BMJ Open

Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080080
Article Type:	Original research
Date Submitted by the Author:	20-Sep-2023
Complete List of Authors:	Shama, Adisu; Wollega University, Department of Public Health, Institute of Health Sciences Terefa, Dufera; Wollega University, Public Health, Institute of Health Sciences Desisa, Adisu; Wollega University, Public Health, Institute of Health Sciences Lema, Matiyos; Wollega University, Public Health, Institute of Health Sciences cheme, Melese chego ; Wollega University, Department of Public Health, Institute of Health Sciences Geta, Edosa; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Jira Wakoya; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Bikila Regassa; Wollega University, Department of Public Health, Institute of Health sciences; Jimma University, Department of Epidemiology, Faculty of Public Health Biru, Bayise; Wollega University, Department of Public Health, Institutes of Health Sciences; Jimma University, Department of Human Nutrition and Dietetics, Faculty of Public Health
Keywords:	Risk Factors, Primary Health Care, PUBLIC HEALTH, Chronic Disease

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Word count=3771

Abstract

Objectives: Breast cancer is the leading cause of cancer morbidity and mortality among women. There is no representative data regarding the magnitude and risk factors of breast cancer in Ethiopia. Hence, this review was intended to identify the determinants of breast cancer in Ethiopia.

Design: A systematic review and meta-analysis was conducted. Databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar were searched to find articles. Low-quality articles were excluded. Heterogeneity was assessed using the I^2 statistics at the value >20% and the p-values <0.01 from the Cochrane Q-test. The effect estimates for pooled proportion and pooled odds ratio along with a 95% confidence interval were determined using the random effect model as a remedial for the heterogeneity problem. **Setting:** The studies conducted in Ethiopian were screened and included in this extended analysis. **Participants:** All people male and females, all age groups were included in this analysis. **Outcomes:** The pooled proportion of breast cancer was the primary outcome of this study whereas the determinants that affect the occurrence of breast cancer were the secondary outcome identified in this study.

Results: The pooled proportion of breast cancer is 22. 98% (95%CI: 19.48, 26.48) in Ethiopia. Consuming packed foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75, 6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27; 95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer (POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92) were the determinants of breast cancer.

Conclusions: The magnitude of breast cancer is high according to this review. Processed food consumption, high cholesterol in the body, lack of physical activity, high body mass index, post-menopause, family history of cancer, and lack of breastfeeding were the risk factors for breast cancer.

Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia

Article Summary

Strengths and limitations of this study

- ❖ This study is the first systematic review and meta-analysis on breast cancer in Ethiopia.
- ❖ The evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies.
- ❖ Only a few studies were found to pool the odds ratio for some factors.
- ❖ Only four out of 11 regions had studies regarding breast cancer with the dominance of Addis Ababa city.

Background

Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups [1]. It is found to be the most common cause of cancer deaths in 11 regions of the world [2]. It is one of the most frequently diagnosed cancers and the leading cause of cancer deaths in females worldwide [3]. The recent global burden of cancer statistics (GLOBOCAN) showed that BC has surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It affects one in four women and contributes to one in six deaths of women [4].

According to GLOBOCAN 2002, breast cancer incidence rates were increasing faster in most low- and middle-income countries (LMICs) than in places previously known for their high incidence rates [5]. In this regard, the global cancer burden by 2040 will be 28.4 million cases, a 47% increase over the cancer burden in 2020 [4]. Most of these expected new occurrences of cancer will be in the developing world [6]. Even if the incidence rate is higher in developed countries than in developing countries [4, 7], the reverse is true regarding the death rate (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000) [4]. In 2019, there

were estimated 5900 incident cases of breast cancer in Ethiopia with the highest age-standardized incidence rate of 12.5 per 100,000 and a death rate of 9.7 per 100,000 [8].

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, early age at menarche, sedentary lifestyles, and poor diet) and improving cancer registration and cancer detection are among the factors for the projected rise of breast cancer count in LMICs [9-11]. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also there for the increasing breast cancer burden in underdeveloped countries [9, 12, 13]. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer [9, 12-15].

Comprehensive identification of the magnitude and determinants of breast cancer is critical for developing nations like Ethiopia, as this will aid in the development and implementation of effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. Different pocket studies done so far may not represent the entire picture of the determinants of breast cancer in Ethiopia because most of them were limited to small sample sizes, limited

populations, and limited research regions. It is critical to disclose information about breast cancer to reduce risk factors. As a result, the purpose of this study was to determine the magnitude of breast cancer and its determinants in Ethiopia.

Methods

Study design

A systematic review and meta-analysis was conducted. The protocol was registered on Prospero with registration number (CRD42023417733). To conduct this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [16] was used.

Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: [“breast” OR “mammary gland” AND “cancer” OR “tumor” OR “malignancy” OR “breast cancer” OR “breast malignancy” OR “breast tumor” AND “Risk factors” OR “Associated factors” OR “Determinants” OR “predictors” AND “Ethiopia” OR “Addis Ababa” OR “Northern Ethiopia” OR “North west Ethiopia” OR “Southern Ethiopia” OR “South Western Ethiopia” OR “Western Ethiopia” OR “East Ethiopia”] were used. The final date of searching was March 6, 2023.

Eligibility criteria

Inclusion criteria

To be included in this review, the study should report either the determinants of breast cancer and/or the magnitude (incidence, prevalence, number) of breast cancer.

Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were part of this systematic review.

Study population: The study involved all human population (male, female, children, and adults) in Ethiopia.

Study design: All observational studies (cross-sectional, case-control, and cohort) that reported the magnitude of breast cancer and its determinants were evaluated to be included.

Publication status: Both published and unpublished studies were considered for inclusion.

Exclusion criteria

Articles with unclear methodologies, studies whose full-text papers were not available after at least two personal email contacts with the corresponding authors, and articles that didn't indicate the outcome of interest were excluded.

Outcome variables assessment

There were two outcomes in this study: the first outcome was the magnitude of confirmed breast cancer based on the operational definition of those studies. The total number of people who had breast cancer was divided by the total number of people participating in the study and multiplied by 100 which was used to determine the magnitude of breast cancer. The second outcome of this review was the determinants of breast cancer.

Study selection and data extraction

All the articles searched from Databases were imported into EndNote version X7, and duplicates were removed. Based on the predefined inclusion criteria, two authors (ATS and AED) independently assessed and identified papers by their titles, abstracts, and full texts. The screened

items were then compiled, and any disagreement was handled by inviting and discussing with the third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data extraction format [17-19]. The data extraction format included the primary author, publication year, study period, region, study area, study setting, study design, study population, publication status, sample size, response rate, and the number of cases/breast cancer. For the second outcome, data were extracted into a two-by-two table.

Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles [19]. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control of confounding. Accordingly, quality was categorized as low (total score of ≤2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood [19]. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy during the quality appraisal of the studies was resolved by the agreement of the two reviewers. Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of interest were excluded from the systematic review and meta-analysis (Additional file 1).

Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I^2 statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used

to indicate the presence of heterogeneity among the studies. The Higgins I^2 test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I^2 value > 20%. As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided as significant at p-value < 0.05. A leave-one-out sensitivity meta-analysis was used to assess the robustness of the findings.

Patient and public involvement: No patient was involved in this study.

Result

About 1644 articles were identified through database searching while 19 of them were included in this systematic review and meta-analysis (Figure 1).

Description of included studies in the systematic review and meta-analysis

Of the total 19 articles included with 96044 participants, the majority of them were from Addis Ababa (AA), followed by southern nations, nationalities and peoples (SNNP) and Amhara regions (Table 1).

Table 1: Descriptive summary of 19 studies included in the meta-analysis to estimate breast cancer magnitude and its determinants in Ethiopia

Studies ID	Author (Year)	Regions	Population	Study design	Sample size	Response rate	Proportion (%)
2	Abebe et al (2017) [20]	AA	Cancer patients	Cross-sectional	112	93.0%	25
3	Ayele et al	SN	General women	Cross-	7,580	99%	0.09

	(2021) [21]	NP		section al			
4	Ayele et al (2022) [22]	Oro mia	Deceased women	Cross-section al	800	98.0%	2.63
5	Duche et al. (2021) [23]	AA	Women with breast cancer	Case-control	226	97.0%	48.67
6	Endalamaw et al (2021) [24]	Am har a	Children attended the OPD	Cross-section al	1270	98.97%	0.08
7	Gebretsadik et al (2021) [25]	SN NP	Cancer patients	Cross-section al	3002	100%	18.62
8	Hailu et al. (2020) [26]	AA	Patients seen for suspicion of cancer	Cross-section al	9,261	100.0%	6.34
9	Hassen et al (2021) [27]	AA	Women with breast cancer	Case-control	460	100%	50
10	Hassen et al (2022) [27]	AA	Women with breast cancer	Case-control	460	100%	50
11	Kibret et al (2022) [28]	SN NP	Cancer patients	Cross-section al	1,810	100%	4.97
12	Kumie et al (2020) [29]	Am har a	Women with breast cancer	Cross-section al	182	100%	50
13	Mekonen et al (2021) [30]	AA	Cancer patients	Case-control	100	100.0%	50
14	Memirie et al. (2018) [31]	AA	Cancer patients	Cross-section al	64,285	100%	21.76
17	Shalamo (2022) [32]	SN NP	Women with breast cancer	Case-control	408	95%	32.11
18	Solomon et al (2019) [33]	AA	Cancer patients	Cross-section al	919	100%	14.8
19	Tefera B et al. (2016) [34]	Am har a	Cancer patients	Cross-section al	540	100.0%	14.07
22	Timotewos et al (2018) [35]	AA	Cancer patients	Cross-section al	4139	100%	22.54
23	Tolessa et al (2021) [36]	AA	Women with breast cancer	Case-control	348	100.0%	33.33
24	Woldu et al	AA	Cancer patients	Cross-	142	100%	14.79

	(2017) [37]			section al			

Prevalence of breast cancer in Ethiopia

Nineteen (19) articles were included to pool the magnitude of breast cancer [20-38]. Accordingly, the pooled proportion of breast cancer in Ethiopia was found to be 22. 98% (95%CI: 19.48, 26.48; I^2=99.9%, p=0.000) (Figure 2).

Subgroup analysis

Since significant heterogeneity was found when pooling the magnitude of breast cancer, subgroup analysis was done to further check for the source of heterogeneity. As of the subgroup analysis by region, the proportion of breast cancer was found to be 30.19%; 95%CI: 23.65, 36.74 in AA, 20.91%;95%CI: 2.59, 39.24 in Amhara, 13.66%;95%CI:4.81, 22.51 in SNNP, and 2.63%;95%CI:1.52,3.73 in Oromia (Additional file 2). The result of subgroup analysis by study setting showed that the pooled magnitude of breast cancer was high for institution-based studies (24.86%;95%CI:20.69, 29.02) while 14.79%; 95%CI: -2.56, 32.15) for population-based studies (Additional file 3). When analyzed by study design, the pooled proportion of breast cancer is highest for studies by case-control study design (43.79%;95%CI: 36.21, 51.38) than studies by cross-sectional design (14.27%; 95%CI: 10.24, 18.3) (Additional file 4). Furthermore, the subgroup analysis was done by the study population. Accordingly, the pooled magnitude of breast cancer is found to be (43.9%; 95%CI: 36.45,51.34), (19.77%; 95%CI: 14.33, 25.21), (6.34%; 95%CI: 5.84, 6.83), (2.63%; 95%CI: 1.52, 3.73), (0.09%; 95%CI: 0.02, 0.16), and (0.08%; 95%CI: -0.08, 0.23) among women participated in case-control studies of breast cancer, among cancer patients, among patients seen for the suspicion of cancer at the oncology unit, among deceased women, among general women and among children attended pediatric

outpatient department (OPD), respectively (Additional file 5). A significant source of heterogeneity was observed across all the sub-group analyses done by region, study design, study setting and study population (Table 2).

Table 2: Subgroup analysis for the pooled proportion of breast cancer in Ethiopia

Variables	subgroup	No of included studies	Sample size	Proportion of Breast cancer	Heterogeneity across the studies	
					I^2 (%)	p-value
Region	Addis Ababa	11	80452	30.19%	99.7%	0.000
	Amhara	3	1992	20.91%	99.3%	0.000
	SNNP	4	12800	13.66%	99.7%	0.000
	Oromia	1	800	2.63%	0.0%	-
Study design	Cros-sectional	13	94042	14.27%	99.9%	0.000
	Case-control	6	2002	43.79%	91.6%	0.000
setting	Population-based	3	76004	14.79%	100%	0.000
	Institution-based	16	20040	24.86%	99.5%	0.000
Population	Women in case-control study of breast cancer	6	2084	43.9%	91.8%	0.000
	Cancer patients	9	75049	19.77%	99.3%	0.000
	suspected patients evaluated at oncology unit	1	9261	6.34%	0.0%	-
	Deceased women	1	800	2.63%	0.0%	-
	General women	1	7580	0.09%	0.0%	-
	Children attended paediatric OPD	1	1270	0.08%	0.0%	-

Publication bias

The funnel plot appeared asymmetric indicating the presence of publication bias (Additional file 6), Egger's test (P = 0.017). Hence, further analysis was done using trim and fill analysis since publication bias was observed (Additional file 7).

Sensitivity Analysis

A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to the sensitivity analyses output, using the random-effects model was robust, and no single study affected the pooled proportion of breast cancer (Additional file 8).

Determinants of breast cancer

In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI:1.41, 3.17, I^2=0.0%, p=0.826) times more odds of breast cancer than their counterparts (Additional file 9). This meta-analysis also revealed that the risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, I^2=0.0%, p=0.888) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file 10). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, , I^2=65.2%%, p=0.090) times more odds of breast cancer than their counterparts (Additional file 11). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, I^2=0.0%, p=0.433) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely

for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 12). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 13). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 14).

DISCUSSION

According to this study, the pooled proportion of breast cancer in Ethiopia is 22. 98 (95%CI: 19.48, 26.48). This finding is high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations) [8]. The observed variation could be due to a difference in the denominator. As it is shown in the subgroup analysis, the proportion of breast cancer varies in different situations. For example, the proportion of pooled breast cancer is higher-19.77% in confirmed cancer patients, 6.34% among patients seen for the suspicion of cancer at the oncology unit, 2.63% among deceased women, 0.09% among general women, and 0.08% among children attended pediatric OPD. This shows that breast cancer varies depending on the study population (male vs female, child versus adult, deceased versus alive, patient versus healthy population).In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study [39, 40] and the study in the United states of America (USA) (29%) [41]. The possible reason might be that the proportion in the current analysis is inclusive of all populations even though dominated by cancer populations. Furthermore, the difference in socio-economic and demographic conditions might be another reason for this variation. Developed countries have improved cancer

detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions.

In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65;95%CI:0.85, 15.71). This finding is consistent with the studies conducted in Iran [42, 43], the United kingdom [44], China [45], and Malaysia [46]. This might be due to the presence of some inherited defect that will facilitate the development of the disease.

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in line with the finding of previous systematic review [47], studies done in China [45], Iran [42], USA ([48, 49] where studies conducted in stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2 [50]. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles [51].

This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study [46, 49, 52-55], and studies in Iran [42, 43] but contrasts with the finding of the study conducted in Northern California [56]. High BMI including

obesity is found to be a risk factor for breast cancer in postmenopausal women [57-59]. Increased body fat might increase the level of circulating estrogens and decrease levels of sex hormone-binding globulin [60]. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development [61].

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies [42, 62, 63]. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies [42, 43] found that obesity is a risk factor for breast cancer.

This study revealed that the use of processed food and/or drink was found as a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America [64], Iran [65] and other reviews [53, 66]. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which implies that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer [67].

In this review, a positive association between high cholesterol level and breast cancer was found. However, studies are contradicting in this regard. Some studies found high cholesterol as a risk factor [68] while some found it as a protective factor [69, 70]. Those studies that found the protective

effect of high cholesterol explained it as "statin-the cholesterol-lowering medication might reduce the breast cancer risk too" [71, 72]. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer [73, 74]. Women with high body fat might have an increased risk of breast cancer though their BMI is normal. Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies [75] where it was indicated as a breast cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women [59]. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study [45]. Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen [53]. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women [47]. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women.

This finding implies that breast cancer is increasing in the country and deserves attention. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat it timely, and minimize the risk of death and economic impact of the disease. Breast cancer screening should be initiated and strengthened in the country. Decentralization of the cancer registry is required.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia. Next, it shares the strengths of systematic review and meta-analysis over a single study as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. The limitation of this study is that only a few studies were found to pool the odds ratio for some factors. In addition, only four out of 11 regions had studies regarding breast cancer with the dominance of Addis Ababa city and were directly included in this systematic review and meta-analysis. However, the big regions of the country were covered.

Conclusion

The magnitude of breast cancer in this study is high compared to the finding from the 2019 cancer burden in Ethiopia [8]. Furthermore, the use of processed foods, high BMI, high cholesterol, physical inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to

practice regular physical exercise to regulate body weight, and body fat and then to protect against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2 years after delivery as this contributes to the minimization of breast cancer risk. Regular breast examination should be practiced to detect and control the problem timely.

List of abbreviations

AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USA-United states of America

Ethics approval and consent to participate

N/A

Consent for publication

N/A

Availability of data and materials

The data extracted from included studies and analyzed in this review are available from the corresponding author based on the reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained to conduct this systematic review and meta-analysis

Authors Contributions

ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript. DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first draft of the result. AED searched, screened, and critically appraised the studies, extracted the data, and interpreted the result. ML searched and screened the studies, drafted the methods and wrote the introduction for the study. MCC and ETG extracted the data and prepared the manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and analyzed the data.

Acknowledgements

Not applicable

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Additional files

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Additional file 3: subgroup analysis of the pooled proportion of breast cancer by study setting in Ethiopia

Additional file 4: subgroup analysis of the pooled proportion of breast cancer by study design in Ethiopia

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Additional file 14: The pooled odds ratio of the association between breast feeding/lack of live birth and breast cancer in Ethiopia

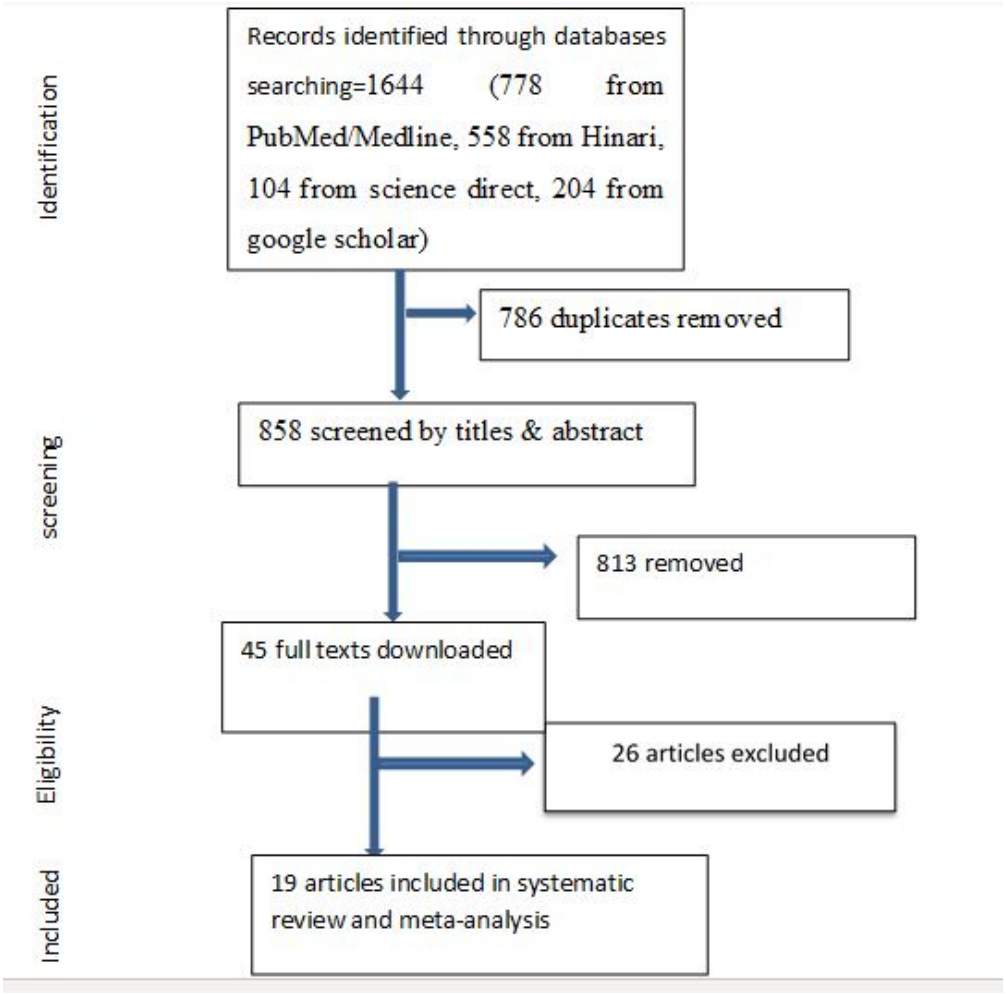

Figure 1: Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

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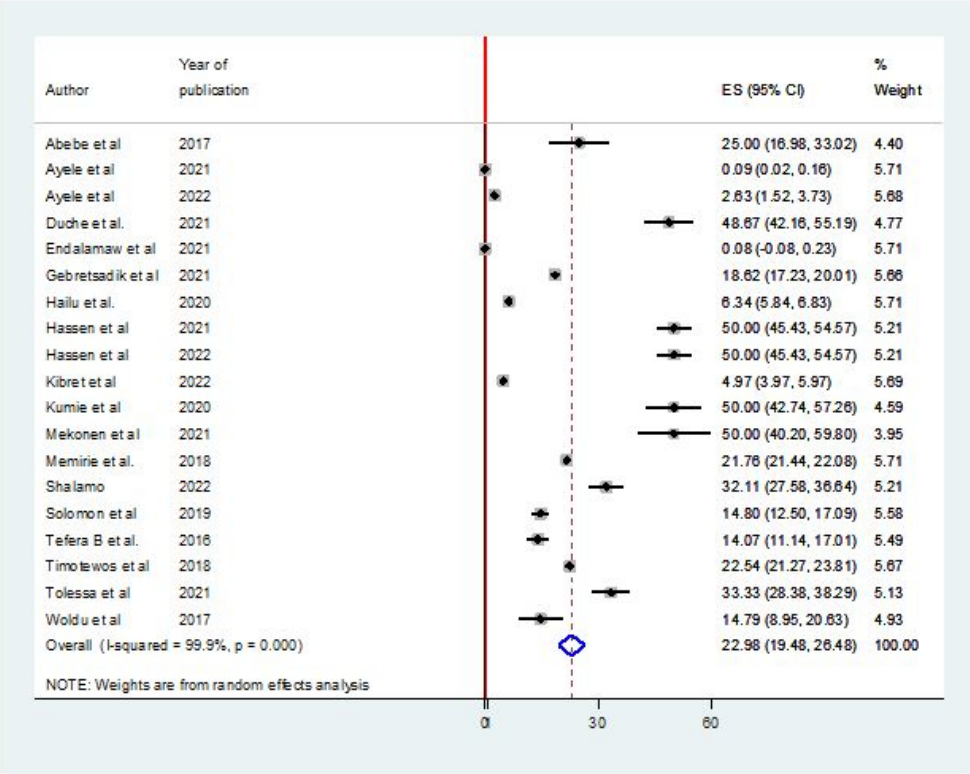

Figure 2: Forest plot of the pooled proportion of breast cancer in Ethiopia

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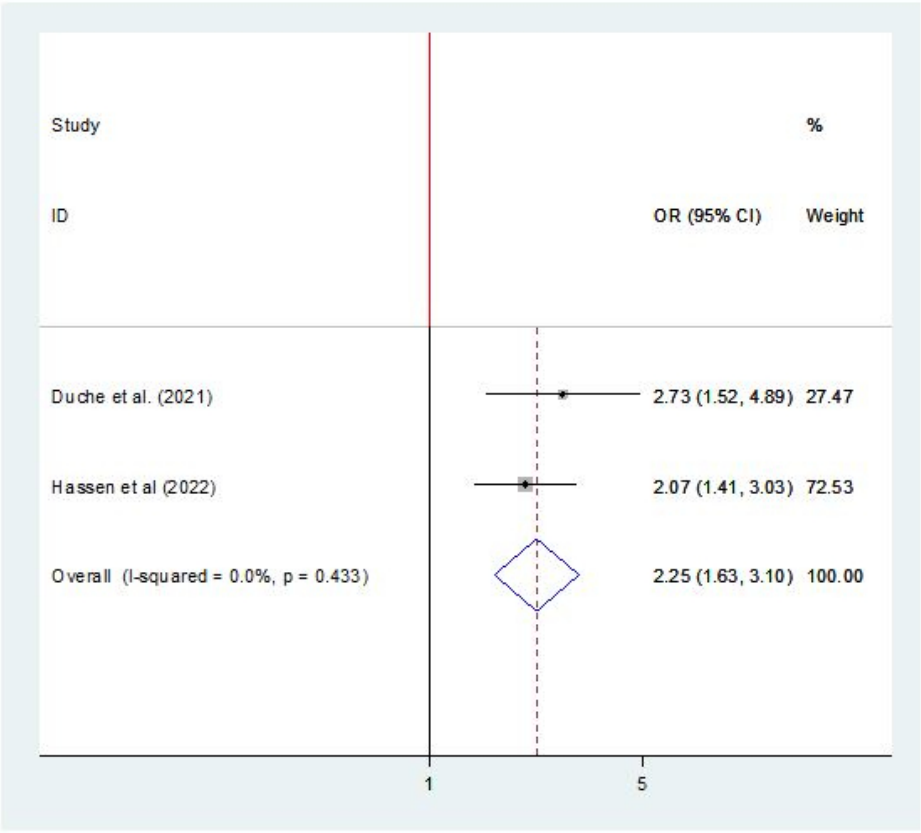

Figure 3: The pooled odds ratio showing the association between menopausal status and breast cancer in Ethiopia

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Reviewers: Adisu Tafari Shama and Dufera Rikitu Terefa, Date: 15-20/3/2023

JBI critical appraisal checklist for analytical cross-sectional studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score	%	Overall appraisal	Reason for exclusion
2.	Abebe (2017)	2	2	1	3	2	2	1	1	3	37.5	Include	
3.	Ayele (2021)	2	1	3	3	3	2	1	1	3	37.5	Include	
4.	Ayele (2022)	1	1	1	1	2	2	2	1	5	62.5	Include	
6.	Endalamaw (2021)	1	1	1	1	2	2	1	1	6	75	Include	
7.	Gebretsadik (2021)	2	2	1	1	2	2	1	1	4	50	Include	
8.	Hailu (2020)	2	1	1	1	2	2	1	1	5	62.5	Include	
11.	Kibret (2022)	1	1	3	3	2	2	1	3	3	37.5	Include	
12.	Kumie (2020)	1	1	1	1	2	2	1	1	6	75	Include	
14.	Memirie (2018)	2	1	1	3	2	2	1	1	4	50	Include	
15.	Schwartz (2020)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
16.	Schwartz (2021)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
18.	Solomon (2019)	1	1	3	3	2	1	1	1	5	62.5	Include	
19	Tefera B (2016)	2	1	3	1	2	2	1	3	3	37.5	Include	
21	Tesfaw (2018)	1	1	1	2	2	2	1	1	5	62.5	Exclude	No outcome of interest reported
24.	Woldu (2017)	1	2	1	3	2	2	3	1	3	37.5	Include	

Q1. Were the criteria for inclusion in the sample clearly defined?
Q2. Were the study subjects and the setting described in detail?
Q3. Was the exposure measured in a valid and reliable way?
Q4. Were objective, standard criteria used for measurement of the condition?

