

# Association between obesity with disease-free survival and overall survival in triple-negative breast cancer

## A meta-analysis

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### Abstract

**Objective:** To investigate the relationship between obesity and disease-free survival (DFS) and overall survival (OS) of triple-negative breast cancer.

**Methods:** Citations were searched in PubMed, Cochrane Library, and Web of Science. Random effect model meta-analysis was conducted by using Revman software version 5.0, and publication bias was evaluated by creating Egger regression with STATA software version 12.

**Results:** Nine studies (4412 patients) were included for DFS meta-analysis, 8 studies (4392 patients) include for OS meta-analysis. There were no statistical significances between obesity with DFS ( $P = .60$ ) and OS ( $P = .71$ ) in triple-negative breast cancer (TNBC) patients.

**Conclusion:** Obesity has no impact on DFS and OS in patients with TNBC.

**Abbreviations:** BMI = body mass index, DFS = disease-free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, OR = odds ratio, OS = overall survival, PR = progesterone receptor, TNBC = triple-negative breast cancer.

**Keywords:** disease-free survival, meta-analysis, obesity, overall survival, triple-negative breast cancer

## 1. Introduction

Breast cancer is a multiple kinds of extremely heterogeneous diseases with the same location of origin, each kind displays distinctive etiology, clinical pathological features, molecular characteristics, and therapeutic response.<sup>[1]</sup> The prognosis of breast tumors with different biological and molecular characteristics is quite diverse.<sup>[2]</sup> Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2

(HER2) and other molecular markers are usually evaluated on breast cancer specimens, which play an important role in the development of optimal treatment strategies for patients with breast cancer.<sup>[3]</sup> Nevertheless, breast cancer is frequently sorted as receptor positive, HER2 overexpression, and triple-negative breast cancer (TNBC) due to modern technologies and these assortments are not yet routinely used in clinical practice.<sup>[4]</sup>

There is not enough expression of ER, PR, and HER-2 in patients with TNBC.<sup>[5]</sup> Compared with other subtypes of breast tumors, TNBC has a shorter recurrence time and more possibilities metastasize to distance by hematogenic channel.<sup>[6,7]</sup> The key drivers of TNBC involve as following: lability of genome, such as p53 functional deletion,<sup>[8–10]</sup> sensitization of pivotal signaling networks,<sup>[11–16]</sup> the function of progenitor cells in driving the transition between epithelium with mesenchyme and plasticity of phenotype,<sup>[17]</sup> and the microenvironment of obesity.<sup>[18,19]</sup>

In accordance with The Centers for Disease Control and Prevention, obesity is defined as body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>.<sup>[2]</sup> The prevalence of obesity (35.5%–40.4%) and severe obesity (BMI  $> 40$  g/m<sup>2</sup> [7.4%–9.9%]) is found more in women than in men.<sup>[20,21]</sup> It is discovered that overweight and obesity are the potential causes carcinoma in esophagus, gastric cardia, thyroid, pancreas, colon, rectum, endometrium, prostate, gallbladder, ovary, and breast by recent researches.<sup>[22]</sup>

The women with higher BMI are more likely to suffer breast cancer, that has been demonstrated by some scientific evidence.<sup>[23]</sup> Recent studies have suggested that obesity is still related with poor outcomes (i.e., decline in overall survival [OS] and disease-free survival [DFS]), OS is computed by the time from

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**Table 1**  
**Characteristic details of the studies involved in meta-analysis.**

Study	Year	Nation	Time nodes	Subjects (N)	Obesity definition	Obesity		No-obesity	
						OS events	DFS events	OS events	DFS events
Yunseon	2016	Korea	3 y	50	BMI $\geq 23$ kg/m <sup>2</sup>	27/31	26/31	19/19	19/19
Sarah	2014	America	5 y	392	BMI $\geq 30$ kg/m <sup>2</sup>	95/146	78/146	141/246	128/246
Shaheenah1	2012	United Arab Emirates	5 y	2311	BMI $\geq 30$ kg/m <sup>2</sup>	520/825	511/825	951/1486	913/1486
Burcu	2015	Turkey	NA	112	BMI $\geq 30$ kg/m <sup>2</sup>		46/52		40/60
Ronny	2013	America	5 y	183	BMI $\geq 30$ kg/m <sup>2</sup>	92/117	83/117	54/66	47/66
Foluso	2011	America	5 y	418	BMI $\geq 30$ kg/m <sup>2</sup>	231/294	221/294	99/124	93/124
Liu	2017	America	NA	44	BMI $\geq 30$ kg/m <sup>2</sup>	9/16	6/16	23/28	20/28
Joseph	2012	America	5 y	878	BMI $\geq 30$ kg/m <sup>2</sup>	250/327	224/327	423/551	386/551
Ouissam	2017	Morocco	5 y	116	BMI $\geq 25$ kg/m <sup>2</sup>	27/82	15/82	20/34	13/34
Shaheenah2	2012	United Arab Emirates	5 y	1486	BMI $\geq 25$ kg/m <sup>2</sup>	443/692	429/692	508/794	484/794

