Risk factors associated with premature myocardial infarction: a systematic review protocol

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Risk factors associated with premature myocardial infarction: a systematic review protocol

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ABSTRACT

Introduction: Premature myocardial infarction (MI) generally refers to MI in men ≤55 years or women ≤65 years. Premature MI is a major contributor to cardiovascular disease (CVD), which claimed 17.6 million lives globally in 2016. Reducing premature MI and CVD is a key priority for all nations; however, there is sparse synthesis of information on risk factors associated with premature MI. To address this knowledge gap, we are conducting a systematic review to describe the association between risk factors (demographics, lifestyle factors, and biomarkers) and premature MI.

Methods and analysis: The following databases were searched from inception to June 2018: CENTRAL, CINAHL, Clinical Trials, EMBASE, and MEDLINE. We will include original research articles (case-control, cohort, and cross-sectional studies) that report a quantitative relationship between at least one risk factor and premature MI. Two investigators will use pre-determined selection criteria and independently screen articles based on title and abstract (primary screening). Articles that meet selection criteria will undergo full-text screening based on criteria used for primary screening (secondary screening). Data will be extracted using pre-determined data extraction forms. The Newcastle-Ottawa Scale for case-control and cohort studies will be used to evaluate the risk of bias, and will be adapted for cross-sectional studies. Whenever feasible, data will be summarised into a random-effects meta-analysis.

Ethics and dissemination: To our knowledge, this will be the first study to synthesize results on the relationship between risk factors and premature MI. These findings will inform health care providers on factors associated with risk of premature MI, and potentially improve primary prevention efforts by guiding development of interventions. These findings will be summarised and presented at conferences and through a peer-reviewed publication.

Systematic review registration PROSPERO CRD42018076862

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This will be the first comprehensive, systematic review of diverse risk factors associated with premature MI.
- The broad search strategy will identify infrequently reported risk factors, and identify new strategies to predict risk of premature MI.
- This study will categorise results by world region, thereby identifying regional variation in association of risk factors with premature MI.
- This study will only identify English-language articles from the peer-reviewed literature.
- This study will exclude articles with fewer than 100 cases of premature MI.

INTRODUCTION

Noncommunicable diseases (NCDs), which generally include cardiovascular disease (CVD), diabetes, respiratory disease, and cancer, are a major driver of global mortality [1]. The World Health Organization estimated that NCDs annually claim approximately 15 million lives within the 30–70 year age group (termed 'premature mortality'), with the major burden concentrated in low- and middle- income countries [2].

Cardiovascular disease is the major contributor to NCD-related morbidity and mortality, and in 2016, it claimed 17.6 million lives globally [3]. The majority of CVD-related deaths comes from ischemic heart disease, which is comprised of acute myocardial infarction (MI) and ischemic heart failure [4]. In 2016, IHD claimed 9.5 million lives, a 19% increase over the prior decade, attributed to aging and a growing population [3]. The high burden of IHD, particularly among young adults, adversely affects personal and economic productivity, health of caregivers, and increases health care costs [1,5,6]. Reducing the burden of IHD is a key priority for all countries.

Although premature mortality refers to mortality in the 30–70 year age group, premature MI generally refers to MI in men ≤55 years or women ≤65 years [7–9]. Although diagnosis, management, and treatment of MI have improved, results on IHD mortality in young adults have been mixed. A United States study showed that IHD mortality in young women (<55 years) has remained unchanged over a 20-year period from 1990–2011 [10]. Similarly, in countries including Australia, Canada, and Scotland, young adults have shown minimal to no improvement, higher IHD mortality, or different IHD mortality for men versus women [11–16]. The reasons for suboptimal IHD mortality in young adults are incompletely understood and require further characterisation.