Q5. Were confounding factors identified?
Q6. Were strategies to deal with confounding factors stated?
Q7. Were the outcomes measured in a valid and reliable way?
Q8. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Case-control studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	%	Overall appraisal	Reason for exclusion
5.	Duche (2021)	1	2	1	1	1	2	3	1	3	1	6	60	Include	
9.	Hassen (2021)	1	1	1	1	1	2	2	1	2	1	7	70	include	
10.	Hassen (2022)	1	3	3	3	1	1	1	1	2	1	6	60	include	
13.	Mekonen (2021)	1	3	1	1	1	2	1	1	3	1	7	70	include	
17.	Shalamo (2022)	1	2	2	1	1	2	1	1	3	1	6	60	include	
23.	Tolessa (2021)	1	2	1	1	1	1	1	1	3	1	8	80	include	

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Cohort studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score	%	Overall appraisal	Reason for exclusion
20	Tekle (2019)	4	4	3	2	2	3	1	2	2	1	1	3	27	exclude	Outcome of interest not reported

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

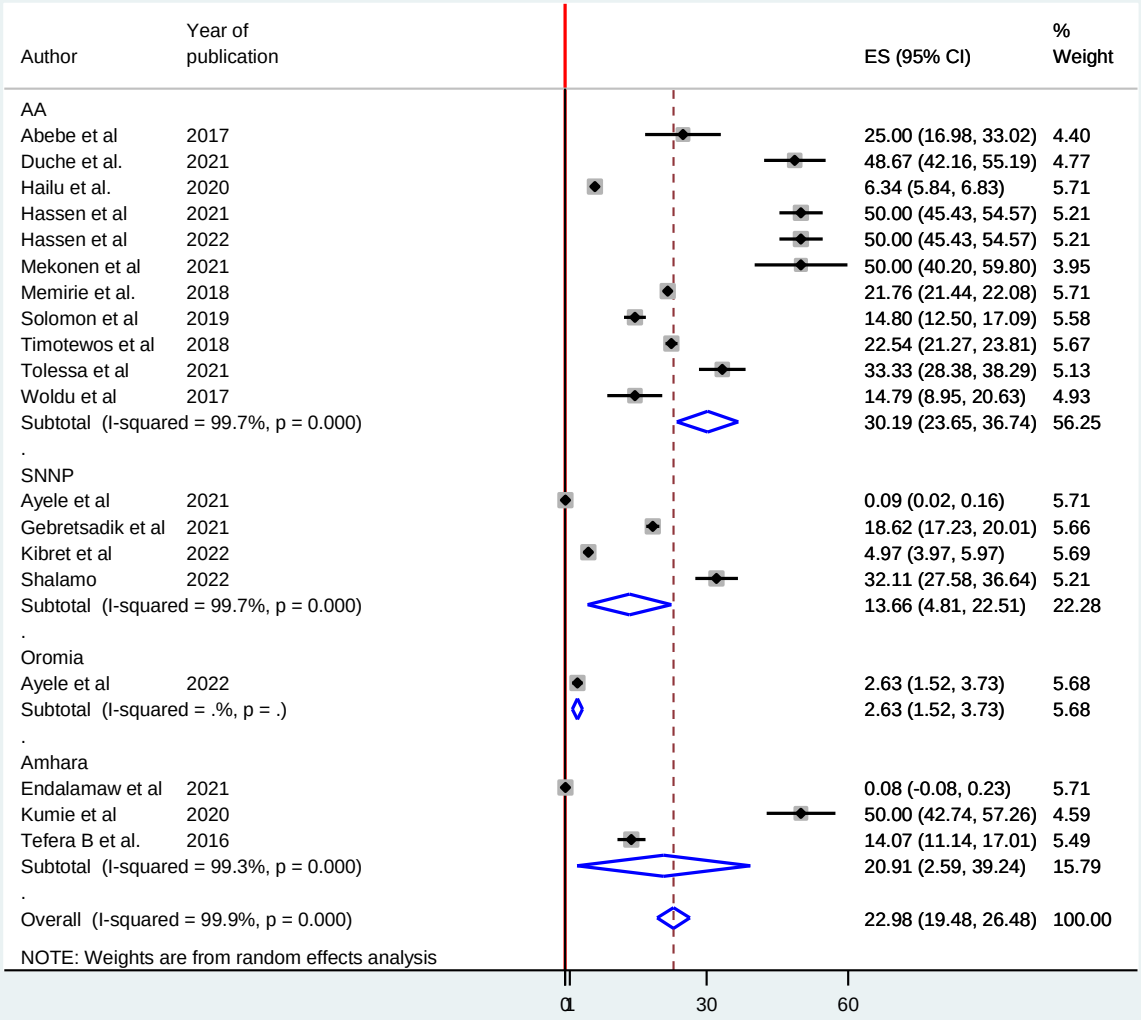
JBI CRITICAL APPRAISAL CHECKLIST FOR STUDIES REPORTING PREVALENCE DATA

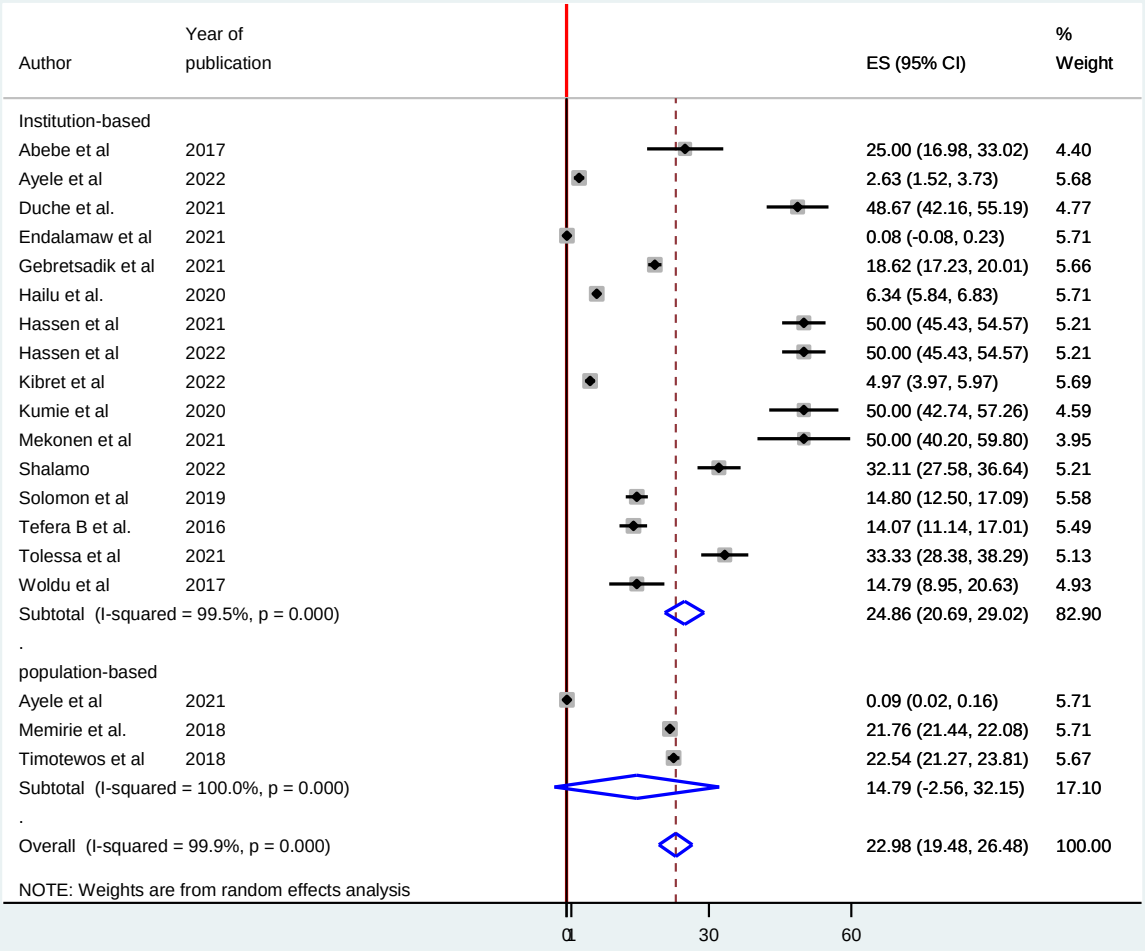
Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total score	%	Overall appraisal	Reason for exclusion
1	Abate (2016)	3	3	3	1	1	3	1	3	3	3	33	exclude	The outcome of interest is not shown in this study. Besides, sample size, sampling techniques and analysis methods were not clearly described.
22	Timotewos (2018)	3	3	3	1	1	1	1	1	3	5	77	Include	

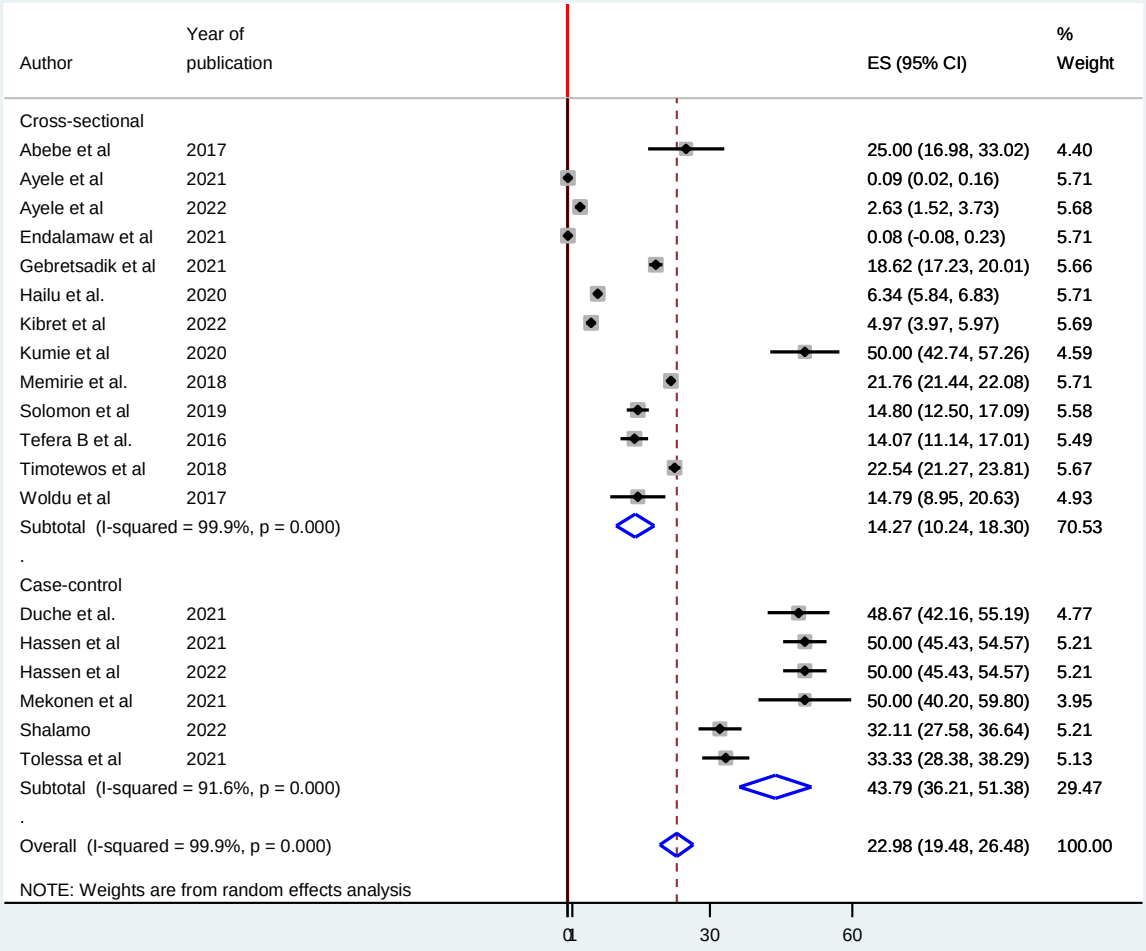
1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?

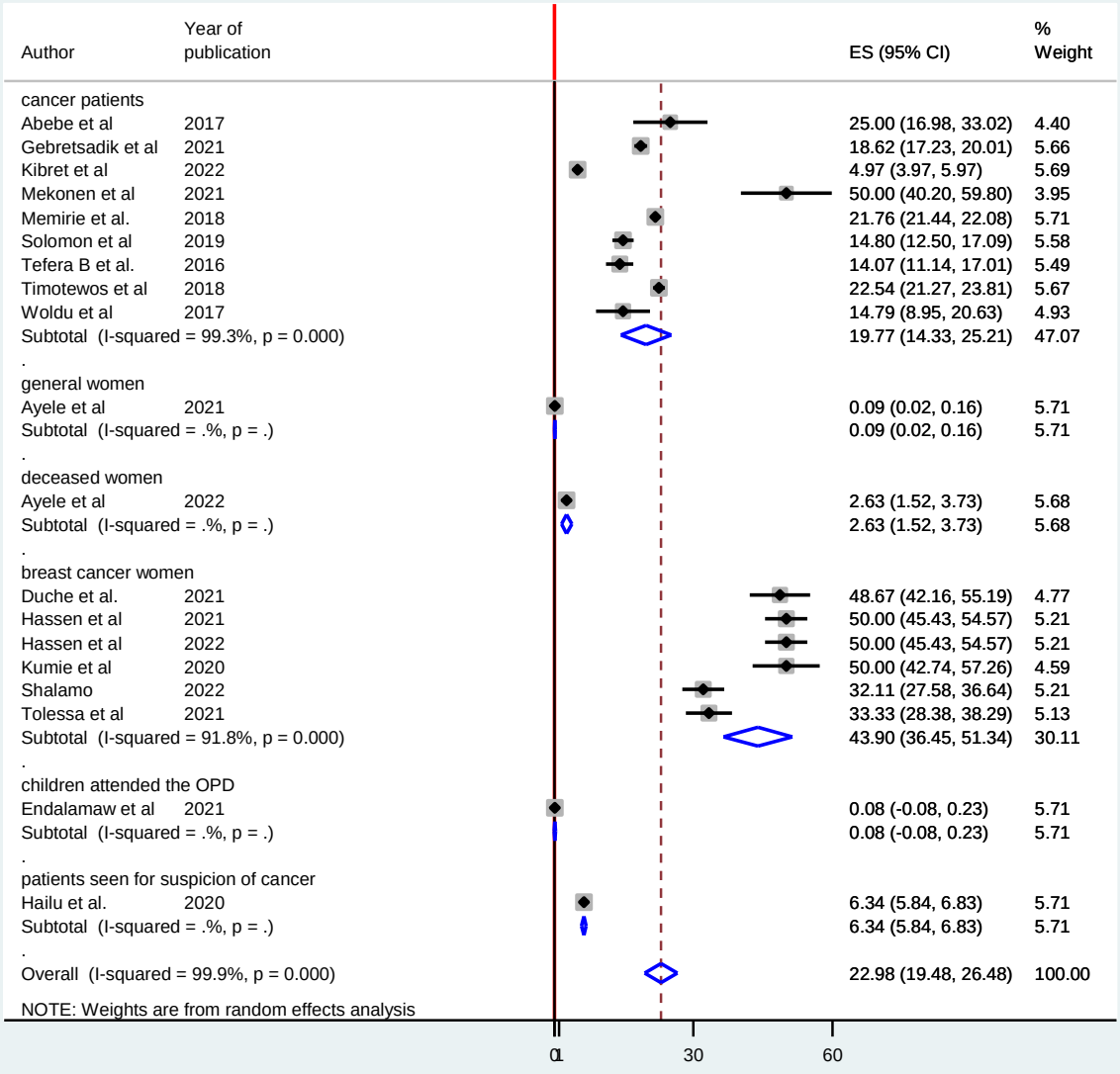
4.	Were the study subjects and the setting described in detail?
5.	Was the data analysis conducted with sufficient coverage of the identified sample?
6.	Were valid methods used for the identification of the condition?
7.	Was the condition measured in a standard, reliable way for all participants?
8.	Was there appropriate statistical analysis?
9.	Was the response rate adequate, and if not, was the low response rate managed appropriately?

