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Meta-analysis

Association between high body mass index and prognosis of patients with early-stage breast cancer: A systematic review and meta-analysis

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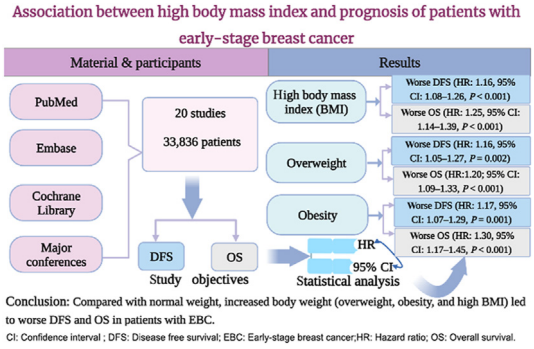
HIGHLIGHTS

- The impact of high body mass index (BMI) on the prognosis of patients with early-stage breast cancer (EBC) was examined.
- A meta-analysis of 20 studies with 33,836 patients with EBC was carried out.
- High BMI (overweight or obesity) had adverse effects on disease-free survival and overall survival in patients with EBC.
- Clinicians should recommend regular physical activity and weight reduction to patients with EBC. This may prolong survival and improve prognosis and quality of life in patients with EBC.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: A high body mass index (BMI) can indicate overweight or obesity and is a crucial risk factor for breast cancer survivors. However, the association between high BMI and prognosis in early-stage breast cancer (EBC) remains unclear. We aimed to assess the effects of high BMI on the prognosis of patients with EBC.

Methods: The PubMed, Embase, and Cochrane Library databases and proceedings of major oncological conferences related to the effects of BMI on the prognosis of breast cancer were searched up to November 2021. Fixed- and random-effects models were used for meta-analyses. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-free survival (DFS) and overall survival (OS) were extracted from the included literature.

Results: Twenty retrospective cohort studies with 33,836 patients with EBC were included. Overweight patients had worse DFS (HR: 1.16, 95% CI: 1.05–1.27, $P = 0.002$) and OS (HR: 1.20; 95% CI: 1.09–1.33, $P < 0.001$). Obesity also had adverse effects on DFS (HR: 1.17, 95% CI: 1.07–1.29, $P = 0.001$) and OS (HR: 1.30, 95% CI: 1.17–1.45, $P < 0.001$). Likewise, patients with high BMI had worse DFS (HR: 1.16, 95% CI: 1.08–1.26, $P < 0.001$) and OS (HR: 1.25, 95% CI: 1.14–1.39, $P < 0.001$). In subgroup analyses, overweight had adverse effects on DFS (HR: 1.11, 95% CI: 1.04–1.18, $P = 0.001$) and OS (HR: 1.18, 95% CI: 1.11–1.26, $P < 0.001$) in multivariate analyses, whereas the relationship that overweight had negative effects on DFS (HR: 1.21, 95% CI: 0.99–1.48,

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$P = 0.058$) and OS (HR: 1.39, 95% CI: 0.92–2.10, $P = 0.123$) was not statistically significant in univariate analysis. By contrast, obesity had adverse effects on DFS (HR: 1.21, 95% CI: 1.06–1.38, $P = 0.004$ and HR: 1.14, 95% CI: 1.08–1.22, $P < 0.001$) and OS (HR: 1.33, 95% CI: 1.15–1.54, $P < 0.001$ and HR: 1.23, 95% CI: 1.15–1.31, $P < 0.001$) in univariate and multivariate analyses, respectively.

Conclusions: Compared with normal weight, increased body weight (overweight, obesity, and high BMI) led to worse DFS and OS in patients with EBC. Once validated, these results should be considered in the development of prevention programs.

Introduction

Breast cancer (BC) is one of the most common malignancies in women worldwide. The global incidence of BC has continued to increase slowly in the last decade.[1] Early detection combined with progress in cancer treatment has greatly improved BC outcomes.[2] However, approximately 15% of patients with BC still experience disease progression and death each year.[1] Some factors that affect the prognosis of BC include axillary lymph nodes, size of the primary tumor, administration of adjuvant systemic therapies, tumor-infiltrating lymphocytes, estrogen receptor, human epidermal growth factor receptor-2 (HER-2), age, menopause status, race, alcohol consumption, and smoking.[3–5]

The prevalence of overweight or obesity is regarded as a public health problem worldwide, and an increasing number of patients with BC are overweight or obese. The World Health Organization (WHO) standards define the following body mass index (BMI) categories: underweight, <18.5 kg/m^2; normal weight, 18.5 to <25.0 kg/m^2; overweight, ≥ 25.0 to <30.0 kg/m^2; and obesity ≥ 30.0 kg/m^2. Up to 75% of women in the United States and 50% in Europe are overweight or obese upon BC diagnosis, and BC treatments often result in additional weight gain.[6–10] A high BMI is associated with a worse clinical outcome in patients with early-stage breast cancer (EBC).[11] The biological mechanisms explaining the association between adiposity and BC survival remain unclear and may involve the interaction among hormones, adipocytokines, and inflammatory cytokines, which are linked to cell survival/apoptosis, migration, and proliferation.[12–15] For example, leptin, an adipocytokine, is produced mainly by the white adipose tissue and acts as a growth factor in various types of cancers, including BC. Leptin promotes angiogenesis, potentially directly stimulating the growth of BC cells and possibly leading to reduced survival.[12–15] Insulin-like growth factor-1 (IGF-1) also inhibits apoptosis, and higher fasting insulin concentrations are associated with increased recurrence and decreased survival in patients with BC.[13]

Numerous studies have examined the relationship between obesity and BC outcomes.[14,16–23] In one meta-analysis, only the effect of weight gain on BC outcomes was examined, and the association between high BMI and BC prognosis was not explored.[24] Another meta-analysis only examined the prognostic role of overweight in triple-negative breast cancer (TNBC) and did not explore the effect of overweight and obesity on the prognosis of all subtypes of BC.[25] Consequently, a systematic review and meta-analysis were conducted to ascertain the association between high BMI and prognosis in patients with EBC.

