xx xx 2022

ADHERENCE TO A MEDITERRANEAN-BASED DIETARY PATTERN AND THE EFFECT ON BREAST CANCER RISK:

FOCUSSING ON THE QUALITY OF EXISTING EVIDENCE

LITERATURE THESIS

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Summary

Introduction – The main aim of this literature thesis is to evaluate the association between adherence to a Mediterranean-based dietary pattern (MBDP) and primary breast cancer (BC) risk in pre- and postmenopausal women. To evaluate this association, a relevant update of the systematic review by Morze J, et al. (2020), including studies published between January 2017 and September 2022, is provided. In addition, strong emphasis is placed on the quality of the included studies and the difference in quality between study designs.

Methods – A computerized search was set up for two electronic databases (PubMed and Embase) to search for existing evidence published between January 2017 and September 2022. Studies were considered relevant when the dietary pattern studied met a MBDP defined as: a diet with a relatively high intake of vegetables, fruits, cereals, nuts, and legumes combined with a relatively low-to-moderate intake of meats (especially red and processed meats), dairy products, and alcohol. No strict criteria need to be met regarding the quantities to be consumed. Furthermore, the outcome should be the primary risk of BC in pre- and/or postmenopausal women, an association between adherence to a MBDP and primary risk of BC should be reported, and the study needs to be observational. Data were extracted and reported in tables. Additionally, a quality assessment was performed using JBI critical appraisal checklists combined with quantitative scores providing an overall quality rating as 'low' (≤50% of total score), 'moderate' (score between 50-75% of total score), or 'high' (score between 75-100% of total score).

Results – In total, 17 articles were identified, of which nine cohort studies and eight case-control studies. Four case-control studies reported inverse associations between adherence to a MBDP and overall BC risk, with the odds of BC risk being reduced by a range of 18-50% (95% CI 5-66%) with adherence to a MBDP. Three case-control studies reported reduced odds of BC risk in postmenopausal women ranging from 28-55% (95% CI 2-77%) when adhering to a MBDP, while one cohort study only reported an inverse association for premenopausal women (HR highest quantile 0.33; 95% CI 0.11-0.99). Of the cohort studies, 37.5% scored a moderate overall quality and 62.5% a high overall quality. The case-control studies were judged as follows: 22.2% scored a low overall quality, 11.1% a moderate overall quality, and 66.7% a high overall quality. Points were lost mainly on the validity of the exposure measurement method, identification and inclusion of confounders, and reporting of incomplete follow-up or too short exposure time-period.

Conclusion – In conclusion, adherence to a MBDP might be inversely associated with BC risk in predominantly postmenopausal women. However, most studies mainly included postmenopausal women resulting in a lack of evidence for premenopausal women. Furthermore, some critical points regarding the validity of the exposure measurement tool, the exposure time-period, and the inclusion of confounders scored poorly in both study designs, for which room for improvement is especially possible in cohort studies. Therefore, further research needs to be done by prospective cohort studies with longitudinal dietary intake measurements using validated tools combined with potential biomarkers reflecting adherence to a MBDP. In addition, potential confounders need to be included and the distribution of pre- and postmenopausal women should ideally be equal.

Keywords: Mediterranean diet, Breast cancer, Primary risk, Premenopausal, Postmenopausal

List with abbreviations

aMD	Adapted Mediterranean Diet
AU	Alcohol unit
BC	Breast cancer
BMI	Body Mass Index
CI	Confidence interval
FFQ	Food-Frequency Questionnaire
HR	Hazard ratio
JBI	Joanna Briggs Institute
MBDP	Mediterranean-based dietary pattern
MD	Mediterranean diet
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
NA	Not applicable
OR	Odds ratio
SES	Socio-economic Status
SR	Systematic review
T2D	Diabetes Mellitus type 2

Introduction

Currently, breast cancer (BC) is one of the most commonly diagnosed cancers in women and the second-leading cause of cancer deaths, after lung cancer. Several possible (non-)modifiable risk factors have emerged from research that are responsible for a large proportion of BC cases, including, for example, hormonal therapy, lifestyle factors (such as alcohol consumption and smoking), and advanced age (1). To reduce this large number of BC cases, a lot of research is being done especially on modifiable risk factors, including lifestyle. This research has shown that more than a third of BC cases in high-income countries can be prevented by lifestyle changes (2).

The already mentioned intake of alcohol and smoking are certain lifestyle factors that can be changed to reduce the risk of BC (3-5). In addition, it is shown that physical activity and weight in combination with adiposity are associated with the risk of BC, with more physical activity and lower weight and fat percentage seen as preventive (6). Nutritional intake, which is related to these lifestyle factors, has been the subject of several observational studies investigating its association with BC risk. These include studies on dietary components, such as fiber intake (7), as well as whole dietary patterns, such as the Mediterranean diet (MD) (8).

There is a lot of interest in the research on the MD because of its healthy composition characterized by an abundance of plant-based foods (vegetables, fruits, whole-grain cereals, nuts, and legumes), intake of olive oil as the main source of fat, intake of bread, fish, and poultry in low-to-moderate amounts, a low intake of red meat, and moderate consumption of alcohol (9). Due to its healthy potential, it is associated with a reduced risk of several chronic diseases, such as diabetes mellitus, cardiovascular diseases, obesity, hypertension, and cognitive diseases. In addition, it is associated with a decreased risk of several cancers (10).

However, contrasting results have been published regarding the association between the traditional MD or dietary patterns derived from it and the risk of BC. A recently published systematic review of Morze J, et al. (2020) focused on the association between dietary patterns derived from the traditional MD and the risk of and mortality from several cancers, including BC. They reported contrasting results between case-control studies and cohort studies regarding the association between adherence to a Mediterranean dietary pattern and the risk of BC. Where moat case-control studies showed an inverse association between the Mediterranean dietary patterns and the risk of BC, most cohort studies showed no association at all. However, little emphasis has been placed on the quality of the included studies, which may have biased the conclusions about the possible association.

Focusing on the quality of the studies investigating the association between a Mediterranean-based dietary pattern (MBDP) and BC risk might give a clearer picture of the possible association and causal effect. This, in turn, could provide clear ideas on possible methodological improvements for these nutritional studies and ultimately provide leads for potential prevention strategies to reduce the incidence of BC.

Research question

Giving a relevant and more recent update on the systematic review of Morze J, et al. (2020) by including articles with a publication date between January 2017 and September 2022, the aim is to give answers on the following questions:

Main research question:
What is the effect of adherence to a Mediterranean-based dietary pattern on the primary risk of breast cancer in pre- and postmenopausal women?

Sub questions:

- What is the quality of performed scientific studies to the association between a Mediterranean-based dietary pattern and the risk of breast cancer in pre- and/or postmenopausal women?
- What is the difference in quality between performed scientific case-control and cohort studies?

Methods

Operationalization concepts

A literature search was set up based on the key components of the main research question including the exposure (MBDP), outcome (BC), the association measure (primary risk) and the population (pre- and postmenopausal women). A MBDP used in this literature thesis is different to a specific MD in that it does not require strict criteria for the amounts to be consumed (e.g. twice daily or weekly). A dietary pattern in which the intake of vegetables, fruits, cereals, nuts, and legumes is high in combination with a low-to-moderate intake of meats, especially red and processed meats, dairy products, and alcohol is considered as typical for a MBDP. A ratio of mono-unsaturated:saturated fat might be included in defining a MBDP, in which olive oil is considered as the main source of (mono-unsaturated) fat. This means that a MBDP is typically low in saturated fat and high in mono-unsaturated fat. Regarding the outcome BC, no distinction was made between different types of BC. The only criterium for the outcome measure is that the study should (also) focus on the risk of BC in women, for which both pre- and postmenopausal women may be included. Lastly, the association between adherence to a MBDP and BC should be focused on the primary risk for BC, not just recurrence, prognosis, or mortality.

Literature search

In addition to the observational articles included in the systematic review of Morze J, et al. (2020) with a publication date after 01 January 2017, a computerized search strategy was set up in two different databases: (I) PubMed and (II) Embase. Mesh terms, Emtree terms, and synonyms used for the search strategy in PubMed and Embase, including the number of results for each search component, are shown in Appendix A. A filter was applied for the search, identifying only articles published between January 2017 and September 2022, to provide a relevant and more recent update on the systematic review by Morze J, et al. (2020). In addition, reference lists of the eligible articles were checked on extra eligible articles.

Selection eligible articles

Identified articles based on the search strategies were first checked on title and/or abstract and thereafter on the full text. For this screening method, specific in- and exclusion criteria were used to identify the most relevant and eligible articles (Table 1).

