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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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ABSTRACT

Introduction:

Type 2 diabetes (T2D) is a leading health priority worldwide. Multimorbidity (MM) is a term describing the co-occurrence of two or more chronic diseases or conditions. The majority of people living with T2D have multimorbidity. The relationship between MM and mortality and glycaemia in people with T2D is not clear.

Methods and analysis:

MEDLINE, EMBASE, CINAHL Complete, The Cochrane Library, and SCOPUS will be searched with a prespecified search strategy. The searches will be limited to quantitative empirical studies in English with no restriction on publication date. One reviewer will perform title screening and two review authors will independently screen the abstract and full texts using Covidence software, with disagreements adjudicated by a third reviewer. Data will be extracted using a using a Population, Exposure, Comparator, and Outcomes (PECO) framework. Two reviewers will independently extract data and undertake the risk of bias (quality) assessment. Disagreements will be resolved by consensus. A narrative synthesis of the results will be conducted and meta-analysis considered if appropriate. Quality appraisal will be undertaken using the Newcastle-Ottawa quality assessment scale and the quality of the cumulative evidence of the included studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This protocol was prepared in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines to ensure the quality of our review.

Dissemination:

This review will synthesise the existing evidence about the impact of MM on mortality and glycaemic outcomes in people living with T2D and increase our understanding of this subject and will inform future practice and policy. Findings will be disseminated via conference presentations, social media and peer-reviewed publication.

Prospero registration number: CRD42017079500

Strength and limitations of this study

- This will be the first systematic review to explore the impact of MM on all-cause mortality and glycaemia in people with T2D and should make a valuable contribution to the literature in this area.
- Our review benefits from a comprehensive search strategy including key terms, synonyms and medical subject headings that describe the research questions with a deliberate

inclusion of the “comorbidity” term to address the identified issue of the terms “comorbidity” and “multimorbidity” being used interchangeably.

- We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely.

INTRODUCTION

Rationale

Type 2 diabetes (T2D) is a major health priority of the 21st century. Worldwide, it is estimated that more than 424 million people live with diabetes, resulting in $727 billion US dollars in healthcare expenditures (1). Approximately 4 million people die from diabetes related causes each year, equivalent to 1 death every 8 seconds, with nearly half of these deaths in people under the age of 60 (1). There is no doubt that T2D imposes a heavy burden on communities.

The management of T2D is complex, requiring continuous efforts to implement recommendations for self-management and pharmacotherapy in a step-wise manner to achieve evidence based targets. This complexity is increased when the patient has other chronic conditions in addition to T2D because T2D rarely occurs on its own. Data suggests that as many as 85% of those with T2D have at least one other chronic condition (2).

For many years, the terms comorbidity and multimorbidity (MM) were used interchangeably (3). It has only been more recently that there has been a clearer distinction and understanding between the two terms. Comorbidity is defined as the existence or occurrence of any additional condition(s) that co-occurs with an index disease (4). MM however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition (5). These established definitions provide the basis of our systematic review which exclusively focuses on MM in T2D.

MM presents multiple challenges. It is associated with a reduced quality of life, increased costs, a reduced ability to make lifestyle changes and may be associated with complex therapeutic regimens which the patient may be challenged to manage (6). For health professionals MM brings increased workload, and the clinical challenges of interactions between multiple conditions and medications (4). Most condition-specific management guidelines do not account for MM, and prioritise management of one condition at the expense of another (6). For people with diabetes, this can lead to clinicians focusing on diabetes only without consideration of the patient's other conditions and patient goals. Similarly, a focus on other conditions may lead to sub-optimal glycaemic management due to a lack of focus on diabetes-specific care goals (7, 8). This is particularly problematic because achieving and maintaining glycaemic targets early is important in reducing downstream complications and all-cause mortality (9).

Currently little is known about the associations between MM and T2D. In particular, there is little information regarding the relationship of the total burden of disease reflected in MM's multiple dimensions to the association between all-cause mortality and glycaemia.

Our systematic review will focus on current knowledge regarding the impact of MM on mortality and glycaemia in people with T2D and provide insights regarding the implications of MM in the context of this chronic disease. It may provide an important foundation of knowledge for improving care for patients with T2D and multiple chronic conditions.

Objectives

The primary objective of our systematic review is to determine the impact of MM reflected in condition count on all-cause mortality and glycaemia in people with T2D. We will have two primary outcomes of equal interest:1) all-cause mortality; and 2) glycaemia (measured by HbA1c). Secondary outcomes of interest include: 1) hypoglycaemia, 2) hyperglycaemia; and 3) glycaemic variability.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines has been used to prepare this protocol (10).

Eligibility criteria

Study characteristics/design:

All quantitative empirical studies published in the English language will be included. Our target studies will be observational studies that use either longitudinal cohort (retrospective and prospective) or cross-sectional designs. While we recognise the limitation of cross-sectional studies in terms of assessment of temporality, cross-sectional studies provide a snapshot of the association between MM count and our glycaemia related outcomes of interest. We will have no restrictions on publication date.

Randomised controlled trials, non-diabetes-drug intervention studies, all qualitative studies, case-reports, review articles and conference abstracts will be excluded as they will not give us information on our primary outcomes of interest. All non-English studies will also be excluded.

Population:

Our target study population be adults (18 years of age or older) with T2D.

Studies including populations of children and adolescents (under 18 years of age) or people without T2D (e.g. people with pre-diabetes, type 1 diabetes/gestational diabetes/monogenic diabetes) will be excluded. Animal studies will also be excluded.

Exposure:

The primary exposure of interest is MM count. Only studies that assess the relationship between a numerical count of MM and our outcomes of interest will be included.

Studies with single nominated specific conditions (i.e. only one comorbid condition) linked with T2D without MM count will be excluded.

Comparators (control):

A comparator/control group is defined by people with T2D with no other chronic conditions. Studies that do not include such a control group will not be excluded.

Outcome:

A study will be included in our review if data is provided regarding either all-cause mortality or glycaemic outcomes. It is expected that glycaemia will be reported in the form of HbA1c, however we will include any measure of glycaemia, for example, hypoglycaemia, hyperglycaemia or glycaemic variability.

Information sources

We will search five electronic databases including MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS with no restrictions on publication date.

We will check the International Prospective Register of Systematic Reviews (PROSPERO) regularly for ongoing and completed systematic reviews for MM and T2D.

Search strategy

The search strategy will include medical subject headings (MeSH), terms and synonyms relating to or describing our primary objectives. These terms will be combined using appropriate Boolean logic operators to create our search strategy. The truncation symbol (*) will also be included at the end of the stem of a word to retrieve all words that start with that stem. Our strategy has been reviewed by a librarian from a biomedical library and members of our review panel with expertise in MM and T2D. A number of test runs will firstly be conducted with MEDLINE, and any necessary adjustments will be made prior to running the search. Once the search strategy is finalised, the searches will be adapted for each of the five electronic databases, prior to conducting the searches. The search terms are listed in Table 1. The full search strategy is available in Supp. 1.