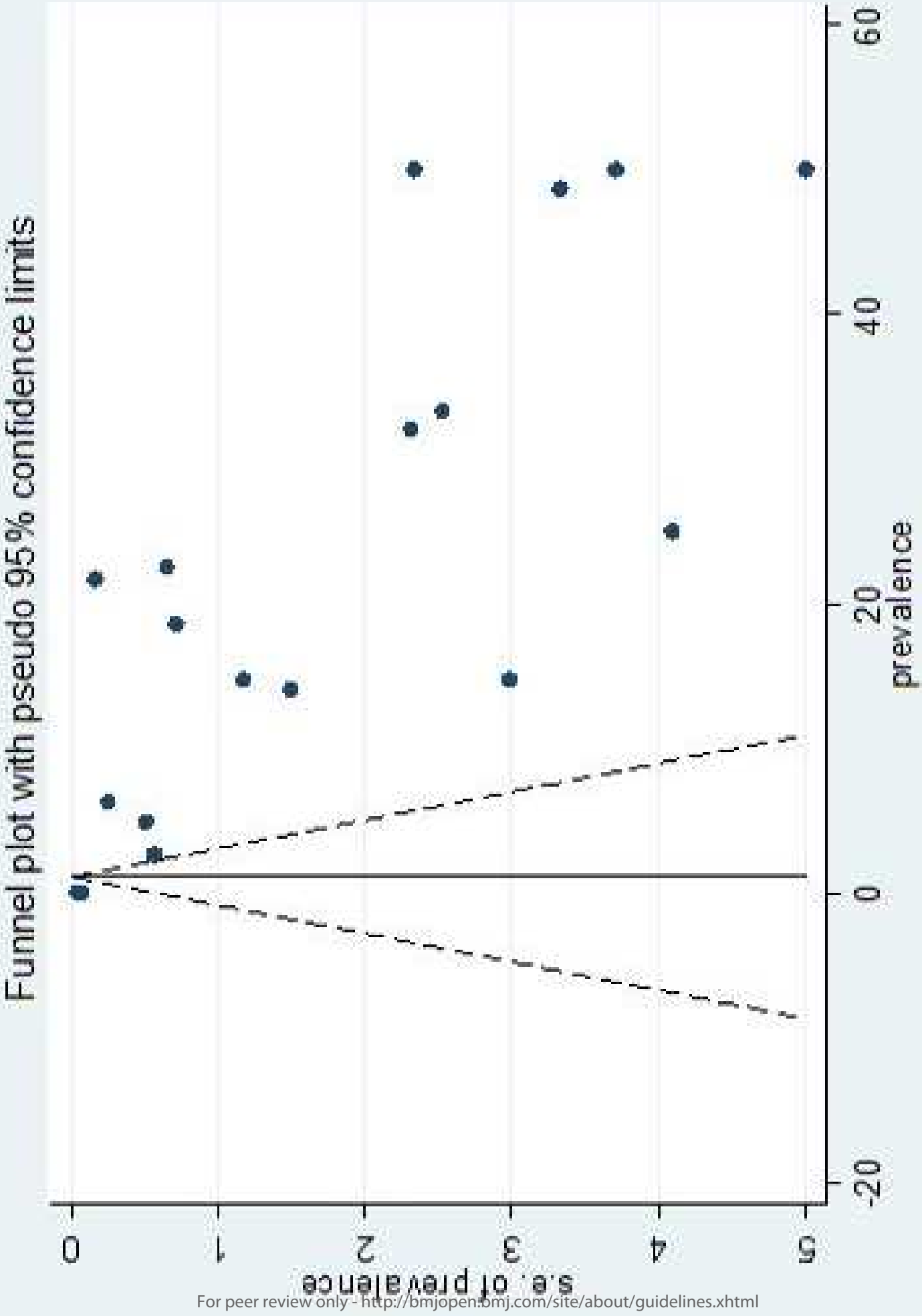
1-Yes 2- No 3-Unclear 4-Not applicable

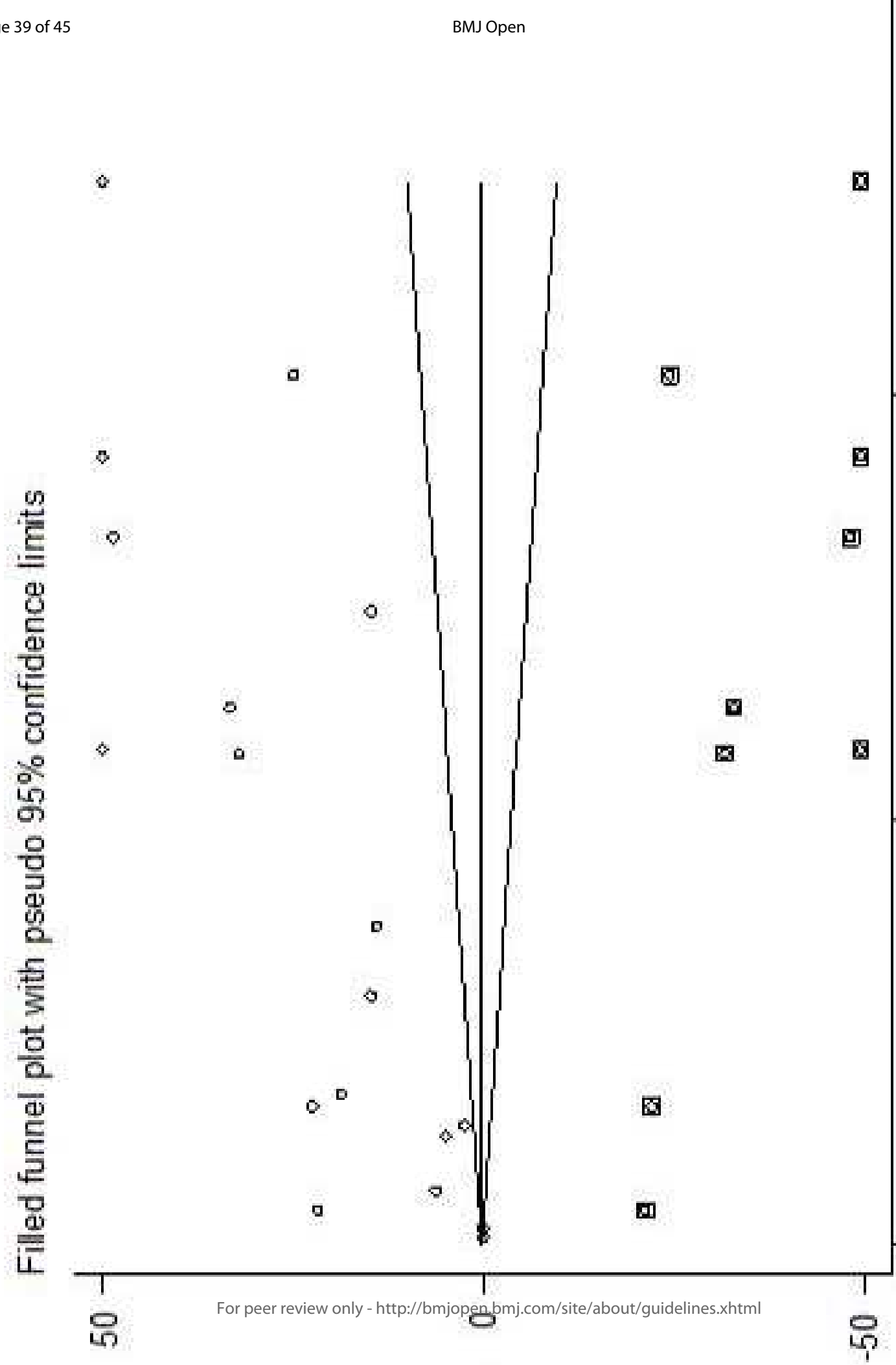


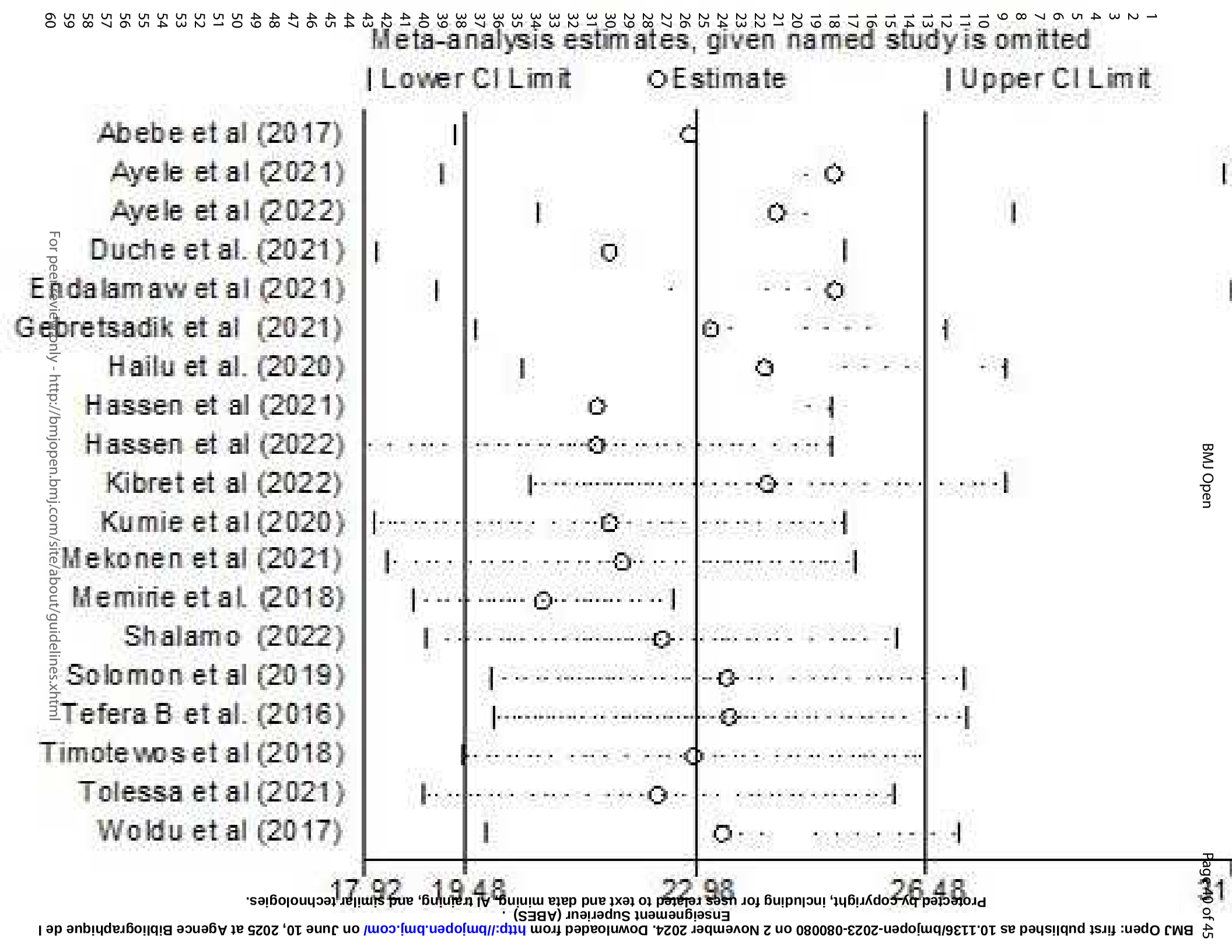












BMJ Open

Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080080.R1
Article Type:	Original research
Date Submitted by the Author:	29-Jul-2024
Complete List of Authors:	Shama, Adisu; Wollega University, Department of Public Health, Institute of Health Sciences Terefa, Dufera; Wollega University, Public Health, Institute of Health Sciences Desisa, Adisu; Wollega University, Public Health, Institute of Health Sciences Lema, Matiyos; Wollega University, Public Health, Institute of Health Sciences cheme, Melese chego ; Wollega University, Department of Public Health, Institute of Health Sciences Geta, Edosa; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Jira Wakoya; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Bikila Regassa; Wollega University, Department of Public Health, Institute of Health sciences; Jimma University, Department of Epidemiology, Faculty of Public Health Biru, Bayise; Wollega University, Department of Public Health, Institutes of Health Sciences; Jimma University, Department of Human Nutrition and Dietetics, Faculty of Public Health
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health policy, Health services research, Oncology, Public health, Nutrition and metabolism
Keywords:	Risk Factors, Primary Health Care, PUBLIC HEALTH, Chronic Disease

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Word count=4737

Abstract

Objectives: Breast cancer is the leading cause of cancer morbidity and mortality among women. Still, there is a paucity of studies to know the magnitude of the problem in the country Ethiopia. Hence, this review was intended to pool the prevalence and identify the determinants of breast cancer in Ethiopia.

Design: A systematic review and meta-analysis was conducted.

Data sources: Databases like PubMed/MEDLINE, HINARI, Science Direct, Google and Google Scholar as well as websites of organizations were searched between 25 February to 6 March 2023.

Eligibility criteria: All observational studies in Ethiopia that reported either the magnitude and/or determinants of breast cancer regardless of publication status were included

Data extraction and synthesis: Two authors independently assessed and extracted the data. Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles. Effect estimates were done by using the random effect model. The meta-analysis results were displayed by using forest plots.

Results: Nineteen 19 articles were reviewed with 24,435 total participants. The pooled proportion of breast cancer was 17.94(95%CI: 12.03, 23.85) in Ethiopia. Consuming packed foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75, 6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27; 95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer (POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92) were the determinants of breast cancer.

Conclusions: The magnitude of breast cancer is high according to this review. Processed food consumption, high cholesterol in the body, lack of physical activity, high body mass index, post-menopause, family history of cancer, and lack of breastfeeding were the risk factors for breast

cancer. The use of healthy food sources such as fruits and vegetables, and homegrown varieties of crops rather than seeking processed foods would help.

PROSPERO Registration Number: CRD42023417733

Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia

Article Summary

Strengths and limitations of this study

- The inclusion of prediction interval is a strong aspect of this study, as it is uncommon in many meta-analyses
- The review included only observational studies.
- The narrow scope of the review (only one country)
- A limited number of studies were found to pool the odds ratio for some factors.

Background

Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups [1]. It is found to be the most common cause of cancer deaths in 11 regions of the world [2]. It is one of the most frequently diagnosed cancers and the leading cause of cancer deaths in females worldwide [3]. The recent global burden of cancer statistics (GLOBOCAN 2020) showed that BC has surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It affects one in four new cancer cases of women and contributes to one in six deaths of women from cancer [4].

The cancer burden is increasing worldwide and is estimated to be 28.4 million cases by 2040, which is a 47% increase over the cancer burden in 2020. A Higher death rate occurs in developing countries than in developed (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000) [4]. In Ethiopia too there were an estimated 5900 incident cases

of breast cancer with the highest age-standardized incidence rate of 12.5 per 100,000 and a death rate of 9.7 per 100,000 in 2019 [5].

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, early age at menarche, sedentary lifestyles, and poor diet) and improving cancer registration and cancer detection are among the factors contributing to the projected rise of breast cancer in LMICs [6-9]. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also contributing factors to the increasing breast cancer burden in underdeveloped countries [6, 10, 11]. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer [6, 10-13].

Comprehensive identification of the magnitude and determinants of breast cancer is critical for developing nations like Ethiopia, as this will aid in the development and implementation of effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. Although there is one recently published review, the focus of that study was more on determinants of the problem [14]. Different pocket studies done so far may not represent the entire

picture of the determinants of breast cancer in Ethiopia. Most of them were limited to small sample sizes, limited portions of populations covered, and limited research regions. In this regard, many of the regions were not addressed in the previous studies and our study also helps to show this gap for further study, let alone intervention. It is critical to shed light on the risk factors for breast cancer. As a result, this study aimed to determine the magnitude of breast cancer and its determinants in Ethiopia.

Methods

Study design

A systematic review and meta-analysis was conducted. The protocol was registered on Prospective Registry of Systematic Reviews (PROSPERO) with registration number (CRD42023417733) and no change made to the protocol. To conduct this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [15] was used.

Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: [“breast” OR “mammary gland” AND “cancer” OR “tumor” OR “malignancy” OR “breast cancer” OR “breast malignancy” OR “breast tumor” AND “Risk factors” OR “Associated factors” OR “Determinants” OR “predictors” AND “Ethiopia” OR “Addis Ababa” OR “Northern Ethiopia” OR “North west Ethiopia” OR “Southern Ethiopia” OR “South Western Ethiopia” OR “Western Ethiopia” OR “East Ethiopia”] were used (Additional

file 1). Searching started on February 25, 2023, and the final date of searching was March 6, 2023.

Eligibility criteria

Inclusion criteria

To be included in this review, the study should report either the determinants of breast cancer and/or the magnitude (incidence, prevalence, number) of breast cancer.

Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were part of this systematic review.

Study population: The study involved all human population (male, female, children, and adults) in Ethiopia who has been evaluated for cancer.

Exposure: those with modifiable or non-modifiable risk factors

Study design: All observational studies (cross-sectional and case-control) that reported the magnitude of breast cancer and its determinants were evaluated to be included.

Publication status: Both published and unpublished studies were considered for inclusion.

Exclusion criteria

Articles with low quality, unclear methodologies and articles that didn't indicate the outcome of interest were excluded (Additional file 2). Excluding the studies whose full-text papers were not available after at least two personal email contacts with the corresponding authors was an exclusion criterion but all full texts were available.

Outcome variables assessment

There were two outcomes in this study: the first outcome was the magnitude of confirmed breast cancer. This outcome can occur in any population group. Therefore, the population for this outcome was a human population of any age who was evaluated for cancer.

Breast cancer: When the diagnosis was confirmed by pathological tests in addition to the history and physical examination [16]. Hence, the data were sought if the diagnosis of breast cancer was confirmed by pathological tests. The total number of people who had breast cancer was divided by the total number of people participating in the study and multiplied by 100 which was used to determine the proportion of breast cancer.

The second outcome/variables of this review were the determinants of breast cancer. Modifiable and non-modifiable factors were searched from the literature to pool their value together. For the variables whose categorization didn't overlap (e.g. age category), the category repeatedly reported in the studies or the established categorization was assumed to get the privilege.

Early age at menarche: this is the starting of menstruation early and mostly before the age of 12 years [17, 18].

Late menopause: it is delayed age at menopause which is after the age of 55 years in most cases [17].

Benign breast disease and breast injury: those breast diseases such as atypical ductal hyperplasia or lobular carcinoma [17].

Menopause status: this is categorized as postmenopausal if the woman has already stopped menstruation (either absence of menstruation for at least 1 year (any age) or due to bilateral oophorectomy or estrogen deprivation therapy) and premenopausal otherwise [16, 19, 20].

Body mass index (BMI): is an index which is determined based on the weight and height measurement and it is classified as high if the value is >25kg/M^2 [16].

Age (<30, 30-49, >50) [17, 20], residence (rural vs urban), occupation (unemployed vs employed), exposure to smoking dried meat, use of industry processed foods, lack of intake of milk, fruits, and sea foods, high cholesterol (total cholesterol >200 mg/dl) [21], energy source; fuel source

(wood/charcoal/kerosene/animal dung vs electricity), lack of physical activity, contraceptive use, family history of cancer, history of abortion, absence of breastfeeding, benign breast disease, and breast injury, radiation exposure, anemia and thrombocytosis were also the variables for which data were sought in the literature.

Study selection and data extraction

All the articles searched from Databases were imported into EndNote version X7, and duplicates were removed. Based on the predefined inclusion criteria, two authors (ATS and AED) independently assessed and identified papers by their titles, abstracts, and full texts. The screened items were then compiled, and any disagreement was handled by inviting and discussing with the third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data extraction format [22-24]. The data extraction format included the primary author, publication year, study period, region, study area, study setting, study design, study population, publication status, sample size, response rate, and the number of cases/breast cancer. For the second outcome, data were extracted into a two-by-two table.

Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles [24]. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control of confounding. Accordingly, quality was categorized as low (total score of ≤2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood [24]. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy

during the quality appraisal of the studies was resolved by the agreement of the two reviewers. Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of interest were excluded from the systematic review and meta-analysis (Additional file 2).

Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I^2 statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used to indicate the presence of heterogeneity among the studies. The Higgins I^2 test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I^2 value > 20% [25]. As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model [26]. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). Moreover, the 95% prediction interval was computed by using the comprehensive meta-analysis to indicate the location of true proportion in comparable population [27]. The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided as significant at p-value < 0.05 [28, 29]. A leave-one-out sensitivity meta-analysis was used to assess the robustness of the findings.

Patient and public involvement: No patient was involved in this study.

Result

Description of included studies in the systematic review and meta-analysis

About 1644 articles were identified through database searching while 19 of them were included in this systematic review and meta-analysis (Figure 1). The total number of participants was 24,435.

Studies covered the period between 2011 to 2021 [16, 18-21, 30-43], 13 were cross-sectional [21, 30-41], six were case-control [16, 18-20, 42, 43], 18 were published [16, 18, 19, 21, 30-43], 1 was unpublished [20], the majority-16 were institution-based [16, 18-21, 30, 32-36, 38, 39, 41-43], and 3 of them were population-based studies [31, 37, 40]. The majority of them-10 were done in Addis Ababa (AA) [16, 18, 19, 30, 35, 37, 38, 40-43], followed by southern nations, nationalities and peoples (SNNP)- four studies [20, 31, 34, 36] and Amhara regions (3 studies) [21, 33, 39] (Table 1).

Table 1: Descriptive summary of 19 studies included in the meta-analysis to estimate breast cancer magnitude and its determinants in Ethiopia

Author (Year)	Age	Study design	Period	Sample size	Proportion (%)	Factors
Abebe et al (2017) [30]	>=18 years	Cross-sectional	June 1-31, 2015	112	26.5	
Ayele et al (2021) [31]	>=15 years	Cross-sectional	Mar- Apr 2018	7,580	10.2	
Ayele et al (2022) [32]	>=15 years	Cross-sectional	2011-2012	800	2.7	
Duche et al. (2021) [16]	>15 years	Case-control	April to September 2017	226		Physical inactivity, postmenopausal, breast feeding, BMI>25,
Endalamaw et al (2021) [33]	<15y ears	Cross-sectional	January 1, 2019 to March 30, 2019	100	10	
Gebretsadik et al (2021) [34]	No age limit	Cross-sectional	January 2013 and Jan. 2019	3002	18.6	
Hailu et al.	No	Cross-	January 2014	200	29.	

(2020) [35]	age limit	sectional	and December 2018	2	3	
Hassen et al (2021) [42]	>18 years	Case-control	May 2018 to June 2019	460		Anemia, thrombocytosis
Hassen et al (2022)	>18 years	Case-control	May 2018 to June 2019	460		Age between 40- 49, Early menarche, unemployment, milk intake, solid oil, use of unclean energy, Physical inactivity, breast disease
Kibret et al (2022) [36]	No age limit	Cross-sectional	Jan to Jun 2021	1,810	25.4	
Kumie et al (2020) [21]	>18 years	Cross-sectional	January 22 to May 26, 2020	182		High cholesterol
Mekonen et al (2021) [43]	>=18 years	Case-control	February to April 2020	100		
Memirie et al. (2018) [37]	>=15 years	Cross-sectional	2012 to 2015	1105	22.9	
Shalamo (2022) [20]	>15 years	Case-control	March 1 – April 30, 2022	408		Age, use of packed food, eating fruits and fish, contraceptive use, History of abortion, Radiation exposure, Breast injury, history of Cancer
Solomon et al (2019) [38]	No age limit	Cross-sectional	Jan 1, 2010 and Dece. 15, 2014	919	14.8	
Tefera B et al. (2016) [39]	N age limit	Cross-sectional	Sept 2014 to Aug 2015	540	14.1	
Timotewos et al (2018) [40]	No age limit	Cross-sectional	2012–2013	4139	22.5	
Tolessa et al (2021) [18]	>20 years	Case-control	Feb 1 to March 30, 2020	348		Early menarche, residence, dried meat, use of packed foods, Family history of

						Cancer, lack of breast feeding, overweight
Woldu et al (2017) [41]	No age limit	Cross-sectional	November 2015 to June 2016	142	14.8	

Prevalence of breast cancer in Ethiopia

Of the total 19 included studies, twelve (12) articles were included to pool the prevalence of breast cancer [16, 18-21, 30-43]. Accordingly, the pooled proportion of breast cancer in Ethiopia was found to be 17. 94% (95%CI: 12.03, 23.85; I^2=98.7%, *p<0.000)*. The 95% prediction interval is located between 8% and 34%. This indicates that the true magnitude in 95% of all comparable populations falls in the interval between 8% and 34% [27] (Figure 2).

Subgroup analysis

Since significant heterogeneity was found when pooling the magnitude of breast cancer, subgroup analysis was done to further check for the source of heterogeneity. As of the subgroup analysis by region, the proportion of breast cancer was found to be 21.51%; 95%CI: 15.91, 27.11 in AA, 18.97%; 95%CI: 12.82, 25.13 in SNNP, 14%;95%CI: 11.10, 16.90 in Amhara, and 2.7%;95%CI:1.57,3.83 in Oromia (Additional file 3). The result of subgroup analysis by study setting showed that the pooled magnitude of breast cancer was high; 21.18%; 95%CI: 18.83, 24.54) for population-based studies while (17.57%; 95%CI: 10.08, 25.06) for institution-based studies (Additional file 4). Furthermore, the subgroup analysis was done by the study population. Accordingly, the pooled magnitude of breast cancer is found to be 26.14%; 95%CI: 19.87, 32.42), (19.05%; 95%CI: 15.91,22.18), (10.10%; 95%CI: 1.73, 18.67), (2.70%; 95%CI: 1.57, 3.83), and (10.0%; 95%CI: -8.59, 28.59), among women with cancer, among cancer patients, among eligible women evaluated with Ultrasound-guided FNAC, among deceased women for whom causes of death were done through verbal autopsy, and among children who had cancer), respectively (Additional file 5).

Publication bias

The funnel plot appeared symmetric indicating the absence of publication bias (Additional file 6). Egger's test (*P = 0.707*) and Begg's test (*p=0.311*) also confirmed this because they both are non-significant being above *p>0.5*.

Sensitivity Analysis

A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to the sensitivity analyses output, using the random-effects model was robust, and no single study affected the pooled proportion of breast cancer (Additional file 7).

Determinants of breast cancer

In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI:1.41, 3.17, I^2=0.0%, *p=0.826*) times more odds of breast cancer than their counterparts (Additional file 8). This meta-analysis also revealed that the risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, I^2=0.0%, p=*0.888*) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file

9). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, , I^2=65.2%%, *p=0.090*) times more odds of breast cancer than their counterparts (Additional file 10). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, I^2=0.0%, *p=0.433*) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 11). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 12). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 13).

DISCUSSION

In total, 24 articles were assessed for inclusion and five (5) were excluded from this review. The reason for exclusion was mainly due to the lack of an intended outcome report. Here are the citations of excluded studies [44-48]. Data of 19 articles were extracted 12 for prevalence and 6 for determinants study. Accordingly, the pooled proportion of breast cancer in Ethiopia is found to be 17. 94 (95%CI: 12.03, 23.85). Although the result seems low when compared with the one in Iranian women (23.6%) [49], it is still high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations) [5]. The observed variation could be due to a difference in the denominator. As shown in the subgroup analysis, the proportion of breast cancer varies in different situations. For example, the proportion of pooled breast cancer is higher-26.14% in cancer-diagnosed women which is even higher than the one in Iranian women [49], 19.05% among general cancer patients, 10.1% in eligible women evaluated by ultrasound-

guided FNAC, and 2.7% among post-death verbal autopsy for deceased women. This shows that breast cancer varies depending on the study population). In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study [50, 51] and the study in the United States of America (USA) (29%) [52]. The difference in socio-economic and demographic conditions might be the possible reason for this variation. Developed countries have improved cancer detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions. Although the prevalence seems low when compared to the developed settings, this result is still high in comparison with the previous estimation. This alerts us that breast cancer deserves attention, especially in women. Because the subgroup analysis indicated a high prevalence of breast cancer among women who suffered from cancer.

In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65; 95%CI: 0.85, 15.71). This finding is consistent with previous studies conducted in Ethiopia [14], Iran [53, 54], the United kingdom [55], China [56], and Malaysia [57]. This might be due to the presence of some inherited defect that will facilitate the development of the disease. Given that biological exposure is non-modifiable, screening and follow-up of the breast condition would help to get timely treatment that can halt the bad consequences of the disease [14].

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in-line with the finding of previous systematic review [14, 58], studies done in China [56], Iran [53], USA [59, 60] where

studies conducted stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2 [61]. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles [62]. The result is a good indication to promote breastfeeding which has dual benefits for both the mother and child.

This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study [57, 60, 63-66], and studies in Iran [53, 54] but contrasts with the finding of the study conducted in Northern California [67]. High BMI including obesity is found to be a risk factor for breast cancer in postmenopausal women [68-70]. Increased body fat might increase the level of circulating estrogens and decrease the levels of sex hormone-binding globulin [71]. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development [72].

