SYSTEMATIC REVIEW

Measure of the Rate at which Mortality in Type 2 Diabetes Mellitus Occurs: Protocol for a Systematic Review

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ABSTRACT

Introduction: Type 2 diabetes is the third largest cause of mortality in the United Kingdom, with about 50% of patients' having developed complications at time of diagnosis. We consider that the evidence which explores the actual hazard ratios of mortality has not been consistent. n this paper we discuss methodology and review the most recent accurate data on mortality in type 2 diabetes. **Methods:** A systematic review will be undertaken aimed at synthesis of evidence of relative risk of mortality in type 2 diabetes, using the Centre for Reviews and Dissemination guidelines. We will explore conflicting and unanswered questions in relation to mortality. The primary outcome is all-cause, overall-cause or total mortality expressed as hazard ratios. Sub-groups will also be explored; age, gender, socio-economic factors and causes of death. We will review abstracts published after 1990 in the English language. Our data source will include electronic databases; the Cochrane library, the Centre for Reviews and Dissemination, Medline/PubMed, and other grey literature. The study populations are type 2 diabetes patients whose mortality outcome, expressed as hazard ratio, has been evaluated. Data extraction will be undertaken by one reviewer and triangulated by the second and third reviewer. The quality of the included studies will be evaluated in accordance with the inclusion/exclusion criteria; methodological quality that meets the critical appraisal framework and the relevance to the research questions. Evidence from data will be synthesised through a descriptive epidemiological review from included studies; meta-analysis will be used if appropriate. **Result & Conclusion:** We expect to pool homogenous studies of large population cohorts which explore the hazard ratio of mortality, and to summarise the evidence of the actual mortality risk in type 2 diabetes, with limited bias. This will help direct future research in areas of unanswered questions and may influence healthcare policy decisions.

Keywords: All-cause mortality, Hazard ratio, Meta-analysis, Systematic review, Type 2 diabetes mellitus

INTRODUCTION

Globally, the 2010 projection is that about 285 million people suffer from type 1 or type 2 diabetes (T2D)[1]; in the United Kingdom (UK), the estimate is of 3 million diagnosed,[2] with undiagnosed diabetes accounting for an additional 1 million individuals.[3] At least 180 million of these patients have T2D.[4] As the life expectancy in the general population in UK is increasing there is limited evidence for a corresponding increase in the diabetic population. Accurate mortality indices of T2D are essential since countries rely on these for resource allocation and health systems prioritization.

The reported low mortality indices of T2D seen in the UK population have been questioned by many, as it is known that inaccuracy in the recorded cause of death on death certificates is widespread.[5] This is because diabetes has been implicated in the mechanisms leading to death in many medical conditions including cardiovascular, cerebrovascular diseases and cancer but diabetes is not always noted. Diabetes is a poor prognostic predictor in patients with cancer, heart failure, acute myocardial infarction, and other medical conditions. Nevertheless, the prognosis for diabetes patients varies greatly.

It has been recognised for many years that T2D is associated with an increase in mortality rate, in the range of between four to five times of those in the general mortality statistics.[6] More recent studies have suggested that it is twice that seen in the non-diabetic population.[7] Even though it is known that diabetes reduces life expectancy by 10-12 years this does not translate to an ability to predict death in patients with T2D.

More recently in Europe and UK an increased incidence of certain carcinomas have been implicated in diabetes-related mortality,[8,9] although not seen in the study from UK Health Information Network.[10] Carcinomas of the liver, pancreas and endometrium were associated with

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more than a two fold increase in relative risks, whereas colo-rectal, breast and bladder cancers were associated with less than 1.5 fold increase in relative risk.[11,12] There was no association with lung cancer while the study was inconclusive for renal and non-Hodgkin's lymphomas. Unexplainably, prostatic carcinoma was less often associated with T2D.[11] It is widely believed that this association is partly due to increasing incidence of both diseases with increasing age and their complex and multi-factorial pathophysiologies.