Table 1: In- and exclusion criteria eligibility of identified articles

Inclusion Criteria	Exclusion Criteria
• Exposure is within the criteria for a MBDP • Outcome is primary risk of BC in pre- and / or postmenopausal women • An association between the adherence to a MBDP and the primary risk of BC is reported • Observational studies	• Exposure was not (total) MBDP • Duplicate in study population / cohort compared to other eligible article • Full text not available

Data extraction

Data of the included studies were reported in tables. The first table contains basic study characteristics of the included articles such as the country in which the study was performed, the study design, the number of female participants, the inclusion of pre- and/or postmenopausal women and the percentages relative to the total female population, the follow-up time (for cohort studies the prospective follow-up time and for case-control studies the retrospectively exposure time), and the inclusion of the article in the systematic review of Morze J, et al. (2020). The second table contains more methodological information, such as assessment of the MBDP, assessment of dietary intake, assessment of BC cases, and statistical outcome measures. Additionally, information regarding the inclusion of potential confounders, results for overall BC risk as well as separate for pre- and postmenopausal women, and the conclusion regarding the association between the MBDP and BC risk is provided in the last table. Data extraction was performed twice, to prevent mistakes in the interpretation of methods and outcomes.

Quality assessment included articles

To assess the quality of the included articles, forms of the Joanna Briggs Institute (JBI) critical appraisal checklists are used (11). An advantage of using the JBI critical appraisal checklist is that it has different checklists for different study designs. This gives the opportunity to score studies specific to their study design but with the same quality score structure. The main topics addressed in the JBI critical appraisal checklists for observational studies are the selection of the study population, exposure measurement (tools and methods), inclusion of confounders, outcome measurement tools, description and strategies regarding (variable) follow-up time, and performed statistical analyses. For each specific question regarding these topics the following answers can be given: ‘Yes’, ‘No’, ‘Unclear’, or ‘Not applicable’. Since some items are more up for discussion, the answer 'moderate' will be added based on clear criteria for the specific critical appraisal topics. The criteria for the answers are provided in Tables 2A and 2B in Appendix B, stratified by study design.

Additionally, a quantitative score is given to get a clear insight in the overall quality assessment. In general, a score of 2 points is given for the answer ‘yes’, 1 point if it’s scored moderate, and 0 points if the answer is ‘no’ or when it is ‘unclear’. The overall quality is the sum of the quality scores per specific question. An overall value judgement is given as follows: (I) ‘low’ when scoring ≤50% of the total sum, (II) ‘Moderate’ when scoring between 50-75% of the total sum, and (III) ‘high’ when scoring between 75-100% of the total sum. The quality assessment of the articles will be visualized in a table by colors with green representing a ‘yes’, orange representing ‘moderate’, and red representing ‘no’/’unclear’.

Results

Literature search and screening process

The literature search in PubMed, including date filter in which articles published before 01 January 2017 were excluded, yielded 342 articles that were subsequently screened for suitability by title and/or abstract. Of the 342 articles screened, 23 articles seemed relevant to our subject and were additionally screened for full text. This resulted in the exclusion of 8 articles based on one of the aforementioned exclusion criteria (Table 1). Of the suitable articles, the reference list was checked from which 1 additional relevant article was identified. Of the articles included in the systematic review of Morze J, et al. (2020), 1 article was not retrieved by the search in PubMed. Based on the search in Embase, no additional relevant articles were identified. In the end, a total of 17 articles were included in this literature thesis. The process of screening and inclusion of articles is shown in Figure 1.

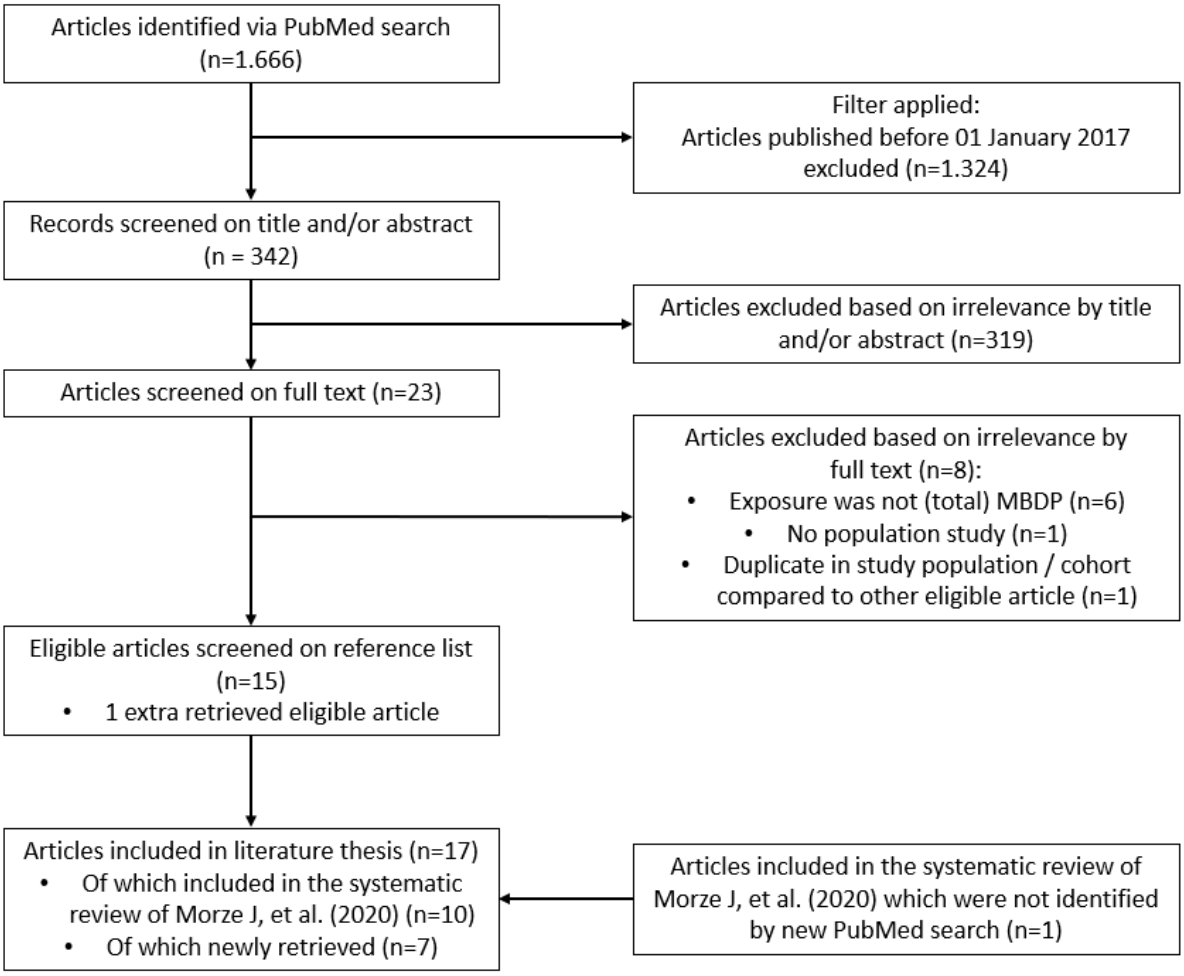

Figure 1: Flowchart literature search and screening process
Abbreviations: MBDP, Mediterranean-based dietary pattern

Study characteristics included articles

Basic study characteristics included articles

The study characteristics of the included articles are shown in Table 2. Of the 17 included articles, eight studies were performed with a prospective cohort design (12-19) and nine studies were performed with a case-control design (20-28). Studies were performed in a variety of countries including Finland, Iran, Poland, Turkey, Italy, China, The United States, French, Sweden, The Netherlands, Spain, and Switzerland. Almost all studies included both pre- and postmenopausal women, except for the studies

of Männistö S, et al. (2021) and van den Brandt P.A, et al. (2017) in which only postmenopausal women were included. In total, 410.320 (range 6.374-101.291) females were included in the cohort studies and 14.171 (range 130-6.426) females were included in the case-control studies. Follow-up time was reported in all the cohort studies, but in different ways using means, medians, or person-years. In contrast, the case-control studies did not always report the retrospectively follow-up time for which dietary data was retrieved (21, 23, 24, 26). Of the case-control studies in which retrospectively follow-up time was reported, dietary intake was assessed for the year preceding enrollment or BC diagnosis (20, 22, 25, 27, 28). In addition, the study of Cao S, et al. (2022) used a 'duration' indicator, assessing how long the participants maintained their current dietary habit in the preceding years.