Shaheenah1: The first compartment of this article reports the survival events according the BMI  $\geq 30$  kg/m<sup>2</sup>; Shaheenah2: The second compartment of this article reports the survival events according the BMI  $\geq 30$  kg/m<sup>2</sup>.

DFS events = defined as disease-free survival numbers in totality during follow-up periods, N = the number of the patients in this study, NA = not assessed, OS events = defined as OS numbers in totality during follow-up periods.

diagnosis to death or final follow-up, and DFS is computed by the time from diagnosis to recurrence) in patients with breast cancer being received doxorubicin chemotherapy.<sup>[2,3]</sup> By contrast, some studies have stated that BMI affects DFS, and merely has a significant impact on OS.<sup>[24]</sup> Some studies show that there is no significant difference in OS and DFS between obese and nonobese patients with breast cancer,<sup>[25–28]</sup> and a study find that there is significant difference in DFS but not in OS.<sup>[29]</sup> Noteworthy, there is a key article justifies that for hormone receptor-positive breast cancer, patients with obesity, when compare with no obesity, display inferior outcomes in OS and DFS, but not for hormone receptor-negative breast cancer.<sup>[30]</sup> Paradoxically, Liu et al<sup>[31]</sup> come to conclude that people with obesity tend to predict worse outcomes for DFS and OS in a study with 44 TNBC patients. There is no comprehensive conclusion in the field at present. The second major reason of carcinoma death in women is mammary cancer, which is the most usually developing one yet, and approximately 12% to 17% of women with breast cancer are diagnosed as TNBC.<sup>[5,32]</sup> Therefore, it is greatly essential to investigate whether obesity is an aggravating factor influencing the DFS and OS in TNBC.

## 2. Methods

### 2.1. Search strategy

In November 2017, 2 authors (LH and MX) independently carried out comprehensive literature searches in PubMed, Web of Science, and Cochrane Library using the predefined keywords ([triple negative breast cancer] and [BMI or body mass index or overweight or underweight or obesity or body weight]). We included the articles with no restrictions on publication language (English or non-English), publication year, geographical location, and the age of the participants. In addition, we augmented the searches with the subject heading terms option as much as possible.

### 2.2. Inclusion criteria and study selection

In order to qualify for meta-analysis, studies needed to content the following criteria: publication language in English, exposure factor was obesity, patients diagnosed with TNBC, and both reported the OS and DFS outcomes.

Two authors (LH and MX) prudentially filtered the retrieved citations, and selected potential researches according to titles, abstracts, and full-texts. If there were some disagreements, the 2 authors resolved them by discussion until reached a consensus.

### 2.3. Data abstraction

In order to collect the data, the 2 authors (LH and MX) used Excel 2016 and abstracted the following components: the first author, publication year, nation, numbers of subjects, obesity definition, OS events (OS numbers vs totality during follow-up periods) in obesity or no-obesity, DFS events (DFS numbers vs totality during follow-up periods) in obesity or no-obesity. If there were any inconsistency, that was resolved by discussion. The details are described in Table 1.

### 2.4. Data analysis

We implemented random-effect meta-analysis and used the odds ratio (OR) value and its 95% confidence interval (CI) to express the data with the Rveman software version 5.3. It was thought to be statistically significant when the  $P < .05$ . Heterogeneity in different group was tested by  $I^2$  test, and we conducted subgroup analysis in terms of different BMI definition. Publication bias was evaluated by Egger regression using the STATA software version 12.