Other studies have suggested a possible increased malignancy risk with insulin therapy or its secretagogues in T2D while other authors provide contradictory evidences.[10,13,14] Sulfonylureas are the most implicated secretagogues amongst oral diabetes medications with possible increased malignancy risk,[10] whereas metformin has been seen to be associated with reduced cancer rates and mortality in patients with T2D.[15]

In 1998 the United Kingdom Prospective Diabetes Study (UKPDS) study identified that sulfonylurea therapy was not associated with increased risk of death, although a more recently published Canadian study identified a possible dose response relationship between sulfonylureas and mortality in T2D.[16] In addition, metformin monotherapy although associated with improved glycaemic control and reduction of all-cause mortality especially in obese T2D, its early addition to sulfonylurea therapy resulted in increased diabetes-related mortality when compared to sulfonylurea alone.[17] There is also additional limited evidence that some therapeutic agents, e.g. long-acting sulfonylureas, some thiazolelinediones and insulin are also associated with increased mortality rates in T2D.[10,14] Thiazolidinediones, especially rosiglitazone have been implicated in their effects on heart failure, myocardial infarction and cardiac mortality.[18]

Barnett et al. from their study in Tayside in UK showed that the age at diagnosis and duration of diabetes in patients with T2D affect both relative and absolute mortality risks and all-cause mortality.[19] Diabetes-related morbidity and mortality is age-related, it tends to be less in patients who develop T2D in their late seventies when compared to those who develop T2D in their mid-forties.[12] The risk of silent myocardial infarction (autonomic neuropathy) and hypoglycaemic unawareness increases with diabetes duration, obesity and hyperglycaemia. In one study in New Zealand it was concluded that in patients who had had myocardial infarction and/or congestive heart failure, the relative risk of death remains high for at least four years after hospitalisation regardless of glycaemic and cardiovascular risk factor regulation.[20]

Gender has been an independent factor in the mortality risks in T2D. Researchers have noted that in people above 49 years of age, females have greater mortality rates than males. This could be due to the risk of death from coronary heart disease (following the loss of cardioprotective effects of circulating oestrogen).[21]

There is also excess mortality associated with social deprivation in T2D.[22] This was stressed by other researchers who noted that diabetes mortality seen in those with poor social deprivation status was twice as high as the national average of those in the wealthiest areas.[23]

Various studies have proposed differing pathophysiological mechanisms in the acute effects of diabetes itself and to the accumulating adverse risks of mortality. The important mechanism implicated in the increase in mortality rate seen in T2D results from vascular and circulatory changes leading to endothelial dysfunction, platelet adhesions, viscosity and increased thrombosis.[24] More recently insulin and insulin-like growth factors (IGFs) receptor dynamics and in their expression of insulin-mediated abnormal cell proliferation have been established.[25] Although other explanatory biological pathways do exist, as documented in the literature on the pathogenesis of carcinomas in T2D there still remains unclear answers especially regarding the role of insulin resistance, hyperinsulinaemia and hyperglycaemia in the aetiology of cancers in T2D, as cancer and diabetes share similar risk factors.

With the ushering in of newer oral hypoglycaemic drugs it was expected that glycaemic regulation and mortality indices would start to normalise. The UKPDS reported that tight glycaemic control should be aimed at, with HbA1c of less than 7% but a more recent meta-analysis whilst showing that tight glycaemic control reduced microvascular complication,[17] and the risk for some cardiovascular disease events such as nonfatal myocardial infarction, it did not decrease the risks of cardiovascular endpoint or all-cause mortality. It also increased the risk of severe hypoglycaemia which is associated with morbidity and mortality.[26]

It is also surprising that even with improved patient education, specialist care, multi-disciplinary team working, technological advances and newer medications which have removed some obstacles, the attainment of improved life expectancy and decreasing mortality remains elusive. This raises questions pertaining to whether this is due to the complex interplay of some other variables, or lack of knowledge of the actual figures.