Table 2: Overview basic study characteristic included articles

	Country	**Female study population size**	**Menopausal status**	**Follow-up time**	**Inclusion SR**
Cohort studies					
Männistö S, et al. (2021) (12)	Finland	N=6.374	Postmenopausal	*Median:* 9.7 years	
Petimar J, et al. (2019) (13)	United States	N=50.884	Pre- and postmenopausal *No percentages*	*Mean:* 7.6 years	SR
Haridass V, et al. (2018) (14)	California	N=96.959	(43.9%) Premenopausal (56.1%) Postmenopausal	1.354.947 person years	SR
Lavalette C, et al. (2018) (15)	French	N=30.525	(39.8%) Premenopausal (50.1%) Postmenopausal	164.052 person years	SR
Boden S, et al. (2019) (16)	Sweden	N=51.001	Pre- and postmenopausal *No percentages*	*Median:* 15 years	SR
Dela Cruz R, et al. (2020) (17)	Hawaii	N=101.291	(27.4%) Premenopausal (72.6%) Postmenopausal	*Mean:* 17.4 years	SR
van den Brandt P.A, et al. (2017) (18)	The Netherlands	N=62.573	Postmenopausal	*Total:* 20.3 years	SR
Gardeazabal I, et al. (2020) (19)	Spain	N=10.713	(~90%) Premenopausal Postmenopausal	*Median:* 10.3 years	SR
Case-control studies				**Exposure time**	
Sheikhhossein F, et al. (2021) (20)	Iran	N=300 [Cases N=150 Controls N=150]	(61.3%) Premenopausal (38.7%) Postmenopausal	1 year	
Aghamohammadi V, et al. (2021) (21)	Iran	N=1.050 [Cases N=350 Controls N=700]	(19.1%) Premenopausal (80.9%) Postmenopausal	Not reported	
Krusinska B, et al. (2018)[1] (22)	Poland	N=420 [Cases N=190 Controls N=230]	(14.8%) Premenopausal (85.2%) Postmenopausal	1 year	
Toklu H, et al. (2018) (23)	Turkey	N=130 [Cases N=65 Controls N=65]	(52.3%) Premenopausal (47.7%) Postmenopausal	Not reported	
La Torre G, et al. (2021) (24)	Italy	N=182 [Cases N=94 Controls N=88]	Pre- and postmenopausal *No percentages*	Not reported	
Cao S, et al. (2022) (25)	China	N=1.753 [Cases N=818 Controls N=935]	(34.2%) Premenopausal (65.8%) Postmenopausal	1 year (duration indicator 25 years)	
Turati F, et al. (2018) (26)	Italy & Switzerland	N=6.426 [Cases N=3.034 Controls N=3.392]	(36.3%) Premenopausal (63.7%) Postmenopausal	Not reported	SR
Krusinska B, et al. (2018)[2] (27)	Poland	N=280 [Cases N=140 Controls N=140]	Pre- and postmenopausal *No percentages*	1 year	SR
Castello A, et al. (2017) (28)	Spain	N=2.714 [Cases N=1.124 Controls N=1.589]	(32.7%) Premenopausal (67.3%) Postmenopausal	1 year	SR

Abbreviations: SR, systematic review; N, number

Methodological characteristics included articles

The methodological characteristics of the included articles in this literature thesis are summarized in Table 3 and more extensively described in the sections below.

Type of MBDP - Almost all studies described the MBDP as a traditional or modified/alternate/country-specific version of the MD, except for Sheikhhossein F, et al. (2021) and Aghamohammadi V, et al. (2021) in which the more specific Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND)-diet was investigated. For the assessment of the MBDP, most studies used the MD index by Trichopoulou A, et al. (2003) and/or modification by Fung T.T, et al. (2006) (29, 30). For the studies investigating the MIND diet, a specific score called the MIND diet score was used. Other methods to assess a MBDP were the MEDI-LITE score (31), the MD score by Panagiotakos D.B, et al. (2007) (32), a PCA derived score or a self-made construction of the MD score. Detailed information regarding the different MBDP assessment scores is described in Appendix C.

Assessment exposure - Of the included cohort studies, assessment of dietary intake was mostly performed using a validated food-frequency questionnaire (FFQ) (12-14, 16, 18, 19). Other methods were a dietary history interview (12) and a validated web-based 24 hours-dietary record (15). Regarding the case-control studies, the most common dietary intake assessment method was a validated and interviewer-administered FFQ (20-22, 26, 27). The study of Cao S, et al. (2022) and Castello A, et al. (2017) also used a validated FFQ but was not administered during an interview. In contrast, La Torre G, et al. (2021) used an FFQ, but was neither validated not interviewer administered. The study by Toklu H, et al. (2018) used a self-made questionnaire.

Assessment outcome - The assessment of BC cases was mostly done by linkage with cancer registries (12, 14, 16-18, 25), followed by histologically confirmation (22, 26-28), self-reportion with confirmation by medical records (13, 15, 19), and physical examination together with mammography findings and/or pathologic verification (20, 21).

Statistical analyses - Except for the studies by Toklu H, et al. (2018), which used the Chi-square test, and La Torre G, et al. (2021), which reported only overall odds ratios (ORs) with 95% confidence intervals (CIs), all the studies reported either hazard ratios (HRs) or ORs (based on study design) with 95% CIs across different diet quality indices.

Table 3: Overview methodological characteristics of the included articles

	Type of MBDP	Assessment MBDP	Assessment dietary intake	Assessment BC cases	Statistical outcome measures
Cohort studies					
Männistö S, et al. (2021)	Modified MD	Based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006)	Dietary history interview method and validated FFQ	Finnish Cancer Registry	HRs (with 95% CIs) according to diet quality indices (scores)
Petimar J, et al. (2019)	Alternative MD	Based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006)	Validated FFQ	After self-reportion verified by medical records for 80%	HRs (with 95% CIs) according to diet quality indices (scores)
Haridass V, et al. (2018)	Alternate MD	Based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006) – alcohol excluded from the index	Validated FFQ	California cancer registry records	HRs according to diet quality indices (scores)
Lavalette C, et al. (2018)	MD	Based on MEDI-LITE by Sofi F, et al. (2014)	Validated web-based 24 hours-dietary records	After self-reportion verified by medical records for >90%	Overall HRs and HRs (with 95% CIs) according to diet quality indices (scores)
Boden S, et al. (2019)	MD	Adapted MD score: vegetables and potatoes, fruit and fresh juices, wholegrain cereals, fish and fish products, ratio of polyunsaturated fatty acids + monounsaturated fatty acids to saturated fat, alcohol intake, meat and meat products, and dairy products.	Validated FFQ	Swedish Cancer Registry	HRs (with 95% CIs) per tertile increase in MD score. Tertiles were distributed avoid ties: T1 score 0-3, T2 score 4, T3 score 5-8
Dela Cruz R, et al. (2020)	Alternate MD	Based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006)	(Validated) FFQ	Cancer registries	HRs (with 95% CIs) according to diet quality indices (scores)
van den Brandt P.A, et al. (2017)	Alternate MD	Alternate MD Score and Modified MD Score, adapted versions of the traditional MD Score of Trichopoulou A, et al. (2003) – alcohol excluded from the index	Validated FFQ	The Netherlands Cancer Registry and PALGA	HRs (with 95% CIs) according to diet quality indices (scores)
Gardeazabal I, et al. (2020)	Mediterranean dietary pattern	PCA derived score identifying main dietary patterns resulted in the following food components: vegetables, fruits, legumes, nuts, eggs, fish, natural fruit juices, processed meats, unprocessed red meat, poultry, olive oil, potatoes and other fruits including canned fruit, dried fruit, avocado and olives	Validated FFQ	Self-reported and validated by medical records	HRs (with 95% CIs) according to diet quality indices (scores)

	Type of MBDP	Assessment MBDP	Assessment dietary intake	Assessment BC cases	Statistical outcome measures
Case-control studies					
Sheikhhossein F, et al. (2021)	MIND diet	MIND diet score	Validated and interviewer administered FFQ	Physical examination and mammography findings	ORs (with 95% CIs) across different tertiles of MIND diet score
Aghamohammadi V, et al. (2021)	MIND diet	MIND diet score	Validated and interviewer administered FFQ	Physical examination ,mammography, and pathologic verification	ORs (with 95% CIs) across different tertiles of MIND diet score
Krusinska B, et al. (2018)[1]	Polish-adapted MD	Altered score based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006) – alcohol excluded from the index and monounsaturated:saturated fat ratio replaced by vegetable-oils:animal fat ratio.	Validated and interviewer administered FFQ	Histologically confirmed	ORs (with 95% CIs) across different tertiles of the Polish-adapted MD score
Toklu H, et al. (2018)	MD	Based on MD score by Panagiotakos D.B, et al. (2007)	Self-made questionnaire	Assessment BC cases not reported	Chi-square test, p-value<0.05
La Torre G, et al. (2021)	MD	Adapted MD score based on intake according to Pyramid of the modern MD	FFQ	Assessment BC cases not reported	OR (with 95% CIs)
Cao S, et al. (2022)	Chinese version of the MD	Alternate Chinese Diet Score based on the MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006) with some other products included in the main food groups.	Validated FFQ	Cancer registries	ORs (with 95% CIs) based on intake ≥ reference of food components compared to intake < reference
Turati F, et al. (2018)	MD	Based on MD index of Trichopoulou A, et al. (2003)	Validated and interviewer administered FFQ	Histologically confirmed	ORs across different tertiles and for an increment of one point in the MD score
Krusinska B, et al. (2018)[2]	Polish-adapted MD	Altered score based on MD index of Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006) – alcohol excluded from the index and monounsaturated:saturated fat ratio replaced by vegetable-oils:animal fat ratio.	Validated and interviewer administered FFQ	Histologically confirmed	ORs (with 95% CIs) across different tertiles of the Polish-adapted MD score
Castello A, et al. (2017)	Mediterranean dietary pattern	PCA derived score identifying main dietary patterns. MD consisted of following food components: fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil, intake of juices.	Validated FFQ	Histologically confirmed	ORs (with 95% CIs) across different tertiles of the MD score

Abbreviations: MBDP, Mediterranean-based dietary pattern; MD, Mediterranean Diet; BC, Breast Cancer; FFQ, Food-Frequency Questionnaire; HR, hazard ratio; CI, confidence interval; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; OR, Odds ratio

Reported results included articles

Table 4 shows the most important findings of the included articles in combination with the potential confounders important for retrieving a valid conclusion about the association between adherence to a MBDP and BC risk.

