Variations in time to breast cancer treatment initiation and survival across ethnoracial groups: a DAG-based protocol for a systematic review and meta-analysis

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Abstract

Background

Racial disparities in access to care are a known driver of differential health outcomes. There is a need to synthesize knowledge on the impact and mechanisms of ethnoracial variations in initiation of breast cancer treatment. The aim of the study described in this protocol is to systematically review the existing evidence on ethnoracial disparities in initiation of breast cancer treatments and their impact on patients’ survival in the United States.

Methods

A comprehensive systematic search of databases including PubMed, Ovid, Web of science, and the Cochran library will be performed. An extra search filtered on the title will be carried out on Google Scholar. Two main keywords, ‘breast cancer’ and ‘time to treatment,’ will be used in search strings. The review process will follow Preferred Reporting Items for Systematic Review and the Meta-Analysis Protocols (PRISMA-P) guidelines and will include studies of cohorts of female breast cancer patients who were diagnosed with stage I-III in the US. The Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) tool will be applied for bias assessment, and only studies with low or moderate risk of bias will be included. A modified checklist for applying the Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs) method is developed to describe the causal relationships between ethnoracial group membership, other study variables, delays to treatment, and survival.

Discussion

This systematic review will summarize the impact of racial disparity on breast cancer survival considering delays in receiving treatments as a mediator. Future directions will be identified to address existing gaps potentially relevant to creating equity for racial and ethnic minority groups. The results can help health authorities to develop approaches for addressing racial disparities in access to breast cancer treatment at the population level.

Background

Racial disparities in breast cancer contribute to needlessly poor health outcomes among members of marginalized racial groups. Many studies have been conducted on racial disparities in breast cancer etiology, incidence, mortality, screening, and treatment in the US over the past three decades [1–4]. Studies have shown higher mortality rates in marginalized breast cancer groups consistent with an independent and fundamental impact of race/ethnicity, even after controlling for biologic and other parameters [2–5]. Although breast cancer mortality has declined due to advances in prevention methods, treatment modalities, and survivorship care worldwide, in the U.S., mortality has decreased less among Black patients compared to other ethnoracial groups. Likewise, other health outcomes including breast cancer incidence and survival have remained less improved in this subpopulation [5, 6]. According to reports using Surveillance Epidemiology and End Result (SEER) data, the 5-year relative survival rate has continued to increase to 90.6% on average across all stages of breast cancer.
between 2012 and 2018, but the distribution of this improvement was unequal within different racial and ethnic groups [7]. In particular, 5-year survival in Black patients was estimated to be 82% relative to whites with 90% survival probability [8].

One essential intermediate predictor of survival is time-to-treatment initiation (TTI) for breast cancer patients. Over the last decades, studies addressed the effect of time to treatment on survival between different racial and ethnic groups in breast cancer patients [9–13]. There is consistent and increasing evidence pertaining to delays in initiation of treatments associated with race or ethnicity [14]. One study found a significant increase in delays in initiation of surgery in people of color, particularly in Black patients rather than other racial/ethnic minorities, when adjusting for biologic and socioeconomic factors [10]. Other studies showed a significant effect of delayed treatments on survival, progression-free survival, or breast cancer specific survival, in this group when compared to other racial and ethnic minorities [15, 16].

**Rationale for the systematic review**

Understanding common risk factors relating to delays in treatment initiation among marginalized groups is of essential importance. Studies showed that factors including biologic, socioeconomic and environmental parameters are associated with differences in time to diagnosis [17], initiation of surgery [10, 18–20], and chemotherapy in the U.S. [11, 21, 22]. One retrospective cohort study highlighted the effect of insurance status on early diagnosis of breast cancer among patients of different races and ethnicities [23]. By assessing inequality in breast cancer patients, we can identify, for different groups (e.g., Hispanic, African American), key characteristics that lead to inequity in access to care, and that must be addressed by policy.

The literature on breast cancer disparity focuses primarily on associations, rather than causal mechanisms [24, 25]. Many existing studies do not consider complex causal relationships between race/ethnicity and factors such as socioeconomic status or quality of life which affect time to surgery and strongly affect the time to initiation of treatments for patients [14]. This review will create new knowledge by synthesizing the potential causal relationships among factors that appear in the literature.