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies [53, 73, 74]. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies [53, 54] found that obesity is a risk factor for breast cancer. Therefore, adherence to regular physical exercise and healthy foods would help

to control weight and reduce body fat given that both overweight and physical inactivity are the two modifiable and related risk factors for breast cancer.

This study revealed that the use of processed food and/or drink was a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America [75], Iran [76] and other reviews [64, 77]. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which imply that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women [75 64, 76, 77]. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development [78]. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer [79].

In this review, a positive association between high cholesterol level and breast cancer was found. However, studies are contradicting in this regard. Some studies found high cholesterol as a risk factor [80] while some found it as a protective factor [81, 82]. Those studies that found the protective effect of high cholesterol explained it as “statin-the cholesterol-lowering medication might reduce the breast cancer risk too” [83, 84]. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer [85, 86]. Women with high body fat might have an increased risk of breast cancer though their BMI is normal.

Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies [14, 87] where it was indicated as a breast

cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women [70]. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study [56]. Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen [64]. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women [58]. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women. Although there are differences in explanation models regarding the postmenopausal stage, it is imperative to care for oneself because age extremes are mostly known to have a high risk for disease including chronic conditions like breast cancer [17].

This study has its own implications for research, practice, and policy. The practical implication is that a program on non-communicable diseases like breast cancer in the country should be strengthened to combat the problem given the prevalence in this study is high. On top of that, a protective effect of breastfeeding found in this study implies that programs that address breastfeeding promotion should incorporate the protective role of breastfeeding in their promotion activities. This research also alerts future research to investigate factors like residence, occupation, smoke-dried meat consumption, unclean energy sources, and the protective effects of

foods like milk, seafood, and fruits including their risk and protective mechanisms. The issue of postmenopausal status is still non-conclusive in the literature. It deserves further analysis to put under its appropriate classification (risk or protective factor for breast cancer). Moreover, researchers and policy-makers should work together on how to intervene and prevent the consumption of globalized and commercially processed foods as they are contributing to the breast cancer burden. The infection prevention-dominated policy of the country should be revisited to incorporate the prevention of non-communicable diseases. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat timely, and minimize the risk of death and economic impact. This may include the initiation and strengthening of breast cancer screening in the country. Decentralization of the cancer registry is also required.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia which pooled the prevalence of breast cancer. Next, it shares the strengths of systematic review and meta-analysis as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. Thirdly, the study estimated the prediction interval for the result obtained which is uncommon in many previous meta-analyses. However, the review was not free of limitations. The first limitation could be the narrow scope of the review in which a single country is covered. Nonetheless, it can still serve the studied country to consider in their policy decisions. The other drawback was that some of the regions had no primary studies regarding breast cancer and were not included in this review. Although the big regions of the country were covered, the majority of the studies were done in Addis Ababa city which is the country's capital. The other is that the

evidence pooled together was merely from observational studies (cross-sectional and case-control studies).

Conclusion

The magnitude of breast cancer in this study is high compared to the finding from the 2019 cancer burden in Ethiopia [5]. On top of that, the subgroup analysis by population in our study showed that the magnitude of breast cancer in cancer affected women (26.14%) is higher than that of women's data analyzed in Iranian study (23.6) [49]. In another way, the use of processed foods, high BMI, high cholesterol, physical inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to practice regular physical exercise to regulate body weight, and body fat and then to protect against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2 years after delivery as this contributes to the minimization of breast cancer risk. Regular breast examination should be practiced to detect and control the problem timely.

List of abbreviations

AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USA-United states of America

Ethics approval and consent to participate

Ethical approval was not applicable because the review of previous studies was done.

Consent for publication

N/A

Availability of data and materials

The data extracted from included studies and analyzed in this review are available from the corresponding author based on the reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained to conduct this systematic review and meta-analysis

Authors Contributions

ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript. DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first draft of the result. AED searched, screened, and critically appraised the studies, extracted the data, and interpreted the result. ML searched and screened the studies, drafted the methods and wrote the introduction for the study. MCC and ETG extracted the data and prepared the manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and analyzed the data. ATS is the guarantor.

Acknowledgements

Not applicable

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List of figures

Additional files

Additional file 1: Search strategies

Additional file 2: Critical appraisal of full texts downloaded for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

Additional file 3: subgroup analysis of the pooled proportion of breast cancer by regions in Ethiopia

Additional file 4: subgroup analysis of the pooled proportion of breast cancer by study setting in Ethiopia

Additional file 5: subgroup analysis of the pooled proportion of breast cancer by study population in Ethiopia

Additional file 6: Funnel plot with 95% confidence limits of the pooled proportion of breast cancer in Ethiopia

Additional file 7: Sensitivity analysis of the level of breast cancer: Prevalence and 95% confidence interval of breast cancer in Ethiopia

Additional file 8: The pooled odds ratio showing the association between processed food and breast cancer in Ethiopia

Additional file 9: The pooled odds ratio of the association between cholesterol level and breast cancer in Ethiopia

Additional file 10: The pooled odds ratio showing the association between physical activity and breast cancer in Ethiopia

Additional file 11: The pooled odds ratio showing the association between family history of cancer and breast cancer in Ethiopia

Additional file 12: The pooled odds ratio of the association between BMI and breast cancer in Ethiopia

Additional file 13: The pooled odds ratio of the association between breast feeding/lack of live birth and breast cancer in Ethiopia

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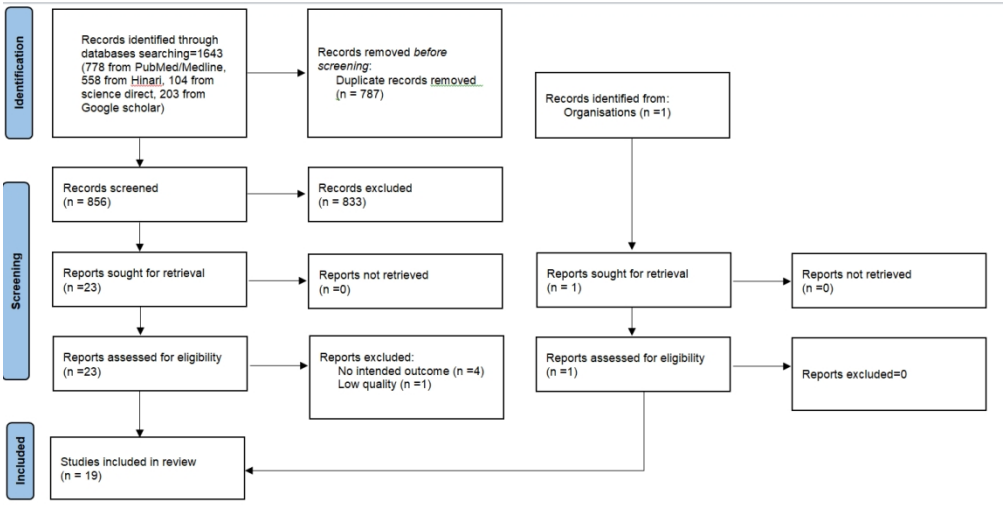
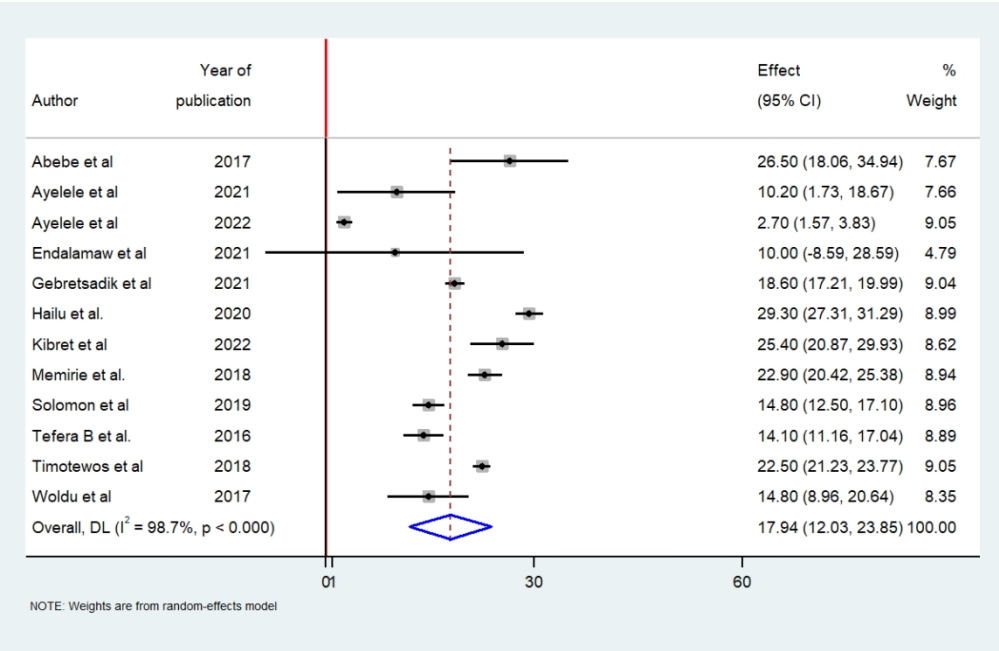


Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

682x345mm (57 x 57 DPI)



Forest plot of the pooled proportion of breast cancer in Ethiopia

532x345mm (57 x 57 DPI)

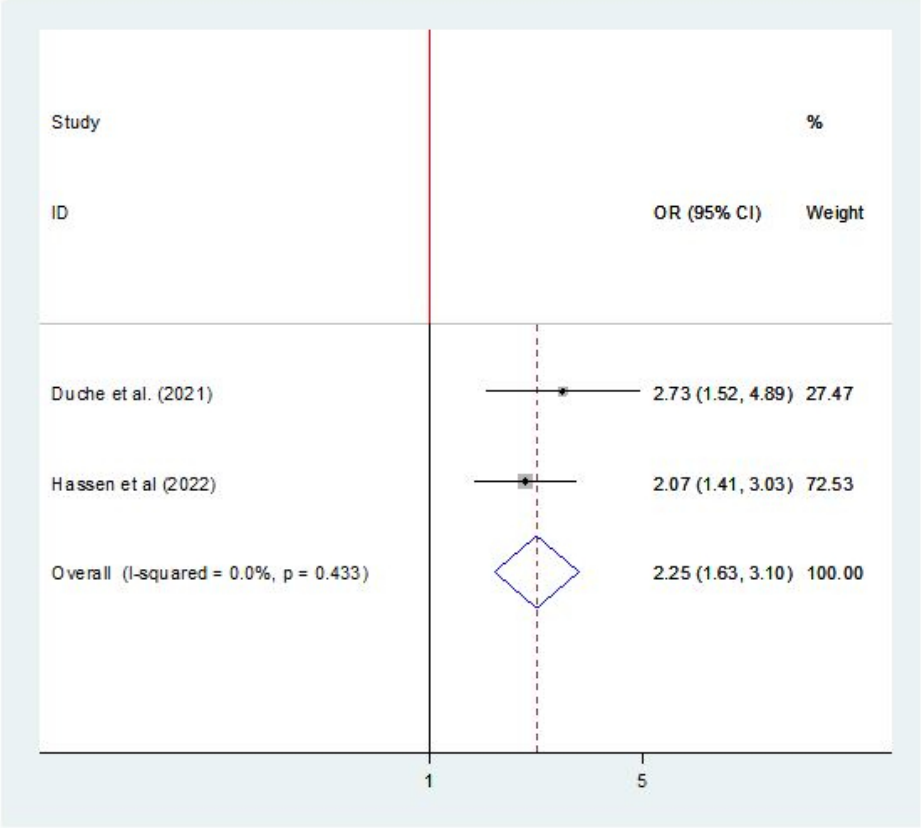


Figure 3: The pooled odds ratio showing the association between menopausal status and breast cancer in Ethiopia

157x138mm (96 x 96 DPI)

Search strategy

PubMed:

["breast" OR "mammary gland"]

AND

["Cancer" OR "tumor" OR "malignancy" OR "breast cancer" OR "breast malignancy" OR "breast tumor"]

AND

["Risk factors" OR "Associated factors" OR "Determinants" OR "predictors"]

AND

["Ethiopia" OR "Addis Ababa" OR "Northern Ethiopia" OR "North west Ethiopia" OR "Southern Ethiopia" OR "South Western Ethiopia" OR "Western Ethiopia" OR "East Ethiopia"]

HINARI:

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Determinants OR Associated factors OR Predictors]

AND

[Ethiopia]

Science Direct:

[Breast cancer] OR breast malignancy OR Breast carcinoma]

AND

[Determinants OR Associated factors]

Google and Google Scholar:

[Prevalence OR Magnitude OR Proportion]

AND

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Associated factors OR Determinants OR Risk factors OR Predictors OR factors OR Causes]

AND

[Ethiopia]

University websites:

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Associated factors of breast cancer OR Risk factors of breast cancer OR Predictors of breast cancer OR factors OR Causes of breast cancer]

AND

Ethiopia OR Western Ethiopia OR Central Ethiopia OR Addis Ababa OR northern Ethiopia OR Eastern Ethiopia OR Southern Ethiopia]

Reviewers: Adisu Tafari Shama and Dufera Rikitu Terefa, Date: 15-20/3/2023

JBI critical appraisal checklist for analytical cross-sectional studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score	%	Overall appraisal	Reason for exclusion
2.	Abebe (2017)	2	2	1	3	2	2	1	1	3	37.5	Include	
3.	Ayele (2021)	2	1	3	3	3	2	1	1	3	37.5	Include	
4.	Ayele (2022)	1	1	1	1	2	2	2	1	5	62.5	Include	
6.	Endalamaw (2021)	1	1	1	1	2	2	1	1	6	75	Include	
7.	Gebretsadik (2021)	2	2	1	1	2	2	1	1	4	50	Include	
8.	Hailu (2020)	2	1	1	1	2	2	1	1	5	62.5	Include	
11.	Kibret (2022)	1	1	3	3	2	2	1	3	3	37.5	Include	
12.	Kumie (2020)	1	1	1	1	2	2	1	1	6	75	Include	
14.	Memirie (2018)	2	1	1	3	2	2	1	1	4	50	Include	
15.	Schwartz (2020)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
16.	Schwartz (2021)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
18.	Solomon (2019)	1	1	3	3	2	1	1	1	5	62.5	Include	
19	Tefera B (2016)	2	1	3	1	2	2	1	3	3	37.5	Include	
21	Tesfaw (2018)	1	1	1	2	2	2	1	1	5	62.5	Exclude	No outcome of interest reported
24.	Woldu (2017)	1	2	1	3	2	2	3	1	3	37.5	Include	

Q1. Were the criteria for inclusion in the sample clearly defined?
Q2. Were the study subjects and the setting described in detail?
Q3. Was the exposure measured in a valid and reliable way?
Q4. Were objective, standard criteria used for measurement of the condition?

Q5. Were confounding factors identified?
Q6. Were strategies to deal with confounding factors stated?
Q7. Were the outcomes measured in a valid and reliable way?
Q8. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Case-control studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	%	Overall appraisal	Reason for exclusion
5.	Duche (2021)	1	2	1	1	1	2	3	1	3	1	6	60	Include	
9.	Hassen (2021)	1	1	1	1	1	2	2	1	2	1	7	70	include	
10.	Hassen (2022)	1	3	3	3	1	1	1	1	2	1	6	60	include	
13.	Mekonen (2021)	1	3	1	1	1	2	1	1	3	1	7	70	include	
17.	Shalamo (2022)	1	2	2	1	1	2	1	1	3	1	6	60	include	
23.	Tolessa (2021)	1	2	1	1	1	1	1	1	3	1	8	80	include	

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Cohort studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score	%	Overall appraisal	Reason for exclusion
20	Tekle (2019)	4	4	3	2	2	3	1	2	2	1	1	3	27	exclude	Outcome of interest not reported

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

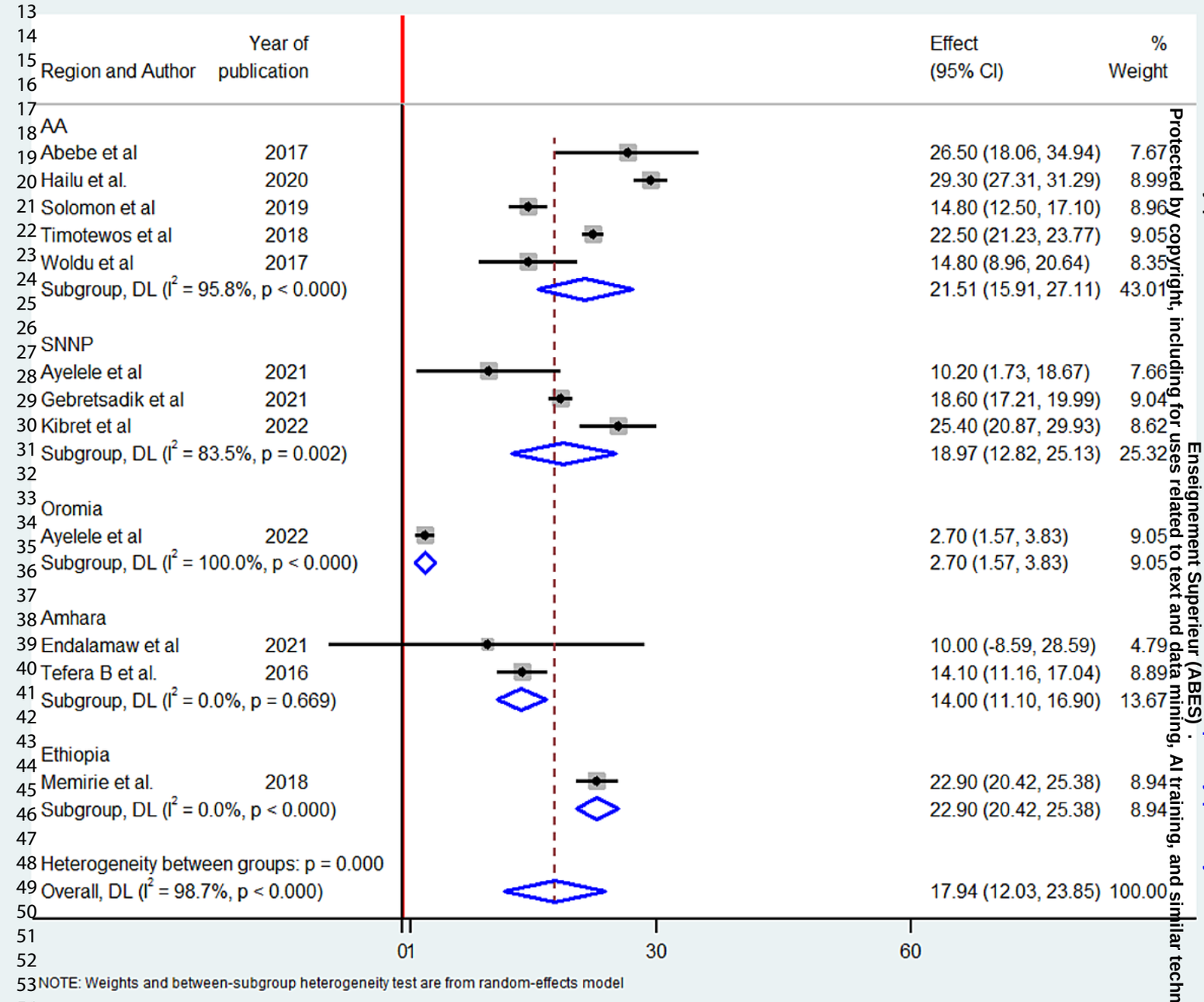
JBI CRITICAL APPRAISAL CHECKLIST FOR STUDIES REPORTING PREVALENCE DATA

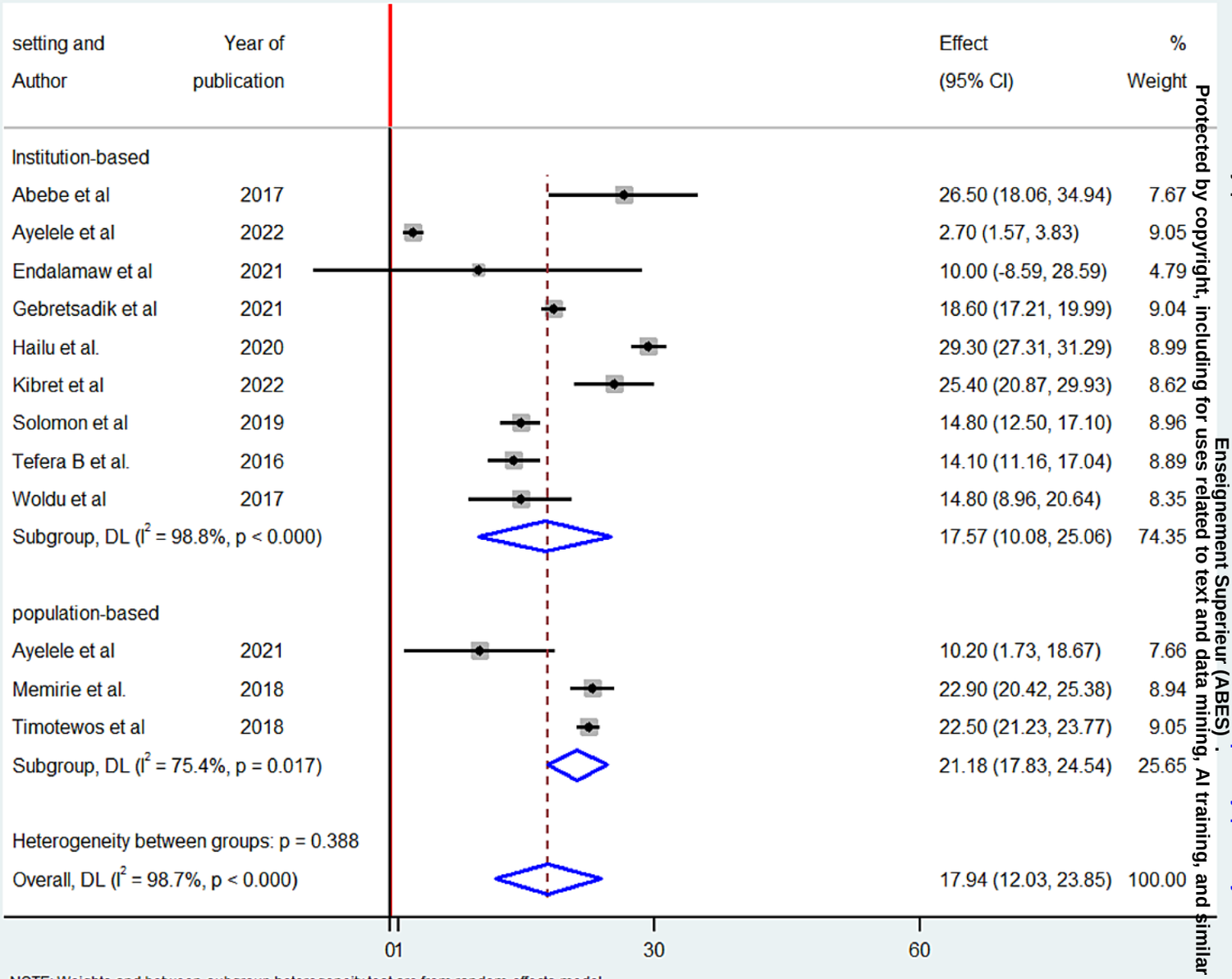
Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total score	%	Overall appraisal	Reason for exclusion
1	Abate (2016)	3	3	3	1	1	3	1	3	3	3	33	exclude	The outcome of interest is not shown in this study. Besides, sample size, sampling techniques and analysis methods were not clearly described.
22	Timotewos (2018)	3	3	3	1	1	1	1	1	3	5	77	Include	

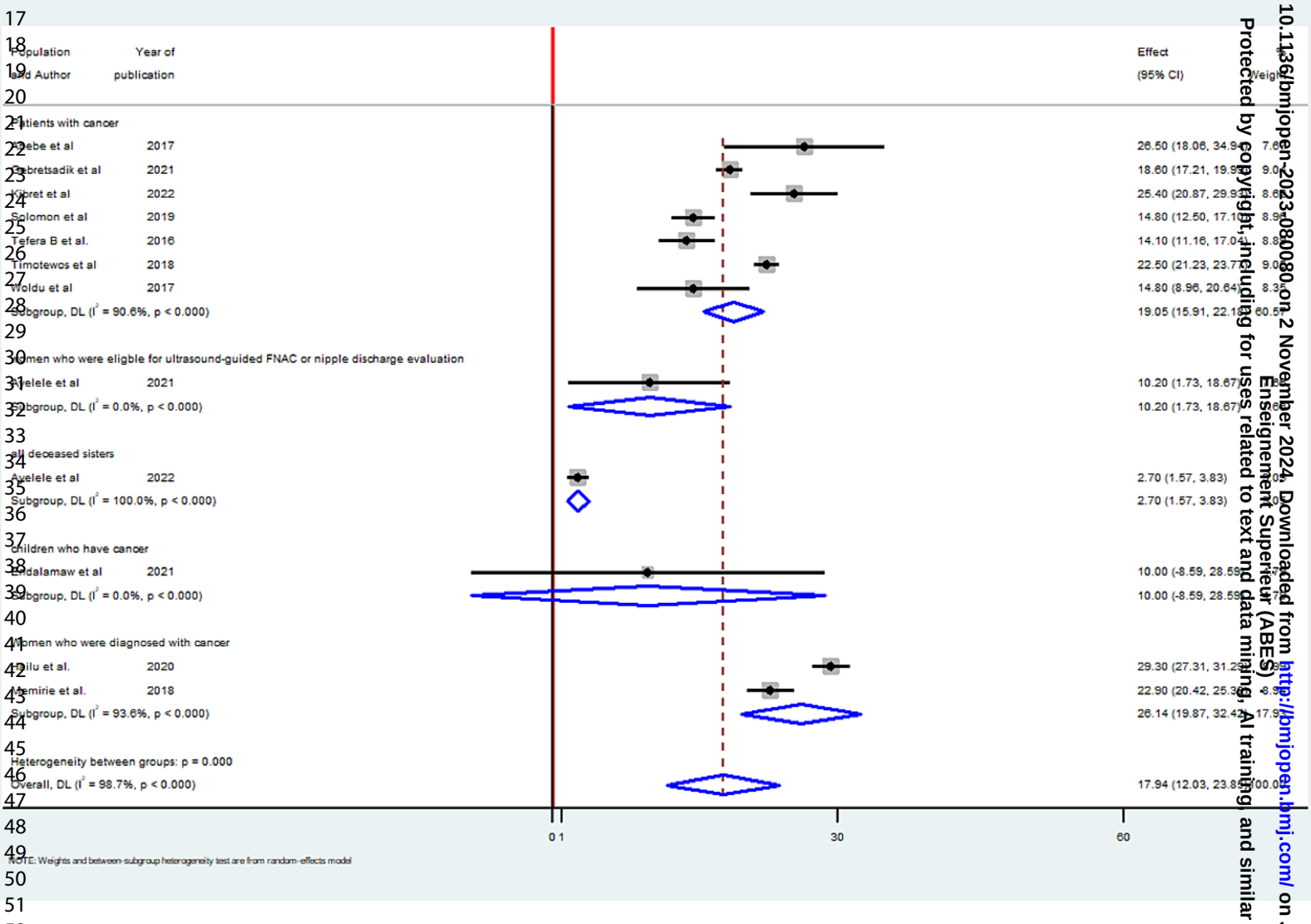
1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?

