based on filled prescriptions from 1998 to 2020	OS	(19)
Shim <i>et al</i> , 2020	South Korea	76,328	47,225	Any AD	Use of AD within the 1st year after diagnosis	OS	(20)
Busby <i>et al</i> , 2018	United Kingdom	4,784	18,885	SSRIs, TCAs and venlafaxine	At least one AD prescription after diagnosis	OS and BCSS	(21)
Wernli <i>et al</i> , 2011	USA	308	2,750	Any AD	Use of AD after diagnosis at least twice weekly for ≥ 3 months	OS and BCSS	(8)
Chubak <i>et al</i> , 2016	USA	2,302	1,914	Any AD	Use of AD after diagnosis	BCSS	(9)
Dumas <i>et al</i> , 2024	France	1,490	233,878	Mianserin	≥ 3 months of the full mianserin dose in the 6 months before breast cancer diagnosis	OS	(22)
Suppli <i>et al</i> , 2017	Denmark	1,450	6,733	Any AD	AD treatment from 3 years to 3 months before breast cancer diagnosis	OS and BCSS	(10)

AD, antidepressant; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; OS, overall survival; BCSS, breast cancer-specific survival.

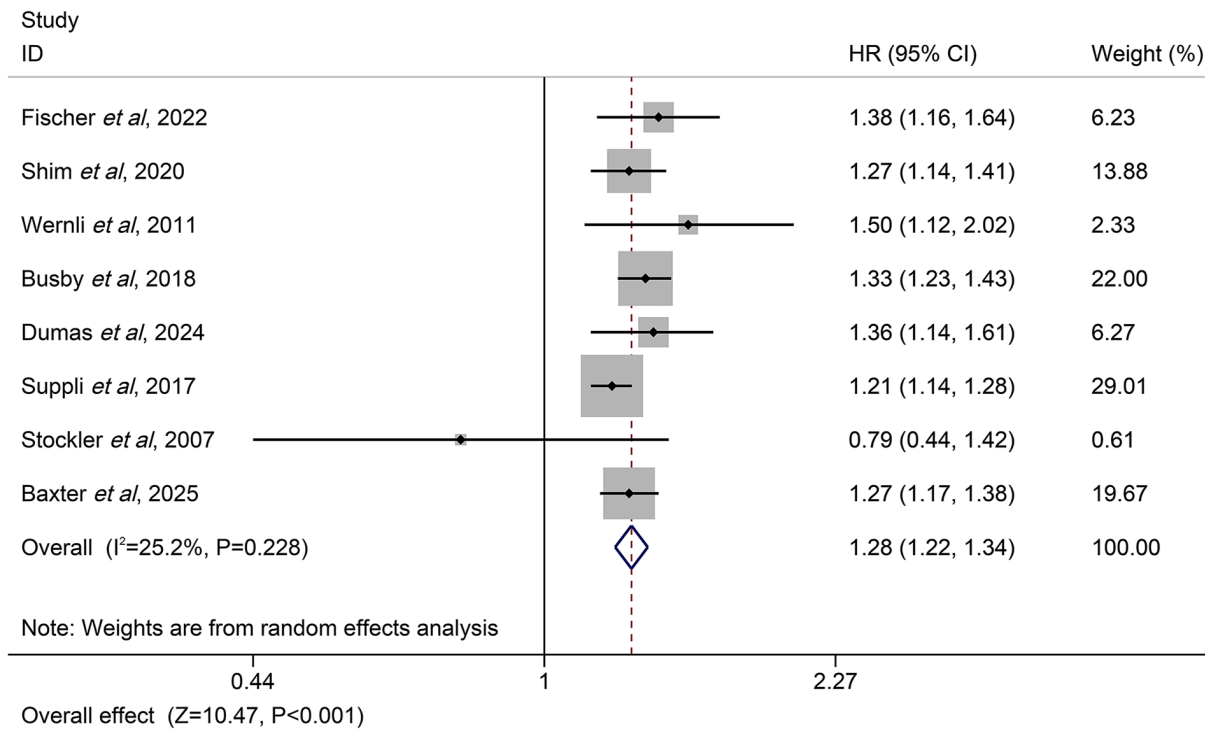


Figure 2. Forest plot demonstrating the effect of antidepressant exposure on overall survival (overall effect, $P<0.001$). HR, hazard ratio.