Tools for causal reasoning, such as directed acyclic graphs (DAGs), can enrich knowledge on health disparities and provide further information about health disparities for health authorities by making assumed causal structures explicit and by supporting estimation of causal effects. This review will extend and apply a new method, termed ESC-DAGs [26] which uses DAGs to synthesize causal assumption information retrieved by a systematic review. To our knowledge, this review will be the first systematic review using this causal approach to assess racial differences in breast cancer survival.

**Research objectives**

This review has three main objectives: 1) The overall objective will be to systematically review the existing evidence to assess variation in TTI across racial/ethnic groups. 2) The result will be a summary DAG showing the causal relationships among race/ethnicity and other factors, especially TTI, and these relationships’ effects on survival in cohort studies. 3) In addition, this review will conduct a meta-analysis with the specific aim of estimating the effect of time to initiation of treatments on survival related outcomes, including overall survival and progression-free survival, within specific race/ethnicity subgroups.
Methods

This protocol of a systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and the Meta-Analysis Protocols (PRISMA-P) guideline [27].

Eligibility criteria

Studies of female breast cancer patients aged over 18 and diagnosed with breast cancer stage I to III between 1995 and 2019 will be eligible for inclusion. Included studies must be cohort studies of breast cancer patients who have received at least one systematic modality (e.g., chemotherapy) or local therapy (e.g., surgery). Studies addressing advanced or metastatic breast cancer patients will be excluded, as treatment in this group of patients mainly involves palliative care.

To be included, a study must include a measure of race/ethnicity, and the measure must be included in the statistical analysis. Peer-reviewed publications of original cohort study findings that appeared in English-language academic journals will be eligible for inclusion. Editorials, letters, reviews, and preprints will be excluded. Moreover, studies covering data on breast cancer patients during the COVID-19 pandemic will also be excluded, because the treatment modalities and management of breast cancer patients changed based on both individual and health system factors.

In terms of further eligibility criteria for the potential meta-analysis, at least one of the outcomes, either survival related outcomes or TTI (see Outcome measure), must be reported in the findings of included studies. Studies reporting hazard ratio will be eligible for inclusion in the meta-analysis. Only studies with low or moderate risk of bias will be included in the meta-analysis.

Outcome measure

We will consider two outcome measures: survival, and time to treatment initiation. The primary outcome will be survival in breast cancer patients, including overall survival and progression free survival. Survival time can be measured using the difference in time interval between time to treatments and either time to death due to breast cancer or time to follow-up of survivors. Within time-to-event data analysis literature, survival has been mainly presented as 5-year survival or 10-year survival. Studies identified in our preliminary search suggested that overall survival, rather than progression-free survival, was measured as an outcome; this is because in most administrative databases, information on cause of death does not have high validity or has a high frequency of missingness [28, 29]. While overall survival was the most common outcome observed in our preliminary search, some studies did examine progression-free survival or 5-year recurrence-free survival in the context of racial disparity and delay in beginning treatments [28, 15].

Time to treatment initiation (TTI) will be the secondary outcome of the study. The definition of TTI varies across studies; in this review, TTI will be defined as the difference between time to diagnosis and time to initiation of a treatment (e.g., surgery, chemotherapy) [15, 30]. According to the studies’ methods for measuring TTI, cut-off points for determining that there has been a delay in accessing systemic therapies have been established based on stage and hormonal receptors in patients younger than 70. Based on the measures for stage II and III chemotherapy patients, the cut-off is less than 120 days. Although there is no established categorization for TTI, this review will examine three categories of intervals between diagnosis and treatment initiation including less
than 30 days, 60 days, and 90 or more days, after diagnosis [14, 15]. However, because previous studies addressed various subjectively-coded categories including binary or multiple categories of time to treatment, this study will also classify binary categories for delay to treatment such as less than 30 days and over 31 days.

**Race/ethnicity measure**

Self-reported race/ethnicity is considered as the gold standard measurement, because there is a low likelihood of misclassification error [17]. In the U.S, the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS) categories for race include: White, Black/African American, American Indian/Alaska Native, Asian Indian, Chinese, Japanese, Korean, Filipino, Vietnamese, Other Asian, Native Hawaiian, Guamanian/Chamorro, Samoan, and Other Pacific Islander [31]. However, as there is no standardized classification of race/ethnicity in studies, the likelihood of misclassification of race and ethnicity can be expected. To avoid this error, narrowing race/ethnicity classification into three categories including Black, white and others may be helpful [10, 11, 16]; however, this review will attempt to maintain more information related to race/ethnicity where possible.