Confounders - Most of the articles reported a clear list of possible confounders including the most important risk factors age, personal history of BC, family history of BC, reproductive risk factors, and exogenous hormone use as possible confounders (33). Different compared to the other studies, the study of La Torre G, et al. (2021) did not adjust for (non-)modifiable risk factors but reported the synergism effect between the MD and modifiable risk factors in association with BC risk. In contrast, the study of Toklu H, et al. (2018) did not report any confounders at all.

Outcome report – Of the studies that included both pre- and postmenopausal women, only six studies (1 cohort study, 5 case-control studies) reported both the overall BC risk and the BC risk stratified by menopausal status (19-21, 25, 26, 28). Eight other studies reported only overall BC risk (12, 13, 15-18, 22-24, 27), while the study by Haridass V, et al. (2018) only reported the BC risk stratified by menopausal status.

Associations cohort studies - Six out of eight cohort studies reported no association between a MBDP and overall BC risk (12, 13, 15-18). The study of Haridass V, et al. (2018) did report a modest association between adherence to a MBDP and BC risk in postmenopausal women (HR highest quantile 0.93; 95% CI 0.83-1.03), but no association was found in premenopausal women (HR highest quantile 1.14; 95% CI 0.95-1.38). In contrast, the study of Gardeazabal I, et al. (2020) was the only study that did report an inverse association for premenopausal women (HR highest quantile 0.33; 95% CI 0.11-0.99) but did not find an association for postmenopausal women (HR highest quantile 1.52; 95% CI 0.33-6.98).

Associations case-control studies – Of the nine case-control studies, eight studies did report an association between adherence to a MBDP and BC risk. Inverse associations between a MBDP and overall BC risk were reported in 4 case-control studies of which the studies by Aghamohammadi V, et al. (2021) and Cao S, et al. (2022) also reported an inverse association for postmenopausal BC risk (OR highest quantile: 0.45; 95% CI (0.30-0.66) and 0.57; 95% CI (0.41-0.80) respectively). The study by Castello A, et al. (2017) reported only an inverse association for postmenopausal BC risk (OR highest quantile 0.72; 95% CI 0.53-0.98). The study by Krusinska B, et al. (2018)[1] reported a weak inverse association with overall BC risk, based on non-significant HRs (HR highest quantile 0.93; 95% CI 0.82-1.05). The other study by Krusinska B, et al. (2018)[2] reported only an inverse association between adherence to a MBDP and breast and lung cancer risk overall, but not separately for these cancer types. In contrast, the study of Sheikhhossein F, et al. (2021) did not report any association between adherence to a MBDP and BC risk.

Table 4: Overview reported confounders, outcomes, and associations of the included articles

	Included confounders	General adjusted results per tertile/quantile (or other mentioned)	Premenopausal outcome	Postmenopausal outcome	Reported association
Cohort studies					
Männistö S, et al. (2021)	Age; education; smoking; height; BMI; leisure time exercise; parity; hormone replacement therapy; energy intake; cohort; T2D	HR (95% CI) [1] 1.00 [2] 0.89 (0.61-1.28) [3] 0.72 (0.49-1.07) [4] 0.69 (0.46-1.02) [5] 0.88 (0.59-1.30)	NA	NA	No association between the MD and postmenopausal BC risk
Petimar J, et al. (2019)	Race/ethnicity; education; income; BMI; physical activity; smoking; energy intake; number of first-degree relatives with a history of BC; parity; age at first live birth; age at menarche; age at menopause; oral contraceptive use; hormone replacement therapy use; lifetime duration of breastfeeding; time since most recent mammogram	HR (95% CI) [1] 1.00 [2] 0.98 (0.86-1.13) [3] 0.92 (0.78-1.08) [4] 0.90 (0.77-1.06)	Not reported	Not reported	MD not significantly inversely associated with risk of invasive BC or BC subtypes
Haridass V, et al. (2018)	Participants' race; menopausal status; hormone replacement therapy; age at menarche; family history of BC; BMI; parity; oral contraceptive use; smoking status; physical activity	Not reported	HR (95% CI) [1] 1.00 [2] 1.06 (0.86-1.29) [3] 1.10 (0.91-1.33) [4] 1.15 (0.96-1.39) [5] 1.14 (0.95-1.38)	HR (95% CI) [1] 1.00 [2] 0.99 (0.89-1.11) [3] 0.95 (0.85-1.05) [4] 0.91 (0.82-1.02) [5] 0.93 (0.83-1.03)	Modest inverse association between higher scores and risk of incident postmenopausal BC. No association found with premenopausal BC risk
Lavalette C, et al. (2018)	Age; height; smoking; number of dietary records; energy intake without alcohol; family history of cancer in first-degree relatives; education; BMI; physical activity	HR (95% CI) [1] 1.00 [2] 1.07 (0.77-1.48] [3] 1.01 (0.77-0.32) [4] 0.96 (0.69-1.33) [5] 1.13 (0.84-1.53)	Not reported	Not reported	No clear association with BC risk
Boden S, et al. (2019)	Smoking; diabetes; BMI; physical activity; education; energy intake	HR (95% CI) 0.98 (0.92-1.05) per tertile increase	Not reported	Not reported	Null findings for BC risk

	Included confounders	General adjusted results per tertile/quantile (or other mentioned)	Premenopausal outcome	Postmenopausal outcome	Reported association
Cohort studies					
Dela Cruz R, et al. (2020)	Age; energy intake, BMI; smoking; physical activity; education; age at menarche; age at first live birth; parity; age at menopause; family history of BC; estrogen and progestin use; diet quality	HR (95% CI) [1] 1.00 [2] 1.00 (0.93-1.07) [3] 1.03 (0.96-1.11] [4] 1.00 (0.92-1.08) [5] 1.01 (0.94-1.09)	Not reported	Not reported	MD quality index did not predict BC incidence
van den Brandt P.A, et al. (2017)	Age; smoking; height; BMI; physical activity; education; family history of BC in mother or sisters; history of benign breast disease; age at menarche; parity; age at first birth; age at menopause; oral contraceptive use; postmenopausal hormone replacement therapy; energy intake	HR (95% CI) [1] 1.00 [2] 0.82 (0.70-0.96) [3] 0.87 (0.72-1.06)	NA	NA	No inverse associations between adherence to MD and risk of total BC
Gardeazabal I, et al. (2020)	Age; height; years at university; family history BC; smoking; physical activity; alcohol; age at menarche; age at menopause; number of pregnancies of more than 6 months; pregnancy before the age of 30; lifetime breastfeeding; use of hormone replacement therapy and duration; diabetes; energy intake	HR (95% CI) [1] 1.00 [2] 0.78 (0.43-1.43) [3] 0.57 (0.28-1.16) [4] 0.63 (0.28-1.45)	HR (95% CI) [1] 1.00 [2] 0.32 (0.13-0.74)* [3] 0.40 (0.16-0.99)* [4] 0.33 (0.11-0.99)*	HR (95% CI) [1] 1.00 [2] 1.96 (0.64-6.00) [3] 1.24 (0.34-4.51) [4] 1.52 (0.33-6.98)	Small changes towards a higher adherence to the MD could be associated with a decreased risk of premenopausal BC. No association was found for postmenopausal BC
Case-control studies					
Sheikhhossein F, et al. (2021)	Age; energy intake; physical activity; education; marital status; menopause status; SES; alcohol use; smoking; vitamin supplements and medicines; medical history; history of hormone and oral contraceptives; age at first menarche; time since menopause in postmenopausal women; weight at age 18 years old; number of children; length of breastfeeding; age at first pregnancy; family history of BC; BMI	OR (95% CI) [1] 1.00 [2] 0.787 (0.211-2.93) [3] 1.32 (0.31-5.64)	OR (95% CI) [1] 1.00 [2] 0.891 (0.342-2.32) [3] 1.02 (0.36-2.94)	OR (95% CI) [1] 1.00 [2] 1.02 (0.247-4.22) [3] 1.66 (0.358-7.77)	No significant association between adherence to the MIND diet and BC in both pre- and postmenopausal Iranian women
Aghamohammadi V, et al. (2021)	Age; energy intake; education; SES; residency; family history of BC; physical activity; marital status; smoking; alcohol; supplement use; breastfeeding; menopausal status; BMI	OR (95% CI) [1] 1.00 [2] 0.73 (0.48-1.09) [3] 0.50 (0.34-0.72)*	OR (95% CI) [1] 1.00 [2] 0.98 (0.28-3.42) [3] 1.28 (0.40-4.09)	OR (95% CI) [1] 1.00 [2] 0.69 (0.44-1.07) [3] 0.45 (0.30-0.66)*	Significant inverse association between adherence to the MIND diet and the odds of BC. This inverse association was also seen in postmenopausal women