Table 1: Search terms

Key terms	Multimorbidity	Diabetes	Mortality	Glycaemia
Other related terms or synonyms	multimorbid* multi mobid* condition count* multiple condition* multiple disease* multiple disorder* multicondition* multidisease* multidisorder*	diabet* diabetes adj2 (type 2 or type ii)	mortality death surviv* surviv* analys*	glycaemia* glycemia* hypoglycaem* hypoglycem* hyperglycaem* hyperglycem* glycem* varia* glycaem* varia*

	multi condition* multi disease* multi disorder* comorbid* co morbid*			

Study records

Data management:

Literature search results will be downloaded to EndNote (Version 7; Clarivate Analytics) and duplicates will be removed. The non-duplicate studies will then be uploaded to Covidence (11), a systematic review management software, for the selection process.

Selection process:

The selection process of the studies for inclusion in our review will be conducted in three stages. First, titles of the studies identified in the five database searches will be screened by the primary researcher (JC) against the predefined eligibility criteria outlined above. A deliberately inclusive approach will be adopted for this title screening stage to reduce the risk of missing potentially relevant studies.

Second, all abstracts will be screened by two reviewers independently. The primary researcher (JC) will screen all abstracts against the predefined eligibility criteria outlined above to identify a subset of potentially relevant studies. This will then be repeated independently by a second reviewer (JMN, JF BN, BJ, AJ, FM). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF).

Finally, we will obtain full text articles for all studies that appear to meet our eligibility criteria after the title and abstract screening stages. Full text screening will be conducted by two reviewers independently. The primary researcher (JC) will screen all full texts against our predefined eligibility criteria. This will then be repeated independently by a second reviewer (JMN, JF, BJ). Online supplementary material will be consulted when necessary. Again, any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF). Reasons for exclusion at the full text screening process will be kept for record.

Data extraction:

Data will be extracted in a structured manner from all included studies and recorded in a predefined data extraction form designed by the primary researcher (JC) following a prespecified Population,

Exposure, Comparator, Outcomes (PECO) framework in the data extraction stage. This is an adapted framework based on the Cochrane PICO statement where "I" for intervention is replaced with an "E" for exposure. We will also be including an extra "Study Characteristics" parameter to record characteristics of the study including study design, setting, period of study, and aims and objectives. (See Supp. 2). The form will be reviewed, refined and adjusted where necessary by the review team. Again, online supplementary material will be consulted when necessary for data extraction.

Data items

We will be extracting relevant data in each of the following five parameters:

Populations:

We will extract data on characteristics of study populations (sample size, sex, age, ethnicity, social economic status, occupation, education, diabetes duration, HbA1c, insulin treatment and oral anti-diabetes drugs), as well as definition/measure of T2D, method of recruitment and sampling, and, inclusion and exclusion criteria.

Exposure:

We will describe the definition/measure of MM count and number of subjects reported.

Comparator:

We will provide details provided in the publication of any comparator groups including the definition/measure of people with T2D with no other chronic/long term conditions and number in group.

Outcomes:

We will provide details as to how all-cause mortality and/or glycaemia is defined/measured, as well as length of follow up, number of subjects, and the statistical analyses employed by the authors to evaluate the relationship between MM count and the measured outcomes.

Study characteristics:

We will extract details of study design, setting, period of study, and aims and objectives.

Outcomes and prioritisation

One of the primary clinical outcomes of interest is all-cause mortality. We expect that studies will calculate the effect estimate as either hazard ratios, odds ratios, incidence rates or survival percentages.

For our other primary outcome, glycaemia, we will prioritise those studies that measure glycaemia in terms of HbA1c. We will further divide studies into one of two groups: those that measure HbA1c into either considering HbA1c as a continuous or categorical variable.

We will accept all other measures of glycaemia as secondary outcomes.

Risk of bias assessment (quality assessment in individual studies)

Two reviewers will independently assess the risk of bias (quality) in each of the included studies.

All studies will be assessed using the Newcastle-Ottawa quality assessment scale (12). The choice of this tool was informed by recommendations from the Cochrane Handbook on assessing the quality of non-randomised studies (13). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer.

The Newcastle-Ottawa quality assessment scale has a star system to judge three broad perspectives of the included studies: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Data synthesis

For data synthesis, we will group the included studies according to the two outcomes of all-cause mortality and glycaemia. Within the glycaemia outcome group, we will further subgroup the studies into the different measures of glycaemia. For our primary analysis we will consider either all-cause mortality or glycaemia each as a composite outcome. However, dependent on the number of studies retrieved an analysis of glycaemia subtype will be conducted. Furthermore, dependent on the characteristics of the study populations, we will consider stratifying our results according to either exposure ascertainment (MM count) or population characteristics (i.e. age group, gender and social economic status).

A narrative synthesis of findings will be conducted which will describe the findings from each of the included studies. For each study we will present details relating to the following:

- The number and characteristics of participants in the study
- Setting
- Study design
- The outcome-level risk of bias of the study
- Findings for quantitative outcomes

- Inconsistent findings within individual studies will be indicated.

A meta-analysis will be conducted if appropriate. Tests for publication bias and heterogeneity will be conducted.

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guideline is recommended by the Cochrane Handbook for grading the quality and strength of evidence (14). We will use the GRADE guidelines to assess the quality of evidence for our research questions.

ETHICS AND DISSEMINATION

Ethics

Ethics was not required for this study as this is a systematic review and it does not contain individual patient data. We will disseminate the results of our review via conference presentations, social media and peer reviewed publication. This review also forms part of the lead investigator's (JC) PhD.

Discussion

This systematic review will aim to synthesise the existing evidence on the effects of MM in T2D on mortality and glycaemic control and will be the first on this subject. Clinical management in patients with T2D and MM is a growing international healthcare challenge and our review will make important contributions to understanding of the impact of MM, if any, in the context of T2D on key clinical outcomes which should enhance the understanding in this field.

Key strengths of our review will be our adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines, our robust search strategy and the fact that all screening and data extraction will be performed by two reviewers independently. We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely which will be a likely limitation. In addition, we have restricted our review to English language publications which is a potential limitation.

As the first review on this subject it will help identify what is known on this subject and whether any gaps in knowledge exist. It will therefore help highlight whether there are areas requiring further investigation as well as clarify the key messages from the evidence, to date, including implications for future guidelines for those with T2D.

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AUTHORS' CONTRIBUTIONS

JC drafted the protocol and developed the search strategy, inclusion/exclusion criteria and the data extraction form with guidance from JMN, JF, FM, BN, BJ, AJ and DO. PC contributed to the development of the search. All co-authors read and provided feedback on the draft manuscript.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

No competing interests.