**Search strategy**

Eligible studies will be identified through searching PubMed, Ovid, Web of science, and the Cochran library. Additionally, a search filtered on the title will be carried out through Google Scholar using keywords ‘breast cancer’ and ‘time to treatment’. An extra search will be manually performed to check the reference lists of included studies. Because the term ‘race’ is not likely to appear in the title/abstract even when a study is relevant to the review, two main keywords will be searched: ‘breast cancer’ and ‘time to treatment’. All databases will be searched using the combination of keywords ‘breast cancer’ and ‘time to treatment’ with their MeSH terms. As an example, search strings in PubMed were as follows: (((((((((((breast cancer[MeSH Terms]) AND (“time to treatment”[Title/Abstract]) OR (“time to surgery”[Title/Abstract]) OR (“time to chemotherapy”[Title/Abstract]) OR (“time to radiotherapy”[Title/Abstract]) OR (“time to hormone therapy”[Title/Abstract]) OR (“time to endocrine therapy”[Title/Abstract]) OR (“delayed treatment”[Title/Abstract]) OR (“delayed treatments”[Title/Abstract])). This review will use the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline [32].

**Study records**

First, duplicated records will be removed from the pooled records using reference manager software (e.g., Mendeley). The remaining studies will be screened based on the title and abstract. Two independent reviewers will extract data. Other reviewers will convene to discuss any uncertainties, including any errors in data collection process or uncertainty regarding inclusion of a study. Finally, in-depth analysis of full texts will be performed to determine the total number of included studies following eligibility criteria. In addition, studies will be searched for correction or retraction notices. Of these, eligible studies will be selected to conduct a meta-analysis. The selection process of studies in the systematic review is shown in Fig. 1.

**Risk of bias assessment**

The Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) will be used to assess risk of bias for included studies. ROBINS-I is a powerful tool which requires methodological and content knowledge and addresses internal validity. The tool assigns each paper one of five judgments: low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias and no information [33]. If a study fails to meet low or moderate risk
of bias, it will be excluded from the meta-analysis. The risk of bias assessment of included studies will be done by two reviewers and in case of controversy, the third reviewer will review the assessment.

A brief on the ESC-DAGs method

This review will use the Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs) guideline on evidence synthesis for constructing directed acyclic graphs (DAGs) to develop an integrated causal graph that summarizes the causal relationships across the study papers from our systematic review [26]. There is evidence that cohort studies frequently suffer from unmeasured factors (e.g., confounders), and DAGs are often used as tools to aid identification of confounders, as well as to help capture the effects of mediators [34]. The ESC-DAGs method uses three major steps to develop an integrated DAG (Fig. 2). The first step is mapping, which begins by drawing an "implied graph" for each study, based on that study's results and conclusions, which may include directed and undirected edges. Then, directed edges corresponding to other known factors and structures (e.g., mediators, confounders etc.) affecting the exposure-outcome association are added to the graph based on relationships implied by the findings of that study. The implied graph will be saturated and complex for each study, as it combines all relationships observed in the implied graph from the first stage. Translation of each implied graph into a DAG is the next step that can be applied through various approaches including causal theory and counterfactual thought experiments. In the ESC-DAGs protocol, three criteria of Hill's guideline, temporality, face validity and resource theory were suggested. The final stage is integration, which includes synthesis and recombination. This stage creates a single DAG by combining the translated DAGs. This is done by combining nodes with the goal of creating consensus and reducing complexity in the final DAG.

The result will be the integrated DAGs which describe the evidence on racial disparity for U.S. adult populations diagnosed with a primary breast cancer.

A workflow to apply ESC-DAG to cohort studies addressing racial disparity

The original ESC-DAG method is presented in general, without regard to study design. Here, we describe in detail our checklist for applying the method to cohort studies, which addresses two issues specific to applying ESC-DAG to cohort studies. First, authors might not specify the causal role of the covariates that are included, for example whether they are considered to be confounder(s) or mediator(s). Because of this, we might not be able to directly draw the causal graph for a study if we do not know the authors' causal assumptions. Second, we expect that studies will be of variable quality in terms of their risk of bias, and we only wish to include studies in the ESC-DAGs process if their risk of bias is low or moderate.

