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PROSPERO International prospective register of systematic reviews

A meta-analysis of type 1 diabetes mellitus, all-cause and cause-specific mortality

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Review question(s)

• What risk factors are associated with mortality in T1DM?

• How do these risk factors affect mortality rates in individuals diagnosed with T1DM as compared to the general population?

• Are there any gender difference in individuals diagnosed with T1DM?

Searches

Relevant studies will be searched for regardless of publication status i.e. published and unpublished studies.

An initial search will cover electronic databases such as PubMed, MEDLINE, Campbell Library of Systematic Reviews, Cochrane Database of Systematic Reviews (CDSR), EMBASE and PAIS International, the Cochrane Central Register of Controlled Trials (CENTRAL), LILACS, World Health Organisation Library and Information Network for Knowledge database (WHOLIS), The Centre for Evidenced-Based Medicine, PsycINFO, Google Scholar, National Library for Health, Ongoing Reviews database, British Nursing Index and Scopus (Higgins & Green, 2011).

The search for unpublished works will be done through assessing grey literature such as UK National Research Register (NRR), ReFeR, Kings Fund and Conference Papers Index. FADE, ProQuest Dissertation and mTheses, and other Indexed Citations up to 2015, National Technical Information Service (NTIS) and Health Management Information Service.

A manual search will be undertaken of reference lists of all studies identified by the above methods.

Non-English language databases like the LILACS (Latin American and Caribbean Health Sciences) will be assessed provided they are translated into English language to reduce the risk of language bias (CRD, 2008). Bibliographic databases such as BIOSIS will also be assessed for previews of materials from conferences.

The search strategy will involve using keywords and phrases, including Medical Subject Headings (MeSH) related to the inclusion criteria for the study.

The search period instituted will be between January, 1960 and March, 2016.

Types of study to be included

• Existing systematic reviews;

• Epidemiological studies;

• Randomised controlled trials of interventions in the management of T1DM.

Condition or domain being studied

Mortality in type 1 diabetes.

Participants/ population

Participants diagnosed with T1DM before the age of 40 years as it becomes increasingly difficult to differentiate between type 1 and type 2 diabetes after this age.

Intervention(s), exposure(s)

The nature of the outcome to be reviewed in this study is mortality after the diagnosis of type 1 diabetes.

Exclusions are as follows;

(1) Any study that has a CASP score (Quality appraisal) less than 8;

(2) Studies in which the participants acquire type 1 diabetes from a secondary cause;

(3) Studies that only have an abstract and the full paper is not accessible;

(4) Studies in which there is no differentiation between type 1 or type 2 diabetes in participants;

(5) Studies that do not have any comparison population (either cohort or general population);

(6) Studies without adequate data for analysis.

Comparator(s)/ control

The studies included will have a comparison population which will be either a comparison cohort or the general population.

Outcome(s)

Primary outcomes

Overall mortality rate/all-cause mortality.

The outcome measures used will be the standardized mortality ratio (SMR) as a form of relative risk (RR).

Secondary outcomes

Secondary outcomes include mortality in relation to:

1. Gender;

2. Year of study publication;

3. Follow-up duration;

4. Cause (overall and according to gender);

a) Cardiovascular disease (inclusive of coronary artery disease, myocardial infarction, heart failure/disease, ischemic heart disease);

b) Cerebrovascular disease (stroke);

c) Renal disease;

d) Cancer;

e) Accidents and suicide.

Data extraction, (selection and coding)

This process entails retrieving the information needed from the studies included in this review. The process can be carried out manually or electronically (CRD, 2008). Forms will be developed, modified, and adapted to the CRD template (CRD, 2008). The following data will be extracted from individually selected studies: author, year of

publication, study design, setting/location, year of study, comparison population, study size, number of deaths, patients' characteristics, follow-up years, outcome measure(s) of mortality, and degree of mortality in standardized mortality ratios (SMRs). The process of data extraction will be carried out by one reviewer (AE) any discrepancies will be addressed by two other reviewers (HC) and (DBJ).

Risk of bias (quality) assessment

Having ensured that studies meet the inclusion/exclusion criteria, the next stage will be to quality appraise the studies using the Critical Appraisal Skill Programme [CASP] tool (Higgins & Green, 2011). The CASP tool uses a check list that assesses systematic reviews, randomized control trials, case controls and cohort studies. The process will be documented and each study will be scored. This process will be carried out by one reviewer (AE) and triangulated by (HC) and (DBJ). CASP scores will be assigned to the study and any study scoring less than 9 out of an overall score of 12 will be excluded from the quantitative analysis.

The quality appraisal will assess the following three broad categories:

• Are the results valid?

• What are the results?

• Will the results help locally?

Strategy for data synthesis

We intend to conduct a narrative synthesis on the studies included in tabular format. This table will include a synthesis of the studies included, a consideration of factors such as study characteristics/type, study participants characteristics, settings and outcomes measured. We will also calculate the risk ratios using standardized mortality ratios (SMR) as a form of relative risk. The estimations of risk ratios (RR) will involve calculating the log (SMR) and standard errors (SE), back transformed to estimate the risk ratios (RR) at 95% confidence limits using the statistical software Review Manager version 5.3. We also intend to conduct a meta-analysis using the outcomes identified, estimating the average pooled effect estimate of the studies included at 95% confidence intervals. The analysis for this study will be either a random or a fixed-effect meta-analysis. It is anticipated that for a study of this nature, there will exist a certain amount of heterogeneity of the studies included because of variations in study populations, settings, and outcome measures. We intend to measure heterogeneity between study characteristics by assessing the I-squared estimate. Any values greater than 60% will considered as having significant levels of heterogeneity and an exclusion sensitivity analysis will be carried out to find out which studies contribute to the degree of heterogeneity observed.

Analysis of subgroups or subsets

We intend to conduct subgroup meta-analyses based on year of study publication and follow-up duration.

The follow-up duration will be categorized into follow-up durations of less than 10 years, between 10 and 20 years and greater than 20 years. Assessing the subgroup analysis on follow-up duration will be done as a proxy to estimate survival with disease progression.

Subgroup analysis based on study publication will consider publication years before the year 2000, publications between 2000 and 2010, and publications after the year 2010. This analysis will be done as a proxy to estimate the temporal trend in the management of type 1 diabetes.

Dissemination plans

We intend to communicate the essential messages of this review in conferences, and seminar meetings.

Contact details for further information

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None

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None known

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English

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England

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Subject indexing assigned by CRD

Subject index terms
Diabetes Mellitus, Type 1; Epidemiology; Humans; Mortality; Risk Factors

Any other information
This review is being undertaken as part of a PhD project in type 1 diabetes. AE, HC and DBJ are investigators for the proposed systematic review. AE and HC proposed the study, HC, DBJ, and MA are reviewers and supervisors of the study.

Stage of review
Ongoing

Date of registration in PROSPERO
11 April 2016

Date of publication of this revision
11 April 2016

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes

Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No