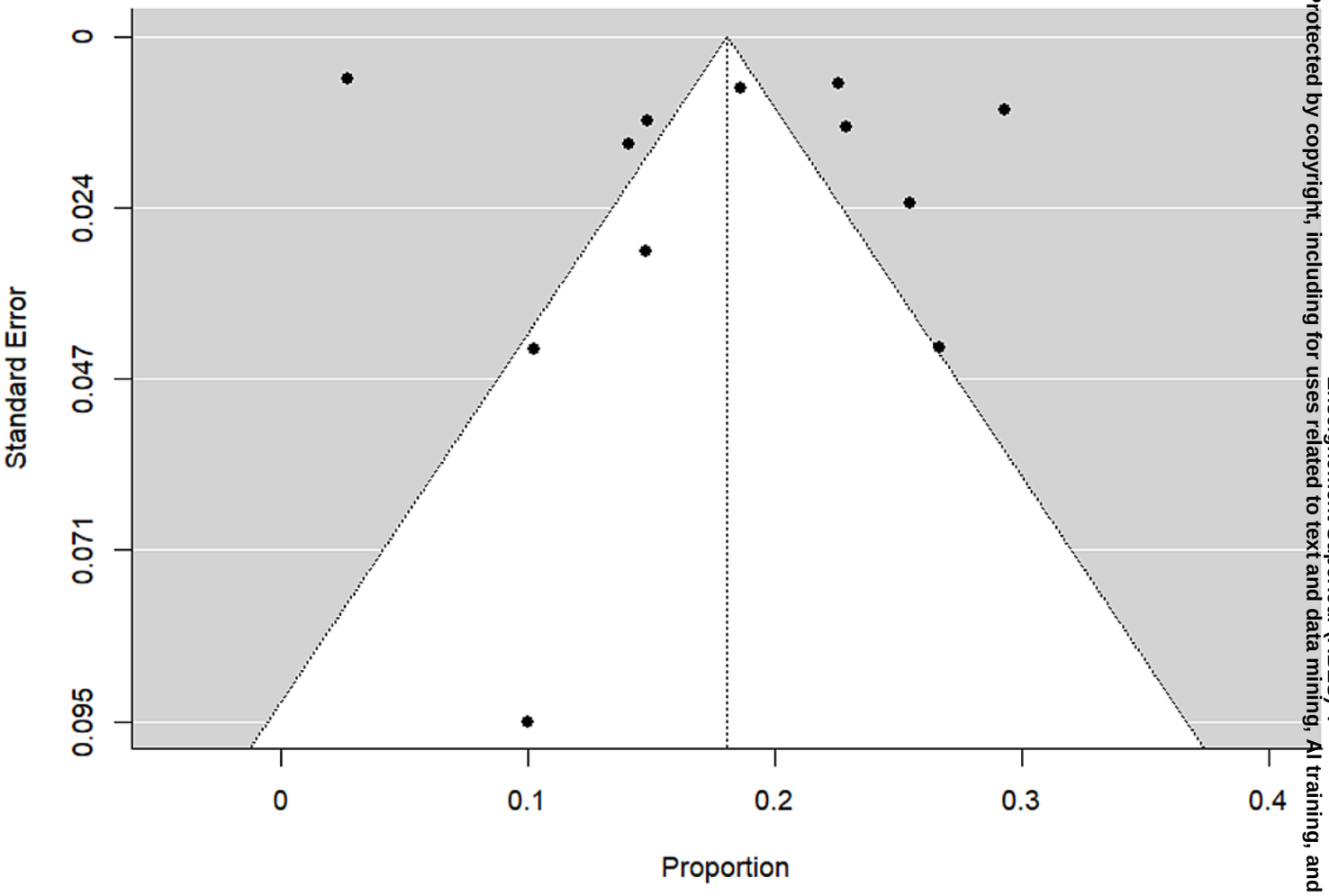
4.	Were the study subjects and the setting described in detail?
5.	Was the data analysis conducted with sufficient coverage of the identified sample?
6.	Were valid methods used for the identification of the condition?
7.	Was the condition measured in a standard, reliable way for all participants?
8.	Was there appropriate statistical analysis?
9.	Was the response rate adequate, and if not, was the low response rate managed appropriately?