	Included confounders	General adjusted results per tertile/quantile (or other mentioned)	Premenopausal outcome	Postmenopausal outcome	Reported association
Case-control studies					
Krusinska B, et al. (2018)[1]	Age; BMI; SES; physical activity; age at menarche; menopausal status; oral contraceptive use; hormone-replacement therapy use; number of children; smoking; alcohol; supplement use; family history of BC in first- or second-degree relative; and molecular BC subtypes.	OR (95% CI) [1] 1.00 [2] 0.52 (0.26-1.01) [3] 0.54 (0.26-1.10) [4] 0.93 (0.82-1.05)	Not reported	Not reported	Weak association between high adherence to the Polish-adapted MD and BC risk
Toklu H, et al. (2018)	Not reported	Chi-square test Diet score ≤29 vs. >29 in case and control group 13.22 (p=0.001)	Not reported	Not reported	Nonadherence to the MD increase the risk of BC
La Torre G, et al. (2021)	Report synergistic effects with smoking, physical activity, and alcohol consumption	OR (95% CI) MD score > 6 0.29 (0.12-0.69)	Not reported	Not reported	The score of MD >6 can be considered as protective factor
Cao S, et al. (2022)	Age; education; smoking; physical activity; oral contraceptives use; hormone replacement therapy; family history of BC; history of benign breast disease; age at menarche; number of full-term births; age at first full-term delivery; breastfeeding; height; BMI; energy intake	OR (95% CI) [1] 1.00 [2] 1.07 (0.83-1.37) [3] 0.95 (0.73-1.24) [4] 0.64 (0.49-0.84)*	OR (95% CI) [1] 1.00 [2] 1.34 (0.85-2.13) [3] 1.40 (0.87-2.24) [4] 0.80 (0.49-1.31)	OR (95% CI) [1] 1.00 [2] 0.97 (0.71-1.33) [3] 0.78 (0.56-1.09) [4] 0.57 (0.41-0.80)*	Adherence to the Chinese version of the MD inversely associated with postmenopausal BC risk
Turati F, et al. (2018)	Study center; age; education; BMI; physical activity; smoking; parity; menopausal status; age at menopause; oral contraceptive use; hormonal replacement therapy; history of diabetes; family history of BC in first degree relatives; non-alcohol energy intake	OR (95% CI) [1] 1.00 [2] 0.86 (0.76-0.98)* [3] 0.82 (0.71-0.95)*	OR (95% CI) [1] 1.00 [2] 0.93 (0.75-1.16) [3] 0.78 (0.61-1.00)	OR (95% CI) [1] 1.00 [2] 0.83 (0.71-0.97)* [3] 0.87 (0.72-1.04)	Adherence to the MD is related to a reduced risk of overall BC
Krusinska B, et al. (2018)[2]	Age; sex, type of cancer, BMI; physical activity; smoking; abuse of alcohol; SES	Not specifically reported for BC only	Not reported	Not reported	Adherence to Polish-aMD score significantly decreased the risk of BC or lung cancer
Castello A, et al. (2017)	Menopausal status; age; education; BMI; age at first delivery; family history of BC; physical activity; smoking; caloric intake; alcohol	OR (95% CI) [1] 1.00 [2] 1.05 (0.83-1.32) [3] 0.97 (0.76-1.23) [4] 0.90 (0.69-1.17)	OR (95% CI) [1] 1.00 [2] 1.36 (0.93-2.00) [3] 1.12 (0.75-1.67) [4] 1.39 (0.92-2.11)	OR (95% CI) [1] 1.00 [2] 0.91 (0.68-1.21) [3] 0.89 (0.67-1.20) [4] 0.72 (0.53-0.98)*	MD seems to be protective against postmenopausal BC

Abbreviations: BMI, body mass index; T2D, diabetes mellitus type 2; HR, hazard ratio; CI, confidence interval; NA, not applicable; MD, Mediterranean Diet; BC, breast cancer; SES, socio-economic status; OR, odds ratio; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; aMD, adapted Mediterranean Diet

*Statistically significant OR/HR

Quality assessment included articles

Cohort studies

The quality of the cohort studies was assessed using the JBI critical appraisal checklist for cohort studies (Appendix D) and is visualized with colors in Table 5. It was noticeable that none of the cohort studies were rated with low overall quality. Five out of the eight cohort studies were rated with high quality and the remaining three cohort studies scored moderate overall quality. All cohort studies received full marks for using the correct strategy to deal with confounders, for validly assessing BC cases, and for using appropriate statistical analyses. Most points were lost for measuring exposure in a validated and reliable way and for describing the characteristics of participants who were lost to follow-up.

Table 5: Quality assessment included cohort studies based on JBI critical appraisal checklist for cohort studies

	Männistö S, et al. (2021)	**Petimar J, et al. (2019)**	**Haridass V, et al. (2018)**	**Lavalette C, et al. (2018)**	**Boden S, et al. (2019)**	**Dela Cruz R, et al. (2020)**	**van den Brandt P.A, et al. (2017)**	**Gardeazabal I, et al. (2020)**
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?	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Total Quality score (score/22)	16	19	20	18	16	16	18	20
Value judgement quality*	Moderate	High	High	High	Moderate	Moderate	High	High

*Low: total quality score ≤ 11; Moderate: total quality score 12 – 17; High: total quality score 18-22

Legend: 🟢 'Yes' 🟡 'Moderate' 🔴 'No'

Case-control studies

The quality of the case-controls studies was assessed by using the JBI critical appraisal checklist for case-control studies (Appendix E) and is visualized with colors in Table 6. Five out of the nine case-control studies were rated with a high overall quality, followed by one study with moderate overall quality and two studies with low overall quality. Only for measuring the exposure similar in cases and controls did all case-control studies receive full marks. The worst scores were obtained for the exposure period for which dietary intake was collected, followed by the identification and reporting of possible confounding factors.

Table 6: Quality assessment included case-control studies based on JBI critical appraisal checklist for case-control studies

	Sheikh-hossein F, et al. (2021)	**Aghamo-hammadi V, et al. (2021)**	**Krusinska B, et al. (2018)[1]**	**Toklu H, et al. (2018)**	**La Torre G, et al. (2021)**	**Cao S, et al. (2022)**	**Turati F, et al. (2018)**	**Krusinska B, et al. (2018)[2]**	**Castello A, et al. (2017)**
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?	🟢	🟢	🟢	🟡	🟡	🟢	🟢	🟢	🟢
Overall quality score (score/20)	18	17	18	5	5	17	13	17	16
Value judgement overall quality score	High	High	High	Low	Low	High	Moderate	High	High

*Low: total quality score ≤ 10; Moderate: total quality score 11-15; High: total quality score 16-20

Legend: 🟢 'Yes' 🟡 'Moderate' 🔴 'No'

Discussion

The main aim of this literature thesis was to assess the effect of adherence to a Mediterranean-based dietary pattern on the primary risk of breast cancer in pre- and postmenopausal women based on existing evidence between January 2017 and September 2022. Of the eight included cohort studies, only the study of Gardeazabal I, et al. (2020) did report a significant inverse association between adherence to a MBDP and premenopausal BC risk (HR highest quantile 0.33; 95% CI 0.11-0.99), but not for overall BC risk (HR highest quantile 0.63; 95% CI 0.28-1.45) or postmenopausal BC risk (HR highest quantile 1.52; 95% CI 0.33-6.98). In contrast, in case-control studies an inverse association was mainly reported for overall BC risk, for which the odds were reduced by 18-50% (95% CI range 5-66%) when high adherence to a MBDP. Additionally, it was found that postmenopausal women had a reduced odds of BC risk by 28-55% (95% CI range 2-70%) when high adherence to a MBDP.

The exact mechanism by which a MBDP can reduce the risk of BC remains to be elucidated, although several hypotheses about it already exist. It is hypothesized that the reduced risk in BC might be related to the most bioactive components of the MBDP: (I) polyphenols (in nuts, vegetables, and olive oil), (II) mono-unsaturated fatty acids (in nuts and olive oil), (III) polyunsaturated fatty acids (in nuts), and (IV) fiber (in vegetables, legumes, fruits, nuts, and grains). These bioactive compounds may lead to altered lipid metabolism, a decrease in oxidative stress and inflammation, and an improvement in endothelial function and coagulation (34).

Although several studies report the same association direction with a potential mechanistic understanding, it is important to keep the quality of the included studies in mind when interpreting the results; therefore, in this literature thesis, much attention was paid to the quality of the included studies. The quality stratified by study design is discussed in the sections below.

Quality cohort studies – Of all the included cohort studies, 37.5% were scored with moderate overall quality and 62.5% with high overall quality. Points were mainly scored on (I) the use of correct strategies to deal with confounders, (II) selecting participants who were free of BC at baseline, (III) assessing BC cases in a valid and reliable way using linkage with cancer registries or self-reportion in combination with high verification percentages by medical records, and (IV) using appropriate statistical analyses like cox proportional hazard models. Therefore, one would say that reliable conclusions can be drawn. However, it is noteworthy to state that some crucial points were lost which could lead to erroneous conclusions regarding the association between adherence to a MBDP and primary BC risk. The main topics on which cohort studies scored poorly are discussed in the sections below.