## 3. Results

### 3.1. Search results

There were 612 citations retrieved after comprehensive literature searches, and 368 were excluded due to patently no pertinent. And we removed 158 studies because they did not meet inclusion criteria, when screening the title and abstract, 58 citations were excluded. The further exclusion via perusing full text led 19 studies to be debarred. Finally, 9 studies were included for DFS meta-analysis, and 8 studies were included for OS meta-analysis (Fig. 1). One of these articles<sup>[26]</sup> reports the OS and DFS events of TNBC patients according to BMI  $\geq 25$  kg/m<sup>2</sup> and BMI  $\geq 30$  kg/m<sup>2</sup> cut-off points, respectively; thus, it can be analyzed by dividing into 2 compartments on the basis of the 2 cut-off points. Overall, we included 5898 patients with triple negative breast tumors who

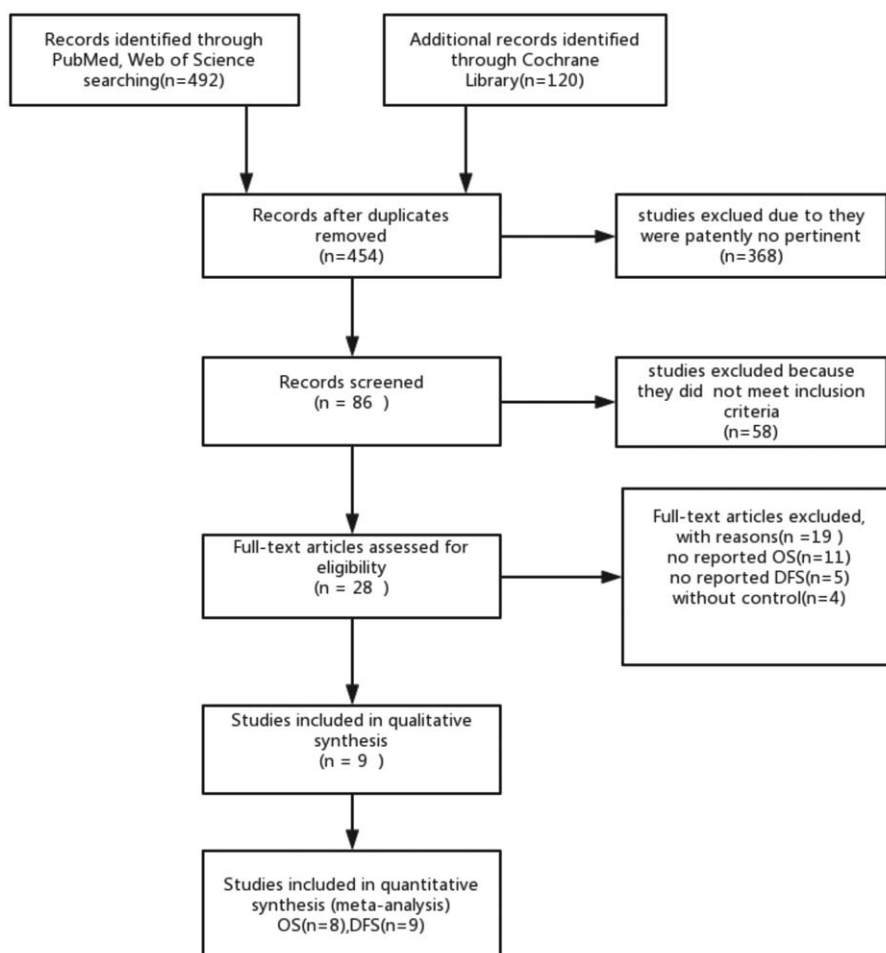


Figure 1. The process of the study selection. DFS = disease-free survival, OS = overall survival.

were reported DFS outcomes for obesity or no-obesity, and 5878 patients with TNBC who were reported OS outcomes for obesity or no-obesity. Although all the retrospective studies were from institutional databases, their quality was satisfactory.

### 3.2. Obesity vs no-obesity for OS

As can be observed in Figure 2, the combination of obesity was no significantly associated with a higher risk of OS than no-obesity in patients with TNBC.