Supplementary Document 1

Full Search Strategy – MEDLINE (OVID)

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to english
9	animal not human
10	8 not 9
11	multimorbid* or multi morbid*
12	condition count*
13	multiple condition* or multiple disease* or multiple disorder*
14	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
15	comorbid* or co morbid*
16	or/11-15
17	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
18	(mortality or death or surviv* or surviv* analys*) or mortality
19	(diabetes adj2 ("type 2" or "type ii"))
20	19 and 16
21	20 and (17 or 18)
22	limit 21 to english
23	10 or 22

Supplementary Document 2

Data extraction form

Reviewer Name	
Review Date	
STUDY	
First author	
Year	

STUDY CHARACTERISTICS

	Response	**Notes**
Setting		
Country		
Study Design		
Period of Study		
Aims and Objectives		

POPULATION and COMPARATOR

POPULATION	**Response**	**Notes**
Total number of participants		
Total number of participants with T2D		
How was T2D defined or measured in this population?		
How was the study population recruited?		
What were the sampling methods? Explain		
Inclusion criteria for study population		
Exclusion criteria for study population		
COMPARATOR		
Was there data on people with T2D with no other chronic condition (only T2D)?	☐Yes ☐No	If yes, please fill in both columns of table 1. If no only fill in the left column.
Total number of participants with T2D		

with no other chronic condition		

Table 1: Characteristics of those with and without type 2 diabetes

Characteristics	**T2D population n =**	**T2D Only (T2D with no other conditions – control group) n =**
Age, mean (SD)		
Female sex, N (%)		
Ethnicity, N (%) - Caucasian - Etc.		
Social economic status -		
Occupation -		
Education -		
Diabetes duration, mean (SD)		
HbA1c, mean (SD)		
Insulin treated, N (%)		
Oral anti-diabetes drugs, N(%) - None - One - Two or more - Etc.		

EXPOSURE

	Response	Notes
How was multimorbidity count defined in this population?		
List the conditions included for multimorbidity count		

Table 2: Multimorbidity characteristics of those with type 2 diabetes
Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**Number of people with MM characteristic recorded n =**
Multimorbidity count	
0 comorbidity, N (%)	
1 comorbidity, N (%)	
2 comorbidities, N (%)	
3 comorbidities, N (%)	
4 comorbidities, N (%)	
5 comorbidities, N (%)	
6+ comorbidities, N (%)	
Comorbid conditions	
e.g. Hypertension, N(%)	
e.g. Cardiovascular disease, N(%)	
Add additional columns and rows if needed	

OUTCOMES

MORTALITY OUTCOME:

	Response	Notes
Is all-cause mortality an outcome?	☐Yes ☐No	
How was all-cause mortality measured?		
Statistical analysis; How was the relationship between multimorbidity count and all-cause mortality explored?		
Length of follow up		

Table 3: Hazard ratios and 95% Confidence Interval (reword if MM count and mortality relationship explored differently) for effect of MM count on Mortality in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**HR (95% CI)**
Multimorbidity count	
0 comorbidity	
1 comorbidity	
2 comorbidities	
3 comorbidities	
4 comorbidities	
5 comorbidities	
6+ comorbidities	
Comorbid conditions	
e.g. Hypertension	
e.g. Cardiovascular disease	

What variables were adjusted in the statistical analysis?: ___

GLYCAEMIC OUTCOME:

	Response	Notes
Are any measures of glycaemia an outcome?	☐Yes ☐No	
How was glycaemia measured?	☐HbA1c ☐Fasting plasma glucose ☐Hypoglycaemic event ☐Hyperglycaemic event ☐Any measure of glycaemic variability Explain:	
Statistical analysis; How was the relationship between multimorbidity count and glycaemia explored?		
What was glycaemic outcome treated as	☐Continuous outcome ☐Categorical outcome ☐Both Explain:	
Length of follow up		this may not be applicable as we are only looking at cross sectional data

If glycaemic outcome is measured as a continuous variable use this: ☐Yes ☐No

Table 4: Estimated mean change, β1 and 95% Confidence Interval, in HbA1c (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (measured in HbA1c) in people with T2D

Or

If glycaemic outcome is measured as a categorical variable use this: ☐Yes ☐No

Table 4: Odds ratios and 95% Confidence Interval (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (if measured in OR, glycaemia most likely measured in hypoglycaemic/hyperglycaemic events) in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

	Reviewer uses 1 of the columns below depending on whether glycaemic outcome is measured as continuous or categorical			
Multimorbidity Characteristics	**Continuous: Estimated mean change, β1 (95% CI)**	**p-value**	**Categorical: OR (95% CI)**	**p-value**
Multimorbidity count				
0 comorbidity, N (%)				
1 comorbidity, N (%)				
2 comorbidities, N (%)				
3 comorbidities, N (%)				
4 comorbidities, N (%)				
5 comorbidities, N (%)				

6+ comorbidities, N (%)				
Comorbid conditions				
e.g. Hypertension, N(%)				
e.g. Cardiovascular disease, N(%)				

What variables were adjusted in the statistical analysis?: ___

OTHER

	Response	Notes
Was there missing data? Explanation	☐Yes, explain: ☐No	
Attrition? Explanation:	☐Yes, explain: ☐No	
Authors' conclusion		
Miscellaneous comments		
Funding source		
Other		
Additional notes		

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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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
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	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	7

		that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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)	8
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	8
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (see 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.**

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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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ABSTRACT

Introduction:

Type 2 diabetes (T2D) is a leading health priority worldwide. Multimorbidity (MM) is a term describing the co-occurrence of two or more chronic diseases or conditions. The majority of people living with T2D have multimorbidity. The relationship between MM and mortality and glycaemia in people with T2D is not clear.

Methods and analysis:

MEDLINE, EMBASE, CINAHL Complete, The Cochrane Library, and SCOPUS will be searched with a prespecified search strategy. The searches will be limited to quantitative empirical studies in English with no restriction on publication date. One reviewer will perform title screening and two review authors will independently screen the abstract and full texts using Covidence software, with disagreements adjudicated by a third reviewer. Data will be extracted using a using a Population, Exposure, Comparator, and Outcomes (PECO) framework. Two reviewers will independently extract data and undertake the risk of bias (quality) assessment. Disagreements will be resolved by consensus. A narrative synthesis of the results will be conducted and meta-analysis considered if appropriate. Quality appraisal will be undertaken using the Newcastle-Ottawa quality assessment scale and the quality of the cumulative evidence of the included studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This protocol was prepared in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines to ensure the quality of our review.

Dissemination:

This review will synthesise the existing evidence about the impact of MM on mortality and glycaemic outcomes in people living with T2D and increase our understanding of this subject and will inform future practice and policy. Findings will be disseminated via conference presentations, social media and peer-reviewed publication.

Prospero registration number: CRD42017079500

Strength and limitations of this study

- This will be the first systematic review to explore the impact of MM on all-cause mortality and glycaemia in people with T2D and has the potential to make a valuable contribution to the literature in this area.
- Our review benefits from a comprehensive search strategy including key terms, synonyms and medical subject headings that describe the research questions with a deliberate

inclusion of the “comorbidity” term to address the identified issue of the terms “comorbidity” and “multimorbidity” being used interchangeably.

- We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely.

INTRODUCTION

Rationale

Type 2 diabetes (T2D) is a major health priority of the 21st century. Worldwide, it is estimated that more than 424 million people live with diabetes, resulting in $727 billion US dollars in healthcare expenditures (1). Approximately 4 million people die from diabetes related causes each year, equivalent to 1 death every 8 seconds, with nearly half of these deaths in people under the age of 60 (1). There is no doubt that T2D imposes a heavy burden on communities.