There are limited international studies on the relationship between risk factors (demographics, lifestyle factors, clinical risk factors, and biomarkers) and premature MI. The INTERHEART study used a case-control design on 27,098 adults from 52 countries to assess the relationship between risk factors and acute MI. Although not designed to exclusively study premature MI, this study showed that the population attributable risk of nine risk factors (*lifestyle factors* [smoking; consumption of fruit and vegetables; exercise; consumption of alcohol; psychosocial stress]; *clinical risk factors* [hypertension; diabetes; abdominal obesity] and, *biomarker*s [ratio of blood levels of apolipoprotein B/apolipoprotein A1 (apoB/apoA)] was higher among younger (≤ 55 years for men and ≤ 65 years for women) versus older adults [17]. The Global Registry of Acute Coronary Events (GRACE) study evaluated 24,165 individuals from 14 countries presenting with acute coronary syndrome (ACS; comprised of MI and unstable angina) and assessed prevalence of risk factors in 10-year age groups (<45 years up to ≥85 years). They showed variable age-related trends for different risk factors (*demographics* [higher proportion of men in younger age groups]; *lifestyle factors* [higher prevalence of smoking in younger individuals]; *clinical risk factors* [lower prevalence of hypertension in younger individuals; prevalence of diabetes peaked in 65–74 year age group]; *biomarkers* [prevalence of hyperlipidemia peaked in 55–64 year age group]) [18].

In addition to INTERHEART and GRACE, other studies have evaluated the relationship between select risk factors and ACS. With respect to lifestyle factors, studies based in Spain and the Middle East have shown higher prevalence of smoking in younger individuals with ACS [19–22]. Smoking was generally more prevalent in men versus women, although this was not observed in a large study based in Canada [23]. In addition to lifestyle factors, few studies have examined the relationship between biomarkers and premature MI. Higher levels of low-density lipoprotein cholesterol and triglycerides, and lower levels of high-density lipoprotein cholesterol were observed in younger versus older individuals with ACS in the Middle East [20]; levels of

high-sensitivity C reactive protein (hsCRP), a marker of inflammation, were persistently higher in younger women versus younger men [24] and levels of ferritin were higher among individuals with premature MI versus controls [25].

To our knowledge, there are no published systematic reviews that describe the association between risk factors and premature MI. To address this gap, we have developed a protocol for a systematic review to describe the relationship between risk factors (demographics, lifestyle factors, and biomarkers) and premature MI. From these articles, we also describe the relationship between clinical risk factors and premature MI.

METHODS AND ANALYSIS

Standards

We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement for the completion of the systematic review. We have adhered to PRISMA protocols (PRISMA-P) for the reporting of this protocol (Appendix A) [26].

Protocol and registration

This review protocol is registered online with the International Prospective Register of Systematic Reviews (PROSPERO CRD42018076862). The online profile will be revised for major protocol amendments.

We searched OVID Medline (1946 to June 2018, including Epub Ahead of Print, In Process & other non-indexed citations), OVID Embase (1947 to June 2018), EBSCO CINAHL Plus with Full Text (1981 to June 2018), OVID AMED (1985 to June 2018), ClinicalTrials.gov and Cochrane Central to identify articles on premature MI. The search strategy was developed by an academic health sciences librarian (APA) with input from the study investigators. The search strategy was translated using each database platform's command language, controlled vocabulary, and search fields. MeSH terms, EMTREE terms, CINAHL headings, and textwords were used for the search concepts of myocardial infarction, young adults, and middle aged adults. The concept of premature was captured using textwords. MeSH headings included: myocardial infarction, acute coronary syndrome, young adult, adult, and middle aged.
A multi-stranded approach was used to search the concept of myocardial infarction in Medline, Embase, CINAHL, and Cochrane Central: search terms for myocardial infarction, heart attack, ST segment elevation MI (STEMI), non-ST segment elevation MI (NSTEMI), and acute coronary syndrome were combined with Boolean OR (strand 1). Search terms for young adults, adults, middle aged were combined with the Boolean OR (strand 2). Search terms for the concept of premature, untimeliness, and early onset were combined with the Boolean OR (string 3). Finally, all strings were combined with the Boolean AND. Our search strategy intentionally did not include risk factors to allow for identification of infrequently described risk factors. All searches were limited to the English language.

Searches were completed by June 2018. The MEDLINE search strategy is shown in Appendix B.

Eligibility criteria

Participants

Men (18–55 years) and women (18–65 years) who have experienced an MI.