Methods

Search strategy

All included studies were observational studies with available survival data, including disease-free survival (DFS) and overall survival (OS). The Meta-analyses of observational studies in epidemiology (MOOSE) guidelines were followed in this study.[26] We searched the databases PubMed, Embase, and Cochrane Library for studies up to November 2021. These studies compared the differences in survival between overweight or obesity and normal weight in patients with BC or TNBC. We also scrutinized the publications of major conferences, including those of the European Society of Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), and the San Antonio Breast Cancer Symposium (SABCS). The following keywords were used in our literature search: (1) "breast neoplasm" OR "breast cancer" OR "breast carcinoma" OR "breast tumor" OR "breast tumor" OR "mammary cancer"; (2) "overweight" OR "obesity" OR "weight gain" OR "body weight"; and (3) "prognosis" OR "outcome" OR "survival". We summarized the detailed information of each identified study, including study name, year of publication, author, patient grouping, basic patient information, and median follow-up time.

Inclusion and exclusion criteria

Studies were eligible if they met the following inclusion criteria: (1) studies that included patients diagnosed with EBC; (2) studies that reported the OS, DFS, relapse-free survival (RFS), or event-free survival (EFS) as clinical endpoints; (3) studies in which the exposure factors were overweight or obesity; and (4) studies published in English. The excluded studies were (1) studies that included patients with advanced BC; (2) studies that did not include OS, DFS, RFS, or EFS as clinical endpoints; (3) studies that did not report hazard ratios (HRs) with 95% confidence intervals (CIs) for OS, DFS, RFS, or EFS; and (4) reviews or duplicate studies.

Data abstraction

The name of the first author, year and country of publication, journal name, total number of patients, DFS and OS of overweight or obese patients, and definitions of overweight and obesity were extracted from all included studies. We also extracted DFS, RFS, EFS, and OS data from the studies and the corresponding HRs and 95% CIs. If HRs and 95% CIs were not provided in the study, we extracted HRs and 95% CIs from the survival curves using GetData Graph Digitizer software or contacted the corresponding author to ask for the original data.

Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was adapted to assess the risk of bias of the included studies.[27] NOS evaluates the risk of systematic errors in a study design by assessing the following characteristics: (I) Representativeness of the exposed cohort, (II) Selection of the non-exposed cohort, (III) Ascertainment of exposure, (IV) Demonstration that the outcome of interest was not present at start of study, (V) Comparability of cohorts on the basis of the design or analysis, (VI) Assessment of outcome, (VII) Was follow-up long enough for outcomes to occur, and (VIII) Adequacy of follow-up cohorts.[27] Two authors (Z.L. and M.S.) independently assessed and scored each study according to the pre-established criteria, and for every present characteristic, one point was dispensed. Disagreements were discussed with a third author (G.S.) until a final score was reached for each study. The risk of bias scores were summarized [Supplementary Table 1] into a bias judgment.[27]

Statistical analysis

We used Stata version 17.0 and GetData Graph Digitizer software for our meta-analysis. The heterogeneity among eligible studies was estimated by I^2 statistic and *P*-value. If $I^2 < 50\%$ and $p > 0.01$, we used the

fixed-effects model. If $I^2 > 50\%$ and $P < 0.01$, we used the random-effects model.[28] A p-value <0.05 was statistically significant, and I^2<25%, I^2 = 25–50%, and I^2>50% were considered to indicate low, moderate, and high heterogeneity.[29] The possibility of publication bias was assessed using funnel plots and Egger's test.

Sensitivity analysis

We also conducted a sensitivity analysis by excluding each study. After excluding each study, we recalculated the hazard ratio (HR).

Results

Study characteristics

After searching and screening all eligible studies, 20 retrospective cohort studies including 33,836 patients with EBC[14,18,21,30–46] were selected; one study[44] was only published in abstract form. Of the 20 retrospective cohort studies included, 12 studies each examined the effects of overweight on DFS and OS, 12 and 15 studies examined the effects of obesity on DFS and OS, respectively, and 16 and 17 studies examined the effects of high BMI on DFS and OS, respectively.

Of the included 20 retrospective cohort studies, 16 studies[18,21,31–39,41,43–46] reported data on DFS, 17 studies[14,18,21,30,32–43,45] reported OS data, and 14 studies[18,21,32–39,41–45] reported both endpoints. However, three studies[21,30,31] reported RFS data, and one study[32] reported EFS data. Because the definition of DFS (defined as the time from diagnosis to first recurrence [local or distant] or last follow-up visit) in the other trials was similar to that of RFS (calculated as the time from diagnosis to first recurrence or last follow-up) and EFS (defined as the time from diagnosis to the first recurrence, distant metastasis, or death from any cause) in these four trials, we combined the RFS and EFS data of these four trials with the DFS data of the other trials to perform a comprehensive analysis.

The included 20 retrospective cohort studies used different BMI categories. In some studies, underweight (BMI <18.5 kg/m^2 according to the WHO international classification) and normal weight (BMI 18.5 to <25.0 kg/m^2) were merged into one category, but in some studies, they were classified separately. Similarly, most studies classified overweight (BMI 25.0 to <30.0 kg/m^2) and obesity (BMI ≥30.0 kg/m^2) separately, but in some studies, overweight and obesity were merged into one category. The reference category was normal or underweight, together with normal weight, depending on the study. In this meta-analysis, we classified BMI as underweight (<18.5 kg/m^2), normal weight (18.5 to <25.0 kg/m^2), overweight (25.0, 30.0 kg/m^2), and obesity (≥30.0 kg/m^2) according to the WHO international classification. The study selection process, including the reasons for exclusion, is shown in Figure 1; the main research features are listed in Table 1.

Pooled analysis of the effects of overweight on disease-free and overall survival

After the pooled analysis of 13 studies,[21,31,33–39,43–46] the results showed that compared with normal weight, overweight has an adverse effect on DFS in patients with EBC (HR: 1.16, 95% CI: 1.05–1.27,