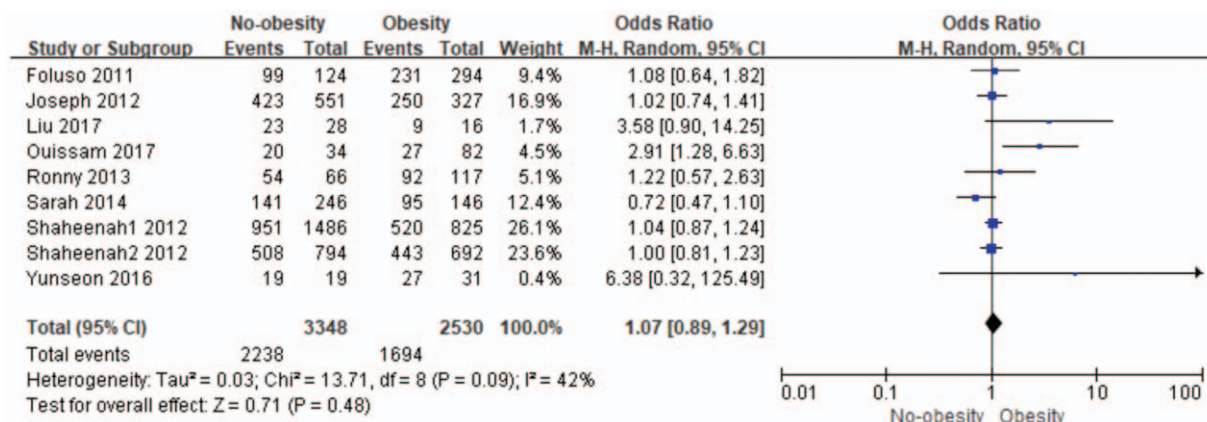


Figure 2. The relationship between obesity and no-obesity for overall survival (OS). CI = confidence interval.

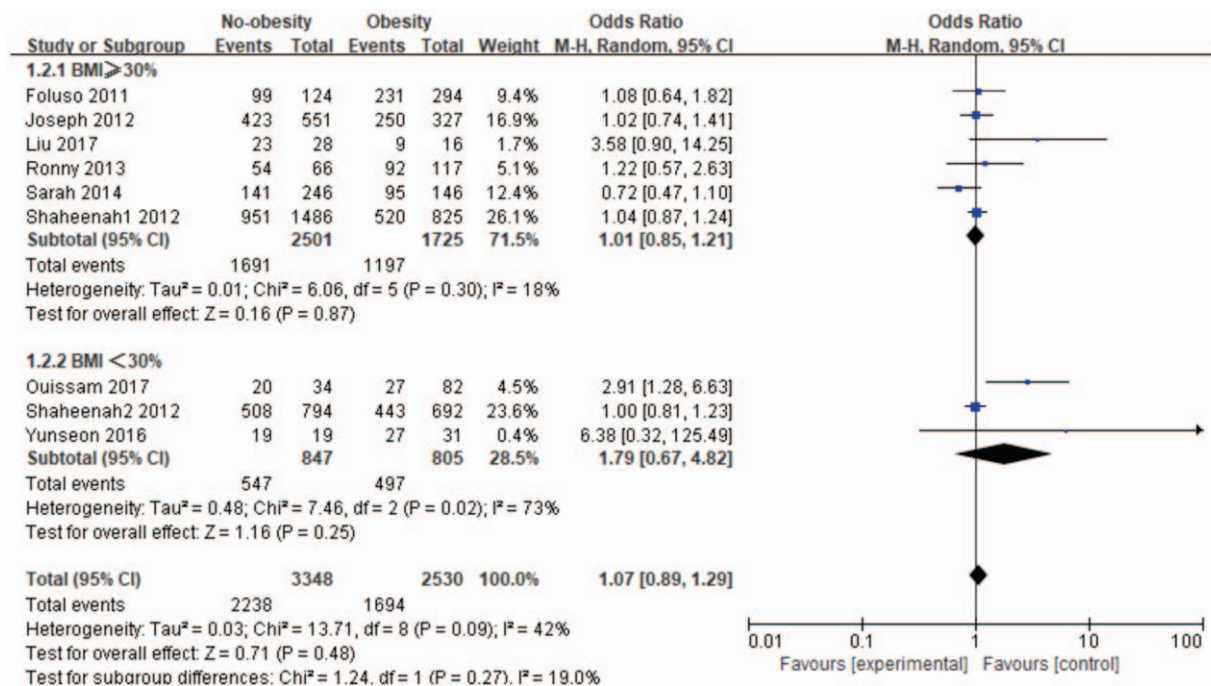


Figure 3. The subgroup analysis in the relationship between obesity and no-obesity for overall survival (OS). CI = confidence interval.

Pooled odds ratio for OS was 1.07 (95% CI: 0.89–1.29; I<sup>2</sup> = 42%; n=5878) for no-obesity, and there was no significant difference of the obesity and no-obesity on impact of OS in TNBC (P = .48).