Risk factors

Demographics, lifestyle factors, clinical risk factors, and biomarkers. Demographics include sex, race or ethnicity, education, income, living area (urban versus rural), and family history of cardiac disease. Lifestyle factors include exercise or physical activity, diet, alcohol consumption, tobacco use including shisha and khat, recreational drug use, and psychological stress. Clinical risk factors include diabetes, hypertension, obesity, and dyslipidemia. Biomarkers include, but are not restricted to, serum cholesterol (total cholesterol, high-density lipoprotein [HDL] cholesterol, non-HDL cholesterol, low-density lipoprotein [LDL] cholesterol), triglycerides, lipoprotein (a), apolipoprotein (Apo) A, ApoB, liver enzymes (aspartate transaminase [AST], alanine transaminase [ALT]), inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], hsCRP), fasting glucose, hemoglobin A1c (HbA1c), and other markers,

including kallikrein, matrix metallopeptidase 9 (MMP9), galectin-3, protein S, protein C, citrate, valine, leucine, isoleucine, alanine, homocysteine, fibrinogen, and iron.

Myocardial infarction
The following events will be included: acute coronary syndrome, STEMI, non-ST elevation–ACS, or, NSTEMI. The following events will be excluded: stable coronary heart disease, stable atherosclerosis, stable coronary artery disease, and heart failure.

Study design
Research articles published in English and that report a quantitative relationship between at least one risk factor (demographics, lifestyle factors, or biomarkers) and premature MI. From these studies, we will also assess the relationship between clinical risk factors and premature MI. Articles that exclusively evaluate clinical risk factors but no other risk factors (demographics, lifestyle factors, or biomarkers) will be described qualitatively but will not be included in quantitative analyses. We will include case-control, cohort, and cross-sectional studies. The following article types will be excluded: conference abstracts, review papers, systematic reviews, reports from organizations, research thesis (e.g., post-graduate, graduate, or undergraduate theses or reports), qualitative articles (e.g., focus groups, interviews, or articles that do not provide a quantitative relationship between risk factors and premature MI), editorials, commentaries, opinion pieces, letters to the editor, viewpoints, and case reports. We will exclude articles with fewer than 100 cases of premature MI.

Creation of database
We used search terms (developed in consultation with an academic health sciences librarian) to identify articles from electronic research databases. Duplicate results were removed, and articles from different databases were merged into a single database and imported to Covidence, an online software product for systematic reviews based on the Cochrane Review process.

Screening, data extraction, and risk of bias
For primary screening, the title and abstract were used to identify eligible studies based on selection criteria described above. For secondary screening, full-text articles were screened using selection criteria for primary screening. If an article meets selection criteria, but is not available online, we will make two attempts to contact authors by electronic mail and obtain the full text. Despite this, if the full-text is not available, we will exclude the study. Only English-language articles will be included, which may influence the precision of pooled estimates but not necessarily result in systematic bias [27]. Dual abstract and full-text screening will be done using standardized forms.

After a final set of articles is obtained, information will be extracted independently by two investigators using a standardized data extraction form. The form will include the following information: study type, study sites (countries), year of study, year of publication, number of participants, risk factor examined, and relationship of risk factor with premature MI (e.g., prevalence, incidence rate, relative risk, odds ratio). We will include risk factors prior to and up to four weeks following premature MI, as risk factors, particularly biomarkers, following that period may not reflect the acute MI phase and also may be modified by pharmacologic treatment. Where possible, we will analyse studies by sex and segregate by world regions defined by the World Bank [28].

For the final set of articles, the Newcastle-Ottawa Scale for case-control and cohort studies will be used to evaluate the risk of bias, and will be adapted for cross-sectional studies [29]. Studies

that do not adjust risk factors for potentially confounding variables will be considered to have higher risk of bias.
For primary and secondary screening, data extraction, and risk of bias assessment, conflicts between reviewers will be resolved by discussion between reviewers, and through consultation with a third reviewer, if necessary.

Data synthesis

Based on the quality of the studies that meet final study criteria, we will determine feasibility to conduct a meta-analysis to determine the relationship between risk factors and premature MI. Where applicable, we will present sex-stratified analyses.

If the relative association measures have similar or close adjustment we will conduct a random-effects meta-analysis (as implemented in the DerSimonian and Laird method) to pool across studies [30]. The random-effects model is chosen *a priori* due to expected variation of studies populations and settings. We will use the I-squared index and Cochrane Q test to determine the extent of heterogeneity and whether it is attributable to chance [31]. We will use STATA version 15 or higher to conduct analyses. Subgroup analyses based on sex or other relevant factors will be conducted and tested using an interaction test as described [32].