As the Diabetes UK and its research Network continues to explore avenues to unveil areas of unanswered research

questions with regards to improving life expectancy and reducing mortality from T2D, several questions need to be answered: these include;

At what stage should T2D patients commence cholesterol lowering agents?

Should calcium-channel blockers be commenced earlier in patients without overt nephrological complications?

In T2D, macrovascular complication is the predominant cause of mortality. As a consequence, preventable and modifiable risk factors such as cardiovascular risks should be aggressively reduced. Modifiable factors are considered to be important in about 70% of cases of mortality. Tight glycaemic regulation has been shown to be difficult to maintain and the evidence shows that in itself it has little effect on morbidity and mortality from cardiovascular disease in T2D. However there are also reports of adverse mortality associations in some patients where glycaemia is reduced after long duration of diabetes., Efforts should be aimed at continual optimisation of treatments for the four atherogenic factors in cardiovascular diseases: hypertension (anti-hypertensives), cholesterol and hyperlipidaemia (cholesterol lowering agents), obesity (weight reduction and diet modification), and smoking (smoking cessation), as well as hyperglycaemia.

Previous systematic reviews have shown varying increased relative mortality in type 2 diabetes combining different proxies of measure of degree of mortality, such as relative risks, standardised mortality ratios, and hazard ratios. These pose uncertainties in the true effect size. Furthermore, they were published prior to the changes in the clinical diagnostic criteria made by the WHO and American Diabetes Association in 1999. This study will update previous reviews and assess the actual relative mortality using the measure of degree of mortality.

In summary, this systematic review will explore the conflicting and unanswered questions in studies involving mortality risk and mortality predictors in T2D in relation to; actual causes of death and risk factors. Sub-groups within the Type 2 population will also be explored in relation to age, gender and socio-economic factors.

The systematic review will aim to answer these questions using the following methodology.

METHODS

A systematic review of the literature will be undertaken using published and unpublished articles including grey literature. The review will follow the Centre for Reviews and Dissemination (CRD) (March 2001) report number 4 guidance on methodological quality scoring criteria[27] and adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on reporting quality.[28]

Ethics approval was approved from the University of Chester Ethics Committee and from the Integrated Research Application System, UK.

Data Source

Electronic database search will be conducted including; The Cochrane Library, Centre for Reviews and Dissemination (CRD; DARE-database of abstracts of reviews of effects, HTA-health technology assessments, and NHS EED databases), Ovid Medline/PubMed, CINAHL, Web of Science (Web of Knowledge), World Health Organisation Library and Information Network for knowledge database (WHOLIS), The Centre for Evidenced-Based Medicine, PsycInfo, Google Scholar, EMBASE, National Library for Health, Ongoing Reviews database, British Nursing Index and SCOPUS. Others would include UK National Research Register (NRR), ReFeR, Kings Fund and Conference Papers Index. Also grey literature search will be conducted for unpublished articles using FADE, Proquest Dissertation and Theses, and other Indexed Citations up to 2014.

References of all retrieved articles will be checked for relevant studies, and if needed experts will be contacted for advice, and to identify additional published and unpublished references. The process of conducting the search will be documented as it develops to ensure transparency.

Search Terms

Keywords and phrases, including Medical Subject Headings (MeSH) to be searched will include; ''Type 2 diabetes mellitus mortality'', "Type 2 diabetes mortality", ''mortality and type 2 diabetes'', ''excess mortality and type 2 diabetes'', ''mortality rates and type 2 diabetes'', ''mortality and diabetes'', "type II diabetes and mortality", "type 2 DM and mortality", "type II DM and mortality", "determinants of mortality and type 2 diabetes", ''mortality predictors and diabetes'', and an effective combination of search terms will be conducted. The details of the search strategies are shown in Table 1.