We continued to conduct subgroup analysis with the obesity definition (BMI ≥30 kg/m<sup>2</sup> group vs BMI <30 kg/m<sup>2</sup> group) which is shown in Figure 3. In the BMI ≥30 mg/m<sup>2</sup> group, pooled odds ratio for OS was 1.01 (95% CI: 0.85–1.21; I<sup>2</sup> = 18%; n = 4226) for no-obesity, and there was no significant difference of the obesity and no-obesity on impact of OS in TNBC (P = .87). In the BMI <30 mg/m<sup>2</sup>, pooled odds ratio for OS was 1.79 (95% CI: 0.67–4.82; I<sup>2</sup> = 73%; n = 1652) for no-obesity, the pooled result was no statistically significant yet (P = .25).

3.3. Obesity vs no-obesity for disease-free survival

As shown in Figure 4, the combination of obesity was not related significantly with a greater risk of DFS than no-obesity in patients with TNBC, either.

Pooled odds ratio for DFS was 0.93 (95% CI: 0.74–1.17; I<sup>2</sup> = 58%; n=5898) for no-obesity, and there was not statistically significant of the obesity or no-obesity on impact of DFS in TNBC (P = .55).

We consequently conducted subgroup analysis with the obesity definition (BMI ≥30 kg/m<sup>2</sup> group vs BMI <30 kg/m<sup>2</sup> group), which is shown in Figure 5. In the BMI ≥30 mg/m<sup>2</sup> group, pooled odds ratio for DFS was 0.98 (95% CI: 0.77–1.24; I<sup>2</sup> = 49%; n = 4338) for no-obesity, and there was no significant difference of

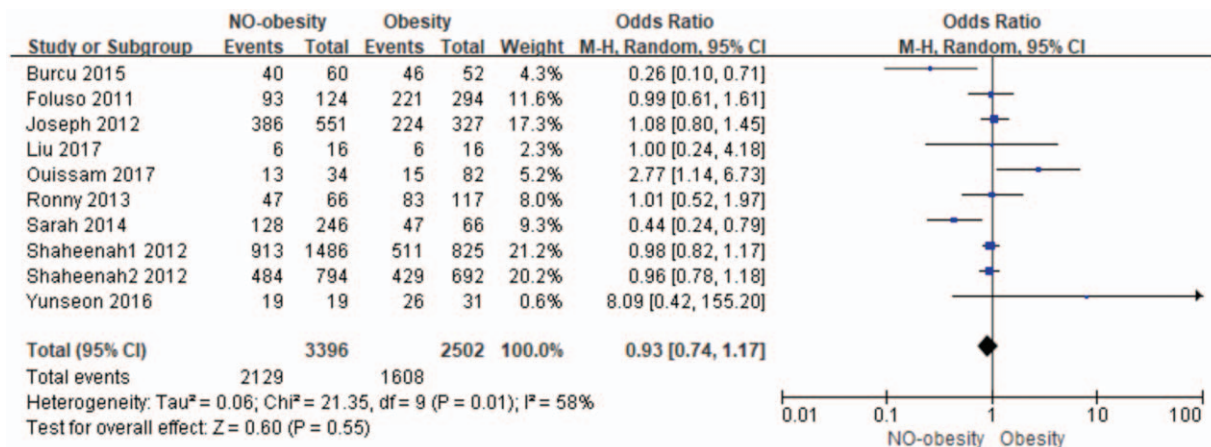


Figure 4. The relationship between obesity and no-obesity for DFS.



the obesity and no-obesity on impact of OS in TNBC ( $P=.87$ ). In the BMI  $<30$  mg/m<sup>2</sup>, pooled odds ratio for DFS was 1.76 (95% CI: 0.64–4.86;  $I^2=71\%$ ;  $n=1650$ ) for no-obesity, and the pooled result was no statistically significant ( $P=.27$ ).

### 3.4. Heterogeneity

In this meta-analysis, moderate-level heterogeneity ( $I^2=42\%$ ,  $P=.09$ ; Fig. 2) and substantial-level heterogeneity ( $I^2=58\%$ ,  $P=.01$ ; Fig. 4) was estimated in the involved studies on the association between obesity with no-obesity for OS and DFS in TNBC. When we narrowed down the group according to different BMI definition and conducted subgroup meta-analysis, the heterogeneity had polarized into 2 diversifications. For the OS in TNBC, there was no heterogeneity ( $P=.30$ ) in BMI  $\geq 30\%$  subgroup and substantial heterogeneity ( $I^2=73\%$ ,  $P=.02$ ) in BMI  $<30\%$ , respectively. It had moderate heterogeneity ( $I^2=49\%$ ,  $P=.07$ ) in BMI  $\geq 30\%$  subgroup and substantial heterogeneity ( $I^2=71\%$ ,  $P=.03$ ) in BMI  $<30\%$  for the DFS in TNBC.