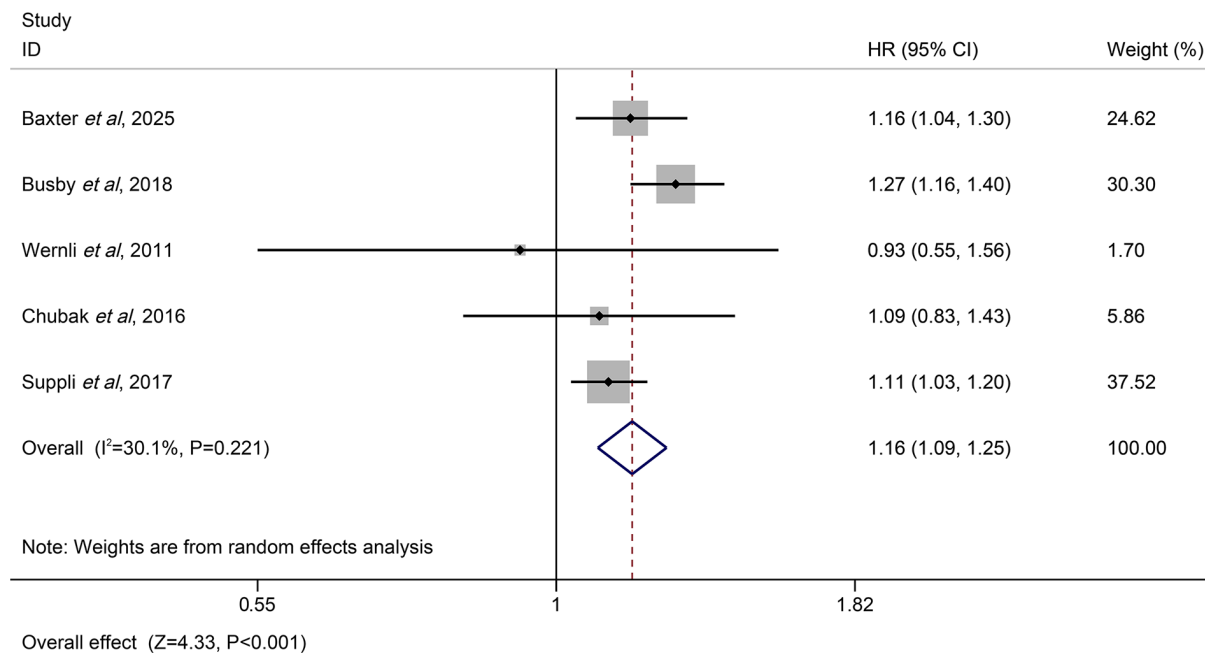


Figure 3. Forest plot demonstrating the effect of antidepressant exposure on breast cancer-specific survival (overall effect, $P<0.001$). HR, hazard ratio.

Meta-analysis. The meta-analysis of OS, based on eight studies reporting this outcome, demonstrated that patients exposed to AD had worse OS compared with the control group (HR=1.28; 95% CI, 1.22-1.34; $P<0.001$), with low heterogeneity ($I^2=25.2\%$; $P=0.228$). The corresponding forest plot is presented in Fig. 2. For BCSS, a pooled analysis of the five studies reporting this outcome revealed that the exposure group had lower survival compared with the control group (HR=1.16; 95% CI, 1.09-1.25; $P<0.001$;

$I^2=30.1\%$; $P=0.221$). The corresponding forest plot is presented in Fig. 3.

Subgroup analysis. In the subgroup analysis of OS, when stratified by ethnicity, the pooled results indicated a significantly worse prognosis in the AD-exposed group compared with their respective control groups within both the European (HR=1.27; 95% CI, 1.21-1.34; $P<0.001$) and Asian (HR=1.30; 95% CI, 1.19-1.42; $P<0.001$) subgroups. The North American subgroup

Table II. Subgroup analysis of the association between AD exposure and overall survival.

Subgroup	No. of studies	HR	95% CI	P-value	I ² , %
Geographical region					
Europe	4	1.27	(1.21, 1.34)	<0.001 ^a	35.3
Asia	2	1.30	(1.19, 1.42)	<0.001 ^a	0.0
Type of AD					
SSRIs	4	1.34	(1.18, 1.51)	<0.001 ^a	31.7
Other ADs	2	1.36	(1.15, 1.59)	<0.001 ^a	0.0
Timing of exposure ^b					
Continuous	5	1.24	(1.19, 1.30)	<0.001 ^a	0.0
Post-diagnosis	5	1.32	(1.23, 1.42)	<0.001 ^a	17.4

^aP<0.05. ^bThe 'continuous use' and 'post-diagnosis use' subgroups each included 5 studies, with 2 studies reporting both exposure definitions and were therefore included in both subgroups. Consequently, the two subgroups overlap, and the combined study entries total 10, although only 8 independent studies provided overall survival data. HR, hazard ratio; AD, antidepressant; SSRIs, selective serotonin reuptake inhibitors.