Study Selection and Eligibility Criteria

Studies will be included if they fulfil the following criteria:

Study design: Existing systematic reviews, epidemiological studies and RCTs of intervention for treating T2D

Participants: People with T2D

Table 1: The search strategy to be used in the systematic review

Search strategy	Combination of free text words and controlled terms (MeSH)
Search #1 Search #2	Type 2 diabetes mellitus mortality, Type 2 diabetes mortality, mortality and type 2 diabetes, excess mortality and type 2 diabetes, mortality rates and type 2 diabetes, mortality and diabetes, type II diabetes and mortality, type 2 DM and mortality, type II DM and mortality, determinants of mortality and type 2 diabetes, mortality predictors and diabetes, type 2 diabetes survival, type 2 diabetes death Diabet* OR type 2 diabet* OR T2DM OR NIDDM OR type II diabet* NOT (type 1 diabet* OR type 1 DM OR type I DM OR IDDM)
Search #3	Mortality OR mortalit* OR mortality indices OR mortality predictors OR survival OR survival* OR death OR death* OR Type 2/*complications/mortality
Search #4 Search #1 AND #2 AND #3 AND #4	Diabetes/*adverse outcome/mortality OR diabetes/*outcome/death OR diabetes/*outcome/mortality OR diabetes/*complications/mortality Limit: English language

Types of outcome: All-cause-, cause-specific mortality in T2D expressed as hazard ratio, or if it is possible to calculate from the data available.

Studies will only be included if they report sufficient detail and constitutes a partial or complete review of mortality in T2D, and the search will be streamlined to research in the English language from 1990 through 2014. Search restriction was limited to studies published after 1990, as previous systematic reviews on mortality in T2D have produced conflicting and inconsistent evidence, and were published prior to the changes in the clinical diagnostic criteria by the World Health Organisation, and American Diabetes Association in 1999.

The following exclusion criteria will be used in this study: studies not published in English language and only available as an abstract; poor quality studies as decided by quality appraisal; and articles published prior to 1990.

Titles and abstracts of articles will be checked by two reviewers (CN and HC). Full texts of selected studies will be assessed for inclusion by one reviewer (CN) and triangulated by the other reviewer (HC and DBJ). Any variations in comments will be resolved by discussion. Figure 1 demonstrates the PRISMA flow chart for the selection of the studies.[28]

Data Extraction

Data extraction will be undertaken by one reviewer (CN, OAU, TO) and triangulated by the second reviewer, (HC) and if possible a third, (DBJ) especially if there are areas of conflicting comments. In the study we will utilise a standard paper format for easy extraction of data from the selected studies. Data from individually selected studies will be extracted as follows: 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 of mortality, and degree of mortality in hazard ratios.

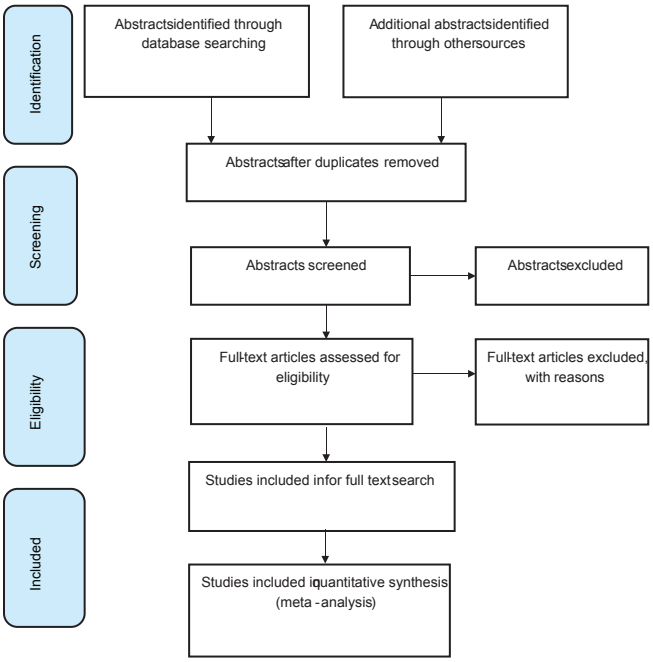

Figure 1: Flow diagram of study selection procedure [28]

The quality of the included studies will be evaluated in accordance with, the inclusion/exclusion criteria; methodological quality that meets the critical appraisal framework; and relevance to the research questions. The criteria used in the assessment of quality of included studies will be documented and clearly stated, and scored.