### 3.5. Publication bias

It is indicated that no publication bias was observed, and there were no statistical differences (both  $P>.05$ ) that is shown in the Egger regression table (appendix, <http://links.lww.com/MD/C241>).

## 4. Discussion

Considering the absence from therapeutic target, TNBC usually leads to worse prognosis, so it is worth to explore the controllable factor, such as obesity. In recent years, a great volume of studies had tested the association of outcomes in TNBC with obesity; however, the conclusions during each other are controversial. Epidemiological studies have proven that obesity increases the risk of breast cancer, and performs an independent risk factor for poor outcome in it.<sup>[31]</sup>

Opposite to hormone receptor-positive breast tumors, obesity has a lower risk of mortality for hormone receptor-negative breast cancer. A key study involving 1238 women with breast cancer, Maehle and Tretli<sup>[33]</sup> examined the impact of BMI on breast cancer mortality, and found that the risk of mortality in women with obesity was generally 49% higher. When using receptor status to check this impact, the risk of death in obese women with hormone receptor-positive tumors was 3 times higher than that in lean women. However, in women with hormone receptor-negative tumors, this effect of obesity was the inverse situation.

There were a large amount of studies concerning the relationship between obesity with the clinical prognosis of TNBC, yet the conclusions of them are controversial.

In a study involved 44 patients with TNBC, Liu et al<sup>[31]</sup> reported that obesity was related to worse DFS (HR 2.62, 95% CI: 1.03–6.66,  $P=.04$ ) and a tendency toward worse OS (HR 3.00, 95% CI 0.95–9.51,  $P=.06$ ). In another study with 2041 TNBC patients, Fontanella et al<sup>[34]</sup> suggested that the mean DFS in obesity and very obesity (68.0 months  $P=.043$  and 42.3 months  $P=.010$ , respectively) and mean OS in obesity and severe obesity (74.5 months  $P=.018$  and 48.0 months  $P=.003$ , respectively) were significantly less than those in normal weight (DFS 77.7 months; OS 85.3 months). Both the studies indicated

that obesity had a huge negative impact on DFS and OS in patients with triple negative breast tumors.

Nevertheless, there are different standpoints. In a study by Ronny et al<sup>[28]</sup> in 2013, which contained 183 patients with TNBC, it is concluded that the OS amount of normal patients was higher than that of overweight or obese patients, and there was no significant difference ( $P=.29$ ), and there was no statistically significant difference in disease-free survival ( $P=.91$ ). Another study that included 418 TNBC patients, Foluso et al<sup>[22]</sup> pointed out that compared with normal or underweight patients, the HR for OS in obesity was 0.94 (95% CI: 0.54–1.64;  $P=.825$ ), and in overweight was 0.60 (95% CI: 0.32–1.14;  $P=.120$ ), as well as the HR for DFS was 0.81 (95% CI: 0.49–1.34;  $P=.416$ ) for patients with obesity and 0.74 (95% CI: 0.43–1.27;  $P=.274$ ) for overweight patients, there was still not significant difference between them, which meant that this single study did not find any clear relationship between higher BMI with OS or DFS in patients with TNBC. Both of these conclusions were consistent with the results of our meta-analysis. When conducting the meta-analysis, we found that the association between obesity and DFS or OS in patients with TNBC was not statistically significant, and the included studies were more than moderate-level heterogeneity. Secondly, we conducted the meta-analysis based on the obesity definition (BMI  $\geq 30$  kg/m<sup>2</sup> group or BMI  $<30$  kg/m<sup>2</sup> group that is equivalent to the occidental race or nonoccidental race, Table 1), and found that the relationship between obesity and DFS or OS in patients with TNBC remained not statistically significant in both subgroups.