As part of this protocol, a workflow was created to describe the steps to apply the ESC-DAGs method to the included retrospective studies: 1) assess each study and create a study-specific DAG, 2) modify and/or simplify the DAGs using established causal criteria, 3) build a combined DAG which describes the existing literature and includes prior knowledge about causal theory, and 4) visualize the resulting DAGs (Fig. 3).

Figure 4 illustrates the steps. The checklist begins with determining the PICO (population, intervention, comparison group and the outcome) and assessing risk of bias. Studies will be removed if either PICOs cannot be determined, or if the study is not determined to have low or moderate risk of bias according to the ROBINS-I tool. For the included studies, the checklist follows the three ESC-DAGs stages: i) The mapping stage includes
drawing the exposure-outcome arrow, adding other covariates that are connected to the outcome and the exposure as nodes and then drawing related arrows from those control variables in the model towards them and vice versa. ii) The translation stage applies causal theory and counterfactual thought experiments to augment the implied graph resulting from mapping stage. For example, just as the exposure proceeds the outcome of interest, based on temporality, we will recognize which causes occur first and direct arrows accordingly. Additionally, based on causal logic, the impact of an exposure such as race, for instance, can be directly related to income or socioeconomic status (SES), and then to initiation of treatment not directly related to TTI. Finally, unmeasured confounders and potential latent variables can be found in the studies’ limitation and then they can be added as unobserved covariates into the DAGs. iii) The integration stage combines and simplifies all of the translated DAGs by grouping similar nodes to a single node. For example, nodes for income, occupation, and education might be combined into a single node that denotes SES. The final stage of our checklist, which is added to ESC-DAGs, will create integrated DAGs for each outcome of interest in the review. In our review we are considering two outcomes, TTI and survival, so we will create two different integrated DAGs.

The following two examples show how the mapping and translation checklist stages are applied to studies on racial disparity and TTI effects on survival.

**Example 1**

**racial disparity and time to surgery [22]**

In a large retrospective cohort study, Jackson et al. examined the differences in time to surgery and low-value care in early-stage non-Hispanic Black and non-Hispanic white breast cancer patients. This study found that time to initiation of surgery (i.e., > two months) was significantly higher among Blacks than in whites. Conduct the mapping stage, based on the variables in the study, a DAG with 29 nodes was created, with the ‘time to surgery’ node and the ‘race’ node considered as the outcome and the exposure, respectively, in the graph. A directed edge was drawn from the outcome node to the exposure node, and edges were drawn from each node corresponding to a variable that was controlled for in the analysis to the exposure node and to the outcome node. We considered genotype as an unmeasured covariate because the genetic information was not measured and was identified by the authors as a limitation. The role of each variable in this study were assessed and as a result, Fig. 5 depicts the incorporation of causal theory into the graph.

**Example 2: racial disparity and survival [23]**

A retrospective cohort study with large administrative data from National Cancer Database addressed the effect of delay in surgery on the likelihood of upstaging and overall survival in primary breast cancer patients. The results showed a significantly lower overall survival in Black patients compared to white patients, with a hazard ratio of 1.33. As time to surgery goes up, the likelihood of upstaging is likely to occur in patients. This study used 21 covariates in the Cox model. The main exposure was race/ethnicity, and the outcome was survival. All covariates as nodes were included in the graph and a directed edge originated from them was drawn to race and time to death (e.g., survival). The associated implied DAG is shown in Fig. 6.