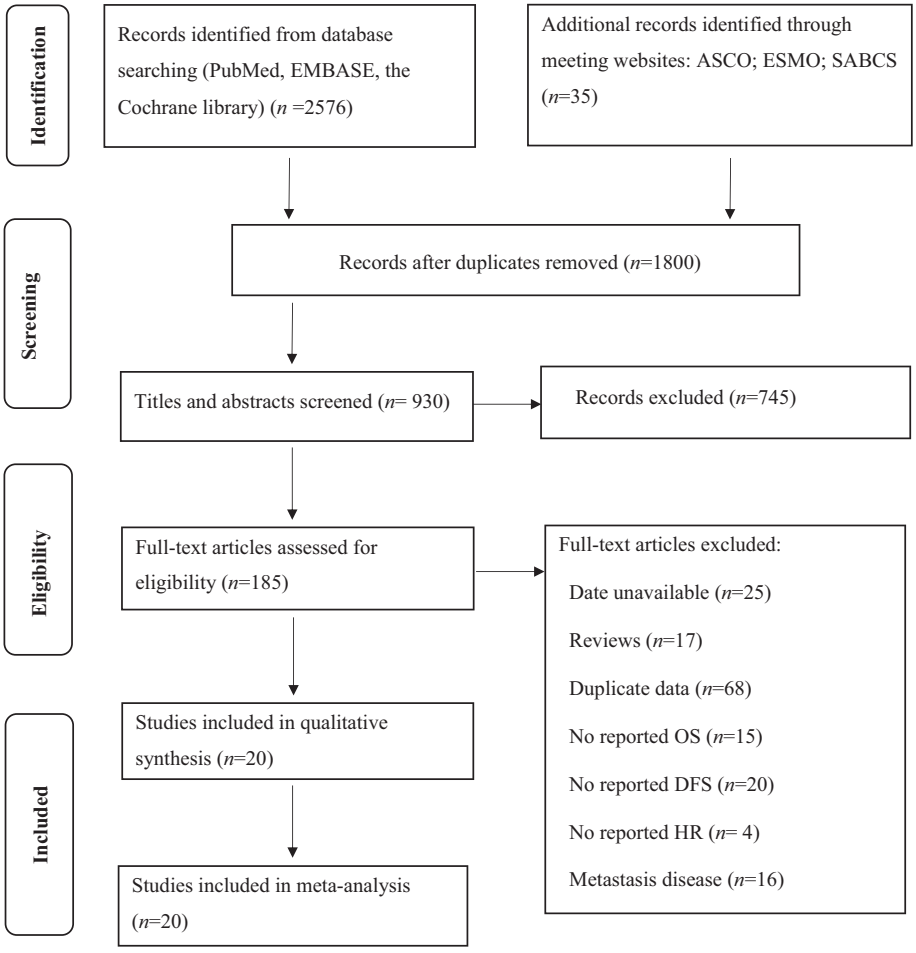


Figure 1. Search strings and flow charts for filtering and research selection. ASCO: American Society of Clinical Oncology; DFS: disease-free survival; ESMO: European Society of Medical Oncology; HR: Hazard ratio; OS: Overall survival; SABCS: San Antonio Breast Cancer Symposium.

Table 1
Characteristics of 20 studies included in this meta-analysis.

Study (First author, year)	Country	Journal	No. of Patients (*n*)	Median follow-up Time (months)	Definition of overweight BMI (kg/m^2)	Definition of obesity BMI (kg/m^2)	Exposure	Primary endpoints
Mantel et al., 1959[29]	China	*J Natl Cancer Inst*	44	32.6		≥30	Obesity	OS, EFS
Tait et al., 2014[35]	USA	*Breast Cancer Research Treatment*	448	40.1	25.0, 30.0	≥30	Overweight Obesity	OS, DFS
Wells et al., 2014[27]	USA	*Symposium on Systematic Reviews: Beyond the Basics*	418	37.2	25.0, 30.0	≥30	Overweight Obesity	OS, RFS
Shang et al., 2021[36]	China	*Breast Cancer Research*	2888	76.8	25.0, 30.0	≥30	Overweight Obesity	OS, DFS
Wang. et al., 2019[37]	China	*Oncology Research and Treatment*	3178	58.0	25.0, 30.0	≥30	Overweight Obesity	OS, DFS
Xing et al., 2013[38]	China	*Clinical and Investigative Medicine*	1192	36.0	≥23.0	≥23	Overweight	OS, DFS
Lin et al., 2021[39]	China	*Journal of Cancer*	5000	NA	24.0, 27.0	≥27	Overweight Obesity	OS, DFS
Schvartsman et al., 2017[40]	USA	*Cancer Medicine*	1998	85.2	25.0, 30.0	≥30	Overweight Obesity	OS
Copson et al., 2015[14]	United Kingdom	*Annals of Oncology*	2843	70.4	25.0, 30.0	≥30	Overweight Obesity	OS
Al Jarroudi et al., 2017[41]	Morocco	*Asian Pacific Journal of Cancer Prevention*	115	36.0	≥25.0	≥25	Overweight Obesity	OS, DFS
Chen et al., 2016[18]	China	*Springer Plus*	206	59.0		≥25	Obesity	OS, DFS
Hao et al., 2015[42]	China	*PLOS ONE*	1106	44.8	> 24.0		Overweight	OS
Mowad et al., 2013[34]	USA	*Journal of Surgical Research*	183	42.5	25.0, 30.0	> 30	Overweight Obesity	OS, DFS
Dawood et al., 2012[21]	USA	*Clinical Breast Cancer*	2311	39.0	25.0, <30.0	≥30	Overweight	OS, RFS
Zintzaras et al., 2005[28]	South Korea	*Genet Epidemiol*	108	60.2	23.0, 25.0	≥25	Overweight Obesity	RFS
Widschwendter et al., 2015[33]	Germany	*Breast Cancer Research*	3754	65.0	25.0, 30.0	≥30	Overweight Obesity	OS, DFS
Wang et al., 2019[46]	China	*BioMed Research International*	1288	NA	<25.0	≥25	Overweight Obesity	DFS
Gennari et al., 2016[43]	Italy	*Breast Cancer Research Treatment*	959	103.0	25.0, 30.0	≥30	Overweight Obesity	OS, DFS
Pfeiler et al., 2022[44]	Austria	*J Clin Oncol.*	5698	NA	25.0, 30.0	≥30	Overweight Obesity	DFS
Modi et al., 2021[45]	Australia	*Npj Breast Cancer*	5099	132.0	25.0, 30.0	≥30	Overweight Obesity	OS, DFS

BMI: Body mass index; DFS: Disease-free-survival; EFS: Event-free survival; NA: Not available; OS: Overall survival; RFS: Relapse-free survival; USA: United States of America.

$P = 0.002$) [Figure 2A]. Based on the pooled analysis of 13 studies,[14,21,30,33–39,42,43,45] overweight has also an adverse effect on OS in patients with EBC (HR: 1.20, 95% CI: 1.09–1.33, $P < 0.001$) [Figure 2B].

Pooled analysis of the effects of obesity on disease-free and overall survival

The results of the pooled analysis of 13 studies[21,31,33–39,43–46] demonstrated that compared with normal weight, obesity has an adverse effect on DFS in patients with EBC (HR: 1.17, 95% CI: 1.07–1.29, $P = 0.001$) [Figure 3A]. Likewise, the pooled analysis of 16 studies[14,18,21,30,32–41,43,45] showed that compared with normal weight, obesity has an adverse effect on OS in patients with EBC (HR: 1.30, 95% CI: 1.17–1.45, $P < 0.001$) [Figure 3B].