The management of T2D is complex, requiring continuous efforts to implement recommendations for self-management and pharmacotherapy in a step-wise manner to achieve evidence based targets. This complexity is increased when the patient has other chronic conditions in addition to T2D because T2D rarely occurs on its own. Data suggests that as many as 85% of those with T2D have at least one other chronic condition (2), this is higher than the 52% in the general population that is multimorbid (3).

For many years, the terms comorbidity and multimorbidity (MM) were used interchangeably (4). It has only been more recently that there has been a clearer distinction and understanding between the two terms. Comorbidity is defined as the existence or occurrence of any additional condition(s) that co-occurs with an index disease (5). MM however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition (6). These established definitions provide the basis of our systematic review which exclusively focuses on MM in T2D.

MM presents multiple challenges. It is associated with a reduced quality of life, increased costs, a reduced ability to make lifestyle changes and may be associated with complex therapeutic regimens which the patient may be challenged to manage (7). For health professionals MM brings increased workload, and the clinical challenges of interactions between multiple conditions and medications (4). Most condition-specific management guidelines do not account for MM, and prioritise management of one condition at the expense of another (7). For people with diabetes, this can lead to clinicians focusing on diabetes only without consideration of the patient's other conditions and patient goals. Similarly, a focus on other conditions may lead to sub-optimal glycaemic management due to a lack of focus on diabetes-specific care goals (8, 9). This is particularly problematic because achieving and maintaining glycaemic targets early is important in reducing downstream complications and all-cause mortality (10).

Currently little is known about the associations between MM and T2D. In particular, there is little information regarding the relationship of the total burden of disease reflected in MM's multiple dimensions to the association between all-cause mortality and glycaemia.

Our systematic review will focus on current knowledge regarding the impact of MM on mortality and glycaemia in people with T2D and provide insights regarding the implications of MM in the context of this chronic disease. It may provide an important foundation of knowledge for improving care for patients with T2D and multiple chronic conditions.

Objectives

The primary objective of our systematic review is to determine the impact of MM reflected in condition count on all-cause mortality and glycaemia in people with T2D. We will have two primary outcomes of equal interest:1) all-cause mortality; and 2) glycaemia (measured by HbA1c). Secondary outcomes of interest include: 1) hypoglycaemia, 2) hyperglycaemia; and 3) glycaemic variability.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines has been used to prepare this protocol (11).

Eligibility criteria

Study characteristics/design:

All quantitative empirical studies published in the English language will be included. Our target studies will be observational studies that use either longitudinal cohort (retrospective and prospective) or cross-sectional designs. While we recognise the limitation of cross-sectional studies in terms of assessment of temporality, cross-sectional studies provide a snapshot of the association between MM count and our glycaemia related outcomes of interest. We will have no restrictions on publication date. The search end date will be 28 July 2017.

Randomised controlled trials, non-diabetes-drug intervention studies, all qualitative studies, case-reports, review articles and conference abstracts will be excluded as they will not give us information on our primary outcomes of interest. Randomised controlled trials and non-diabetes-drug intervention studies have primary objectives of testing particular interventions so the effect of MM will not be captured, thus inappropriate for our review which is focused on the effects on MM. All non-English studies will also be excluded.

Population:

Our target study population is adults (18 years of age or older) with T2D.

Studies including populations of children and adolescents (under 18 years of age) or people without T2D (e.g. people with pre-diabetes, type 1 diabetes/gestational diabetes/monogenic diabetes) will be excluded. Animal studies will also be excluded.

Exposure:

The primary exposure of interest is MM count. We will accept any type of MM count, which may include a list of chronic conditions from a variety of datasets including electronic medical records, administrative and prescription datasets. Only studies that assess the relationship between a numerical count of MM and our outcomes of interest will be included.

Studies with single nominated specific conditions (i.e. only one comorbid condition) linked with T2D without MM count will be excluded.

Comparators (control):

A comparator/control group is defined by people with T2D with no other chronic conditions. Studies that do not include such a control group will not be excluded.

Outcome:

A study will be included in our review if data is provided regarding either all-cause mortality or glycaemic outcomes. It is expected that glycaemia will be reported in the form of HbA1c, however we will include any measure of glycaemia, for example, hypoglycaemia, hyperglycaemia or glycaemic variability.

Information sources

We will search five electronic databases including MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS with no restrictions on publication date.

We will check the International Prospective Register of Systematic Reviews (PROSPERO) regularly for ongoing and completed systematic reviews for MM and T2D.

Search strategy

The search strategy will include medical subject headings (MeSH), terms and synonyms relating to or describing our primary objectives. These terms will be combined using appropriate Boolean logic operators to create our search strategy. The truncation symbol (*) will also be included at the end of the stem of a word to retrieve all words that start with that stem. Our strategy has been reviewed by a librarian from a biomedical library and members of our review panel with expertise in MM and T2D. A number of test runs will firstly be conducted with MEDLINE, and any necessary adjustments will be made prior to running the search. Once the search strategy is finalised, the searches will be adapted for each of the five electronic databases, prior to conducting the searches. The search terms are listed in Table 1. The full search strategy is available in Supp. 1.

Table 1: Search terms

Key terms	**Multimorbidity**	**Diabetes**	**Outcomes of interest:** **Mortality** **Glycaemia**
Other related terms or synonyms	multimorbid* multi morbid* condition count*	diabet* diabetes adj2 (type 2 or type ii)	mortality death surviv*

	multiple condition* multiple disease* multiple disorder* multicondition* multidisease* multidisorder* multi condition* multi disease* multi disorder* comorbid* co morbid*		surviv* analys* glycaemia* glycemia* hypoglycaem* hypoglycem* hyperglycaem* hyperglycem* glycem* varia* glycaem* varia*

Study records

Data management:

Literature search results will be downloaded to EndNote (Version 7; Clarivate Analytics) and duplicates will be removed. The non-duplicate studies will then be uploaded to Covidence (12), a systematic review management software, for the selection process.

Selection process:

The selection process of the studies for inclusion in our review will be conducted in three stages. First, titles of the studies identified in the five database searches will be screened by the primary researcher (JC) against the predefined eligibility criteria outlined above. A deliberately inclusive approach will be adopted for this title screening stage to reduce the risk of missing potentially relevant studies.

Second, all abstracts will be screened by two reviewers independently. The primary researcher (JC) will screen all abstracts against the predefined eligibility criteria outlined above to identify a subset of potentially relevant studies. An independent second screening of the abstracts will be completed between the following reviewers (JMN, JF, BN, BJ, AJ, FM). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF).

Finally, we will obtain full text articles for all studies that appear to meet our eligibility criteria after the title and abstract screening stages. Full text screening will be conducted by two reviewers independently. The primary researcher (JC) will screen all full texts against our predefined eligibility criteria. This will then be repeated independently by a second reviewer (JMN, JF, BJ). Online supplementary material will be consulted when necessary. Again, any inter-reviewer disagreements

will be discussed and resolved by a third reviewer (JMN, JF). Reasons for exclusion at the full text screening process will be recorded.