Table III. Subgroup analysis of the association between AD exposure and breast cancer-specific survival.

Subgroup	No. of studies	HR	95% CI	P-value	I ² , %
Geographical region					
Europe	3	1.18	(1.08, 1.28)	<0.001 ^a	58.1
North America	2	1.05	(0.83, 1.34)	0.671	0.0
Type of AD					
SSRIs ^b	4	1.21	(1.13, 1.31)	<0.001 ^a	0.0
Sertraline	2	1.31	(0.55, 3.11)	0.547	64
Paroxetine	2	1.25	(0.99, 1.57)	0.063	0.0
Fluoxetine	2	1.11	(0.71, 1.72)	0.647	36.3
Citalopram	2	1.29	(1.14, 1.46)	<0.001 ^a	0.0
TCAs	3	1.26	(1.14, 1.40)	<0.001 ^a	3.5
Other ADs	2	1.14	(0.82, 1.59)	0.421	53.3
Timing of exposure					
Continuous	3	1.14	(1.07, 1.20)	<0.001 ^a	0.0
Post-diagnosis	3	1.22	(1.08, 1.37)	0.001 ^a	12.3

^aP<0.05. ^bThe SSRI subgroup included 4 studies reporting any SSRI use. The specific drug subgroups (sertraline, paroxetine, fluoxetine and citalopram) are not mutually exclusive, as a single study may report more than one SSRI. Therefore, the number of studies in each specific drug subgroup is not necessarily 1 and these subgroup counts do not sum to the total number of studies in the SSRI subgroup. HR, hazard ratio; AD, antidepressant; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic ADs.

was not analyzed separately because it contained only one study (8), precluding a meaningful meta-analysis. Stratified by drug class, the AD exposure group had significantly worse OS compared with the control group for both SSRIs (HR=1.34; 95% CI, 1.18-1.51; P<0.001) and other ADs (HR=1.36; 95% CI, 1.15-1.59; P<0.001). Regarding timing of exposure, patients in the exposure group demonstrated significantly worse survival outcomes compared with the control group for both continuous exposure (HR=1.24; 95% CI, 1.19-1.30; P<0.001) and post-diagnosis exposure (HR=1.32; 95% CI, 1.23-1.42; P<0.001). Detailed results are presented in Table II.

An analysis of BCSS was performed across subgroups. Among European patients, those in the exposed group

demonstrated a significantly worse prognosis compared with the control groups (HR=1.18; 95% CI, 1.08-1.28; P<0.001); however, no significant difference in BCSS was observed between both groups in the North American cohort (HR=1.05; 95% CI, 0.83-1.34; P=0.671). In the analysis stratified by drug class, patients exposed to SSRIs (HR=1.21; 95% CI, 1.13-1.31; P<0.001) and TCAs (HR=1.26; 95% CI, 1.14-1.40; P<0.001) demonstrated significantly worse BCSS compared with the control groups. However, no statistical difference in survival outcomes was observed between the two groups for other ADs (HR=1.14; 95% CI, 0.82-1.59; P=0.421). Further subgroup analysis within SSRIs revealed a significantly worse prognosis with

citalopram exposure vs. non-exposure (HR=1.29; 95% CI, 1.14-1.46; $P<0.001$), whereas no significant differences were identified for exposure to sertraline, paroxetine and fluoxetine [sertraline (HR=1.31; 95% CI, 0.55-3.11; $P=0.547$); paroxetine (HR=1.25; 95% CI, 0.99-1.57; $P=0.063$); fluoxetine (HR=1.11; 95% CI, 0.71-1.72; $P=0.647$)]. Regarding timing of exposure, both continuous exposure (HR=1.14; 95% CI, 1.07-1.20; $P<0.001$) and post-diagnosis exposure (HR=1.22; 95% CI, 1.08-1.37; $P=0.001$) to AD had significantly lower BCSS in patients compared with the control groups. Complete data are presented in Table III.