Pooled analysis of the effects of high BMI on disease-free and overall survival

After the pooled analysis of 16 studies,[18,21,31–39,41,43–46] the results demonstrated that compared with normal weight, high BMI has an adverse effect on DFS in patients with EBC (HR: 1.16, 95% CI: 1.08–1.26, $P < 0.001$) [Figure 4A]. The results of the pooled analysis of 17 studies[14,18,21,30,32–43,45] showed that compared with normal weight, high BMI also has an adverse effect on OS in patients with EBC (HR: 1.25, 95% CI: 1.14–1.39, $P < 0.001$) [Figure 4B].

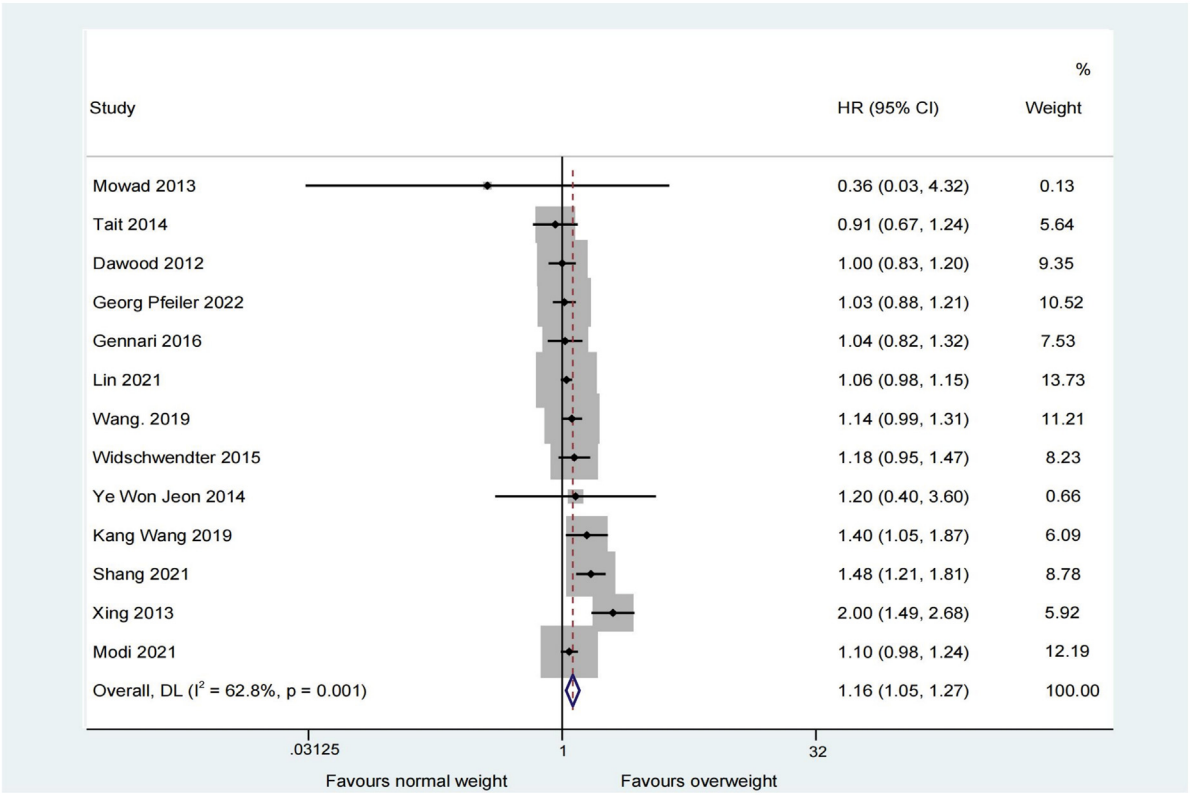
Subgroup survival analysis between overweight and normal-weight patients

After the pooled analysis of 12[21,31,33–37,37,39,43,45,46] and 13[14,21,30,33–39,42,43,45] studies, the results showed that compared with normal weight, overweight had adverse effects on DFS (HR: 1.11, 95% CI: 1.04–1.18, $P = 0.001$) [Supplementary Figure 1B] and OS (HR: 1.18, 95% CI: 1.11–1.26, $P < 0.001$) [Supplementary Figure 1D], respectively, in multivariate analysis. However, the results of the pooled analysis of six[30,35–39] and eight[14,30,35–40] studies showed that compared with normal weight, overweight had negative effects on DFS (HR: 1.21, 95% CI: 0.99–1.48, $P = 0.058$) [Supplementary Figure 1A] and OS (HR: 1.39, 95% CI: 0.92–2.10, $P = 0.123$) [Supplementary Figure 1C], respectively, but these differences were not statistically significant in univariate analysis.

Subgroup survival analysis between obese and normal-weight patients

Based on the pooled analysis of 15[18,21,31–39,41,43,45,46] and 15[14,18,21,30,32–39,41,43,45] studies, the results showed that compared with normal weight, obesity had adverse effects on DFS (HR: 1.14, 95% CI: 1.08–1.22, $P < 0.001$) [Supplementary Figure 2B] and OS (HR: 1.23, 95% CI: 1.15–1.31, $P < 0.001$) [Supplementary Figure 2D], respectively, in multivariate analysis. According to the pooled analysis of six[32,35–39] and nine[14,30,32,35–40] studies, the results showed that compared with normal weight, obesity had a negative effect on DFS (HR: 1.21, 95% CI: 1.06–1.38, $P < 0.001$) [Supplementary Figure 2A] and OS (HR: 1.33,