Data extraction:

Data will be extracted in a structured manner from all included studies and recorded in a predefined data extraction form designed by the primary researcher (JC) following a prespecified Population, Exposure, Comparator, Outcomes (PECO) framework in the data extraction stage. This is an adapted framework based on the Cochrane PICO statement where "I" for intervention is replaced with an "E" for exposure. We will also be including an extra "Study Characteristics" parameter to record characteristics of the study including study design, setting, period of study, and aims and objectives. (See Supp. 2). The form will be reviewed, refined and adjusted where necessary by the review team. Again, online supplementary material will be consulted when necessary for data extraction.

Data items

We will be extracting relevant data in each of the following five parameters:

Populations:

We will extract data on characteristics of study populations (sample size, sex, age, ethnicity, social economic status, occupation, education, diabetes duration, HbA1c, insulin treatment and oral anti-diabetes drugs), as well as definition/measure of T2D, method of recruitment and sampling, and inclusion and exclusion criteria.

Exposure:

We will describe the definition/measure of MM count and number of subjects reported.

Comparator:

We will provide details provided in the publication of any comparator groups including the definition/measure of people with T2D with no other chronic/long term conditions and numbers in group.

Outcomes:

We will provide details as to how all-cause mortality and/or glycaemia is defined/measured, as well as length of follow up, number of subjects, and the statistical analyses employed by the authors to evaluate the relationship between MM count and the measured outcomes.

Study characteristics:

We will extract details of study design, setting, period of study, and aims and objectives.

Outcomes and prioritisation

One of the primary clinical outcomes of interest is all-cause mortality. We expect that studies will calculate the effect estimate as either hazard ratios, odds ratios, incidence rates or survival percentages.

For our other primary outcome, glycaemia, we will prioritise those studies that measure glycaemia in terms of HbA1c. We will further divide studies into one of two groups: those that measure HbA1c as a continuous variable and those that measure HbA1c as a categorical variable.

We will accept all other measures of glycaemia as secondary outcomes.

Risk of bias assessment (quality assessment in individual studies)

Two reviewers will independently assess the risk of bias (quality) in each of the included studies.

All studies will be assessed using the Newcastle-Ottawa quality assessment scale (13). The choice of this tool was informed by recommendations from the Cochrane Handbook on assessing the quality of non-randomised studies (14). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer.

The Newcastle-Ottawa quality assessment scale has a star system to judge three broad perspectives of the included studies: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Data synthesis

For data synthesis, we will group the included studies according to the two outcomes of all-cause mortality and glycaemia. Within the glycaemia outcome group, we will further subgroup the studies into the different measures of glycaemia. For our primary analysis we will consider either all-cause mortality or glycaemia each as a composite outcome. However, dependent on the number of studies retrieved an analysis of glycaemia subtype will be conducted. Furthermore, dependent on the characteristics of the study populations, we will consider stratifying our results according to either exposure ascertainment (MM count) or population characteristics (i.e. age group, gender and socialeconomic status).

A narrative synthesis of findings will be conducted which will describe the findings from each of the included studies. For each study we will present details relating to the following:

- The number and characteristics of participants in the study
- Setting
- Study design
- The outcome-level risk of bias of the study
- Findings for quantitative outcomes
- Inconsistent findings within individual studies will be indicated.

If further information relevant to our review is required, we will attempt to contact the authors of the included studies.

A meta-analysis will be conducted if appropriate. Tests for publication bias and heterogeneity will be conducted. If the included studies are sufficiently homogenous in terms of study design, study population, outcomes and data analysis, a meta-analysis will be considered. I^2 statistic will be used to assess statistical heterogeneity and to guide the choice of either fixed or random effects model. Given sufficient numbers of included studies, a funnel plot will be used to assess publication bias and other reporting bias, and a Begg's test will be utilised to test for asymmetry. A sensitivity analysis will also be used to determine the consistency of the results. However, if a meta-analysis and the above tests are not possible, possible sources of bias across studies will be discussed in the narrative synthesis and this limitation will be considered when drawing conclusions.

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guideline is recommended by the Cochrane Handbook for grading the quality and strength of evidence (15). We will use the GRADE guidelines to assess the quality of evidence for our research questions.

Patient and public involvement

Patients were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Ethics

Ethics was not required for this study as this is a systematic review and it does not contain individual patient data. We will disseminate the results of our review via conference presentations, social media and peer reviewed publication. This review also forms part of the lead investigator's (JC) PhD.

Discussion

This systematic review will aim to synthesise the existing evidence on the effects of MM in T2D on mortality and glycaemic control and will be the first on this subject. Clinical management in patients with T2D and MM is a growing international healthcare challenge and our review will make important contributions to understanding of the impact of MM, if any, in the context of T2D on key clinical outcomes which should enhance the understanding in this field. We hypothesise that increasing MM will be associated with increased all-cause mortality, however the effects on glycaemic outcomes may vary. Our review will be the first to bring together existing literature exploring associations between MM and T2D, and therefore clarifying the effects of increasing MM on mortality and glycaemia in people with T2D.

Key strengths of our review will be our adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines, our comprehensive search strategy and the fact that all screening and data extraction will be performed by two reviewers independently. We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely which may be a limitation. In addition, we have restricted our review to English language publications which is a potential limitation.

As the first review on this subject it will help identify what is known on this subject and whether any gaps in knowledge exist. It will therefore help highlight whether there are areas requiring further investigation as well as clarify the key messages from the evidence, to date, including implications for future guidelines for those with T2D.

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AUTHORS' CONTRIBUTIONS

JC drafted the protocol and developed the search strategy, inclusion/exclusion criteria and the data extraction form with guidance from JMN, JF, FM, BN, BJ, AJ and DO. PC contributed to the development of the search. All co-authors read and provided feedback on the draft manuscript.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

No competing interests.

Supplementary Document 1

Full Search Strategy – MEDLINE (OVID)

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to english
9	animal not human
10	8 not 9
11	multimorbid* or multi morbid*
12	condition count*
13	multiple condition* or multiple disease* or multiple disorder*
14	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
15	comorbid* or co morbid*
16	or/11-15
17	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
18	(mortality or death or surviv* or surviv* analys*) or mortality
19	(diabetes adj2 ("type 2" or "type ii"))
20	19 and 16
21	20 and (17 or 18)
22	limit 21 to english
23	10 or 22

Supplementary Document 2

Data extraction form

Reviewer Name	
Review Date	
STUDY	
First author	
Year	

STUDY CHARACTERISTICS

	Response	Notes
Setting		
Country		
Study Design		
Period of Study		
Aims and Objectives		

POPULATION and COMPARATOR

POPULATION	Response	Notes
Total number of participants		
Total number of participants with T2D		
How was T2D defined or measured in this population?		
How was the study population recruited?		
What were the sampling methods? Explain		
Inclusion criteria for study population		
Exclusion criteria for study population		
COMPARATOR		
Was there data on people with T2D with no other chronic condition (only T2D)?	☐Yes ☐No	If yes, please fill in both columns of table 1. If no only fill in the left column.
Total number of participants with T2D		

with no other chronic condition		

Table 1: Characteristics of those with and without type 2 diabetes

Characteristics	**T2D population n =**	**T2D Only (T2D with no other conditions – control group) n =**
Age, mean (SD)		
Female sex, N (%)		
Ethnicity, N (%) - Caucasian - Etc.		
Social economic status -		
Occupation -		
Education -		
Diabetes duration, mean (SD)		
HbA1c, mean (SD)		
Body mass index, kg/m^2, mean (SD)		
Insulin treated, N (%)		
Oral anti-diabetes drugs, N(%) - None - One - Two or more - Etc.		