**Challenges of causal effects of race in the context of disparity**

In the context of health disparity, the interpretation of “effects of race” can be challenging [35]. Based on counterfactual theory, it is not causally supported to evaluate the effect of race on the health outcomes.
Vanderweele and Robinson identify two methods for interpreting race effects in the presence of control variables, depending on whether or not the control variables mediate the effect of race on the outcome [35]. If the included control variables do not mediate the effect of race on the outcome, then the race/ethnicity coefficient in the regression model estimates the direct effect of race, assuming no unmeasured confounders. However, if the control variables mediate the effect of race on the outcome, then the interpretation of the race/ethnicity coefficient will subject to whether interaction between race and mediator is considered in the model or not. If there is no interaction, the interpretation of the race/ethnicity coefficient is the direct effect of race on the outcome, and the mediated effect can be captured using the difference in the coefficients in models with and without mediators [35]. If an interaction between race and the mediator is included in the model, the interpretation of the effect of the race coefficient corresponds to the natural indirect effect and controlled direct effect. Therefore, the interpretation of race/ethnicity effect depends on what controls have included in the regression model and their causal roles. In fact, multiple regression models can be considered to assess the effect of race/ethnicity as different controls combination can capture different aspects of race/ethnicity. This review will consider both methods as studies might include different control variables in the regression model.

Data synthesis

Data obtained from each single study will be synthesized by providing descriptive tables reporting authors’ names, publication year, main objective, sample size and period, defined race/ethnicity group, type of treatment(s), minimum causal components (e.g., covariates included in the multivariable model), and limitations related to internal validity (i.e., selection bias, information bias, and confounding). The findings of included studies will be presented chronologically. Because we expect effect measures to mainly be expressed as hazard ratios, the estimate of the hazard ratio, its 95% confidence interval, number of people in each race/ethnicity category, and any related information will be extracted from studies.

To perform the meta-analysis, based on the results of heterogeneity (i.e., \(I^2\) statistic), either a random effect (e.g., if \(I^2 > 50\%\)) or fixed effect model will be used. The potential effect measure will be the hazard ratio (e.g., hazard ratio for all-cause mortality) which will be presented for each single study as well as its pooled estimate with 95% confidence interval. Publication bias of included studies will be assessed using a funnel plot. In addition, 5- or 10-year survival probabilities will be reported from included studies if they are classified by race/ethnicity categories. Finally, as some studies might report odds ratios or regression coefficients, we will convert them to hazard ratios as much as possible.

Two additional analyses are proposed. First, a sensitivity analysis will be performed to evaluate the robustness of primary findings. This will help to identify and exclude low-quality studies if they have a significant impact on the results. As there is a likelihood of different included studies using the same or overlapping data sources, sensitivity analysis can aid to assess whether the proposed systematic review can rely on the results of pooled data or reduced data (i.e., excluding few studies which lead to less robust results). Moreover, subgroup analyses defined by essential risk factors such as stage of disease, hormone receptors (e.g., estrogen receptor, progesterone receptor and HER-2) and age will be conducted if studies provide information on same subcategories of mentioned risk factors. All statistical analyses will be performed using R software.

Discussion
This systematic review will summarize the impact of racial disparity on breast cancer survival. By investigating racial disparity considering delay in initiation of treatment in breast cancer patients, this review will demonstrate how causal analysis can be applied in health disparity research.

In terms of strengths, to our knowledge, this will be the first systematic review and meta-analysis addressing differences in TTI in marginalized racial/ethnic groups, in addition to survival. The result of this review will not only provide a summary of existing knowledge on TTI, but also the result of pooled analysis will provide estimates of essential effect sizes, including hazard ratios for different race/ethnicity groups. In addition, studies on the topic have been generally conducted on large samples of breast cancer patients, so pooled data are expected to be robust enough to perform statistical analysis and provide robust estimates. In this review we will use state-of-the-art measurements and statistical methods including powerful guidelines for appraising quality of studies, DAGs based causal assessment, and sensitivity analysis.

However, this study is prone to multiple limitations. Definition and classification of race/ethnicity differ across published studies. As a result, differences in race/ethnicity definition and its categorization between studies may require us to restrict the review to two main groups, Black and whites. Another limitation will be expected from eligibility criteria as end staged patients (i.e., stage > IV) will not recruit in this review. This can result in a lack of generalizability. Additionally, based on the eligibility criteria, studies will be restricted to the U.S. breast cancer population, where most studies on racial or ethnic disparities in breast cancer have been conducted. The representativeness of the pooled cohort might be violated, as some studies do not have external validity, and our quality assessment will address only internal validity. One another limitation is that the review will not include patients who fail to receive the treatments, because the reasons for not accessing assigned treatments are not clear. For example, this could be due to inequity in the health system across ethnoracial groups and would be impossible to capture through included studies. Finally, as retrospective cohort studies will be included in this review, some selection bias (e.g., lead-time bias) and misclassification of race/ethnicity and time to treatment will remain in the information incorporated into our systematic review and meta-analysis.