A



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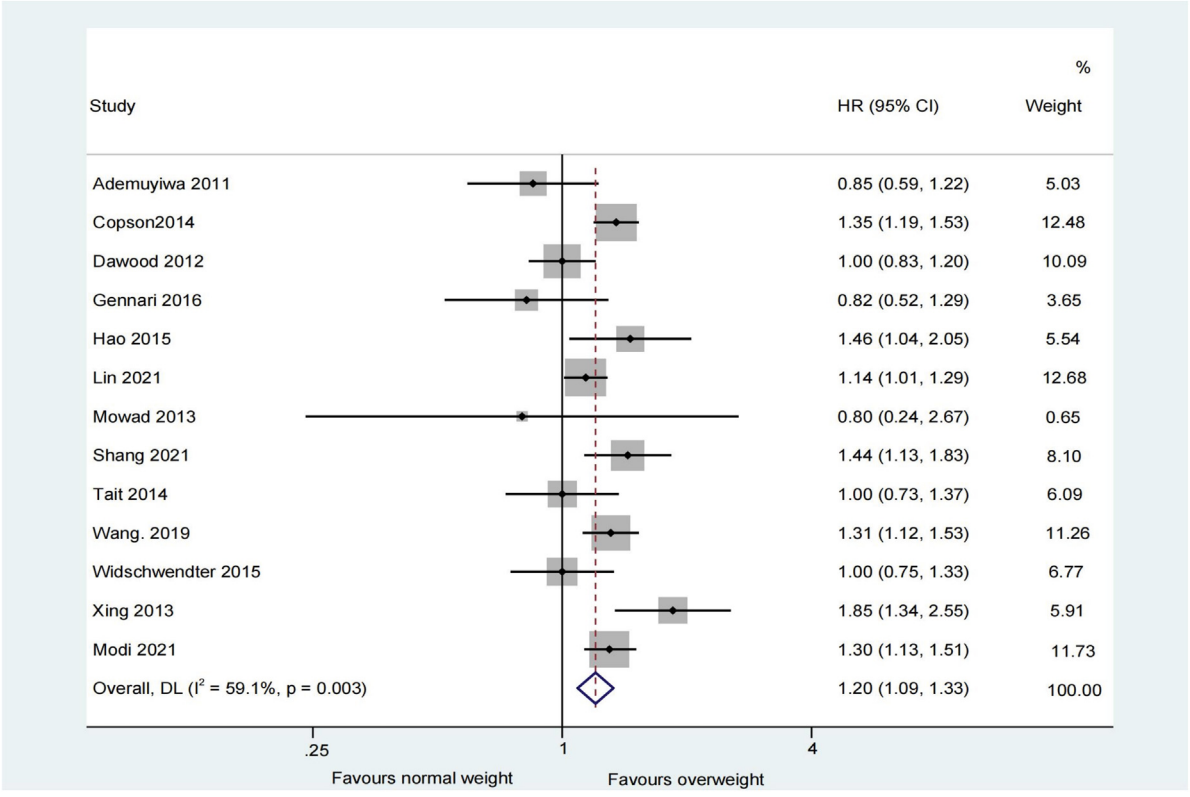
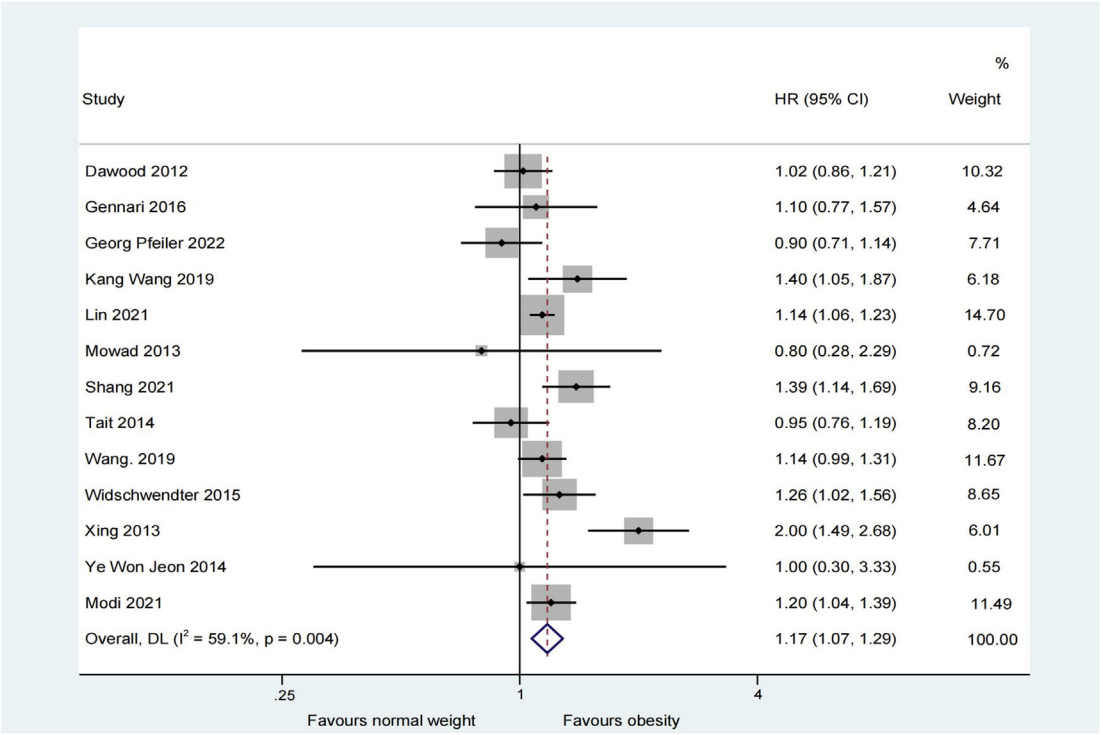


Figure 2. Forest plots of pooled analyses comparing the survival between overweight and normal-weight groups. (A) Forest plot of pooled analysis for disease-free survival. (B) Forest plot of pooled analysis for overall survival. CI: Confidence interval; HR: Hazard ratio.