EXPOSURE

	Response	Notes
How was multimorbidity count defined in this population?		
List the conditions included for multimorbidity count		

Table 2: Multimorbidity characteristics of those with type 2 diabetes
Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**Number of people with MM characteristic recorded n =**
Multimorbidity count	
0 comorbidity, N (%)	
1 comorbidity, N (%)	
2 comorbidities, N (%)	
3 comorbidities, N (%)	
4 comorbidities, N (%)	
5 comorbidities, N (%)	
6+ comorbidities, N (%)	
Comorbid conditions	
e.g. Hypertension, N(%)	
e.g. Cardiovascular disease, N(%)	
Add additional columns and rows if needed	

OUTCOMES

MORTALITY OUTCOME:

	Response	Notes
Is all-cause mortality an outcome?	☐Yes ☐No	
How was all-cause mortality measured?		
Statistical analysis; How was the relationship between multimorbidity count and all-cause mortality explored?		
Length of follow up		

Table 3: Hazard ratios and 95% Confidence Interval (reword if MM count and mortality relationship explored differently) for effect of MM count on Mortality in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**HR (95% CI)**
Multimorbidity count	
0 comorbidity	
1 comorbidity	
2 comorbidities	
3 comorbidities	
4 comorbidities	
5 comorbidities	
6+ comorbidities	
Comorbid conditions	
e.g. Hypertension	
e.g. Cardiovascular disease	

What variables were adjusted in the statistical analysis?: ___

GLYCAEMIC OUTCOME:

	Response	Notes
Are any measures of glycaemia an outcome?	☐Yes ☐No	
How was glycaemia measured?	☐HbA1c ☐Fasting plasma glucose ☐Hypoglycaemic event ☐Hyperglycaemic event ☐Any measure of glycaemic variability Explain:	
Statistical analysis; How was the relationship between multimorbidity count and glycaemia explored?		
What was glycaemic outcome treated as	☐Continuous outcome ☐Categorical outcome ☐Both Explain:	
Length of follow up		this may not be applicable as we are only looking at cross sectional data

If glycaemic outcome is measured as a continuous variable use this: ☐Yes ☐No

Table 4: Estimated mean change, β1 and 95% Confidence Interval, in HbA1c (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (measured in HbA1c) in people with T2D

Or

If glycaemic outcome is measured as a categorical variable use this: ☐Yes ☐No

Table 4: Odds ratios and 95% Confidence Interval (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (if measured in OR, glycaemia most likely measured in hypoglycaemic/hyperglycaemic events) in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

	Reviewer uses 1 of the columns below depending on whether glycaemic outcome is measured as continuous or categorical			
Multimorbidity Characteristics	**Continuous: Estimated mean change, β1 (95% CI)**	**p-value**	**Categorical: OR (95% CI)**	**p-value**
Multimorbidity count				
0 comorbidity, N (%)				
1 comorbidity, N (%)				
2 comorbidities, N (%)				
3 comorbidities, N (%)				
4 comorbidities, N (%)				
5 comorbidities, N (%)				

6+ comorbidities, N (%)				
Comorbid conditions				
e.g. Hypertension, N(%)				
e.g. Cardiovascular disease, N(%)				

What variables were adjusted in the statistical analysis?: ___

OTHER

	Response	Notes
Was there missing data? Explanation	☐Yes, explain: ☐No	
Attrition? Explanation:	☐Yes, explain: ☐No	
Authors' conclusion		
Miscellaneous comments		
Funding source		
Other		
Additional notes		

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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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
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	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	7

		that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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)	8
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	8
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (see 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.**

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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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Impact of multimorbidity count on all-cause mortality and glycaemic outcomes in people with type 2 diabetes: a systematic review protocol

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ABSTRACT

Introduction:

Type 2 diabetes (T2D) is a leading health priority worldwide. Multimorbidity (MM) is a term describing the co-occurrence of two or more chronic diseases or conditions. The majority of people living with T2D have multimorbidity. The relationship between MM and mortality and glycaemia in people with T2D is not clear.

Methods and analysis:

MEDLINE, EMBASE, CINAHL Complete, The Cochrane Library, and SCOPUS will be searched with a prespecified search strategy. The searches will be limited to quantitative empirical studies in English with no restriction on publication date. One reviewer will perform title screening and two review authors will independently screen the abstract and full texts using Covidence software, with disagreements adjudicated by a third reviewer. Data will be extracted using a using a Population, Exposure, Comparator, and Outcomes (PECO) framework. Two reviewers will independently extract data and undertake the risk of bias (quality) assessment. Disagreements will be resolved by consensus. A narrative synthesis of the results will be conducted and meta-analysis considered if appropriate. Quality appraisal will be undertaken using the Newcastle-Ottawa quality assessment scale and the quality of the cumulative evidence of the included studies will be assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. This protocol was prepared in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines to ensure the quality of our review.

Dissemination:

This review will synthesise the existing evidence about the impact of MM on mortality and glycaemic outcomes in people living with T2D and increase our understanding of this subject and will inform future practice and policy. Findings will be disseminated via conference presentations, social media and peer-reviewed publication.

Prospero registration number: CRD42017079500

Strength and limitations of this study

- This will be the first systematic review to explore the impact of MM on all-cause mortality and glycaemia in people with T2D and has the potential to make a valuable contribution to the literature in this area.
- Our review benefits from a comprehensive search strategy including key terms, synonyms and medical subject headings that describe the research questions with a deliberate

inclusion of the “comorbidity” term to address the identified issue of the terms “comorbidity” and “multimorbidity” being used interchangeably.

- We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so that a narrative synthesis may be likely.

INTRODUCTION

Rationale

Type 2 diabetes (T2D) is a major health priority of the 21st century. Worldwide, it is estimated that more than 424 million people live with diabetes, resulting in $727 billion US dollars in healthcare expenditures (1). Approximately 4 million people die from diabetes related causes each year, equivalent to 1 death every 8 seconds, with nearly half of these deaths in people under the age of 60 (1). There is no doubt that T2D imposes a heavy burden on communities.

The management of T2D is complex, requiring continuous efforts to implement recommendations for self-management and pharmacotherapy in a step-wise manner to achieve evidence based targets. This complexity is increased when the patient has other chronic conditions in addition to T2D because T2D rarely occurs on its own. Data suggests that as many as 85% of those with T2D have at least one other chronic condition (2), which is higher than the 52% in the general population that is multimorbid (3).