Publication bias and sensitivity analysis. For OS, no significant publication bias was observed using Egger's test ($P=0.271$; Fig. S1). Sensitivity analysis further confirmed the robustness of the OS results and the leave-one-out analysis excluding the RCT by Stockler *et al* (18) did not materially alter the pooled estimate (HR=1.28; 95% CI, 1.23-1.33; Fig. S2). Similarly, Egger's test for BCSS revealed no significant publication bias ($P=0.223$; Fig. S3), and sensitivity analysis also indicated robust results (Fig. S4; Table SV).

Discussion

The present meta-analysis demonstrated that patients with BC with exposure to AD had a worse prognosis compared with non-exposed patients. Sensitivity analysis demonstrated the robustness of these findings. Before interpreting the observed association as a direct effect of AD exposure, it is key to consider the primary confounding effect of depression. Notable evidence has associated depressive states with increased tumor aggressiveness, immune suppression, poor treatment adherence and elevated risk of recurrence and metastasis (23-26). According to a previous meta-analysis of 65 cohort studies published in 2025, depression is markedly associated with increased cancer-specific mortality across multiple cancer types, such as colorectal cancer, lung cancer and prostate cancer, with a 23% higher hazard for poor survival (27). Therefore, the observed associations in the present study cannot rule out the potential confounding effect of depression, and the findings should be interpreted primarily as reflecting the prognostic impact of the underlying depressive disorder rather than a direct pharmacological effect of the drugs themselves.

Several pathophysiological pathways may mediate this association, such as neuroendocrine dysregulation, chronic inflammation and alterations in the gut microbiota. Firstly, in depressive states, persistent activation of the hypothalamic-pituitary-adrenal (HPA) axis leads to chronically elevated cortisol levels, which can result in glucocorticoid receptor dysfunction and impaired cortisol regulation (28,29). Epidemiological studies suggested that patients with flattened cortisol rhythms have a higher risk of cancer mortality (29,30). In addition to HPA axis dysregulation, emotional stress associated with depression can activate the sympathetic nervous system and promote the release of the neurotransmitter norepinephrine (31), which has been implicated in BC pathogenesis (32). For example, a previous study by Szpunar *et al* (33) demonstrated that chronic administration of TCAs suppresses norepinephrine reuptake, thereby stimulating the proliferation

of mammary adenocarcinoma cell lines. This dual neuroendocrine dysregulation may collectively contribute to the observed association between depression and worse cancer outcomes.

Secondly, several studies have demonstrated that postoperative depressive symptoms in patients with BC are markedly associated with elevated levels of pro-inflammatory cytokines, including IL-1 β , IL-6 and TNF- α (34,35). These cytokines serve a key role in tumor angiogenesis, metastatic dissemination and therapeutic resistance. For instance, IL-6 promotes cancer stem cell properties and induces epithelial-mesenchymal transition via the Janus kinase (JAK)/STAT3 signaling pathway (36), while also remodeling the immunosuppressive tumor microenvironment by modulating the regulatory T/T helper 17 cell balance (37). Clinically, elevated IL-6 levels are associated with a 2.25 times higher risk of mortality in patients with BC, compared with patients without elevated IL-6 levels (38).

Thirdly, depression alters gut microbiota composition and reduces microbial diversity, which in turn promotes BC progression (23,39). A mechanistic study by Cui *et al* (40) revealed that a reduction in beneficial bacteria may decrease butyrate levels, a key microbial metabolite. Butyrate deficiency can aberrantly activate the low-density lipoprotein receptor-related protein 5/ β -catenin pathway, thereby enhancing cancer stem cell properties and promoting tumor growth and metastasis. Furthermore, gut-derived microbial metabolites including short-chain fatty acids, secondary bile acids and aromatic amino acid metabolites, have been implicated in BC development via the circulatory system (41). Furthermore, gut microbiota dysbiosis may contribute to immune dysfunction, affecting the response to antitumor therapy and facilitating tumor progression (42).