A



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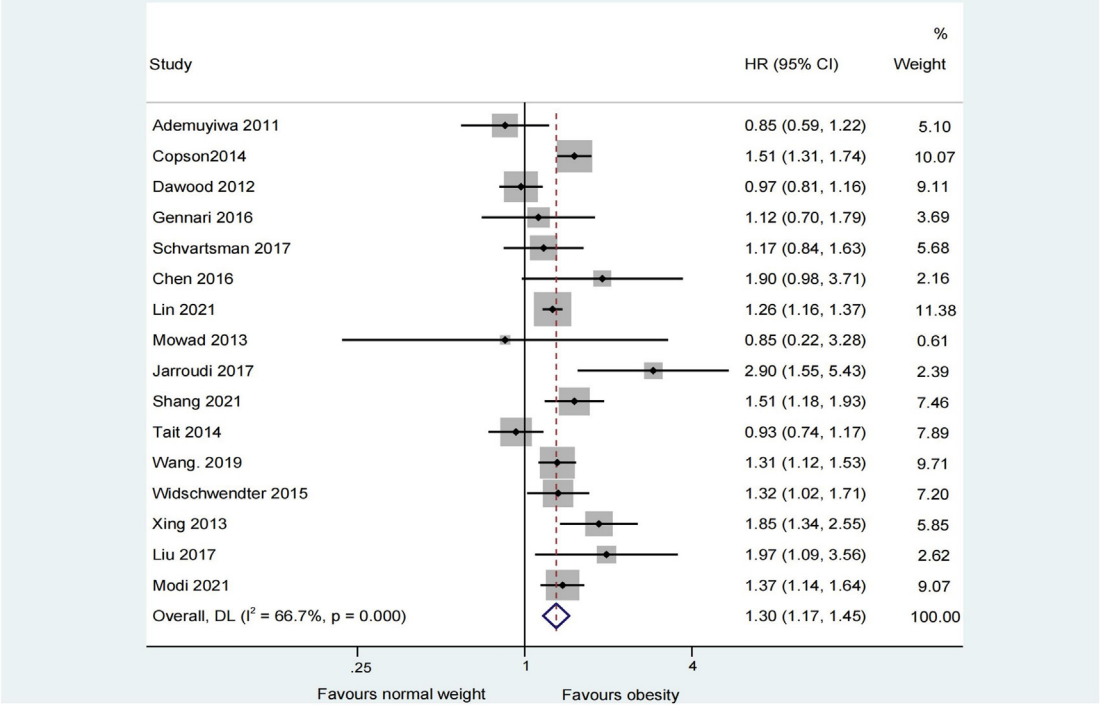
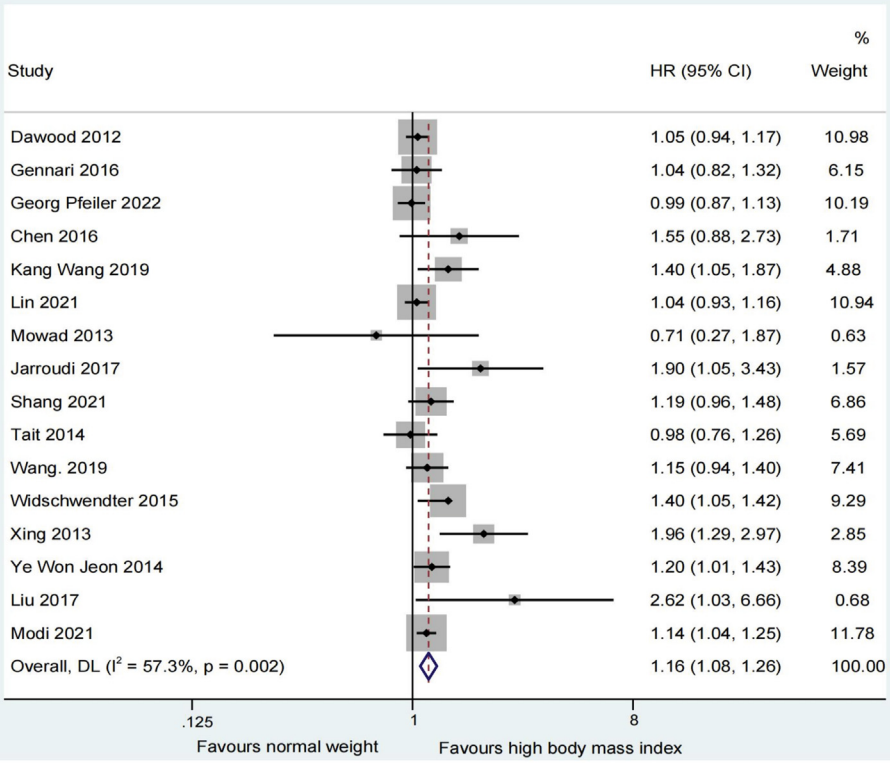


Figure 3. Forest plots of pooled analyses comparing the survival between obesity and normal-weight groups. (A) Forest plot of pooled analysis for disease-free survival. (B) Forest plot of pooled analysis for overall survival. CI: Confidence interval; HR: Hazard ratio.

A



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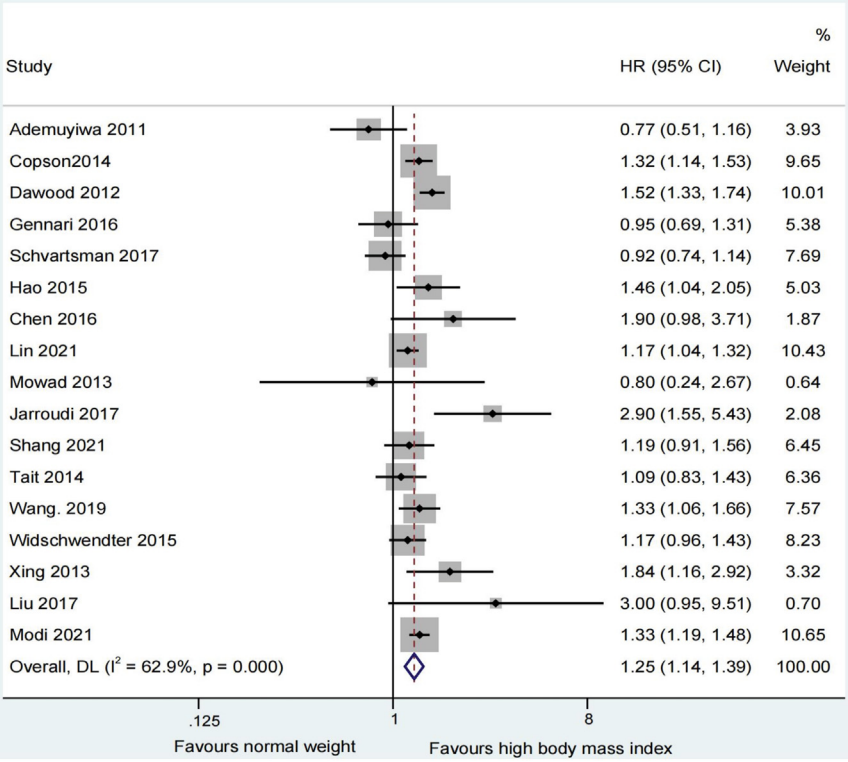

Figure 4. Forest plots of pooled analyses comparing the survival between patients with high body mass index and those with normal weight. (A) Forest plot of pooled analysis for disease-free survival. (B) Forest plot of pooled analysis for overall survival. CI: Confidence interval; HR: Hazard ratio.