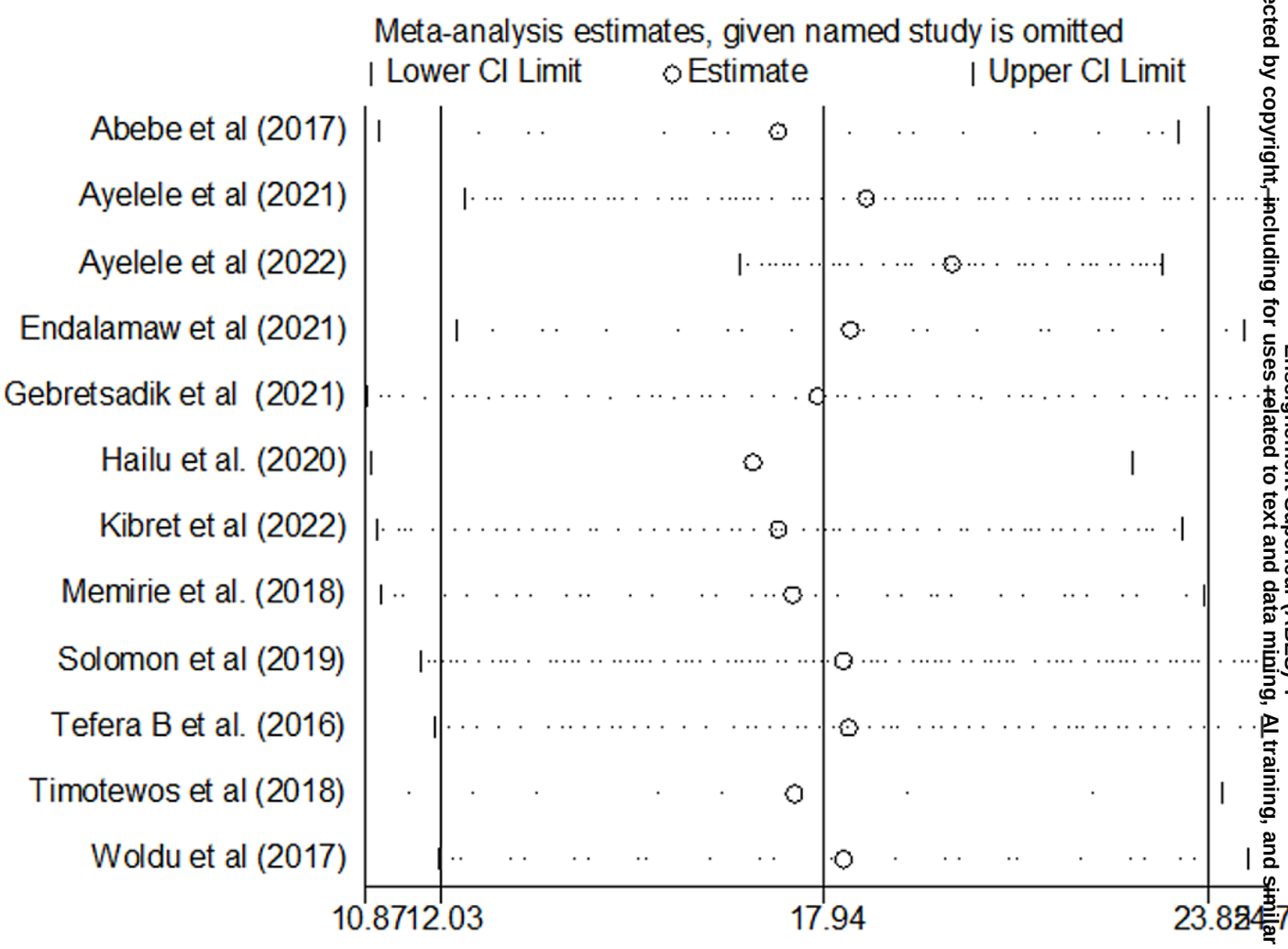
1-Yes 2- No 3-Unclear 4-Not applicable

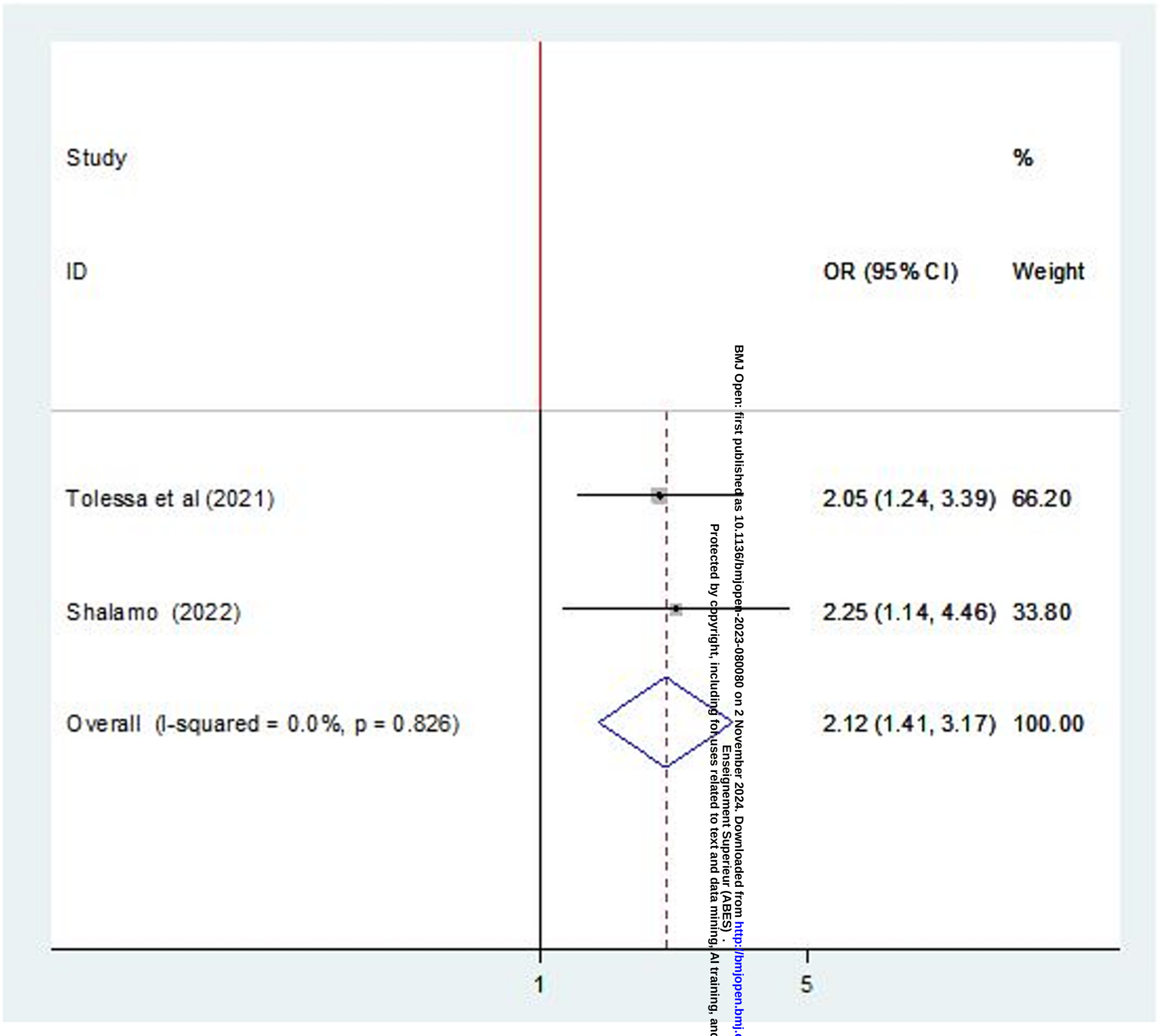


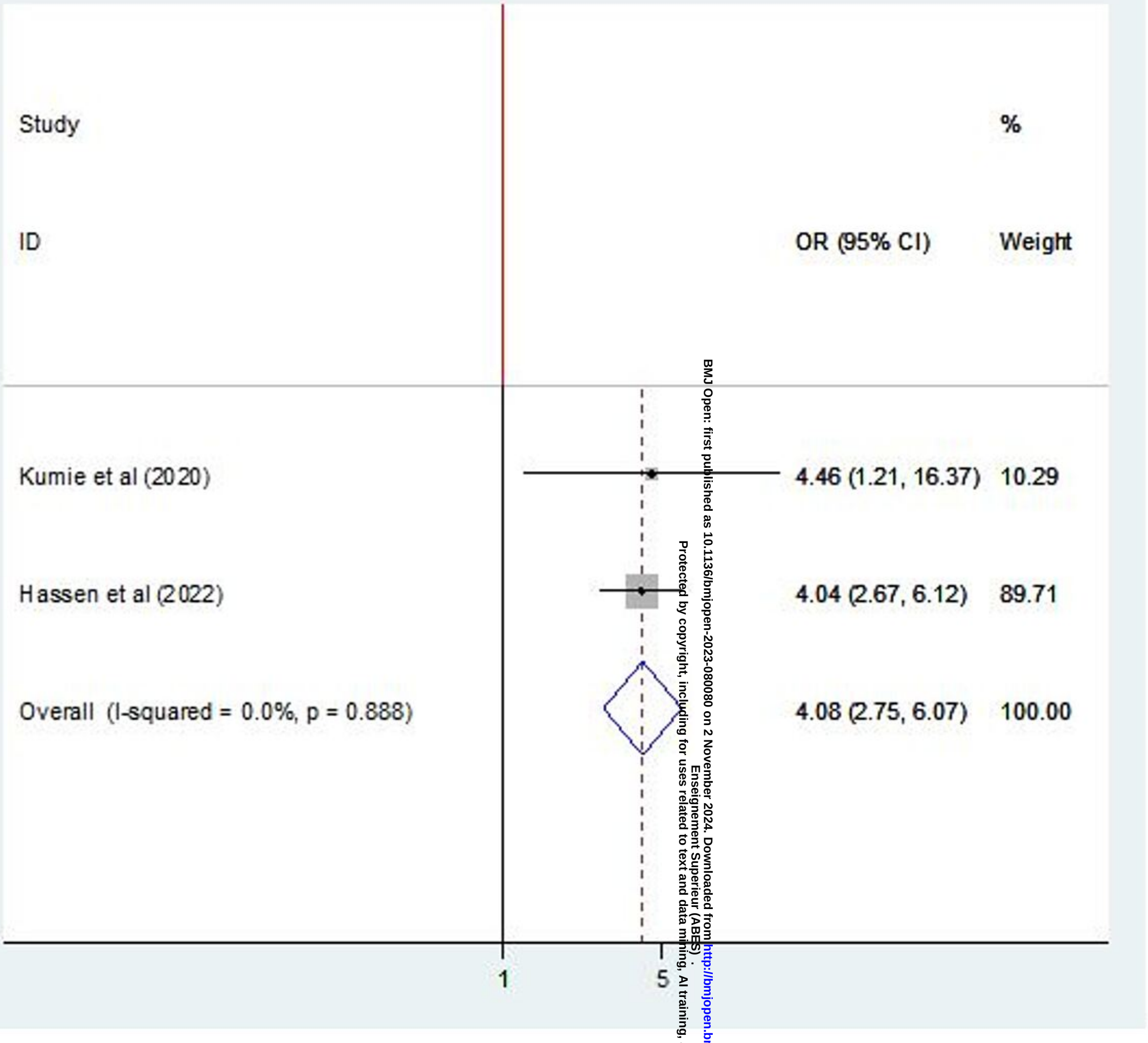


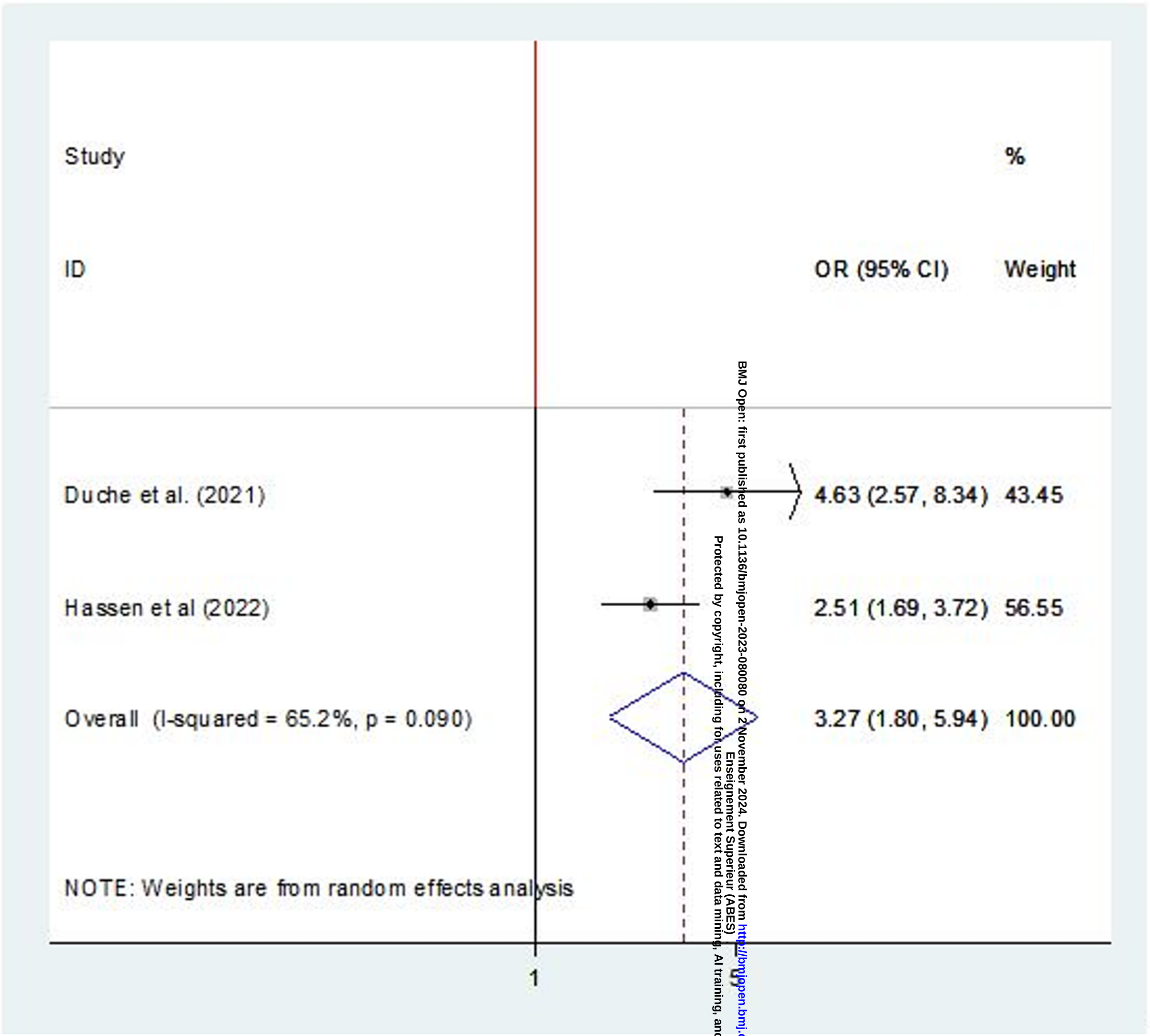


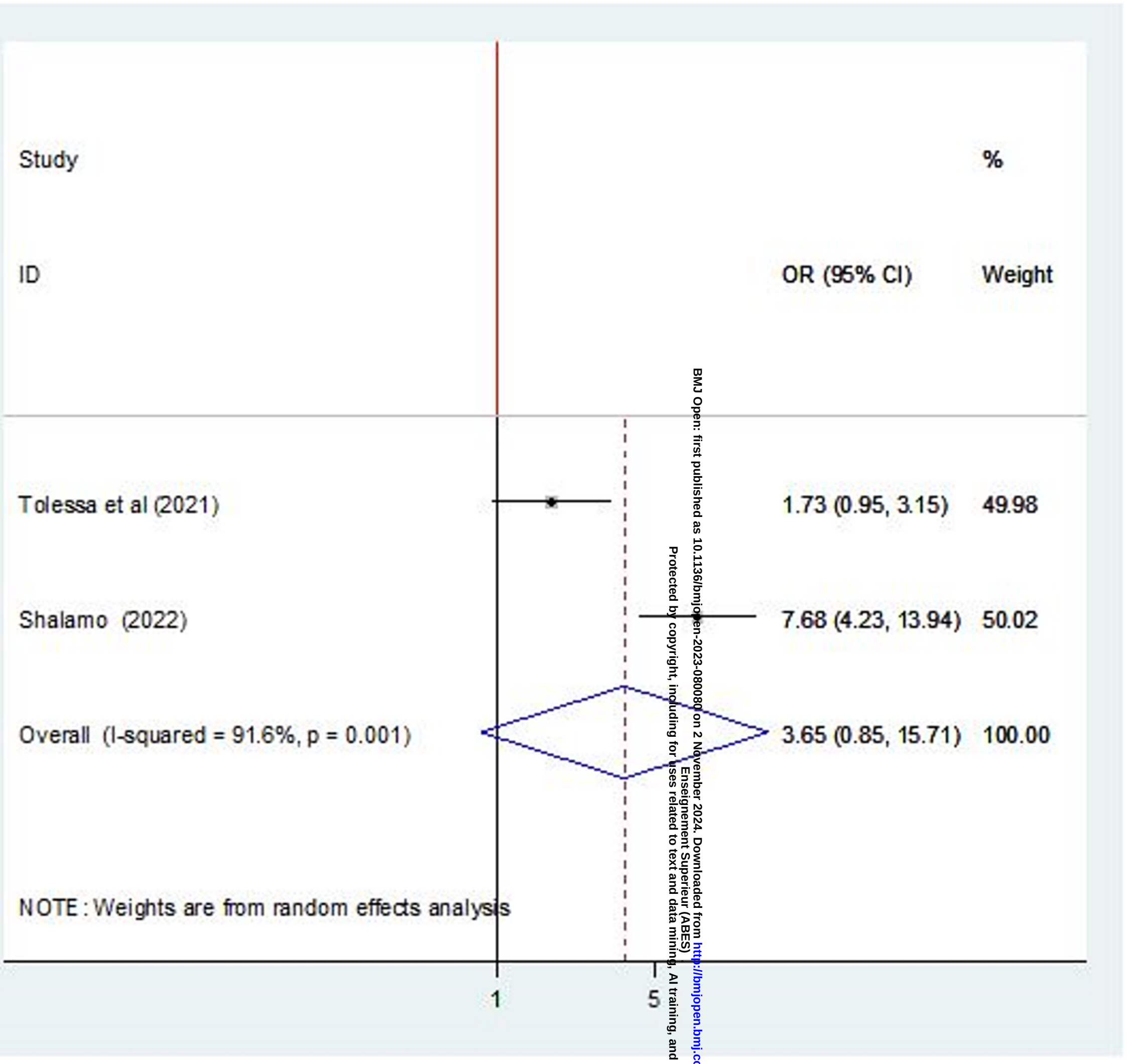


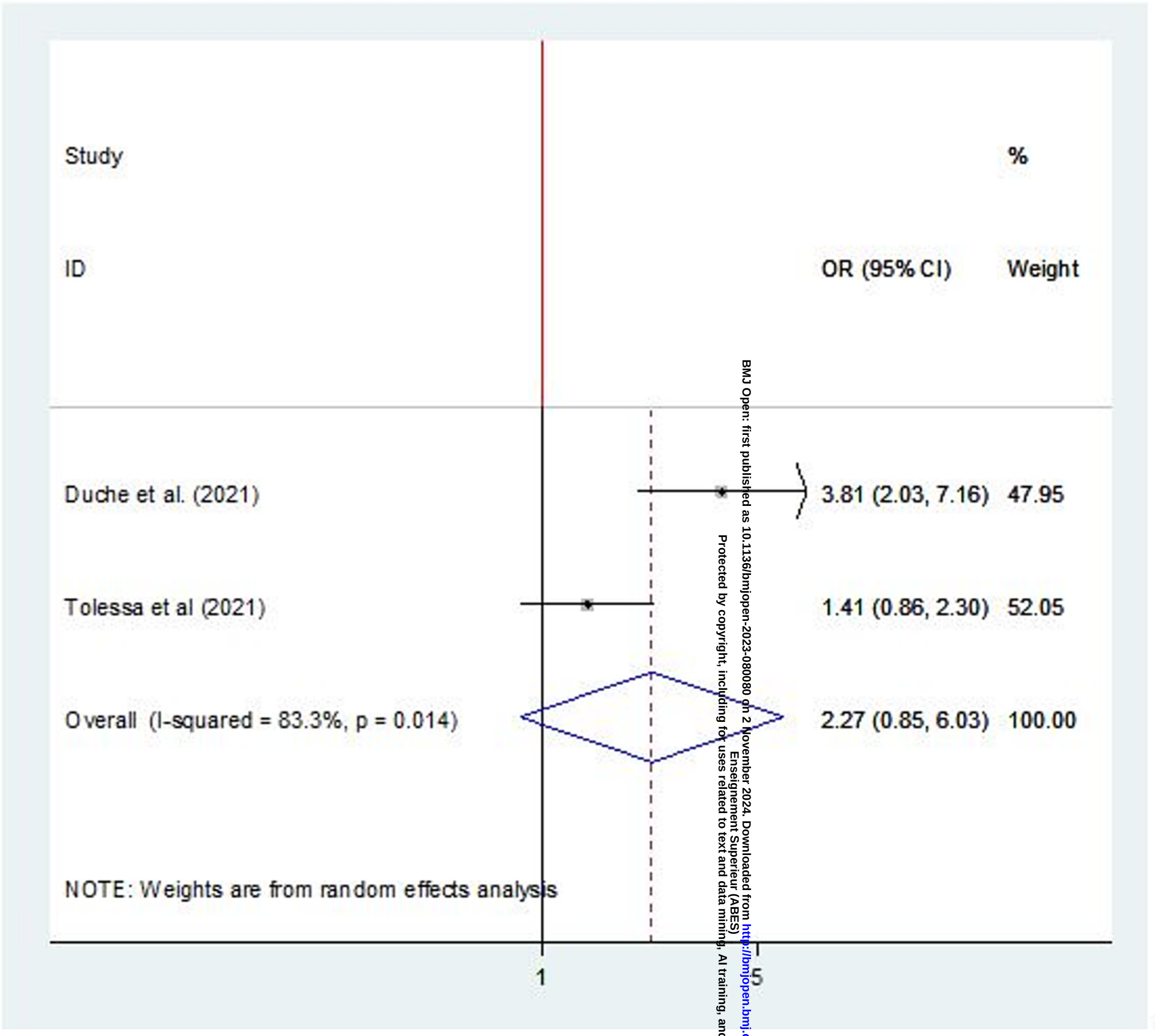


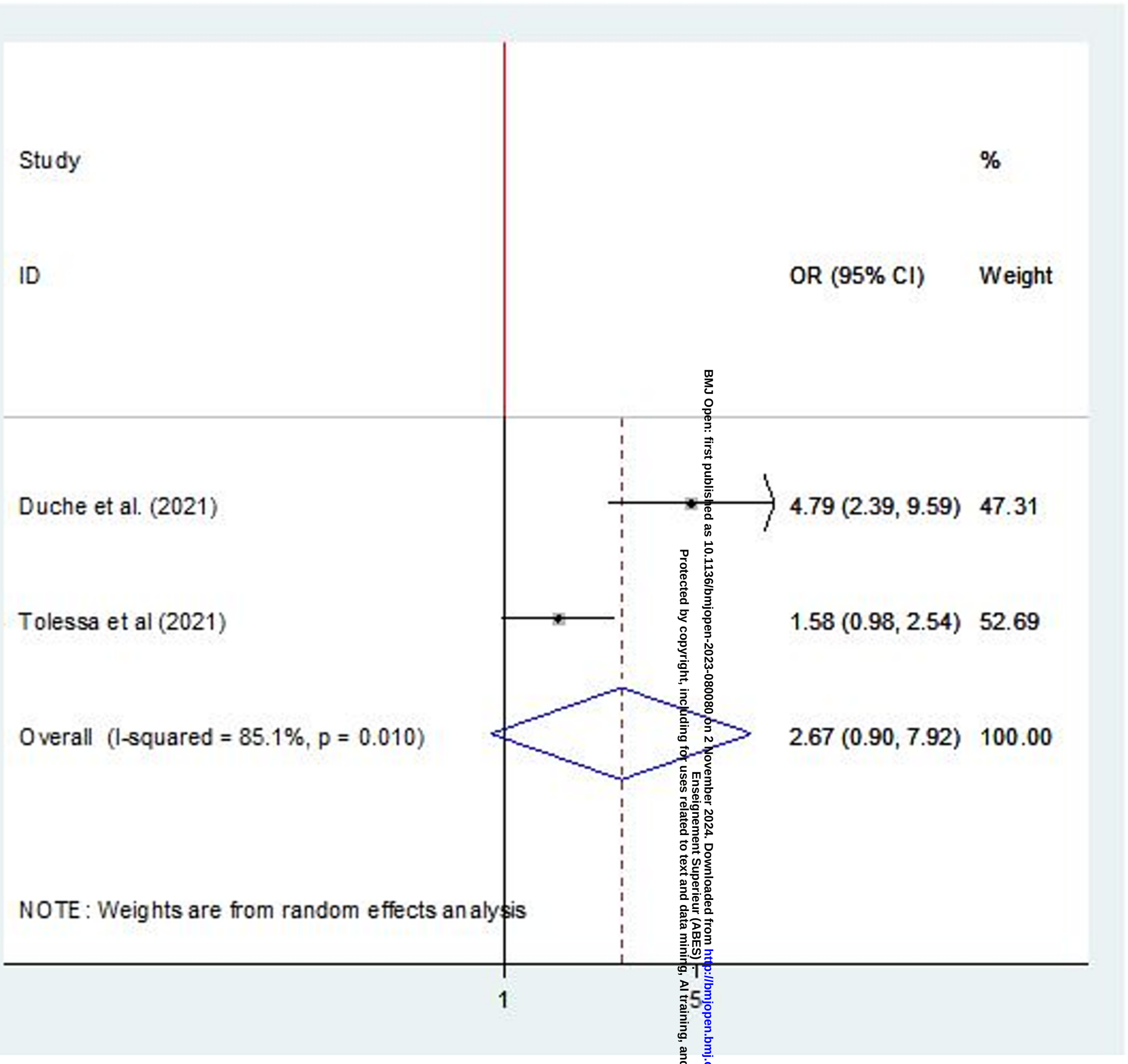












BMJ Open

Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-080080.R2
Article Type:	Original research
Date Submitted by the Author:	02-Oct-2024
Complete List of Authors:	Shama, Adisu; Wollega University, Department of Public Health, Institute of Health Sciences Terefa, Dufera; Wollega University, Public Health, Institute of Health Sciences Desisa, Adisu; Wollega University, Public Health, Institute of Health Sciences Lema, Matiyos; Wollega University, Public Health, Institute of Health Sciences cheme, Melese chego ; Wollega University, Department of Public Health, Institute of Health Sciences Geta, Edosa; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Jira Wakoya; Wollega University, Department of Public Health, Institute of Health Sciences Feyisa, Bikila Regassa; Wollega University, Department of Public Health, Institute of Health sciences; Jimma University, Department of Epidemiology, Faculty of Public Health Biru, Bayise; Wollega University, Department of Public Health, Institutes of Health Sciences; Jimma University, Department of Human Nutrition and Dietetics, Faculty of Public Health
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Health policy, Health services research, Oncology, Public health, Nutrition and metabolism
Keywords:	Risk Factors, Primary Health Care, PUBLIC HEALTH, Chronic Disease

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Breast Cancer and Its Determinants in Ethiopia: A Systematic Review and Meta-Analysis

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Word count=4648

Abstract

Objectives: Breast cancer is the leading cause of cancer morbidity and mortality among women. Still, there is a paucity of studies to know the magnitude of the problem in Ethiopia. Hence, this review was intended to pool the prevalence and identify the determinants of breast cancer in Ethiopia.

Design: A systematic review and meta-analysis was conducted.

Data sources: Databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar as well as websites of organizations were searched between 25 February to 6 March 2023.

Eligibility criteria: All observational studies in Ethiopia that reported either the magnitude and/or determinants of breast cancer regardless of publication status were included

Data extraction and synthesis: Two authors independently assessed and extracted the data. Joanna Briggs Institute (JBI) meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles. Effect estimates were done by using the random effect model. The meta-analysis results were displayed by using forest plots.

Results: Seventeen 17 articles were reviewed with 24,435 total participants. The pooled proportion of breast cancer morbidity among cancer patients was 20. 58% (95%CI: 17.25, 23.90) in Ethiopia. Consuming packed foods (POR=2.12, 95%CI:1.41, 3.17), presence of high cholesterol (POR=4.08; 95%CI: 2.75, 6.07), physical inactivity (POR=3.27; 95%CI: 1.80, 5.94), high body mass index (POR=2.27; 95%CI: 0.85, 6.03), post-menopause (POR=2.25; 95%CI: 1.63, 3.10), family history of cancer (POR=3.65; 95%CI: 0.85, 15.71), and lack of breastfeeding (POR=2.76; 95%CI: 0.90, 7.92) were the determinants of breast cancer.

Conclusions: One of five cancer patients is diagnosed with breast cancer in Ethiopia. Furthermore, more than one quarter of women with cancer suffer from breast cancer. Processed food consumption, high cholesterol in the body, lack of physical activity, high body mass index, post-menopause, family history of cancer, and lack of breastfeeding were the risk factors for

breast cancer. The use of healthy food sources such as fruits and vegetables, and homegrown varieties of crops rather than seeking processed foods would help.

PROSPERO Registration Number: CRD42023417733

Keywords: breast cancer, cancer, determinants of breast cancer, risk factors, Ethiopia

Article Summary

Strengths and limitations of this study

- The inclusion of prediction interval is a strong aspect of this study, as it is uncommon in many meta-analyses
- The review included only observational studies.
- The narrow scope of the review (only one country)
- A limited number of studies were found to pool the odds ratio for some factors.

Background

Breast cancer (BC) is a diverse disease with numerous morphological and molecular subgroups [1]. It is found to be the most common cause of cancer deaths in 11 regions of the world [2]. It is one of the most frequently diagnosed cancers and the leading cause of cancer deaths in females worldwide [3]. The recent global burden of cancer statistics (GLOBOCAN 2020) showed that BC has surpassed lung cancer and accounted for 2.3 million (11.7%) of all new cancer cases globally. It affects one in four new cancer cases of women and contributes to one in six deaths of women from cancer [4].

The cancer burden is increasing worldwide and is estimated to be 28.4 million cases by 2040, which is a 47% increase over the cancer burden in 2020. A Higher death rate occurs in developing countries than in developed (15 BC deaths in developing countries versus 12.8 in developed countries per 100,000) [4]. In Ethiopia too there were an estimated 5900 incident cases

of breast cancer with the highest age-standardized incidence rate of 12.5 per 100,000 and a death rate of 9.7 per 100,000 in 2019 [5].

Previous studies identified that the incidence of BC varies widely across the world due to differences in the level of education, economic status, environmental conditions, eating habits, lifestyle variables, and other cultural traditions. Early age at menarche, westernized lifestyles (namely delayed pregnancies/childbirth, reduced breastfeeding, sedentary lifestyles, and poor diet), and improving cancer registration and cancer detection are among the factors associated with the breast cancer in LMICs [6-9]. Lack of knowledge about the disease, improper screening programs, delayed diagnosis, and insufficient medical facilities are also contributing factors to the increasing breast cancer burden in underdeveloped countries [6, 10, 11]. Widespread urbanization, shifting patterns of reproductive and environmental risk factors, obesity, decreased physical activity, and rising life expectancy are among the major factors contributing to the steady rise in breast cancer incidence in low-income nations. Low socio-economic level, on the other hand, is related to an increased incidence of aggressive premenopausal breast cancers, as well as late-stage diagnosis and lower survival. Late menopause and early menarche are also among the risk factors that could increase the exposure of breast tissue to estrogen hormone. In contrast to this, pregnancy and appropriate breastfeeding help to reduce the risk of breast cancer [6, 10-13].

Comprehensive identification of the magnitude and determinants of breast cancer is critical for developing nations like Ethiopia, as this will aid in the development and implementation of effective breast cancer prevention initiatives. Breast cancer is not well studied in Ethiopia. Although there is one recently published review, the focus of that study was more on determinants of the problem [14]. Different pocket studies done so far may not represent the entire

picture of the determinants of breast cancer in Ethiopia. Most of them were limited to small sample sizes, limited portions of populations covered, and limited research regions. In this regard, many of the regions were not addressed in the previous studies and our study also helps to show this gap for further study, let alone intervention. It is critical to shed light on the risk factors for breast cancer. As a result, this study aimed to determine the magnitude of breast cancer and its determinants in Ethiopia.

Methods

Study design

A systematic review and meta-analysis was conducted. The protocol was registered on Prospective Registry of Systematic Reviews (PROSPERO) with registration number (CRD42023417733) and no change made to the protocol. To conduct this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [15] was used.

Searching strategy

A comprehensive search of databases like PubMed/MEDLINE, HINARI, Science Direct, and Google Scholar was used to find the relevant articles. The searches were limited to articles written using the English language. In addition to the electronic database search, grey literature was searched using Google search, and the Digital Libraries of Universities. Finally, the reference lists of the included articles for related studies were searched. To facilitate the article searching process, the keywords: [“breast” OR “mammary gland” AND “cancer” OR “tumor” OR “malignancy” OR “breast cancer” OR “breast malignancy” OR “breast tumor” AND “Risk factors” OR “Associated factors” OR “Determinants” OR “predictors” AND “Ethiopia” OR “Addis Ababa” OR “Northern Ethiopia” OR “North west Ethiopia” OR “Southern Ethiopia” OR “South Western Ethiopia” OR “Western Ethiopia” OR “East Ethiopia”] were used (Additional

file 1). Searching started on February 25, 2023, and the final date of searching was March 6, 2023.

Eligibility criteria

Inclusion criteria

To be included in this review, the study should report either the determinants of breast cancer and/or the magnitude (incidence, prevalence, number) of breast cancer morbidity.

Study setting: Studies conducted in Ethiopia (both institution-based and population-based) were part of this systematic review.

Study population: The study involved all human population (male, female, children, and adults) in Ethiopia who has been evaluated for cancer and confirmed to be cancer patients.

Exposure: those with modifiable or non-modifiable risk factors.

Study design: All observational studies (cross-sectional and case-control) that reported the magnitude of breast cancer morbidity and its determinants were evaluated to be included.

Publication status: Both published and unpublished studies were considered for inclusion.

Exclusion criteria

Articles with low quality, unclear methodologies and articles that didn't indicate the outcome of interest were excluded (Additional file 2). Excluding the studies whose full-text papers were not available after at least two personal email contacts with the corresponding authors was an exclusion criterion but all full texts were available.

Outcome variables assessment

There were two outcomes in this study: the first outcome was the magnitude of confirmed breast cancer disease/morbidity among patients with cancer diagnosis. This outcome can occur in any

population group. Therefore, the population for this outcome was a human population of any age who was evaluated for cancer disease.

Breast cancer: When the diagnosis was confirmed by pathological tests in addition to the history and physical examination [16]. Hence, the data were sought if the diagnosis of breast cancer was confirmed by pathological tests. The total number of people who had breast cancer was divided by the total number of people participating in the study and multiplied by 100 which was used to determine the proportion of breast cancer morbidity.

The second outcome/variables of this review were the determinants of breast cancer. Modifiable and non-modifiable factors were searched from the literature to pool their value together. For the variables whose categorization didn't overlap (e.g. age category), the category repeatedly reported in the studies or the established categorization was assumed to get the privilege.

Early age at menarche: this is the starting of menstruation early and mostly before the age of 12 years [17, 18].

Late menopause: it is delayed age at menopause which is after the age of 55 years in most cases [17].

Benign breast disease and breast injury: those breast diseases such as atypical ductal hyperplasia or lobular carcinoma [17].

Menopause status: this is categorized as postmenopausal if the woman has already stopped menstruation (either absence of menstruation for at least 1 year (any age) or due to bilateral oophorectomy or estrogen deprivation therapy) and premenopausal otherwise [16, 19, 20].

Body mass index (BMI): is an index which is determined based on the weight and height measurement and it is classified as high if the value is >=25kg/M^2 [16].

Age (<30, 30-49, >50) [17, 20], residence (rural vs urban), occupation (unemployed vs employed), exposure to smoking dried meat, use of industry processed foods, lack of intake of milk, fruits, and sea foods, high cholesterol (total cholesterol >200 mg/dl) [21], energy source; fuel source (wood/charcoal/kerosene/animal dung vs electricity), lack of physical activity, contraceptive use, family history of cancer, history of abortion, absence of breastfeeding, benign breast disease, and breast injury, radiation exposure, anemia and thrombocytosis were also the variables for which data were sought in the literature.

Study selection and data extraction

All the articles searched from Databases were imported into EndNote version X7, and duplicates were removed. Based on the predefined inclusion criteria, two authors (ATS and AED) independently assessed and identified papers by their titles, abstracts, and full texts. The screened items were then compiled, and any disagreement was handled by inviting and discussing with the third author (DRT). Data extraction was performed using the Joanna Briggs Institute (JBI) data extraction format [22-24]. The data extraction format included the primary author, publication year, study period, region, study area, study setting, study design, study population, publication status, sample size, response rate, and the number of cases/breast cancer. For the second outcome, data were extracted into a two-by-two table.

Quality assessment

JBI meta-analysis of statistics assessment and review instrument (MAStARI) quality appraisal tool was used to assess the quality of the articles [24]. The JBI parameters included an appropriate sampling frame, proper sampling technique, study subject and setting description, sufficient time to exposure measurement, use of valid methods for the identified conditions, a valid measurement for variables and conditions, using appropriate statistical analysis including control

of confounding. Accordingly, quality was categorized as low (total score of ≤2), moderate (total score of 3–4), or high (total score of >5) in terms of their likelihood [24]. The quality of the included studies was assessed by two independent authors (ATS and DRT). The discrepancy during the quality appraisal of the studies was resolved by the agreement of the two reviewers. Finally, papers with an overall quality score of <37.5% and/or those not reporting the outcome of interest were excluded from the systematic review and meta-analysis (Additional file 2).

Data synthesis strategy

The data were extracted into Microsoft Excel. Then it was exported to the STATA software, version 14, for further analysis. The standard errors of the included studies were calculated using the formula $SE = \sqrt{p(1-p)}/n$. The I^2 statistics and the p-values of the Cochrane Q-test were used to identify the heterogeneity problem. The p-values of the Cochrane Q test < 0.1 were used to indicate the presence of heterogeneity among the studies. The Higgins I^2 test statistics was used to calculate the percentage of total variance due to heterogeneity across the studies. Heterogeneity was declared for the I^2 value > 20% [25]. As a remedial for the heterogeneity among the studies by the test statistic, the DerSimonian-Laird's impact was evaluated using a random-effects model [26]. Moreover, the subgroup analysis by region, study design, study setting, and study population was done to identify the possible source of heterogeneity. The effect sizes were expressed as proportion and odds ratio along with a 95% confidence interval (CI). Moreover, the 95% prediction interval was computed by using the comprehensive meta-analysis to indicate the location of true proportion in comparable population [27]. The forest plots were used to display the meta-analysis results. Publication bias was investigated graphically using a funnel plot and statistically using Egger's weighted regression and/or Begg's rank correlation tests and decided

as significant at p-value < 0.05 [28, 29]. A leave-one-out sensitivity meta-analysis was used to assess the robustness of the findings.

Patient and public involvement: No patient was involved in this study.

Result

Description of included studies in the systematic review and meta-analysis

About 1644 articles were identified through database searching while 17 of them were included in this systematic review and meta-analysis (Figure 1). The total number of participants was 16055.

Studies covered the period between 2011 to 2021 [16, 18-21, 30-41], 11 were cross-sectional [21, 30-39], six were case-control [16, 18-20, 40, 41], 16 were published [16, 18, 19, 21, 30-41], 1 was unpublished [20], the majority-15 were institution-based [16, 18-21, 30-34, 36, 37, 39-41], and 2 of them were population-based studies [35, 38]. The majority of them-10 were done in Addis Ababa (AA) [16, 18, 19, 30, 33, 35, 36, 38-41], followed by southern nations, nationalities and peoples (SNNP)- three studies [20, 32, 34] and Amhara regions (3 studies) [21, 31, 37] (Table 1).