For many years, the terms comorbidity and multimorbidity (MM) were used interchangeably (4). It has only been more recently that there has been a clearer distinction and understanding between the two terms. Comorbidity is defined as the existence or occurrence of any additional condition(s) that co-occurs with an index disease (5). MM however refers to the presence of two or more chronic conditions in an individual, with no reference to an index condition (6). These established definitions provide the basis of our systematic review which exclusively focuses on MM in T2D.

MM presents multiple challenges. It is associated with a reduced quality of life, increased costs, a reduced ability to make lifestyle changes and may be associated with complex therapeutic regimens which the patient may be challenged to manage (7). For health professionals MM brings increased workload, and the clinical challenges of interactions between multiple conditions and medications (4). Most condition-specific management guidelines do not account for MM, and prioritise management of one condition at the expense of another (7). For people with diabetes, this can lead to clinicians focusing on diabetes only without consideration of the patient's other conditions and patient goals. Similarly, a focus on other conditions may lead to sub-optimal glycaemic management due to a lack of focus on diabetes-specific care goals (8, 9). This is particularly problematic because achieving and maintaining glycaemic targets early is important in reducing downstream complications and all-cause mortality (10).

Currently little is known about the associations between MM and T2D. In particular, there is little information regarding the relationship of the total burden of disease reflected in MM's multiple dimensions to the association between all-cause mortality and glycaemia.

Our systematic review will focus on current knowledge regarding the impact of MM on mortality and glycaemia in people with T2D and provide insights regarding the implications of MM in the context of this chronic disease. It may provide an important foundation of knowledge for improving care for patients with T2D and multiple chronic conditions.

Objectives

The primary objective of our systematic review is to determine the impact of MM reflected in condition count on all-cause mortality and glycaemia in people with T2D. We will have two primary outcomes of equal interest:1) all-cause mortality; and 2) glycaemia (measured by HbA1c). Secondary outcomes of interest include: 1) hypoglycaemia, 2) hyperglycaemia; and 3) glycaemic variability.

METHODS AND ANALYSIS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines has been used to prepare this protocol (11).

Eligibility criteria

Study characteristics/design:

All quantitative empirical studies published in the English language will be included. Our target studies will be observational studies that use either longitudinal cohort (retrospective and prospective) or cross-sectional designs. While we recognise the limitation of cross-sectional studies in terms of assessment of temporality, cross-sectional studies provide a snapshot of the association between MM count and our glycaemia related outcomes of interest. We will have no restrictions on publication date. The search end date will be 28 July 2017.

Randomised controlled trials, non-diabetes-drug intervention studies, all qualitative studies, case-reports, review articles and conference abstracts will be excluded as they will not give us information on our primary outcomes of interest. Randomised controlled trials and non-diabetes-drug intervention studies have primary objectives of testing particular interventions so the effect of MM will not be captured, thus inappropriate for our review which is focused on the effects on MM. All non-English studies will also be excluded.

Population:

Our target study population is adults (18 years of age or older) with T2D.

Studies including populations of children and adolescents (under 18 years of age) or people without T2D (e.g. people with pre-diabetes, type 1 diabetes/gestational diabetes/monogenic diabetes) will be excluded. Animal studies will also be excluded.

Exposure:

The primary exposure of interest is MM count. We will accept any type of MM count, which may include a list of chronic conditions from a variety of datasets including electronic medical records, administrative and prescription datasets. Only studies that assess the relationship between a numerical count of MM and our outcomes of interest will be included.

Studies with single nominated specific conditions (i.e. only one comorbid condition) linked with T2D without MM count will be excluded.

Comparators (control):

A comparator/control group is defined by people with T2D with no other chronic conditions. Studies that do not include such a control group will not be excluded.

Outcome:

A study will be included in our review if data is provided regarding either all-cause mortality or glycaemic outcomes. It is expected that glycaemia will be reported in the form of HbA1c, however we will include any measure of glycaemia, for example, hypoglycaemia, hyperglycaemia or glycaemic variability.

Information sources

We will search five electronic databases including MEDLINE (OVID interface), EMBASE (OVID interface), CINAHL Complete (EBSCO interface), The Cochrane Library (OVID interface), and SCOPUS with no restrictions on publication date.

We will check the International Prospective Register of Systematic Reviews (PROSPERO) regularly for ongoing and completed systematic reviews for MM and T2D.

Search strategy

The search strategy will include medical subject headings (MeSH), terms and synonyms relating to or describing our primary objectives. These terms will be combined using appropriate Boolean logic operators to create our search strategy. The truncation symbol (*) will also be included at the end of the stem of a word to retrieve all words that start with that stem. Our strategy has been reviewed by a librarian from a biomedical library and members of our review panel with expertise in MM and T2D. A number of test runs will firstly be conducted with MEDLINE, and any necessary adjustments will be made prior to running the search. Once the search strategy is finalised, the searches will be adapted for each of the five electronic databases, prior to conducting the searches. The search terms are listed in Table 1. The full search strategy is available in Supp. 1.

Table 1: Search terms

Key terms	**Multimorbidity**	**Diabetes**	**Outcomes of interest:** **Mortality** **Glycaemia**
Other related terms or synonyms	multimorbid* multi morbid* condition count*	diabet* diabetes adj2 (type 2 or type ii)	mortality death surviv*

	multiple condition* multiple disease* multiple disorder* multicondition* multidisease* multidisorder* multi condition* multi disease* multi disorder* comorbid* co morbid*		surviv* analys* glycaemia* glycemia* hypoglycaem* hypoglycem* hyperglycaem* hyperglycem* glycem* varia* glycaem* varia*

Study records

Data management:

Literature search results will be downloaded to EndNote (Version 7; Clarivate Analytics) and duplicates will be removed. The non-duplicate studies will then be uploaded to Covidence (12), a systematic review management software, for the selection process.

Selection process:

The selection process of the studies for inclusion in our review will be conducted in three stages. First, titles of the studies identified in the five database searches will be screened by the primary researcher (JC) against the predefined eligibility criteria outlined above. A deliberately inclusive approach will be adopted for this title screening stage to reduce the risk of missing potentially relevant studies.

Second, all abstracts will be screened by two reviewers independently. The primary researcher (JC) will screen all abstracts against the predefined eligibility criteria outlined above to identify a subset of potentially relevant studies. An independent second screening of the abstracts will be completed between the following reviewers (JMN, JF, BN, BJ, AJ, FM). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer (JMN, JF).

Finally, we will obtain full text articles for all studies that appear to meet our eligibility criteria after the title and abstract screening stages. Full text screening will be conducted by two reviewers independently. The primary researcher (JC) will screen all full texts against our predefined eligibility criteria. This will then be repeated independently by a second reviewer (JMN, JF, BJ). Online supplementary material will be consulted when necessary. Again, any inter-reviewer disagreements

will be discussed and resolved by a third reviewer (JMN, JF). Reasons for exclusion at the full text screening process will be recorded.

Data extraction:

Data will be extracted in a structured manner from all included studies and recorded in a predefined data extraction form designed by the primary researcher (JC) following a prespecified Population, Exposure, Comparator, Outcomes (PECO) framework in the data extraction stage. This is an adapted framework based on the Cochrane PICO statement where "I" for intervention is replaced with an "E" for exposure. We will also be including an extra "Study Characteristics" parameter to record characteristics of the study including study design, setting, period of study, and aims and objectives. (See Supp. 2). The form will be reviewed, refined and adjusted where necessary by the review team. Again, online supplementary material will be consulted when necessary for data extraction.