Quality Appraisal

The methodological quality of included studies will be assessed using CRD's guidance check list (critical quality appraisal programme, CASP) for quantitative research: systematic reviews, case control and cohort studies.[27] With little variations in the CASP's tool for various types of study, there are still 3 broad areas common to all; validity, results and relevance of results locally. The CASP tools for case control, systematic review and cohort studies comprise of 11-item, 10-item, and 12-item questions respectively as shown in Table 2.[29] We defined the quality of methodology as low, medium and high using the parameters from CASP

Table 2: A 12-item questionnaire to assess the methodological quality of systematic review[29]

SECTION A: Screening questions (Are the results of the study valid?)
Did the study address a clearly a clearly focused issue?
□ Yes □ No □ Unclear
Did the authors use an appropriate method to answer their questions?
□ Yes □ No □ Unclear
If 'Yes' in both questions 1 & 2, then it is worth proceeding with the remaining questions
Was the cohort or cases recruited in an acceptable way?
□ Yes □ No □ Unclear
Was the exposure accurately measured to minimise bias?
□ Yes □ No □ Unclear
Was the outcome accurately measured to minimise bias?
□ Yes □ No □ Unclear
A) Have the authors identified all important confounding factors? (B) Have they taken account of the confounding factors in the design and/or analysis?
□ Yes □ No □ Unclear
A) Was the follow-up of subjects complete enough? (B).Was the follow-up of subjects long enough?
□ Yes □ No □ Unclear
SECTION B: What are the results?
What are the results of the study?
□ Yes □ No □ Unclear
A) How precise are the results? B) How precise is the estimate of the risk?
□ Yes □ No □ Unclear
Do you believe the results?
□ Yes □ No □ Unclear
SECTION C: Will the results help me locally?
Was the follow-up of subjects complete enough?
□ Yes □ No □ Unclear
Do the results of this study fit with other available evidence?
□ Yes □ No □ Unclear

tool to categorise the papers based on their measurement properties. The CASP tool contains 12-item questions that assess reliability, content-, criterion-, and construct validity, measurement error, responsiveness and generalizability of the results. Each of these measurement properties were evaluated separately and scored for each study. An item was scored 'high' if the relevant aspect of methodological quality was presented clearly and adequately. Whereas a score of 'medium' indicated that there was evidence of adequacy of the methodological quality but not overtly stated. An item scored 'poor', if there was doubt or lack of clarity in the adequacy of the methodological quality and/or flaws in the design or statistical analysis. For uniformity and transparency PRISMA checklist tools will be used to assess the quality of reporting. Three reviewers will do this independently based on the availability of the data in the articles. The quality assessment and risk of bias will further be carried out using the Newcastle-Ottawa Scale.[30] Funnel plots will be explored for assessment of publication and related biases (language bias, poor methodological quality, and clinical heterogeneity), therefore the external validity of the data analysis.

Synthesis of Evidence

Evidence from data on mortality in T2D will be synthesised through a descriptive epidemiological review from included studies; meta-analysis will be used if appropriate as we expect the studies to be heterogenous in nature judging from the wide variations of population, and variability in complications and co-morbidities of the population. Data synthesis comprising of an overview of the included studies with respect to characteristics of the populations, interventions, designs and outcomes will be narrated. Data from included studies will be summarised in a table to maintain evidence. The point of estimate derived from each of the study design will then be taken for data synthesis. In addition, the quality of design and their effects will be included. In the data synthesis, hazard ratios were appropriate as measures of risks, and were illustrated using tables, figures and other computations. This will highlight the possible comparisons to be analysed, and the outcomes to be used in the meta-analysis, if appropriate. The summary evidence will be tabulated to help in ascertain and enhance transparency and precision.