Table 1: Descriptive summary of 17 studies included in the meta-analysis to estimate breast cancer magnitude and its determinants in Ethiopia

Author (Year)	Age	Study design	Period	Sample size	Proportion (%)	Factors
Abebe et al (2017) [30]	>=18 years	Cross-sectional	June 1-31, 2015	112	26.5	
Duche et al. (2021) [16]	>15 years	Case-control	April to September 2017	226		Physical inactivity, postmenopausal, breast feeding, BMI>=25,
Endalamaw et al (2021) [31]	<15y ears	Cross-sectional	January 1, 2019 to March 30, 2019	100	10	

Gebretsadik et al (2021) [32]	No age limit	Cross-sectional	January 2013 and Jan. 2019	3002	18.6	
Hailu et al. (2020) [33]	No age limit	Cross-sectional	January 2014 and December 2018	2002	29.3	
Hassen et al (2021) [40]	>18 years	Case-control	May 2018 to June 2019	460		Anemia, thrombocytosis
Hassen et al (2022)	>18 years	Case-control	May 2018 to June 2019	460		Age between 40- 49, Early menarche, unemployment, milk intake, solid oil, use of unclean energy, Physical inactivity, breast disease
Kibret et al (2022) [34]	No age limit	Cross-sectional	Jan to Jun 2021	1,810	25.4	
Kumie et al (2020) [21]	>18 years	Cross-sectional	January 22 to May 26, 2020	182		High cholesterol
Mekonen et al (2021) [41]	>=18 years	Case-control	February to April 2020	100		
Memirie et al. (2018) [35]	>=15 years	Cross-sectional	2012 to 2015	1105	22.9	
Shalamo (2022) [20]	>15 years	Case-control	March 1 – April 30, 2022	408		Age, use of packed food, eating fruits and fish, contraceptive use, History of abortion, Radiation exposure, Breast injury, history of Cancer
Solomon et al (2019) [36]	No age limit	Cross-sectional	Jan 1, 2010 and Dece. 15, 2014	919	14.8	
Tefera B et al. (2016) [37]	N age limit	Cross-sectional	Sept 2014 to Aug 2015	540	14.1	
Timotewos et al (2018) [38]	No age limit	Cross-sectional	2012–2013	4139	22.5	

Tolessa et al (2021) [18]	>20 years	Case-control	Feb 1 to March 30, 2020	348		Early menarche, residence, dried meat, use of packed foods, Family history of Cancer, lack of breast feeding, overweight
Woldu et al (2017) [39]	No age limit	Cross-sectional	November 2015 to June 2016	142	14.8	

Prevalence of breast cancer in Ethiopia

Of the total 17 included studies, twelve (10) articles were included to pool the prevalence of breast cancer [16, 18-21, 30-41]. Accordingly, the pooled proportion of breast cancer morbidity among those patients evaluated for cancer in Ethiopia was found to be 20. 58% (95%CI: 17.25, 23.90; I^2=93.8%, *p<0.000)*. The 95% prediction interval is located between 8% and 34%. This indicates that the true magnitude in 95% of all comparable populations falls in the interval between 8% and 34% [27] (Figure 2).

Subgroup analysis

Since significant heterogeneity was found when pooling the magnitude of breast cancer morbidity, subgroup analysis was done to further check for the source of heterogeneity. As of the subgroup analysis by region, the proportion of breast cancer was found to be 21.76%; 95%CI: 17.27, 26.2 in AA, 21.64%; 95%CI: 15.02, 28.27 in SNNP, and 14%; 95%CI: 11.10, 16.90 in Amhara (Additional file 3). The result of subgroup analysis by study setting showed that the pooled magnitude of breast cancer morbidity was high; 22.58%; 95%CI: 21.45, 23.72 for population-based studies while 19.84%; 95%CI: 15.03, 24.65 for institution-based studies (Additional file 4). Furthermore, the subgroup analysis was done by the study population. Accordingly, the pooled magnitude of breast cancer is found to be 26.14%; 95%CI: 19.87, 32.42, 19.05%; 95%CI: 15.91, 22.18, and 10.0%; 95%CI: -8.59, 28.59 among women with cancer,

among general cancer patients, and among children who had cancer, respectively (Additional file 5).

Publication bias

The funnel plot appeared symmetric indicating the absence of publication bias (Additional file 6). Egger's test (*P = 0.533*) and Begg's test (*p=0.727*) also confirmed this because they both are non-significant being above *p>0.5*.

Sensitivity Analysis

A leave-one-out sensitivity analysis was done to test the reliability of the findings. According to the sensitivity analyses output, using the random-effects model was robust, and no single study affected the pooled proportion of breast cancer morbidity (Additional file 7).

Determinants of breast cancer

In individual studies, factors like young age, age at menarche, residence, occupation, exposure to smoking dried meat, use of processed foods, lack of intake of milk, fruits, and eating sea foods, high cholesterol, fuel source (wood, charcoal, kerosene, animal dung), lack of physical activity, menopause, contraceptive use, family history of cancer, history of abortion, benign breast disease and breast injury, radiation exposure, absence of breastfeeding, high body mass index (BMI), anemia and thrombocytosis were found to be the determinants of breast cancer. From these, age, age at menarche, use of processed foods, high cholesterol, lack of physical activity, menopause status, family history of cancer, absence of breastfeeding, and BMI were reported to be significant in more than one study and pooled together. However, only seven (7) factors showed statistical significance in the meta-analysis. Accordingly, those people who consume processed foods/drinks have 2.12 (POR=2.12, 95%CI: 1.41, 3.17, I^2=0.0%, *p=0.826*) times more odds of breast cancer than their counterparts (Additional file 8). This meta-analysis also revealed that the

risk of breast cancer is increased by 4 (POR=4.08; 95%CI: 2.75, 6.07, I^2=0.0%, p=*0.888*) in the presence of high cholesterol including solid oil as compared to low cholesterol (Additional file 9). Those individuals who are physically inactive had 3.27 (POR=3.27; 95%CI: 1.80, 5.94, , I^2=65.2%%, *p=0.090*) times more odds of breast cancer than their counterparts (Additional file 10). The pooled odds of breast cancer is 2.25 (POR=2.25; 95%CI: 1.63, 3.10, I^2=0.0%, *p=0.433*) times more likely in post-menopausal women than premenopausal women (Figure 3). In another way, the pooled odds of breast cancer is 3.65 (POR=3.65; 95%CI: 0.85, 15.71) times more likely for those people who have a family history of cancer as compared to those without a family history of cancer (Additional file 11). Regarding the BMI, when compared to those people having normal BMI, high BMI was associated with 2.27 (POR=2.27; 95%CI: 0.85, 6.03) times increased odds of breast cancer (Additional file 12). Those women who had no history of breastfeeding have 2.76 (POR=2.76; 95%CI: 0.90, 7.92) times more odds of breast cancer compared to their counterparts (Additional file 13).

DISCUSSION

In total, 24 articles were assessed for inclusion and seven (7) were excluded from this review. The reason for exclusion was mainly due to the lack of an intended outcome report and non-similarity of study population. Here are the citations of excluded studies [42-48]. Data of 17 articles were extracted 10 for prevalence and 7 for determinants study. Accordingly, the pooled proportion of breast cancer morbidity in Ethiopia is found to be 20. 58% (95%CI: 17.25, 23.90). Although the result seems low when compared with the one in Iranian women (23.6%) [49], it is still high when compared to the age-standardized incidence rate of breast cancer in Ethiopia (12.1 per 100,000 populations) [5]. The observed variation could be due to a difference in the denominator. As shown in the subgroup analysis, the proportion of breast cancer morbidity

varies in different situations. For example, the proportion of pooled breast cancer morbidity is higher-26.14% in cancer-diagnosed women which is even higher than the one in Iranian women [49] and 19.05% among general cancer patients. This shows that breast cancer varies depending on the study population. In another way, this finding is low as compared to the breast cancer cases (25%) among women newly diagnosed with cancers in the GLOBOCAN 2012 and 2018 study [50, 51] and the study in the United States of America (USA) (29%) [52]. The difference in socio-economic and demographic conditions might be the possible reason for this variation. Developed countries have improved cancer detection, registration, and reporting than Ethiopia which could make a difference between countries regarding breast cancer proportions. Although the prevalence of breast cancer morbidity seems low when compared to the developed settings, this result is still high in comparison with the previous estimation. This alerts us that breast cancer deserves attention, especially in women. Because the subgroup analysis indicated a high prevalence of breast cancer disease among women who suffered from different forms of cancer.

In this systematic review and meta-analysis, factors such as the use of processed foods/drinks, high cholesterol, lack of physical activity, post-menopausal status, family history of cancer, absence of breastfeeding, and high BMI including obesity were reported as risk factors for breast cancer. Accordingly, a family history of cancer including breast cancer was reported as a risk factor for breast cancer (pooled OR=3.65; 95%CI: 0.85, 15.71). This finding is consistent with previous studies conducted in Ethiopia [14], Iran [53, 54], the United kingdom [55], China [56], and Malaysia [57]. This might be due to the presence of some inherited defect that will facilitate the development of the disease. Given that biological exposure is non-modifiable, screening and follow-up of the breast condition would help to get timely treatment that can halt the bad consequences of the disease [14].

This study also revealed non-breastfeeding as a risk factor for breast cancer which is in-line with the finding of previous systematic review [14, 58], studies done in China [56], Iran [53], USA [59, 60] where studies conducted stated that breastfeeding minimizes the risk of breast cancer. The possible reason could be because of the hormonal effect of breastfeeding for the protection or reduction of breast cancer. Both the current study and previous studies revealed the protective effect of breastfeeding for breast cancer. The possible mechanism for the observed protective probability of breast cancer in this study might be attributed to the differentiation induced to the breast lobe by lactation that might transform cancer-prone stem cell 1 to refractive stem cell 2 [61]. There might also be less exposure of breast tissues to hormones as breastfeeding inhibits ovulation and the hormones from the ovulation cycles [62]. The result is a good indication to promote breastfeeding which has dual benefits for both the mother and child.

This current finding also showed that high BMI is the risk factor for breast cancer in which people with high BMI were about 2.27 times more likely to develop breast cancer than their counterparts. This finding is similar to the previous study [57, 60, 63-66], and studies in Iran [53, 54] but contrasts with the finding of the study conducted in Northern California [67]. High BMI including obesity is found to be a risk factor for breast cancer in postmenopausal women [68-70]. Increased body fat might increase the level of circulating estrogens and decrease the levels of sex hormone-binding globulin [71]. Besides, the inflammation that accompanies obesity might also contribute to breast cancer development [72].

In this study, it was also found that lack of physical activity is a risk factor for breast cancer and it was reported by previous studies [53, 73, 74]. The possible explanation for the association between breast cancer and lack of physical activity might be that physical inactivity could increase the probability of fat accumulation in the body as some studies [53, 54] found that obesity is a risk factor

for breast cancer. Therefore, adherence to regular physical exercise and healthy foods would help to control weight and reduce body fat given that both overweight and physical inactivity are the two modifiable and related risk factors for breast cancer.

This study revealed that the use of processed food and/or drink was a risk factor for breast cancer. This is consistent with the finding of the individual studies conducted in Latin America [75], Iran [76] and other reviews [64, 77]. According to this study, consumption of packed food/drinks was found to be the risk factor for breast cancer. This result is in line with the study findings of other countries which imply that a decrease in the intake of packed or ultra-processed food or drink should be encouraged to reduce the incidence of breast cancer among women [75 64, 76, 77]. The possible reason for this association might be due to the presence of different additives to processed foods during the processes that could initiate cancer development [78]. Other reasons might be that packed foods are rich in energy/added sugar, saturated and trans-fatty acids, and salt and have low content in fibers and vitamins that would increase the risk of breast cancer [79].

In this review, a positive association between high cholesterol level and breast cancer was found. However, studies are contradicting in this regard. Some studies found high cholesterol as a risk factor [80] while some found it as a protective factor [81, 82]. Those studies that found the protective effect of high cholesterol explained it as "statin-the cholesterol-lowering medication might reduce the breast cancer risk too" [83, 84]. In this study, the total cholesterol including the use of hard oil was used as high cholesterol and was found to be associated with increased breast cancer risk. The possible reason for the positive association between high cholesterol and breast cancer is that cholesterol is the precursor for estrogen which is the cause of breast cancer [85, 86]. Women with high body fat might have an increased risk of breast cancer though their BMI is normal.

Moreover, the current study revealed that post-menopausal status is one of the risk factors for breast cancer which is consistent with the previous studies [14, 87] where it was indicated as a breast cancer risk is higher in postmenopausal than premenopausal women. However, this result seems to contradict the finding in another meta-analysis in which premenopausal women had about 43% higher risk of breast cancer than postmenopausal women of the same age. In another way, that study added that postmenopausal women with high body fat had an increased risk of breast cancer than premenopausal women [70]. Hence, the association between the increased possibility of breast cancer and postmenopausal status in this study might be justified as those postmenopausal women could have high body fat as well. Another possible explanation is that post-menopausal women in this study might have reached menopause at late age commonly after 50 years as late menopause is found to be a risk factor in another study [56]. Because extended menstruation could expose the breast tissue to increased exposure to hormones like estrogen [64]. Besides, the use of postmenopausal hormone replacement therapy couldn't be ruled out from the possible reasons as this might increase the breast cancer risk in postmenopausal women [58]. This implies that the hormonal change in pre-and post-menopausal contributes to a risk or solution for breast cancer among women. Although there are differences in explanatory models regarding the postmenopausal stage, it is imperative to care for oneself because age extremes are mostly known to have a high risk for disease including chronic conditions like breast cancer [17].

This study has its own implications for research, practice, and policy. The practical implication is that a program on non-communicable diseases like breast cancer in the country should be strengthened to combat the problem given the prevalence in this study is high. On top of that, a protective effect of breastfeeding found in this study implies that programs that address breastfeeding promotion should incorporate the protective role of breastfeeding in their

promotion activities. This research also alerts future research to investigate factors like residence, occupation, smoke-dried meat consumption, unclean energy sources, and the protective effects of foods like milk, seafood, and fruits including their risk and protective mechanisms. The issue of postmenopausal status is still non-conclusive in the literature. It deserves further analysis to put under its appropriate classification (risk or protective factor for breast cancer). Moreover, researchers and policy-makers should work together on how to intervene and prevent the consumption of globalized and commercially processed foods as they are contributing to the breast cancer burden. The infection prevention-dominated policy of the country should be revisited to incorporate the prevention of non-communicable diseases. Although the disease is partly due to non-modifiable risk factors, the presence of modifiable factors calls for all concerned bodies to focus on the disease to prevent the disease, diagnose and treat timely, and minimize the risk of death and economic impact. This may include the initiation and strengthening of breast cancer screening in the country.

The strengths of this study are that it is the first systematic review and meta-analysis on breast cancer in Ethiopia which pooled the prevalence of breast cancer. Next, it shares the strengths of systematic review and meta-analysis as the evidence generated from this systematic review and meta-analysis might be more representative of the country's situation than pocket studies. Thirdly, the study estimated the prediction interval for the result obtained which is uncommon in many previous meta-analyses. However, the review was not free of limitations. The first limitation could be the narrow scope of the review in which a single country is covered. Nonetheless, it can still serve the studied country to consider in their policy decisions. The other drawback was that some of the regions had no primary studies regarding breast cancer and were not included in this review. The majority of the studies were done in Addis Ababa city which is

the country's capital. The other is that the evidence pooled together was merely from observational studies (cross-sectional and case-control studies).

Conclusion

In Ethiopia, out of five patients evaluated for cancer disease, one received a diagnosis of breast cancer. Additionally, more than a quarter of cancer disease in women is breast cancer, according to this study. In another way, the use of processed foods, high BMI, high cholesterol, physical inactivity, post-menopausal status, family history of cancer, and lack of breastfeeding were the facilitators of breast cancer development.

Post-menopausal women, in particular, late menopause women should stick to the lifestyle modifications that help to control body fat. It would be better if the people of Ethiopia use food sources such as fruits and vegetables, homegrown varieties of crops, and the like rather than seeking to adopt the Westernized food culture (processed foods). It is highly recommended to practice regular physical exercise to regulate body weight, and body fat and then to protect against the risk of breast cancer. Appropriate breastfeeding should be practiced for at least 2 years after delivery as this contributes to the minimization of breast cancer risk. Regular breast examination should be practiced to detect and control the problem timely.

List of abbreviations

AA-Addis Ababa, BC-breast cancer, BMI- Body mass index, GLOBOCAN-Global burden of cancer, JBI-Joanna Briggs Institute, LMICs- low- and middle-income countries, OPD- outpatient department, POR-pooled odds ratio, SNNP- Southern nations, nationalities and peoples, USA-United states of America

Ethics approval and consent to participate

Ethical approval was not applicable because the review of previous studies was done.

Consent for publication

N/A

Availability of data and materials

The data extracted from included studies and analyzed in this review are available from the corresponding author based on the reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was obtained to conduct this systematic review and meta-analysis

Authors Contributions

ATS conceptualized the study, designed the methods, wrote the protocol, searched, screened critically evaluated the studies, extracted the data, analyzed the data, and wrote the manuscript. DRT was involved in the critical appraisal of the studies, and data extraction and wrote the first draft of the result. AED searched, screened, and critically appraised the studies, extracted the data, and interpreted the result. ML searched and screened the studies, drafted the methods and wrote the introduction for the study. MCC and ETG extracted the data and prepared the manuscript. JWF, BRF, and BB designed the methods, searched the studies, and extracted and analyzed the data. ATS is the guarantor.

Acknowledgements

Not applicable

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Additional files

Additional file 1: Search strategies

Additional file 2: Critical appraisal of full texts downloaded for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

Additional file 3: subgroup analysis of the pooled proportion of breast cancer by regions in Ethiopia

Additional file 4: subgroup analysis of the pooled proportion of breast cancer by study setting in Ethiopia

Additional file 5: subgroup analysis of the pooled proportion of breast cancer by study population in Ethiopia

Additional file 6: Funnel plot with 95% confidence limits of the pooled proportion of breast cancer in Ethiopia

Additional file 7: Sensitivity analysis of the level of breast cancer: Prevalence and 95% confidence interval of breast cancer in Ethiopia

Additional file 8: The pooled odds ratio showing the association between processed food and breast cancer in Ethiopia

Additional file 9: The pooled odds ratio of the association between cholesterol level and breast cancer in Ethiopia

Additional file 10: The pooled odds ratio showing the association between physical activity and breast cancer in Ethiopia

Additional file 11: The pooled odds ratio showing the association between family history of cancer and breast cancer in Ethiopia

Additional file 12: The pooled odds ratio of the association between BMI and breast cancer in Ethiopia

Additional file 13: The pooled odds ratio of the association between breast feeding/lack of live birth and breast cancer in Ethiopia

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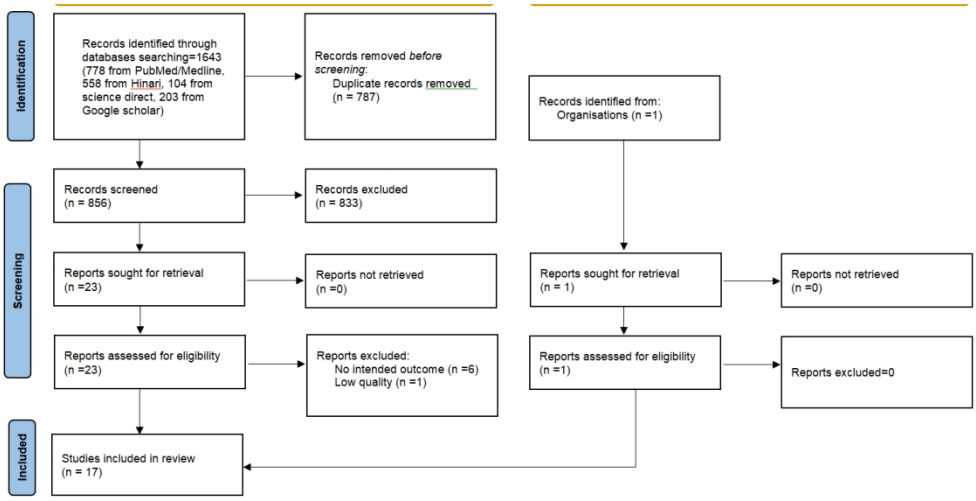

Figure 1: Flow chart of studies selection for the systematic review and meta-analysis of breast cancer and its determinants in Ethiopia

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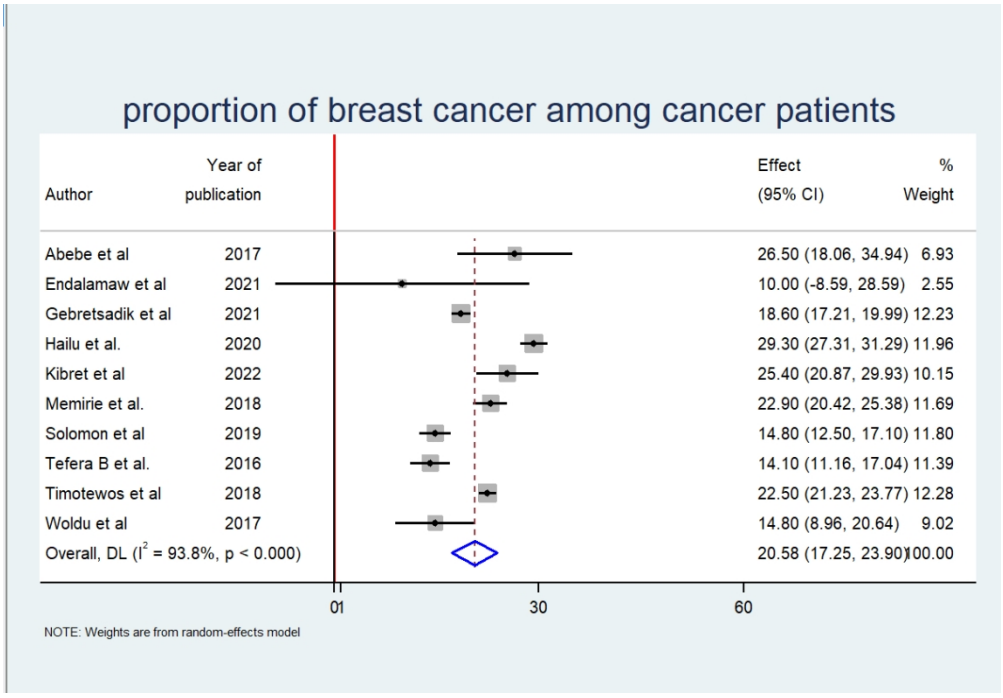


Figure 2: Forest plot of the pooled proportion of breast cancer in Ethiopia

102x70mm (300 x 300 DPI)

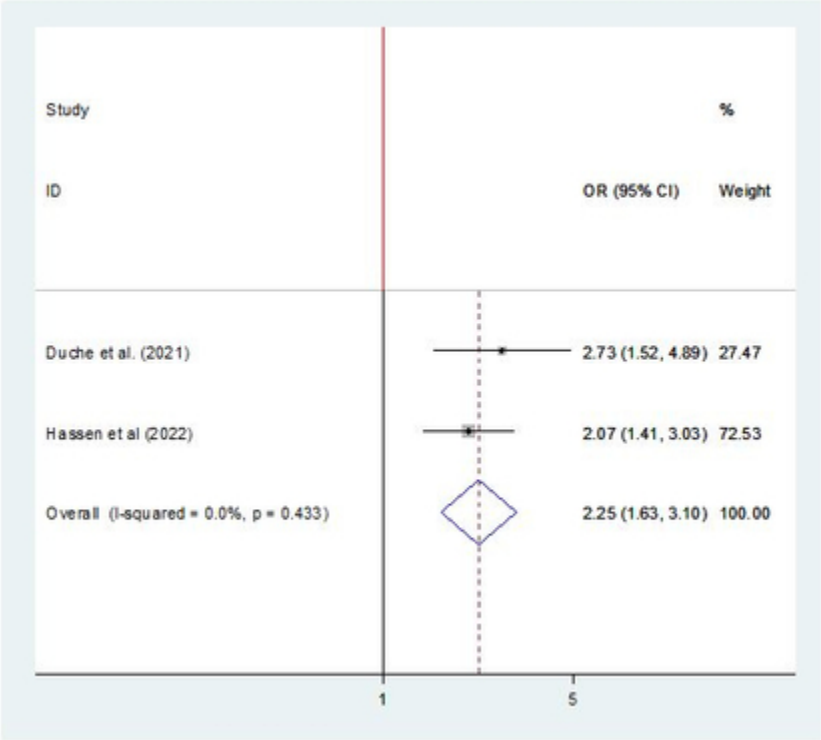


Figure 3: The pooled odds ratio showing the association between menopausal status and breast cancer in Ethiopia

37x33mm (300 x 300 DPI)

Search strategy

PubMed:

["breast" OR "mammary gland"]

AND

["Cancer" OR "tumor" OR "malignancy" OR "breast cancer" OR "breast malignancy" OR "breast tumor"]

AND

["Risk factors" OR "Associated factors" OR "Determinants" OR "predictors"]

AND

["Ethiopia" OR "Addis Ababa" OR "Northern Ethiopia" OR "North west Ethiopia" OR "Southern Ethiopia" OR "South Western Ethiopia" OR "Western Ethiopia" OR "East Ethiopia"]

HINARI:

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Determinants OR Associated factors OR Predictors]

AND

[Ethiopia]

Science Direct:

[Breast cancer] OR breast malignancy OR Breast carcinoma]

AND

[Determinants OR Associated factors]

Google and Google Scholar:

[Prevalence OR Magnitude OR Proportion]

AND

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Associated factors OR Determinants OR Risk factors OR Predictors OR factors OR Causes]

AND

[Ethiopia]

University websites:

[Breast cancer OR breast malignancy OR Breast carcinoma]

AND

[Associated factors of breast cancer OR Risk factors of breast cancer OR Predictors of breast cancer OR factors OR Causes of breast cancer]

AND

Ethiopia OR Western Ethiopia OR Central Ethiopia OR Addis Ababa OR northern Ethiopia OR Eastern Ethiopia OR Southern Ethiopia]

Reviewers: Adisu Tafari Shama and Dufera Rikitu Terefa, Date: 15-20/3/2023

JBI critical appraisal checklist for analytical cross-sectional studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total score	%	Overall appraisal	Reason for exclusion
2.	Abebe (2017)	2	2	1	3	2	2	1	1	3	37.5	Include	
3.	Ayele (2021)	2	1	3	3	3	2	1	1	3	37.5	Exclude	Different Population
4.	Ayele (2022)	1	1	1	1	2	2	2	1	5	62.5	Exclude	Different Population
6.	Endalamaw (2021)	1	1	1	1	2	2	1	1	6	75	Include	
7.	Gebretsadik (2021)	2	2	1	1	2	2	1	1	4	50	Include	
8.	Hailu (2020)	2	1	1	1	2	2	1	1	5	62.5	Include	
11.	Kibret (2022)	1	1	3	3	2	2	1	3	3	37.5	Include	
12.	Kumie (2020)	1	1	1	1	2	2	1	1	6	75	Include	
14.	Memirie (2018)	2	1	1	3	2	2	1	1	4	50	Include	
15.	Schwartz (2020)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
16.	Schwartz (2021)	2	2	3	1	2	2	1	3	2	25	Exclude	Outcome of interest not reported
18.	Solomon (2019)	1	1	3	3	2	1	1	1	5	62.5	Include	
19	Tefera B (2016)	2	1	3	1	2	2	1	3	3	37.5	Include	
21	Tesfaw (2018)	1	1	1	2	2	2	1	1	5	62.5	Exclude	No outcome of interest reported
24.	Woldu (2017)	1	2	1	3	2	2	3	1	3	37.5	Include	

Q1. Were the criteria for inclusion in the sample clearly defined?
Q2. Were the study subjects and the setting described in detail?
Q3. Was the exposure measured in a valid and reliable way?
Q4. Were objective, standard criteria used for measurement of the condition?