This was the first meta-analysis that focused on the obesity as a predictor affecting the DFS and OS events in patients with TNBC, as well as conducted the subgroup meta-analysis according to different obesity definition. Our study still had its limitation as followings: first, we chose only English literatures which could lead to selection bias and measurement bias, although we did not find publication bias; second, in the involved studies, there might be clinical heterogeneity, such as different chemotherapy regimens, demographic baseline, pathological stage, histology, menopausal status, lymphovascular invasion, and median follow-up, this was why we using the random effect model for the purpose to merge and reduce the impact of heterogeneity; third, the number of included literatures was too small to provide effective information for meta-analysis, and might lead to the results bias of meta-analysis, although we did not find statistically significant publication bias in the Egger' regression; finally, the survival analysis was calculated by OR value that might lead to a unauthentic conclusion.

In the clinical treatment, in addition to considering the obesity as an impact factor on the survival of patients with TNBC, there are amounts of non-negligible factors needed to be taken into account, incorporating the patients age, clinical stage, tumor size, histological type, lymphatic node positivity, chemotherapy administration (adjuvant chemotherapy or neoadjuvant chemotherapy), etc. Therefore, we intend to analyze these factors in the oncoming future.

## 5. Conclusion

The result of this meta-analysis study indicates that there is no statistical significance between obesity with DFS and OS in patients with TNBC. However, due to the limited number of literature review, further analysis will be necessary to confirm this conclusion.

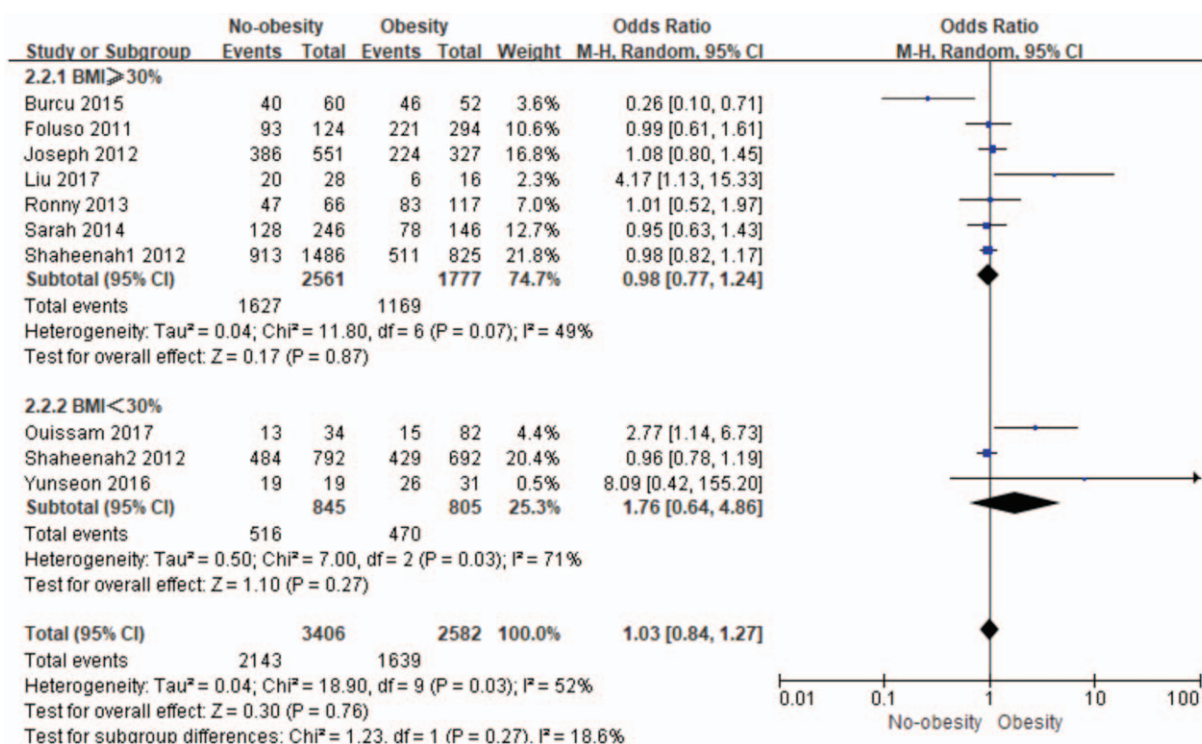


Figure 5. The subgroup analysis in relationship between obesity with no-obesity for disease-free survival (DFS). CI = confidence interval.

**Author contributions**

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**Validation:** Lin He.  
**Writing – original draft:** Lin Mei.  
**Writing – review and editing:** Lin Mei.

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