Notably, when interpreting the present study findings, it is key to consider not only the neuroendocrine-immunological mechanisms of depression, but also the potential impact of psychological comorbidities in patients with BC receiving AD treatment. At the prevention and early detection stage, depression may lead patients to avoid preventive medical services. Baeker Bispo *et al* (43) reported that women with untreated depression or anxiety had a 14-17% lower rate of timely BC screening compared with women without depression or anxiety, suggesting that psychological distress may impair cancer prevention engagement and lead to delayed diagnosis and worse prognosis. In the treatment stage, psychological states such as fear of recurrence, treatment concerns and loss of confidence may reduce adherence to standard therapies (44,45). Patients who use ADs have been reported to be 1.14 times more likely to forego standard BC treatment compared with patients who do not use ADs (10), and a TAILORx trial (46) sub analysis reported that patients with BC with a history of depression had an 82% higher risk of prematurely discontinuing adjuvant endocrine therapy, compared with those without a history of depression (47). By contrast, positive psychological resources, such as belief in treatment effectiveness and optimism, are associated with improved outcomes (48). Mindfulness-based interventions also markedly reduce depressive symptoms, such as persistent sadness, fatigue and loss of appetite (49), as well as improve the quality of life of patients with BC, highlighting the clinical relevance of addressing psychological well-being (50,51).

Beyond the confounding effect of depression, the impact of AD on malignant tumors is complex, encompassing both pro-tumorigenic and antitumorigenic potential, with inconsistent findings from *in vitro* and *in vivo* experiments. Certain ADs have reported intrinsic antitumor properties, including the induction of cancer cell apoptosis and inhibition of the PI3K/AKT/mTOR signaling axis to trigger autophagy (52-54). However, the translational relevance of these preclinical findings remains to be elucidated. The concentrations used in most *in vitro* studies exceed therapeutic doses, and cell line systems fail to replicate the complex *in vivo* microenvironment, immune surveillance and pharmacokinetics. A previous study by Taler *et al* (55) demonstrated that while sertraline significantly inhibited BC tumor growth *in vitro*, it paradoxically promoted tumor growth *in vivo*.

Furthermore, several studies have suggested that AD may carry a potential risk of promoting tumorigenesis (56,57). This finding was replicated in the present meta-analysis, which demonstrated that exposure to AD is associated with worse prognosis in patients with BC. Firstly, tamoxifen is a common adjuvant endocrine therapy for patients with hormone receptor-positive (HR⁺) BC (58). As a prodrug, tamoxifen is metabolized primarily by the hepatic cytochrome P450 (CYP) enzyme system, particularly CYP family 2 subfamily D member 6 (CYP2D6), which converts it into its active metabolite endoxifen to inhibit BC tumor growth (59-61). In patients receiving tamoxifen, concomitant use of certain SSRIs that are potent to moderate CYP2D6 inhibitors may interfere with this activation pathway (60), leading to reduced endoxifen concentrations and potentially diminished therapeutic efficacy. This pathway is relevant only to HR⁺ patients treated with tamoxifen and cannot explain the associations observed in HR⁻ subtypes or in patients receiving aromatase inhibitors. In the present study, although the overall findings are consistent with this hypothesis, the limited subgroup data do not allow robust confirmation.

Secondly, SSRIs block the serotonin transporter, promoting increased extracellular 5-hydroxytryptamine (5-HT) levels, which drive tumor cell proliferation through multiple mechanisms. 5-HT activates the JAK1/STAT3 signaling cascade to drive glycolysis and the cAMP/protein kinase A cascade to promote mitochondrial biogenesis (62), both closely associated with aggressive tumor behavior and poor prognosis in BC (62,63). Furthermore, 5-HT effects are partially mediated by the upregulation of G-protein-coupled receptor 30 (GPR30) (64), which activates PI3K/AKT and ERK signaling to promote BC cell proliferation (65). Notably, certain SSRIs, such as fluoxetine, paroxetine and sertraline, may directly interact with estrogen receptors (ERs), including GPR30 and ER α (66), exerting estrogen-like effects that activate these downstream pathways.

Furthermore, the category of other ADs in the subgroup analyses of the present study warrants particular attention. This group combined mianserin with other agents. Pharmacologically, mianserin is a tetracyclic AD with a mechanism fundamentally distinct from that of SSRIs or TCAs. Ideally, mianserin would have been analyzed as a separate category; however, the limited number of studies precluded a notable subgroup analysis for this agent alone, so this classification was adopted for analytical feasibility.