***Exposure measurement* -** All the cohort studies described the exposure measurement tool in a detailed manner, however the validity and mainly the timepoints at which dietary intake was measured can be questioned. Using self-reported dietary intake data, by for example an FFQ, could lead to measurement errors. Therefore, researchers integrate sub-studies for the validation of the used dietary questionnaires (35). As no gold standard is available for dietary intake, it is important to assess the validity of the exposure measurement tool, mostly an FFQ, with a reference method, such as 24-hour dietary intakes or dietary records. Moreover, it is important to assess the reliability of the FFQ by using repeated measurements (36). Although the study by Dela Cruz R, et al. (2020) reported the use of a so-called validated FFQ, no reference was made to an actual validation study. In addition to the validity of the exposure measurement tool, it is important to keep in mind that dietary intake might vary over time and therefore longitudinal dietary intake measurements would be preferable. However, except for the studies by Lavalette C, et al. (2018), in which dietary intake was measured every 6 months, and Boden S, et al. (2019), in which nutrient intake was measured at least twice, the remaining cohort studies measured nutrient intake only at baseline for the preceding year before enrolment. With reported follow-up times up to 20 years, it is questionable if this measured dietary

intake is representative for the whole follow-up time.

Confounders **-** Reporting the most important risk factors such as age, personal history of BC, family history of BC, reproductive risk factors, and exogenous hormone use as potential confounders is important to demonstrate a possible causal effect of a MBDP on the primary risk of BC (33). The studies by Männistö S, et al. (2021) and Lavalette C, et al. (2018) did report some important confounders, but family history of BC and/or reproductive risk factors were not included. In contrast, the study by Boden S, et al. (2019) reported none of the risk factors belonging to the important above-mentioned categories as potential confounders.

Follow-up **–** Three of the eight cohort studies were clear about the response rates and reported response rates above 90% for which is assumed that it does not affect the validity of the studies (13, 14, 19). However, the remaining studies were not clear about drop-out rates or characteristics of participants lost to follow-up. The study by Lavalette C, et al. (2020) reported the number of participants finally included, but not the total number of participants who were included at baseline. In the study by Boden S, et al. (2019), only ~65% of the participants who completed baseline questionnaires also completed follow-up questionnaires. As the drop-out rate is above 20%, this is considered as a high drop-out rate and characteristics of participants lost to follow-up should be described, but this is not done. As the study by Männistö S, et al. (2021) included multiple cohorts, response rates were ranging between 72% and 99%, but no more details were given for cohorts with drop-out rates above 20%. In contrast, the studies by Dela Cruz R, et al. (2020) and van den Brandt P.A, et al. (2017) didn't report anything at all about drop-out rates. It is important to gain insight in the drop-out rate and the characteristics of the participants who were lost-to follow-up when the drop-out rate is high, as bias can result if dropout rates are different between exposed and non-exposed groups or when the participants lost to follow-up are different from those maintained in the study (37).

General limitations **-** Unfortunately, we couldn't assess the BC risk separately for pre- and postmenopausal women from all studies, because only two cohort studies reported the outcome measures stratified by menopausal status. Furthermore, it is noteworthy that the studies by Krusinska B, et al. (2018)[1&2] and Aghamohammadi V, et al. (2021) chose their control samples by convenient and non-random selection, which might influence the generalizability to the whole population (38).

Quality case-control studies – In contrast to the cohort studies, more clear differences are seen in the overall quality scores: 22.2% scored a low overall quality, 11.1% a moderate overall quality, and 66.7% scored high overall quality. The low overall quality of two studies was mainly based on poor reporting about the inclusion/exclusion criteria and the recruitment procedure of the study population, the assessment of BC cases, and the instrument and method for measuring the exposure. Therefore, no judgements could be made on these methods and 0 points were obtained. The main topics on which case-control studies generally scored poorly were the exposure measurement, identification of confounders, and the exposure time. The discussion of these topics is described in the sections below.

Exposure measurement **-** It is also important for case-control studies that the method of exposure measurement has been validated through a validation study, as described in the 'exposure measurement' section for cohort studies. However, the study by Toklu H, et al. (2018) used a self-constructed questionnaire and the study by La Torre G, et al. (2021) used an FFQ type to collect dietary intake data, both without reporting a validation study. While most of the case-control studies used an interviewer-administered validated FFQ, the studies by Cao S, et al. (2022) and Castello A, et al. (2017) used a self-administered validated FFQ, which is more prone to overreporting than an interviewer-administered FFQ (39). Due to the lack of (reporting) proper validation studies, interpretation of the results should be done with caution as measurement errors may have affected the results.

Confounders **–** In order to obtain reliable results about a possible association between a MBDP and primary BC risk, it is also of high importance for case-control studies to identify and include

potential confounders in the analyses. It is a limitation that the studies by Aghamohammadi V, et al. (2021), Krusinska B, et al. (2018)[2], and Castello A, et al. (2017) couldn't adjust for reproductive risk factors, as these are found to be associated with BC risk (33, 40). The studies scoring a low overall quality didn't adjust for any confounders at all, which strongly influence the reliability of the reported association and the truly causal effect (23, 24).

Exposure time **-** Considering the exposure time for which data was collected, most studies reported that dietary intake data was collected only at baseline over the preceding year before diagnosis or enrollment (20-25, 27, 28), which is assumed as a too short exposure-time to investigate a possible association between a MBDP and BC risk. In contrast, the study by Turati F, et al. (2018) did not even mention the time-period over which dietary intake was collected. The only study that included a 'duration' factor in the analyses was the study by Cao S, et al. (2022), where they asked the participants how long they had been following their current dietary pattern over the previous years. However, this method is still very prone to recall bias.

General limitations **–** Most case-control studies, especially those reporting an inverse association with postmenopausal BC risk, had a study population which also consist mostly of postmenopausal women and therefore it was hard to assess an association for premenopausal women.

Comparing quality cohort and case-control studies – Minor differences were seen regarding the quality of cohort studies compared to case-control studies. From the overall quality assessment point of view, cohort studies scored slightly better on their methodology compared to case-control studies. For example, cohort studies clearly scored better on the assessment of BC cases and using appropriate statistical analyses. However, it is remarkable that both study designs score worse on two same critical appraisal topics: (I) exposure measurement and (II) the identification and adjustment for confounders.

Exposure measurement **-** Regarding the measurement of exposure, it is notable that the use of validated measurement tools could be improved in both study designs. An addition could be to verify adherence to the MBDP using blood biomarkers reflecting the intake of the most important bioactive ingredients of the MBDP, such as lipid (41) and fibre biomarkers (42). Moreover, most cohort and case-control studies scored poorly on the time for which dietary intake data were collected. However, it is difficult to include a much longer exposure time in case-control studies, as the risk of recall bias is then greatly increased. In cohort studies, on the other hand, there is much more room for improvement in terms of collecting dietary intake data by using longitudinal measurement methods.

Confounders **-** Furthermore, in both study designs there is room for improvement regarding the identification of confounders. However, some confounders such as physical activity and smoking can be tracked much more reliably in prospective cohort studies compared to case-control studies by also using longitudinal measurement methods.

Finally, case-control studies clearly showed that postmenopausal women were predominant in the study population, which can be inferred from the association between higher age and higher risk of BC (1). Cohort studies, on the other hand, have the ability to equalise the distribution between pre- and postmenopausal women, so a possible association in premenopausal women can also be reported. However, it was notable that case-control studies were much clearer in describing outcomes stratified by menopausal status, while cohort studies certainly have room for improvement in describing these outcomes.

Strengths and limitations literature thesis – This literature thesis distinguishes itself from previously published reviews in that it has included the most recent articles and that a major focus is placed on the quality of the included articles to examine the reliability of the existing evidence, thus providing leads for future research. Furthermore, the quality assessment of the articles was separately based on study design with a comprehensive critical appraisal checklist covering different types of bias.

However, there are also some limitations that should be noted. First, the literature process was restricted to only two databases which might have resulted in missing eligible articles. Second, only articles with an available free full text and written in the English language were included, which might have resulted in the exclusion of relevant articles. Lastly, the screening process for eligible articles and the quality assessment procedure was carried out by only one reviewer.

Conclusion

In conclusion, adherence to a MBDP might be inversely associated with BC risk in mostly postmenopausal women. However, these associations were mainly reported in case-control studies including a high percentage of postmenopausal women compared to premenopausal women. Therefore, conclusions regarding premenopausal women are lacking. In addition, these results are very prone to recall bias and confounding bias based on the quality assessment of the articles. Therefore, further research is needed with prospective cohort studies using longitudinal dietary intake measurements in which dietary intake is collected through a validated method in combination with the collection of possible blood biomarkers reflecting the adherence to a MBDP. In addition, it is very important that correction for potential confounders takes place to demonstrate a possible causal relationship. Finally, a good distribution of both pre- and postmenopausal women in the cohort would allow stratification of associations by menopausal status, as these might differ. This could provide reliable conclusions regarding the association between an MBDP and the risk of BC which, in turn, could ultimately have an impact on potential prevention strategies for certain subgroups.