Although publication bias assessment methods have been developed for randomised controlled trials, we will attempt to evaluate publication bias in cases where we have more than 10 studies in a meta-analysis. We will visually inspect the funnel plots for symmetry and conduct the Egger regression test [33].

Summarising evidence

Based on the GRADE Working Group recommendations, we will use GRADEpro (http://ims.cochrane.org/gradepro) to build evidence of profiles that meet final eligibility criteria. We will evaluate the quality of evidence (certainty in estimates) using the GRADE approach for each association separately. We will examine the limitations of inclusion studies and whether any elements of indirectness, inconsistency, imprecision or publication bias were present. We will consider increasing the certainty level if the association is strong (i.e., large relative effect size over 2.0).

We will include the following elements: number of participants and country where the study is based; type of study (e.g., case-control, prospective cohort); prevalence and association of risk factors with premature MI, including relationships that are not statistically significant; analysis of prevalence and association of risk factors by sex and by world region; and additional comments or notes related to the study. If data are available, we will conduct a subgroup analysis based on different age thresholds or other factors.

Current study status

At the time of writing this manuscript, primary and secondary screening was completed independently by two investigators, and data extraction was in progress.

Ethics and dissemination

This study involves analysis of data from published literature and does not involve individual-level identifiable data. Given this, there were no privacy concerns that required ethical approval.

Results from this study will be presented at conferences and through publication in a peer-reviewed journal.

Patient and public involvement

There was no patient or public involvement in this study.

DISCUSSION

To our knowledge, this will be the first systematic review on the relationship between risk factors and premature MI. Information from this study may be useful for policy makers, government and non-government stakeholders, and health care providers to develop and implement strategies to reduce the burden of risk factors, and consequently, of premature MI, IHD, and CVD.

Several global declarations have focused on tackling the growing NCD burden. For instance, the United Nations World Health Assembly adopted the '25 × 25' resolution to reduce premature NCD-related mortality by 25% by the year 2025 [2] and the United Nations sustainable development goals aim to reduce premature NCD-related mortality by one-third by the year 2030 [34,35]. In this context, our study will identify knowledge gaps with sparse information on risk factors. This will guide development of a strategic research program to address the rising burden of premature MI and CVD. This is particularly relevant given the sobering update that many countries are not on track to achieve their NCD targets [2,36].

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AUTHORS CONTRIBUTIONS

- **Conceptualization:** AAA, SBD, SM
- **Formal analysis:** APA, RR, SBD, SNM, YMH
- **Investigation:** APA, RR
- **Methodology:** AAA, APA, MHM, SBD, YMH, SM
- **Project administration:** SBD
- **Supervision:** AAA, SM
- **Validation:** SBD, YMH
- **Writing–original draft:** APA, RR, SBD
- **Writing–review & editing:** AAA, APA, MHM, RR, SBD, SM, SNM, YMH
- **Guarantor:** AAA, SBD, SM

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COMPETING INTERESTS
The authors do not have competing interests.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 6
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	6
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	15
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	15
INTRODUCTION			

Rationale	6	Describe the rationale for the review in the context of what is already known	4 – 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6 – 7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6 – 7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix B
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7–8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8

	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	8

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (citc when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

APPENDIX B

Database(s): Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-June 2018

Search Strategy:

#	Searches
1	exp Myocardial Infarction/
2	acute coronary syndrome/
3	(AMI or MI or STEMI or NSTEMI).tw,kf.
4	((heart or coronary or cardiovasc* or cardiac* or myocard*) adj3 (attack* or infarc*)).tw,kf.
5	(acute adj2 coronary adj2 syndrome).tw,kf.
6	Young Adult/
7	Adult/
8	middle aged.sh.
9	adult.mp.
10	((early or premature or pre-mature or young* or earliest or earlier) adj2 (MI or (myocardial adj2 infarc*) or (heart adj2 attack*))).tw,kf.
11	(early or young* or premature* or earlie* or youth or untimely or oversoon).tw,kf.
12	or/1-5 [MI MeSH headings and textwords]
13	or/6-9 [Adults MeSH and textwords]
14	12 and 13 [MI AND Adults]
15	14 and 11 [MI AND Adults AND premature concept textwords]
16	15 or 10 [(MI AND Adults AND premature concept textwords) OR Premature NEAR MI]
17	exp Animals/ not (Humans/ and exp Animals/)
18	16 not 17 [Remove animal studies]
19	limit 18 to english language