Due to the limited number of studies in the drug-specific subgroup analyses, the null findings for certain SSRIs should be interpreted with caution and may reflect insufficient statistical power to detect a true association. Therefore, these results should be considered inconclusive rather than evidence of no effect. The pro-tumorigenic effects of SSRIs such as fluoxetine, paroxetine and sertraline, which are mediated via 5-HT-associated mechanisms, do not provide a complete understanding of these drugs. Of note, previous studies have also revealed antitumorigenic mechanisms: Fluoxetine inhibits eukaryotic elongation factor 2 kinase and activates the AMP-activated protein kinase-mTOR-Unc-51-like kinase complex axis (67), inducing autophagic cell death; both sertraline and paroxetine have been reported to enhance the sensitivity of tumor cells to apoptosis (52,68). This duality of pro-tumor and antitumor effects may offer a plausible explanation for the lack of a notable association observed in the subgroup analysis for these three specific agents, although this interpretation requires further investigation. By contrast, citalopram demonstrated a notable association with worse BCSS. This discrepancy may be partly explained by the intermediate CYP2D6 inhibitory potency of citalopram and its documented impact on tamoxifen metabolism (69), which could be clinically relevant in patients receiving this endocrine therapy. Furthermore, citalopram has been associated with prolongation of the QT interval (the time from the start of the QRS complex to the end of the T wave on an electrocardiogram) (70), a potential risk factor for sudden cardiac death. Nevertheless, the precise mechanism underlying this association remains speculative and warrants further study.

In the present study, geographical variation was observed in the association between AD use and BC survival. Subgroup analysis revealed that this association reached statistical significance in Europe and Asia, whereas no such association was observed in North America. However, this null finding should be interpreted with caution, as it may reflect limited statistical power due to the small number of included studies and extensive CIs, rather than a true absence of effect. Several factors may contribute to the observed geographical differences. The prevalence of depression in patients with BC is 24.9% in North America, compared with 28.9% in Europe and 34.2% in Asia (3). Therefore, the influence of depression on prognosis may be smaller in the North American cohort. Furthermore, CONCORD study data indicated that the incidence rate of locally advanced tumors in Europe is double that in North America (71), suggesting later-stage diagnosis and greater tumor burden, which inherently worsens prognosis. Similarly, in Asia, a majority of patients with BC are diagnosed at advanced stages, with limited national data available for precise quantification (72). Therefore, these findings should not be overgeneralized as evidence that AD use is safe in North American patients with BC.

To the best of our knowledge, the present meta-analysis is the first systematic evaluation of the association between AD exposure and BC prognosis. Comprehensive subgroup analyses were performed, revealing differential effects across specific AD classes and geographical regions. However, several limitations should be considered. The majority of the studies included were observational cohort designs, with only one

RCT included. The inherent heterogeneity among the included studies combined with the weak causal evidence reduces the credibility of the pooled estimates. The limited number of studies precluded subgroup analyses stratified by key pathological factors, including molecular subtype (ER/progesterone receptor/HER2 status) and TNM stage. Due to the notable heterogeneity of BC in terms of prognosis across these subtypes, the inability to perform such analyses represents a major methodological constraint. Therefore, the generalizability of the present study findings across different molecular subtypes and disease stages remains to be elucidated. Notably, confounding by indication cannot be ruled out in the present meta-analysis, as the underlying depression leading to AD exposure may account for the observed survival disadvantage rather than the medication. Furthermore, a majority of the included studies lacked comprehensive adjustment for depression severity. Therefore, the observed associations should be interpreted with caution and causality cannot be inferred from the present study findings. This represents a major limitation of the present study.

In conclusion, the present study observed a statistical association between AD exposure and worse OS and BCSS in patients with BC. However, this association is hypothesized to be largely driven by depression and its associated psychosocial factors, rather than by a direct pharmacological effect of AD. The independent effects of AD could not be distinguished from those of the underlying depressive disorder based on the findings of the present study. Due to the limited sample size and the key confounding by indication, these findings should be interpreted with caution and warrant confirmation in larger-scale, well-designed prospective studies that adequately control for depression severity in the future.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QC conceptualized the present study, conducted literature screening, collected the data, conducted the formal analysis of data, devised the methodology, wrote the original draft and reviewed and edited the manuscript. YS collected the data, conducted literature screening, conducted the formal analysis of data, devised the methodology and reviewed and edited the manuscript. XZ conceptualized the present study, conducted literature screening, collected the data, verified the accuracy of the extracted data and reviewed and edited the manuscript. TJ collected the data, conducted the formal analysis of data,

visualized the data, reviewed and edited the manuscript. SZ collected the data, conducted literature screening, reviewed and edited the manuscript. XY collected the data, conducted literature screening, reviewed and edited the manuscript. FH conceptualized the present study, acquired funding, devised the methodology, participated in project administration, obtained resources, provided supervision, reviewed and edited the manuscript. QC and YS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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