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Appendices

Appendix A – search strings

Table 1A: Search strategy PubMed for retrieving literature investigating the association between a MBDP and the risk of BC in pre- and postmenopausal women

#	Search query	Number of results on 26 September 2022
1	"diet, mediterranean"[MeSH Terms] OR "diet mediterranean"[Title/Abstract] OR "mediterranean diet*"[Title/Abstract] OR "diets mediterranean"[Title/Abstract] OR "Diet"[MeSH Terms:noexp]	186.384
2	"Primary Prevention"[Mesh] OR “Primary prevention”[tiab] OR “Disease Prevention, Primary”[tiab] OR “Disease Preventions, Primary”[tiab] OR “Primary Disease Prevention”[tiab] OR “Primary Disease Preventions”[tiab] OR “Prevention, Primary”[tiab] OR “Primordial Prevention”[tiab] OR “Preventions, Primordial”[tiab] OR “Primordial Preventions”[tiab] OR “Prevention, Primordial”[tiab] OR "Risk Factors"[Mesh] OR “Factor, Risk”[tiab] OR “Risk Factor*”[tiab] OR “Health Correlates”[tiab] OR “Correlates, Health”[tiab] OR “Risk Scores”[tiab] OR “Risk Score”[tiab] OR “Score, Risk”[tiab] OR “Risk Factor Scores”[tiab] OR “Risk Factor Score”[tiab] OR “Score, Risk Factor”[tiab] OR "Risk"[Mesh] OR Risk*[tiab] OR “Relative Risk*”[tiab] OR “Risk, Relative”[tiab] OR “Risks, Relative”[tiab]	3.359.972
3	"Breast Neoplasms"[Mesh:noexp] OR "Breast Neoplasms/epidemiology"[Mesh] OR "Breast Neoplasms/prevention and control"[Mesh] OR "Breast Neoplasm*"[tiab] OR "Neoplasm, Breast"[tiab] OR "Neoplasms, Breast"[tiab] OR "Breast Tumors"[tiab] OR "Breast Tumor"[tiab] OR "Tumor, Breast"[tiab] OR "Tumors, Breast"[tiab] OR "Breast Cancer"[tiab] OR "Cancer, Breast"[tiab] OR "Malignant Tumor of Breast"[tiab] OR "Breast Malignant Tumor"[tiab] OR "Breast Malignant Tumors"[tiab] OR "Cancer of the Breast"[tiab] OR "Cancer of Breast"[tiab] OR "Malignant Neoplasm of Breast"[tiab] OR "Breast Malignant Neoplasm"[tiab] OR "Breast Malignant Neoplasms"[tiab] OR "Mammary Cancer"[tiab] OR "Cancer, Mammary"[tiab] OR "Cancers, Mammary"[tiab] OR "Mammary Cancers"[tiab] OR "Mammary Carcinoma, Human"[tiab] OR "Carcinoma, Human Mammary"[tiab] OR "Carcinomas, Human Mammary"[tiab] OR "Human Mammary Carcinomas"[tiab] OR "Mammary Carcinomas, Human"[tiab] OR "Human Mammary Carcinoma"[tiab] OR "Mammary Neoplasms, Human"[tiab] OR "Human Mammary Neoplasm"[tiab] OR "Human Mammary Neoplasms"[tiab] OR "Neoplasm, Human Mammary"[tiab] OR "Neoplasms, Human Mammary"[tiab] OR "Mammary Neoplasm, Human"[tiab] OR "Breast Carcinoma"[tiab] OR "Breast Carcinomas"[tiab] OR "Carcinoma, Breast"[tiab] OR "Carcinomas, Breast"	431.707
4	"Postmenopause"[Mesh] OR “Postmenopaus*”[Text Word] OR "Postmenopausal Period"[Text Word] OR "Period, Postmenopausal"[Text Word] OR "Post-Menopaus*"[Text Word] OR "Post Menopaus*"[Text Word] OR "Post-menopausal Period"[Text Word] OR "Period, Post-menopausal"[Text Word] OR "Post menopausal Period"[Text Word] OR "Premenopause"[Mesh] OR “Premenopaus*”[Text Word] OR "Premenopausal Period"[Text Word] OR "Pre-Menopaus*"[Text Word] OR "Pre-menopausal Period"[Text Word] OR Female*[Mesh] OR Female*[tiab]	10.171.694
5	#1 AND #2 AND #3 AND #4	1666
6	Filter: 01 January 2017 through September 2022	342

Table 1B: Search strategy Embase for retrieving literature investigating the association between a MBDP and the risk of BC in pre- and postmenopausal women

#	Search query	Number of results on 11 October 2022
1	Mediterranean diet/ or diet/ or mind diet/ or ('Mediterranean diet' or 'diet, Mediterranean' or 'MedDiet' or 'diet' or 'MIND diet').ti,ab,kf.	588.374
2	Primary prevention/ or risk factor/ or ('primary prevention' or 'risk factor' or 'relative risk' or 'risk factors').ti,ab,kf.	1.729.127
3	Breast cancer/ or ('Breast Cancer' or 'Breast Gland Cancer' or 'Breast Gland Neoplasm' or 'Breast Malignancies' or 'Breast Tumor' or 'Ca Breast' or 'Cancer in the Mammary Gland' or 'Cancer of the Breast' or 'Cancer of the Mammary Gland' or 'Cancer, Breast' or 'Malignancies of the Breast' or 'Malignancy of the Breast' or 'Malignant Breast Neoplasm' or 'Malignant Breast Tumor' or 'Malignant Neoplasm of the Breast' or 'Malignant Tumor of the Breast' or 'Mamma Cancer' or 'Mammary Cancer' or 'Mammary Gland Cancer' or Mammary Gland Malignancy' or 'Mammary Malignancies' or 'Mammary Malignancy').ti,ab,kf.	591.112
4	Premenopause/ or postmenopause/ or female/ or ('premenopause' or 'menopause, pre' or 'pre menopause' or 'premenopausal female' or 'premenopausal woman' or 'premenopausal period' or 'postmenopause' or 'post menopause' or 'postmenopausal female' or 'postmenopausal woman' or 'postmenopausal period' or 'female' or 'females' or 'woman' or 'women').ti,ab,kf.	11.164.209
5	#1 AND #2 AND #3 AND #4	1663
6	Filter: 2017 through 2022	490

Appendix B – Criteria answers quality assessment

Table 2A: Criteria answers and scoring system based on the JBI critical appraisal checklist for case-control studies

Critical appraisal topic	Criteria for answers	Scoring system
1.Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	**Yes**: control group is representative of the source population that produced the cases **Moderate**: Other source population is used but similar characteristics except for outcome are clearly described **No**: control group is not representative of the source population that produced the cases	Yes: 2 points Moderate: 1 point No: 0 points Total score: 20
2.Were cases and controls matched appropriately?	**Yes**: Sources from which cases and controls are recruited is clearly described and defined and matches appropriately **No**: Sources from which cases and controls are recruited does not match appropriately / not described or defined	
3.Were the same criteria used for identification of cases and controls?	**Yes**: same criteria were used for identification of cases and controls **No**: other criteria were used for identification of cases and controls / not mentioned	
4.Was exposure measured in a standard, valid and reliable way?	**Yes:** Exposure measured with validated FFQ and administered during an interview **Moderate**: Exposure measured with as self-administered validated FFQ **No:** Exposure measured with non-validated tool / exposure measurement not described	
5.Was exposure measured in the same way for cases and controls?	**Yes**: exposure measured in the same way for cases and controls **No**: exposure not measured in the same way for cases and controls / not mentioned	
6. Were confounding factors identified?	**Yes**: Reporting at least the most important risk factors for BC including age, personal history of BC, family history of BC, reproductive risk factors, and exogenous hormone use as possible confounders (33). **Moderate**: Some confounders reported but missing some of the most important risk factors **No**: No confounders reported	
7. Were strategies to deal with confounding factors stated?	**Yes**: Adjustment for confounders in statistical analysis **No**: No adjustment for confounders in statistical analysis / not mentioned	
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	**Yes**: Confirmed cases through by pathology/histology findings or verified cancer registries **Moderate**: Confirmed cases by verified method but not specified **No**: Cases are not confirmed / outcome measurement not described	
9. Was the exposure period of interest long enough to be meaningful?	**Yes**: exposure period between 2-5 years **Moderate**: exposure period ≤ 1 year but duration factor included **No**: exposure period ≤ 1 year / not mentioned	
10.Was appropriate statistical analysis used?	**Yes**: regression analysis used stratified by quantiles of the diet scale **Moderate**: statistical analysis used without providing OR for different quantiles of the diet scale **No**: no appropriate statistical analysis used for case-control studies / not mentioned	

Table 2B: Criteria answers and scoring system based on the JBI critical appraisal checklist for cohort studies