95% CI: 1.15–1.54, $P < 0.001$) [Supplementary Figure 2C], respectively, in univariate analysis.

Risk of bias

The Newcastle-Ottawa scale (NOS) assesses each study in the categories of "selection", "comparability", and "outcome", in which a maximum of 4, 2, and 3 stars can respectively be scored.[27] A higher score is intended to translate to a lower risk of within-study bias.[27] The risk of bias assessment for each study is shown in Supplementary Table 1. No study was considered to have a "high risk" of bias. Four studies did not adjust for age and six did not adjust for treatment in their statistical analyses.

Publication bias

The visual inspection of the funnel plots revealed a slight asymmetry, suggesting that publication bias may be an influential factor, but this publication bias may have little effect on the results [Supplementary Figure 3].

Sensitivity analysis

The sensitivity analysis demonstrated that the combined HR estimates were stable with only small fluctuations when excluding each individual study [Supplementary Figure 4].

Discussion

This meta-analysis is the most comprehensive study with the largest sample size and includes the latest studies compared with previous meta-analyses. Our study analyzed the association between high BMI and survival outcomes in 33,836 patients with EBC from 20 studies. Unlike previous studies, not only the effects of obesity on DFS and OS in patients with EBC but also the effects of high BMI and overweight on survival endpoints were analyzed. The summary results indicated that high BMI was associated with poor DFS and OS in patients with EBC. Furthermore, both overweight and obesity groups had worse DFS and OS compared with the high BMI group, with obese patients having the poorest OS.

Numerous clinical studies have demonstrated that excessive adiposity may worsen the incidence, prognosis, and mortality rate of patients with BC. Moreover, obesity has been associated with an increased risk of developing contralateral BC or a second primary malignancy in other sites in women who had been previously diagnosed with BC.[47] In recent years, an increasing number of studies have shown a negative correlation between obesity and survival rate in patients diagnosed with EBC. Sufficient evidence showed that high BMI ($\geq$25.0 kg/m2) is related to poor prognosis in patients with EBC. A meta-analysis including 12 studies conducted on 23,832 women reported that weight gain after diagnosis of BC was associated with higher all-cause mortality.[48] However, the clinical outcomes were all-cause mortality and BC-specific mortality, rather than DFS and OS.

Based on the data characteristics of the 20 included retrospective cohort studies, we extracted survival data for univariate and multivariate analysis. Univariate analysis used standard statistical methods to examine the associations of BMI with clinicopathological variables of patients such as age at diagnosis, menopausal status, tumor size, nodal status, grade and systemic therapy. After adjusting for clinicopathologic significant variables with statistical significance in the univariate analysis, multivariate analysis used the Cox proportional hazards model to compare survival outcomes among BMI categories. Accordingly, we performed univariate and multivariate subgroup analyses for overweight and obesity. The subgroup analyses showed that the adverse effects of overweight on DFS and OS were not statistically significant in univariate analysis, but statistically significant in multivariate analysis. By contrast, the adverse effects of overweight on DFS and OS were statistically significant in both univariate and multivariate analyses. Based on these results, we speculated that high BMI (overweight or obesity) may be a significant predictor of survival and obesity may have a worse effect on DFS and OS than overweight in patients with EBC.

However, it should be noted that, first, the 19 included studies all used the Cox proportional hazards regression models to estimate the adjusted HRs and 95% CIs in association with high BMI and prognosis of patients with early-stage breast cancer. Unfortunately, one included study was published as an abstract at the ASCO 2022 conference, and the multivariate analysis model was not mentioned in the methods section. Second, in the multivariate model of the included studies, although four studies did not adjust for age and six did not adjust for treatment, the remaining studies all adjusted for age at diagnosis, systemic therapy, lymphovascular invasion and clinicopathological characteristics of the tumor. Third, for pooled effect size HR, the pooled effect value HR was unadjusted in the univariate subgroup analysis, and the pooled effect value HR was adjusted for mixed in the multivariate subgroup analysis. This result should be interpreted with caution because some heterogeneity between studies.

Sufficient evidence shows that obesity is associated with a worse prognosis in patients with EBC.[14,18,23,30,32–34,49,50] Recently, a meta-analysis on the association between obesity and survival outcomes reported that patients with BC and obesity had higher overall mortality (HR: 1.26, 95% CI: 1.20–1.33, $P < 0.001$) and worse DFS (HR: 1.14, 95% CI: 1.10–1.19, $P < 0.001$) than those without obesity.[51] Furthermore, in a study by Ladoire et al., obesity was moderately associated with poorer DFS (HR: 1.18, 95% CI: 1.01–1.39, $P = 0.04$), but mostly with poorer OS (HR: 1.38, 95% CI: 1.13–1.69, $P = 0.002$) based on the results of their univariate analysis.[52] These results are consistent with those of our meta-analysis suggesting that obesity is associated with inferior survival in patients with EBC. Nevertheless, this observation needs further large-scale clinical trials to prove its accuracy.

Additionally, numerous studies have shown that the effect of obesity on BC prognosis is related to other factors including menopausal status, age, molecular subtype, and treatment. Unfortunately, due to the limited number of studies included in this meta-analysis and the small number of studies evaluating these factors, subgroup analyses of these factors were not conducted. However, according to the results of previous high-quality studies, obesity increased the risk of BC in postmenopausal and older patients but decreased the risk in premenopausal and younger patients.[19,49,53] Besides, obesity was associated with a poor prognosis in patients with HER2-positive (HER2+) EBC, whereas it was associated with better survival in those with HER2+ advanced BC, called the "obesity paradox."[45] Moreover, several randomized studies reported that endocrine therapy was less effective in obese patients,[8,54–56] whereas obese patients treated with neoadjuvant or adjuvant chemotherapy had a worse prognosis.[31,32,40,57] However, the results of some studies contradict the above conclusions.[8,52,58,59] In summary, further clinical studies are warranted to explore the impact of obesity and other factors on BC prognosis.