Abbreviations

PRISMA-P
Preferred Reporting Items for Systematic Review and the Meta-Analysis Protocols
ROBINS-I
The Risk Of Bias In Non-randomised Studies – of Interventions
ESC-DAGs
Evidence synthesis for constructing directed acyclic graphs
SEER
Surveillance Epidemiology and End Result
TTI
Time-to-treatment initiation
DAGs
Directed acyclic graphs
NCHS
the Centers for Disease Control and Prevention's National Center for Health Statistics
PRISMA
Preferred reporting items for systematic reviews and meta-analyses

PICO
population, intervention, comparison group and the outcome

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
The idea of the protocol was initiated by PMH. All authors conceptualized the research plan for the proposed potential systematic review and meta-analysis. PMH wrote the initial draft. All authors critically reviewed the methodology and the content and assisted with the writing of the manuscript. The final manuscript was approved by all authors.

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References


Figures
Figure 1

process of identification and data extraction of studies on racial disparity and time to treatment effect on survival in breast cancer
1. Set the outcome and the exposure in DAGs and direct edge from the exposure to the outcome.
2. Enter all control variables in DAGs and draw directed edges from each control to the exposure and the outcome (based on the result of the study).
3. Find the mediators, confounders, instrumental variables etc. based on study’s conclusion.
4. The resulted implied graph is saturated by drawing directed and undirected. (No matter of direction in this stage until translation stage)

5. Create DAG, apply causal theory in the implied graph. In this stage, four major considerations on causal criteria can be applied using below questions:
   a. does the outcome proceed with the exposure? (i.e., temporality)
   b. is the suggested relationship plausible? (i.e., Coherence)
   c. is the suggested relationship supported by existing theory? (i.e., plausibility)
   d. is the suggested relationship supported by counterfactual thought experiments?
6. Assess each relationship between all variables in the implied graph, apply causal criteria and counterfactual thought experiments.
7. Directed and reverse edges should be assessed, and the relationships may be as directed, reversed or bidirectional in the graph.

8. Synthesis all indexed directed edges to create one integrated DAGs
   a. start with the focal relationship of exposure \(\rightarrow\) outcome (step 1-3 of mapping phase)
   b. add each indexed edge related to focal relationship
   c. add each indexed directed edge related to other nodes such as between confounders
   d. group similar nodes to help recombination process
9. Recombine nodes for the purpose of reducing complexity or establishing consistency

**Figure 2**

Process of ESC-DAGs protocol
Figure 3

A workflow on the process of building causal DAGs
Mapping:

1. Determining PICO (study Population, Exposure/Intervention, Comparison group, Outcome including primary and/or secondary outcome).
2. Enter all control variables in the graph and draw directed edges from each variable to the exposure and the outcome based on the result of the study.
3. Determine the role of covariates such as the mediator and confounder. Then, draw arrows from the covariates towards exposure and outcome and vice versa.

Translation:

5. Create DAG, apply causal theory in the implied graph. Check temporality, coherence, and plausibility of Hill’s guideline.
6. Check all suggested relationships (i.e., directed, reversed, or bidirectional) using counterfactual thought.
7. Search for unmeasured covariates (e.g., confounders) in the studies’ limitation and add those variables into the DAGs as unobserved covariates.

Integration:

8. Create one integrated DAGs based on all indexed directed edges
   i. start with the principal relationship of exposure → outcome
   ii. add each indexed edge related to the relationship
   iii. add each indexed directed edge related to other nodes
   iv. group similar nodes to help recombination process
9. Recombine nodes for the purpose of reducing complexity or establishing consistency

10. To create an integrated DAGs for each outcome of interest (primary and secondary outcomes)

Figure 4

A developed checklist to build a causal DAGs for reviewing evidence in cohort designs
Figure 5

Example causal DAG: Jackson et al study, “Racial disparities in low-value surgical care and time to surgery in high-volume hospitals”

Figure 6
Example causal DAG: Khader et al study, “Delay in surgery is associated with axillary upstaging of clinically node negative breast cancer patients”

**Supplementary Files**

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- Additionalfile.docx