Meta-analysis will be carried out to show precise estimate of mortality risk. Adjustments for confounding factors and sub-analyses of the effects of gender, drugs, cardiovascular diseases, smoking and alcohol, age at diagnosis and cancer on mortality risks will be also assessed. We will then narrate the results of the systematic review in line with the outcome of the meta-analysis. Tables of the selected studies will be shown as well as the figures of the meta-analysis. In addition it will show precision and statistical significance, measured by p-values. The point estimate, lower and upper limits of 95% confidence intervals will be log scaled and the effects observed in the studies will be pooled to produce a weighted average effect of all the studies. If there is a large effect size, meta-analysis may not be appropriate as nothing new would be added to inference. During the meta-analysis in order to check for the robustness of summary effect, larger studies are weighted preferentially by fixed effect models, whereas smaller studies are weighted preferentially by random effect models.[32] This therefore produces wider confidence intervals around the summary effect as they take into account variability in studies. However, the most precise tests of heterogeneity, the Cochran's Q score (Q-statistics), Inconsistency Index (I^2), Tau-square estimate (t^2), will be used and with a p-value < 0.1 indicating a statistically significant difference between studies. A high value of I^2

and Q-statistics translates to high heterogeneity. The Chi-square, a statistical test that defines the degree of freedom and goodness to fit within a distribution of independent variables, can also aid in the interpretations. An attempt will be made to explain the possible reasons for the heterogeneity.

Subgroup Analysis

Further exploration of heterogeneity results will be carried out using subgroup analysis.[31] Subgroup analysis will also be explored with respect to age, gender, socioeconomic status and cause of death, if adequate data are obtained from the selected studies. We will separately synthesise the results of subgroup of studies with different designs to ascertain if differences exist in the summary effect.

Sensitivity analysis will be used to ascertain the effects of different assumptions on the results i.e. repetition of analysis using the best and worst outcomes for the missing observations in each subgroup studied to ascertain the degree to which they affect the summary effect. Reviewers independently will triangulate the narrative write up by the lead reviewer with comments.

DISCUSSION

The results are expected to show the degree of mortality risks in T2D when compared with the general population. The strengths and limitations of the included studies will also be presented. The outcome of this study will help policy makers and healthcare managers direct resources for quality care in patients with diabetes.

EDITOR'S COMMENT

Upon completion, the result will be disseminated both locally and internationally through peer-reviewed journal.

AUTHOR'S CONTRIBUTION

OAU, TO, CN, HC and DBJ are principal investigators for the systematic review. CN and HC proposed the study. DBJ and HC are reviewers and supervisors of the study. All authors read and approved the final manuscript. We intend to re-evaluate and update the review after 2 years.

LISTS OF ABBREVIATIONS

- T2D: Type 2 Diabetes
- UK: United Kingdom
- UKPDS: United Kingdom Prospective Diabetes Study
- HbA_{1C}: Glycated haemoglobin
- CRD: Centre for Reviews and Dissemination
- DARE: Database of Abstracts of Reviews of Effects
- HTA: Health Technology Assessment
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- CASP: Critical Quality Appraisal Programme
- DPP-4 inhibitors: Dipeptidyl peptidase 4-inhibitors

COMPETING OF INTEREST

OAU is a postgraduate student at the University of Chester. TO is researcher at the Clinical Sciences and Nutrition department of the University of Chester. CNwas doctoral student under the auspices of Gladstone Fellowship, University of Chester and The Wirral University Teaching Hospital Foundation Trust, and presently a visiting Senior Lecturer in the Faculty of Health & Social Care. No financial and non-financial competing interest.

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