Critical appraisal topic	Criteria for answers	Scoring system
1.Were the two groups similar and recruited from the same population?	**Yes**: Two groups were similar and recruited from the same population / cohort **Moderate**: Different cohorts from the same country were combined **No**: Groups were recruited from different populations or cohorts / not mentioned	Yes: 2 points Moderate: 1 point No: 0 points Total score: 22
2.Were the exposures measured similarly to assign people to both exposed and unexposed groups?	**Yes**: exposures measured similarly **No**: exposures measured different / not mentioned	
3.Was the exposure measured in a valid and reliable way?	**Yes:** Exposure measured longitudinal with validated tool **Moderate**: Exposure measured at one timepoint with validated tool **No:** Exposure measured with non-validated tool / exposure measurement not described	
4.Were confounding factors identified?	**Yes**: Reporting at least the most important risk factors for BC including age, personal history of BC, family history of BC, reproductive risk factors, and exogenous hormone use as possible confounders (33). **Moderate**: Some confounders reported but missing some of the most important risk factors **No**: No confounders reported	
5.Were strategies to deal with confounding factors stated?	**Yes**: Adjustment for confounders in statistical analysis **No**: No adjustment for confounders in statistical analysis / not mentioned	
6.Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	**Yes**: groups/participants were free of the outcome at baseline **No**: groups/participants were not free of the outcome at baseline / not mentioned	
7.Were the outcomes measured in a valid and reliable way?	**Yes**: >90% confirmed cases through medical records or pathology findings **Moderate**: <90% confirmed cases through medical records or pathology findings but appropriate analytic strategies used to deal with the lower confirmed percentage **No**: Cases are not confirmed / outcome measurement not described	
8.Was the follow up time reported and sufficient to be long enough for outcomes to occur?	**Yes:** mean or median follow-up time reported and ≥10 years **Moderate:** mean or median follow-up time reported and between 5-10 years **No:** mean or median follow-up time reported and <5 years / not mentioned	
9.Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	**Yes**: Follow-up complete (>90% response rates) and reported **Moderate**: Follow-up not complete (<80% response rates) but reasons were reported **No**: Follow-up time incomplete (<80% response rates) but no reasons were reported/ not mentioned	
10.Were strategies to address incomplete follow up utilized?	**Yes**: person-years were calculated for whole cohort and included in statistical analyses **Moderate**: person-years were calculated for a subcohort and included in statistical analyses **No**: no person-years were calculated / not mentioned	
11.Was appropriate statistical analysis used?	**Yes:** appropriate statistical analyses used (cox proportional hazard model) **No**: no appropriate statistical analyses used / not mentioned	

Appendix C – detailed information regarding MBDP-assessment methods

Table 3: Detailed information regarding the MBPD assessment methods used in the included articles

MD scale	Beneficial components	Detrimental components	Alcohol intake
Trichopoulou A, et al. (2003)	0 points when consumption below sex-specific median 1 point when consumption above sex-specific median - Vegetables - Legumes - Fruits and nuts - Cereal - Fish	0 points when consumption above sex-specific median 1 point when consumption below sex-specific median - Meat - Poultry - Dairy products	1 point assigned when men consumed between 10 and 50 g per day 1 point assigned when women consumed between 5 and 25 g per day
Trichopoulou A, et al. (2003) and modification by Fung T.T, et al. (2006)	0 points when consumption below sex-specific median 1 point when consumption above sex-specific median - Vegetables - Potatoes - Legumes - Fruits - Nuts - Whole-grain cereals - Fish	0 points when consumption above sex-specific median 1 point when consumption below sex-specific median - Red and processed meats - Poultry	1 point assigned for intake between 5 and 15 g per day
Panagiotakos D.B, et al. (2007)	0 points when no consumption Scores 1 to 5 for rare to daily consumption - Vegetables - Potatoes - Legumes - Fruits - Non-refined cereals - Fish - Olive oil	5 points when no consumption 0 points when almost daily consumption - Red meat products - Poultry - Full fat dairy products	5 points when consumption less than 300 ml per day, 0 points when no consumption or >700 ml per day

MD scale	Beneficial components	Detrimental components	Alcohol intake
MEDI-LITE score by Sofi F, et al. (2013)	0 points when no to almost no consumption 2 points when high consumption - Fruit - Vegetables - Legumes - Cereals - Fish - Olive oil	2 points when no to almost no consumption 0 points when high consumption - Meat and meat products - Dairy products	1 point <1 AU/day 2 points 1-2 AU/day 0 points >2 AU/day
MIND diet score	Lowest tertile – 0 points Middle tertile – 0.5 points Highest tertile – 1 point - Vegetables - Nuts - Berries - Beans - Whole grain - Fish - Poultry	Lowest tertile – 1 point Middle tertile – 0.5 points Highest tertile – 0 points - Red meats - Butter and stick margarine - Cheese - Pastries and sweets - Fried/fast food intake	Excluded

Abbreviations: MBPD, Mediterranean-based dietary pattern; MD, Mediterranean Diet; MIND, Mediterranean-DASH Intervention for Neurodegenerative Delay; AU, alcohol unit

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____

Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
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?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

EXPLANATION OF COHORT STUDIES CRITICAL APPRAISAL

Cohort Studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the two groups similar and recruited from the same population?

Check the paper carefully for descriptions of participants to determine if patients within and across groups have similar characteristics in relation to exposure (e.g. risk factor under investigation). The two groups selected for comparison should be as similar as possible in all characteristics except for their exposure status, relevant to the study in question. The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants.

2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?

A high quality study at the level of cohort design should mention or describe how the exposures were measured. The exposure measures should be clearly defined and described in detail. This will enable reviewers to assess whether or not the participants received the exposure of interest.

3. Was the exposure measured in a valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

5. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of statistical methods as regression methods such as logistic regression are usually employed to deal with confounding factors/variables of interest.

6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

The participants should be free of the outcomes of interest at the start of the study. Refer to the 'methods' section in the paper for this information, which is usually found in descriptions of participant/sample recruitment, definitions of variables, and/or inclusion/exclusion criteria.

7. Were the outcomes measured in a valid and reliable way?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?

The appropriate length of time for follow up will vary with the nature and characteristics of the population of interest and/or the intervention, disease or exposure. To estimate an appropriate duration of follow up, read across multiple papers and take note of the range for duration of follow up. The opinions of experts in clinical practice or clinical research may also assist in determining an appropriate duration of follow up. For example, a longer timeframe may be needed to examine the association between occupational exposure to asbestos and the risk of lung cancer. It is important, particularly in cohort studies that follow up is long enough to enable the outcomes. However, it should be remembered that the research question and outcomes being examined would probably dictate the follow up time.

9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?

It is important in a cohort study that a greater percentage of people are followed up. As a general guideline, at least 80% of patients should be followed up. Generally a dropout rate of 5% or less is considered insignificant. A rate of 20% or greater is considered to significantly impact on the validity

of the study. However, in observational studies conducted over a lengthy period of time a higher dropout rate is to be expected. A decision on whether to include or exclude a study because of a high dropout rate is a matter of judgement based on the reasons why people dropped out, and whether dropout rates were comparable in the exposed and unexposed groups.

Reporting of efforts to follow up participants that dropped out may be regarded as an indicator of a well conducted study. Look for clear and justifiable description of why people were left out, excluded, dropped out etc. If there is no clear description or a statement in this regards, this will be a 'No'.

10. Were strategies to address incomplete follow up utilized?

Some people may withdraw due to change in employment or some may die; however, it is important that their outcomes are assessed. Selection bias may occur as a result of incomplete follow up. Therefore, participants with unequal follow up periods must be taken into account in the analysis, which should be adjusted to allow for differences in length of follow up periods. This is usually done by calculating rates which use person-years at risk, i.e. considering time in the denominator.

11. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section of cohort studies should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

JBI CRITICAL APPRAISAL CHECKLIST FOR CASE CONTROL STUDIES

Reviewer_____

Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
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?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

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EXPLANATION OF CASE CONTROL STUDIES CRITICAL APPRAISAL

Case Control Studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. Were the groups comparable other than presence of disease in cases or absence of disease in controls?

The control group should be representative of the source population that produced the cases. This is usually done by individual matching; wherein controls are selected for each case on the basis of similarity with respect to certain characteristics other than the exposure of interest. Frequency or group matching is an alternative method. Selection bias may result if the groups are not comparable.

2. Were cases and controls matched appropriately?

As in item 1, the study should include clear definitions of the source population. Sources from which cases and controls were recruited should be carefully looked at. For example, cancer registries may be used to recruit participants in a study examining risk factors for lung cancer, which typify population-based case control studies. Study participants may be selected from the target population, the source population, or from a pool of eligible participants (such as in hospital-based case control studies).

3. Were the same criteria used for identification of cases and controls?

It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics. A case should be defined clearly. It is also important that controls must fulfil all the eligibility criteria defined for the cases except for those relating to diagnosis of the disease.

4. Was exposure measured in a standard, valid and reliable way?

The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.

Case control studies may investigate many different ‘exposures’ that may or may not be associated with the condition. In these cases, reviewers should use the main exposure of interest for their review to answer this question when using this tool at the study level.

Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

5. Was exposure measured in the same way for cases and controls?

As in item 4, the study should clearly describe the method of measurement of exposure. The exposure measures should be clearly defined and described in detail. Assessment of exposure or risk factors should have been carried out according to same procedures or protocols for both cases and controls.

6. Were confounding factors identified?

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of case control design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

7. Were strategies to deal with confounding factors stated?

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured. Look out for a description of statistical methods as regression methods such as logistic regression are usually employed to deal with confounding factors/ variables of interest.

8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity. Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

9. Was the exposure period of interest long enough to be meaningful?

It is particularly important in a case control study that the exposure time was sufficient enough to show an association between the exposure and the outcome. It may be that the exposure period may be too short or too long to influence the outcome.

10. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured. For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.