Q5. Were confounding factors identified?
Q6. Were strategies to deal with confounding factors stated?
Q7. Were the outcomes measured in a valid and reliable way?
Q8. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Case-control studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Total score	%	Overall appraisal	Reason for exclusion
5.	Duche (2021)	1	2	1	1	1	2	3	1	3	1	6	60	Include	
9.	Hassen (2021)	1	1	1	1	1	2	2	1	2	1	7	70	include	
10.	Hassen (2022)	1	3	3	3	1	1	1	1	2	1	6	60	include	
13.	Mekonen (2021)	1	3	1	1	1	2	1	1	3	1	7	70	include	
17.	Shalamo (2022)	1	2	2	1	1	2	1	1	3	1	6	60	include	
23.	Tolessa (2021)	1	2	1	1	1	1	1	1	3	1	8	80	include	

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

JBI critical appraisal checklist for Cohort studies

Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total score	%	Overall appraisal	Reason for exclusion
20	Tekle (2019)	4	4	3	2	2	3	1	2	2	1	1	3	27	Exclude	Outcome of interest not reported

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10. Were strategies to address incomplete follow up utilized?
11. Was appropriate statistical analysis used?

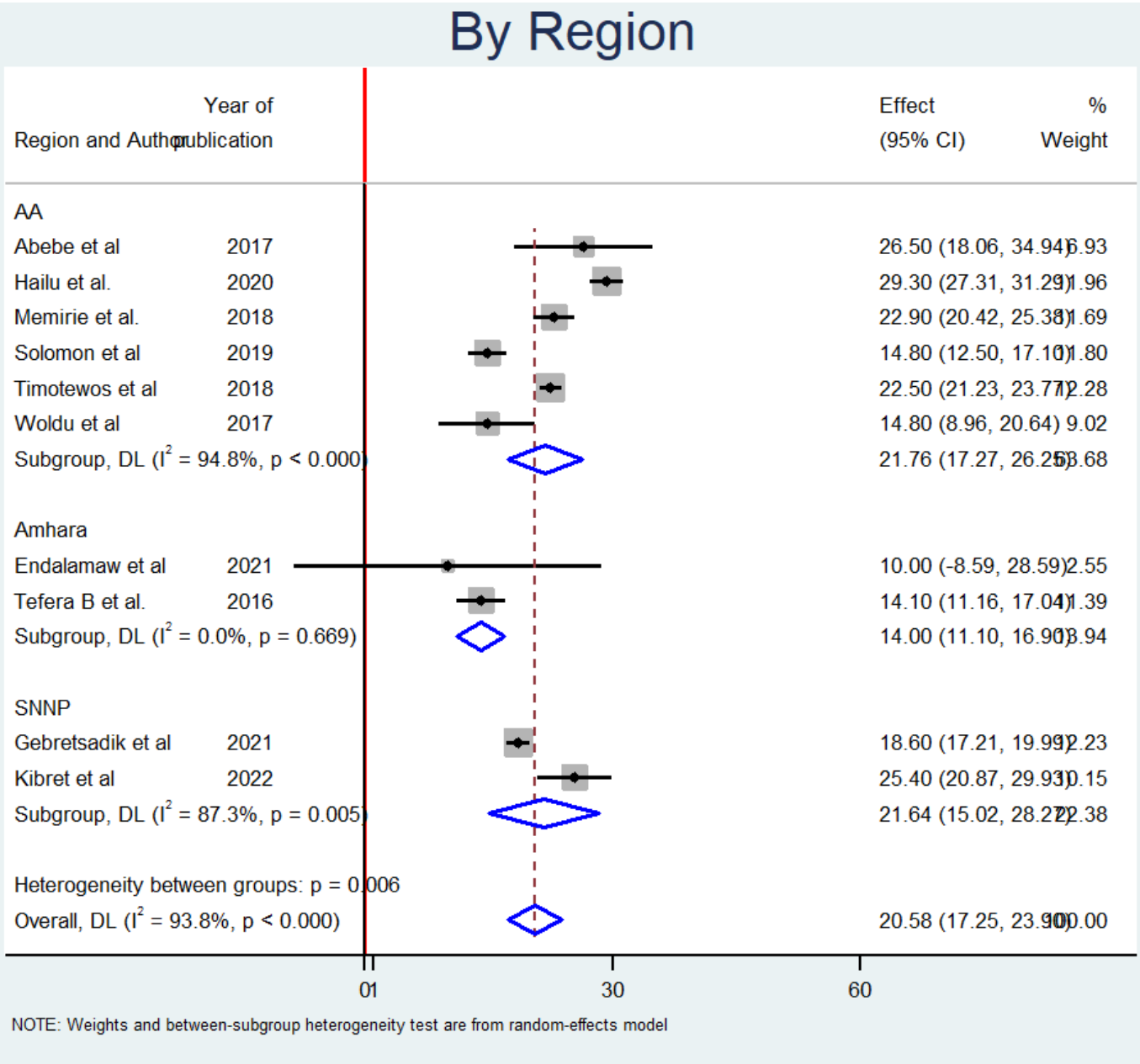
JBI CRITICAL APPRAISAL CHECKLIST FOR STUDIES REPORTING PREVALENCE DATA

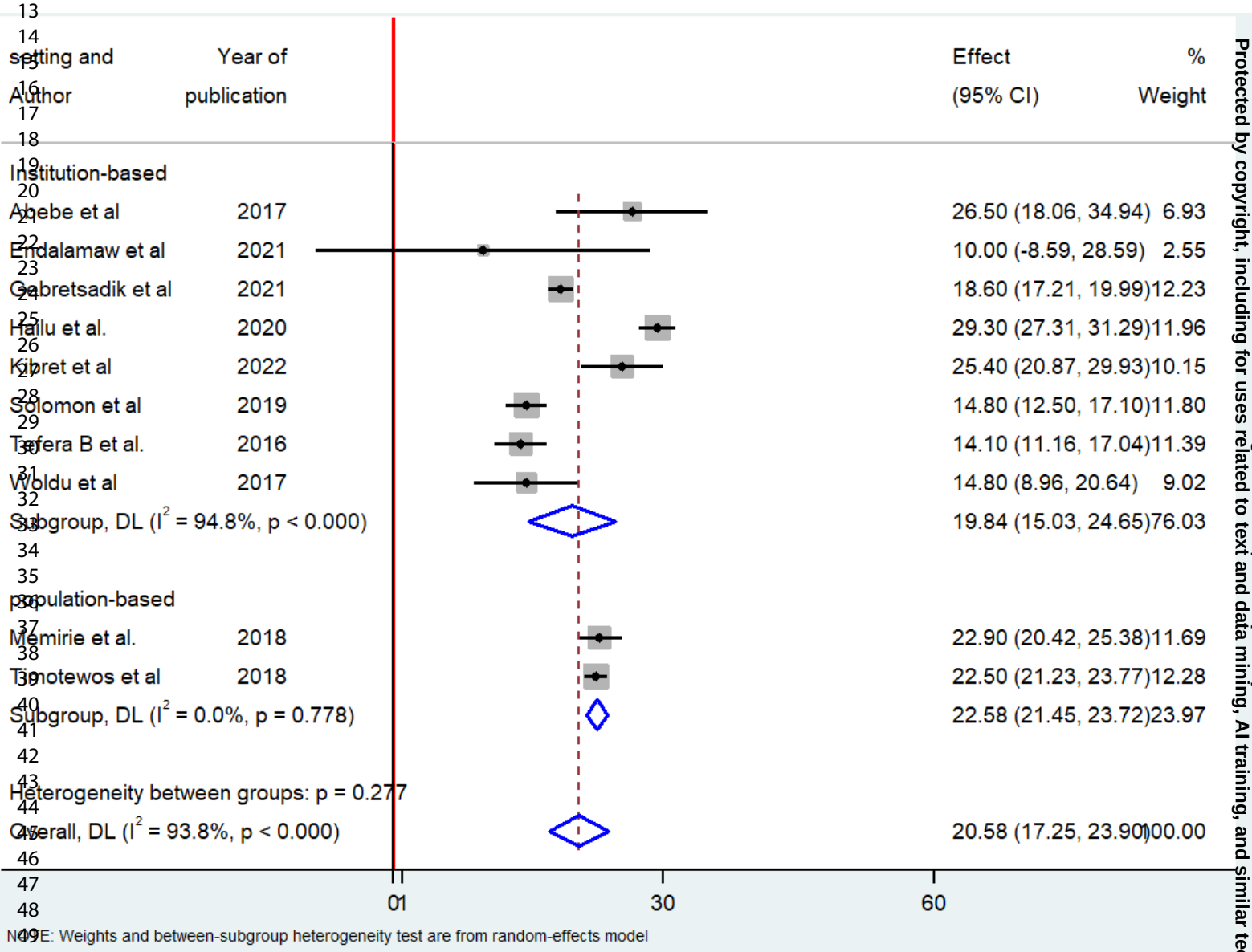
Record no.	Author (year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total score	%	Overall appraisal	Reason for exclusion
1	Abate (2016)	3	3	3	1	1	3	1	3	3	3	33	exclude	The outcome of interest is not shown in this study. Besides, sample size, sampling techniques and analysis methods were not clearly described.
22	Timotewos (2018)	3	3	3	1	1	1	1	1	3	5	77	Include	

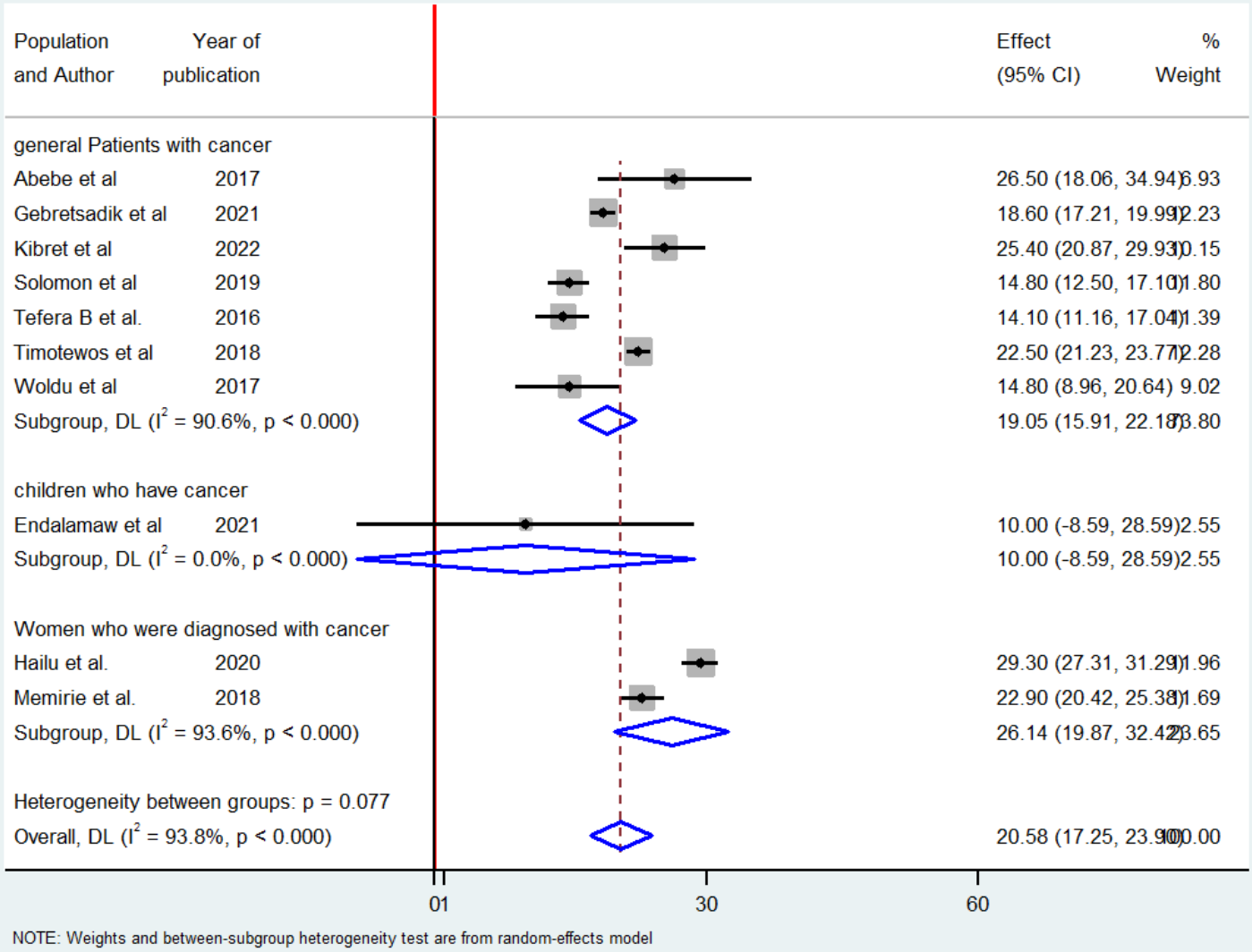
1. Was the sample frame appropriate to address the target population?
2. Were study participants sampled in an appropriate way?
3. Was the sample size adequate?

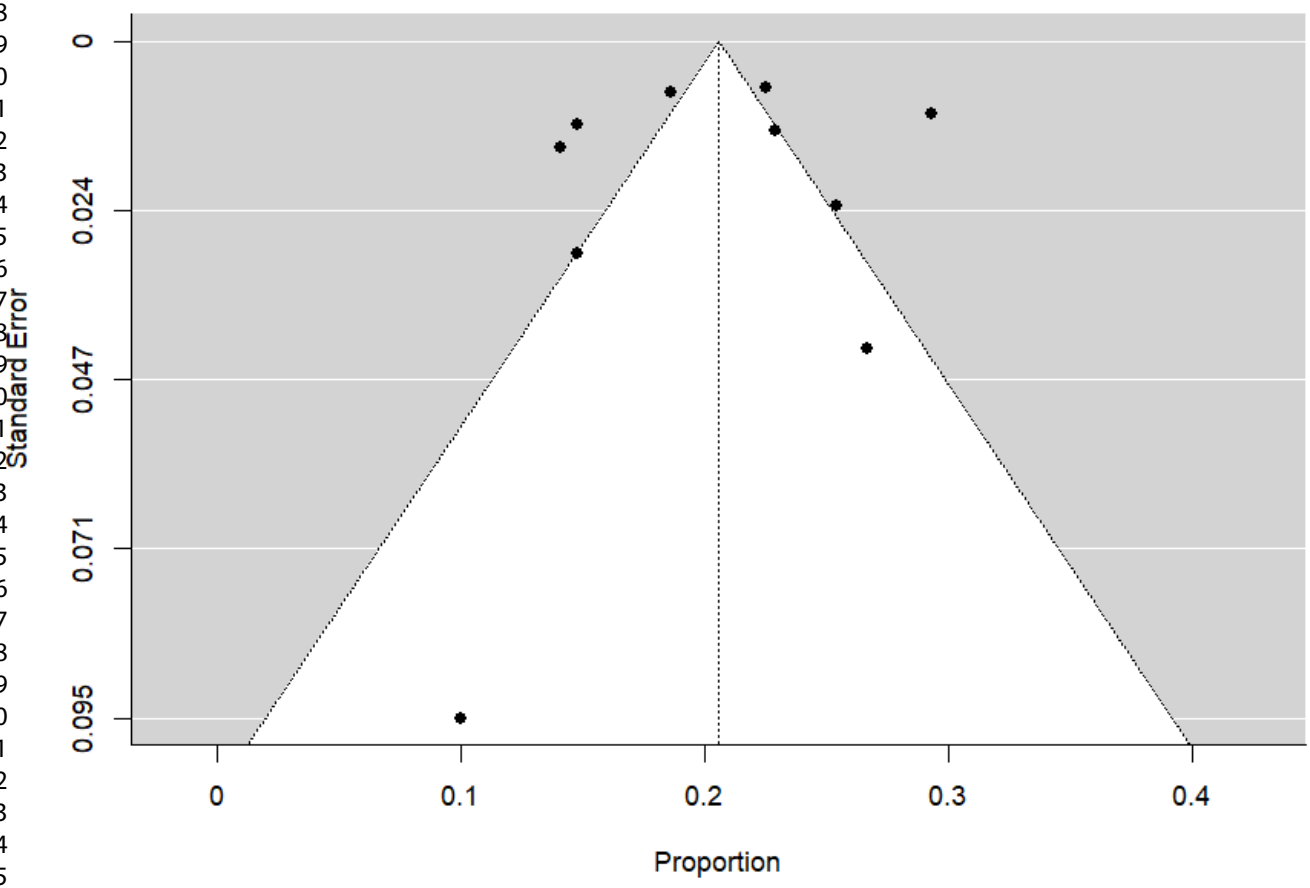
4.	Were the study subjects and the setting described in detail?
5.	Was the data analysis conducted with sufficient coverage of the identified sample?
6.	Were valid methods used for the identification of the condition?
7.	Was the condition measured in a standard, reliable way for all participants?
8.	Was there appropriate statistical analysis?
9.	Was the response rate adequate, and if not, was the low response rate managed appropriately?

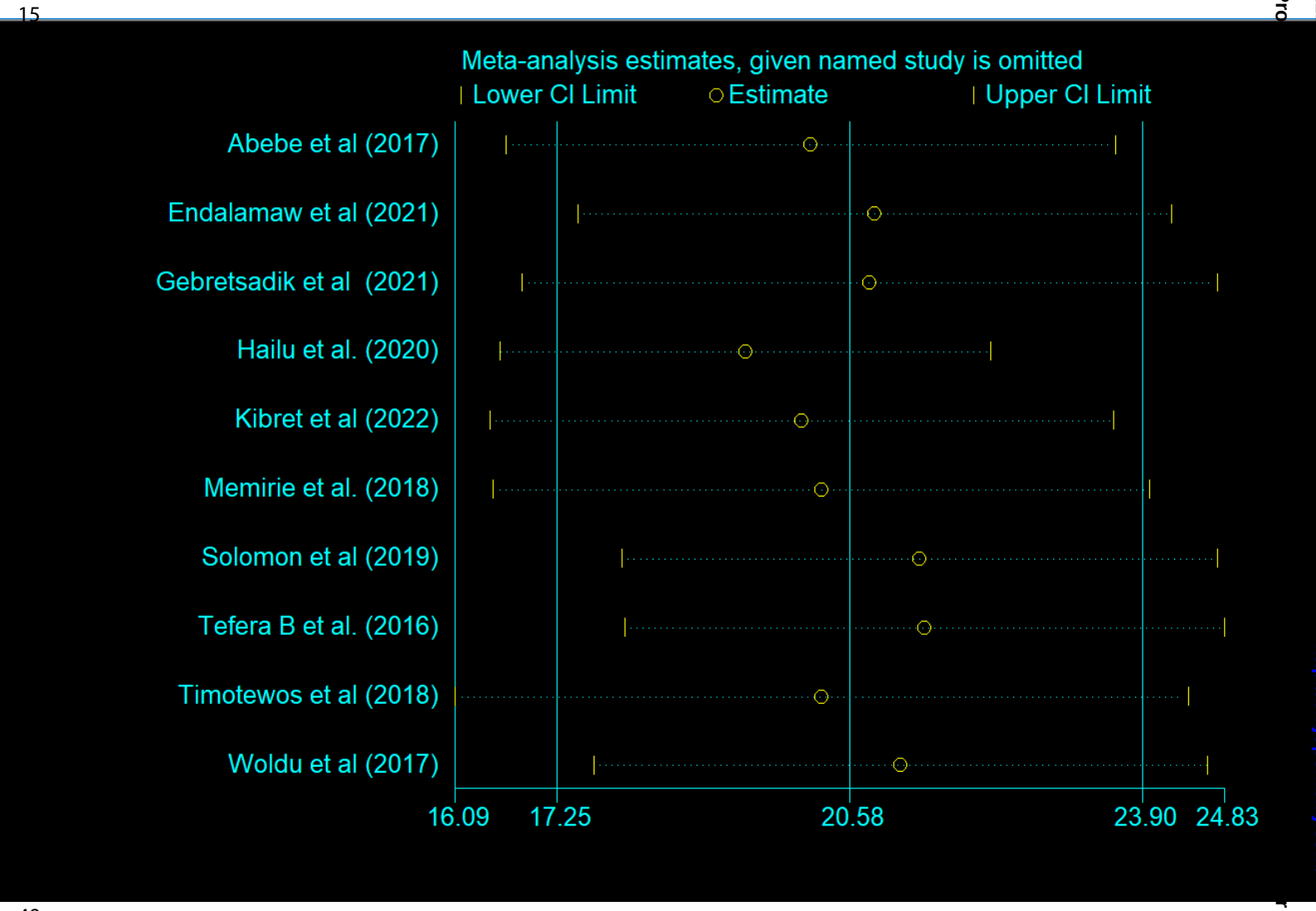
1-Yes 2- No 3-Unclear 4-Not applicable







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Estimate
Upper CI Limit
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Kibret et al (2022)
Memirie et al. (2018)
Solomon et al (2019)
Tefera B et al. (2016)
Timotewos et al (2018)
Woldu et al (2017)
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