A previous meta-analysis conducted by Harborg et al.[25] indicated that overweight was associated with shorter OS and DFS among patients with TNBC. However, Harborg et al. only found a relationship between overweight and prognosis in TNBC. Based on the results of a pooled analysis of 12 studies, overweight patients with EBC had worse OS and DFS. In the multivariable analysis, overweight had a negative effect on the OS and DFS in patients with EBC compared with those in normal-weight patients. The results of our study are consistent with those of several other reports in the literature. The present study found a positive association between BMI at the time of diagnosis and mortality not only in women with postmenopausal BC but also in those with premenopausal BC.[60–63] The results of six cohort studies provide convincing evidence that weight gain after BC diagnosis increases all-cause mortality and BC-specific mortality rates.[17,20,62,64–66] Furthermore, overweight can increase the risk of BC recurrence by 30–40%.[67,68] In the univariate analysis, no significant difference was observed between overweight and

OS and DFS in EBC. Moon et al.[69] found no significant difference in the DFS and OS among overweight (BMI >25.0 kg/m^2) individuals compared with the DFS and OS of the normal-weight group ($P = 0.927$ and $P = 0.336$, respectively). This may be related to the fact that only a few studies were included and that the sample size was relatively small. In addition, the results of subset analyses are usually less trustworthy than those of the main outcome analysis.

Taken together, these findings provide convincing evidence regarding the association between high BMI and poor prognosis and suggest that managing overweight and obesity in patients with EBC is vital for controlling relapse or metastases and improving the prognosis and quality of life (QOL).

Weight gain is a common and persistent problem among patients with breast cancer. It increases the risk of fatigue, cardiovascular disease, diabetes mellitus, functional decline, and inferior QOL.[22,67,68,70] Interestingly, a recent prospective multicenter cancer toxicities (CANTO) cohort study reported that high BMI is a risk factor for severe cancer-related fatigue (CRF), which is one of the most common and persistent sequelae of BC treatment.[71,72] High BMI has been associated with poor health outcomes in patients with breast cancer survivors. Therefore, weight loss is recommended for overweight and obese breast cancer survivors. In a more recent study, Motivating to Exercise and Diet, and Educating to healthy behaviuors After breast cancer (MEDEA), which investigated the impact of weight loss on CRF in overweight or obese survivors of BC, Di Meglio et al.[73] found that an elevated BMI is a risk factor for CRF in breast cancer survivors. Thus, weight loss interventions are feasible and safe for these patients, leading to improved cardiometabolic and QOL outcomes. Furthermore, Reeves et al.[74] systematically reviewed 14 trials on the efficacy of weight loss interventions in patients with breast cancer, including diet, exercise, and cognitive-behavioral therapy. They suggested that weight loss is feasible and safe in overweight and obese breast cancer survivors following BC treatment. Weight loss interventions such as diet management and physical activity (PA) are the best practices for the management of overweight and obesity.[75,76] In a recent systematic review and meta-analysis, Wang et al.[77] described and evaluated 10 randomized controlled trials using diet and exercise interventions for breast cancer survivors. Weight loss programs could significantly reduce high BMI and body fat, thereby greatly improving the outcomes of overweight and obese breast cancer survivors. Overall, increasing evidence supports the role of weight management, improving dietary quality, and PA in the prevention and control of BC, which will contribute to establishing weight loss support as a new standard of clinical care. However, more clinical trials are required to evaluate the effect of weight loss interventions (PA and diet management) on the prognosis of overweight and obese breast cancer survivors.

The pathways involved in the relationship between high BMI and BC outcomes remain unclear, but high BMI affects several hormones and growth factors that are potentially associated with BC.[16] One potential mechanism involves sex hormones. Overweight and obese women have higher endogenous serum estrogen levels than normal-weight women, especially in the postmenopausal period.[78–80] Sex steroids regulate the balance between cellular differentiation, proliferation, and apoptosis and may also favor the selective growth of preneoplastic and neoplastic cells.[81] Among postmenopausal women, estrone, estradiol, and free estradiol levels are significantly associated with increased BMI.[82–87] Estrogen facilitates cancer through the following mechanisms: the mitogenic or anti-apoptotic activity of estrogen in breast and other tissues and the mutagenic effects of estrogen on metabolites.[88] Another potential mechanism involves insulin and IGF-1. Previous literature reported that high levels of tumor necrosis factor (TNF)-α and interleukin (IL)-6in adipose tissue of obese patients impair the activation of insulin receptor subunits and decrease glucose transport and fatty acid metabolism, mediating insulin resistance and upregulating the insulin and IGF-1 levels.[89–91] Insulin and IGF-1 also strongly stimulate cell proliferation, inhibit apoptosis, and enhance angiogenesis.[13] Elevated fasting insulin levels are associated with a poor prognosis in patients with BC.[92] Hyperinsulinism reduces the level of sex hormone-binding globulin and increases the bioavailability of estrogen, thus increasing the risk of BC.[93] Overweight and obesity can alter leptin and adiponectin levels and lead to abnormal glucose metabolism. Collectively, these factors have been associated with poorer outcomes in patients with BC.[92,94,95]

The potential limitations of our study should be considered when interpreting these results. First, all of the included studies were retrospective in nature or were retrospective analyses of prospective studies that may have bias. Second, the included studies showed some heterogeneity considering the difference of classification criteria for BMI, inclusion criteria for participants, systemic treatment, demographic baseline, pathological stage, histology, menopausal status, lymphovascular invasion and median follow-up, but we used the random effect model for the purpose to merge and reduce the impact of heterogeneity. Third, although the definitions of RFS and EFS are similar to DFS, there are still some differences. Therefore the conclusions of this article have certain limitation.

Conclusions

The results of this meta-analysis indicate that high BMI (overweight or obesity) is a risk factor for the prognosis of patients with EBC. Furthermore, obese patients with EBC have worse prognoses than overweight patients with EBC. These findings suggest that patients with BC should maintain a healthy weight throughout their lives. In particular, EBC patients with high BMI should regularly perform PA and undergo dietary management to improve their prognosis and QOL. Nevertheless, this conclusion still needs large-scale studies to prove its accuracy.

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Author contributions

Zhoujuan Li: Methodology, Formal analysis, Data Curation, Writing - Original Draft. Guoshuang Shen: Formal analysis, Writing - Original Draft. Mingqiang Shi: Methodology, Formal analysis, Data Curation, Writing - Original Draft. Yonghui Zheng: Data Curation. Yumei Guan: Data Curation. Yuanfang Xin: Data Curation. Miaozhou Wang: Writing - Review & Editing. Fuxing Zhao: Writing - Review & Editing. Dengfeng Ren: Writing - Review & Editing. Jiuda Zhao: Conceptualization, Writing - Review & Editing, Supervision. All authors critically revised successive drafts of the paper and approved the final version. The corresponding author attests that all listed authors meet the authorship criteria and that no other persons meeting these criteria have been omitted.

Ethics statement

None.

Data availability statement

All data generated or analyzed during this study are included in this published article.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2023.03.002.

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