Data items

We will be extracting relevant data in each of the following five parameters:

Populations:

We will extract data on characteristics of study populations (sample size, sex, age, ethnicity, social economic status, occupation, education, diabetes duration, HbA1c, insulin treatment and oral anti-diabetes drugs), as well as definition/measure of T2D, method of recruitment and sampling, and inclusion and exclusion criteria.

Exposure:

We will describe the definition/measure of MM count and number of subjects reported.

Comparator:

We will provide details provided in the publication of any comparator groups including the definition/measure of people with T2D with no other chronic/long term conditions and numbers in group.

Outcomes:

We will provide details as to how all-cause mortality and/or glycaemia is defined/measured, as well as length of follow up, number of subjects, and the statistical analyses employed by the authors to evaluate the relationship between MM count and the measured outcomes.

Study characteristics:

We will extract details of study design, setting, period of study, and aims and objectives.

Outcomes and prioritisation

One of the primary clinical outcomes of interest is all-cause mortality. We expect that studies will calculate the effect estimate as either hazard ratios, odds ratios, incidence rates or survival percentages.

For our other primary outcome, glycaemia, we will prioritise those studies that measure glycaemia in terms of HbA1c. We will further divide studies into one of two groups: those that measure HbA1c as a continuous variable and those that measure HbA1c as a categorical variable.

We will accept all other measures of glycaemia as secondary outcomes.

Risk of bias assessment (quality assessment in individual studies)

Two reviewers will independently assess the risk of bias (quality) in each of the included studies.

All studies will be assessed using the Newcastle-Ottawa quality assessment scale (13). The choice of this tool was informed by recommendations from the Cochrane Handbook on assessing the quality of non-randomised studies (14). Any inter-reviewer disagreements will be discussed and resolved by a third reviewer.

The Newcastle-Ottawa quality assessment scale has a star system to judge three broad perspectives of the included studies: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

Data synthesis

For data synthesis, we will group the included studies according to the two outcomes of all-cause mortality and glycaemia. Within the glycaemia outcome group, we will further subgroup the studies into the different measures of glycaemia. For our primary analysis we will consider either all-cause mortality or glycaemia each as a composite outcome. However, dependent on the number of studies retrieved an analysis of glycaemia subtype will be conducted. Furthermore, dependent on the characteristics of the study populations, we will consider stratifying our results according to either exposure ascertainment (MM count) or population characteristics (i.e. age group, gender and socioeconomic status).

A narrative synthesis of findings will be conducted which will describe the findings from each of the included studies. For each study we will present details relating to the following:

- The number and characteristics of participants in the study
- Setting
- Study design
- The outcome-level risk of bias of the study
- Findings for quantitative outcomes
- Inconsistent findings within individual studies will be indicated.

If further information relevant to our review is required, we will attempt to contact the authors of the included studies.

A meta-analysis will be conducted if appropriate. Tests for publication bias and heterogeneity will be conducted. If the included studies are sufficiently homogenous in terms of study design, study population, outcomes and data analysis, a meta-analysis will be considered. I^2 statistic will be used to assess statistical heterogeneity and to guide the choice of either fixed or random effects model. Given sufficient numbers of included studies, a funnel plot will be used to assess publication bias and other reporting bias, and a Begg's test will be utilised to test for asymmetry. A sensitivity analysis will also be used to determine the consistency of the results. However, if a meta-analysis and the above tests are not possible, possible sources of bias across studies will be discussed in the narrative synthesis and this limitation will be considered when drawing conclusions.

Confidence in cumulative evidence

Grading of Recommendations, Assessment, Development and Evaluation (GRADE) guideline is recommended by the Cochrane Handbook for grading the quality and strength of evidence (15). We will use the GRADE guidelines to assess the quality of evidence for our research questions.

Patient and public involvement

Patients were not involved in the development of this protocol.

ETHICS AND DISSEMINATION

Ethics

Ethics was not required for this study as this is a systematic review and it does not contain individual patient data. We will disseminate the results of our review via conference presentations, social media and peer reviewed publication. This review also forms part of the lead investigator's (JC) PhD.

Discussion

This systematic review will aim to synthesise the existing evidence on the effects of MM in T2D on mortality and glycaemic control and will be the first on this subject. Clinical management in patients with T2D and MM is a growing international healthcare challenge and our review will make important contributions to understanding of the impact of MM, if any, in the context of T2D on key clinical outcomes which should enhance the understanding in this field. We hypothesise that increasing MM will be associated with increased all-cause mortality, however the effects on glycaemic outcomes may vary. Our review will be the first to bring together existing literature exploring associations between MM and T2D, and therefore clarifying the effects of increasing MM on mortality and glycaemia in people with T2D.

Key strengths of our review will be our adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines, our comprehensive search strategy and the fact that all screening and data extraction will be performed by two reviewers independently. We expect the literature to be quite heterogeneous in terms of how MM is defined and the way outcomes are reported so a narrative synthesis may be likely which may be a limitation. In addition, we have restricted our review to English language publications which is a potential limitation.

As the first review on this subject it will help identify what is known on this subject and whether any gaps in knowledge exist. It will therefore help highlight whether there are areas requiring further investigation as well as clarify the key messages from the evidence, to date, including implications for future guidelines for those with T2D.

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AUTHORS' CONTRIBUTIONS

JC drafted the protocol and developed the search strategy, inclusion/exclusion criteria and the data extraction form with guidance from JMN, JF, FM, BN, BJ, AJ and DO. PC contributed to the development of the search. All co-authors read and provided feedback on the draft manuscript.

FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

No competing interests.

Supplementary Document 1

Full Search Strategy – MEDLINE (OVID)

#	Searches
1	multimorbid* or multi morbid*
2	condition count*
3	multiple condition* or multiple disease* or multiple disorder*
4	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
5	or/1-4
6	diabet*
7	5 and 6
8	limit 7 to english
9	animal not human
10	8 not 9
11	multimorbid* or multi morbid*
12	condition count*
13	multiple condition* or multiple disease* or multiple disorder*
14	multicondition* or multidisease* or multidisorder* or multi condition* or multi disease* or multi disorder*
15	comorbid* or co morbid*
16	or/11-15
17	glycaem* or glycem* or hyperglycaem* or hyperglycem* or hypoglycaem* or hypoglycem* or glycem* varia* or glycaem* varia*
18	(mortality or death or surviv* or surviv* analys*) or mortality
19	(diabetes adj2 ("type 2" or "type ii"))
20	19 and 16
21	20 and (17 or 18)
22	limit 21 to english
23	10 or 22

Supplementary Document 2

Data extraction form

Reviewer Name	
Review Date	
STUDY	
First author	
Year	

STUDY CHARACTERISTICS

	Response	Notes
Setting		
Country		
Study Design		
Period of Study		
Aims and Objectives		

POPULATION and COMPARATOR

POPULATION	Response	Notes
Total number of participants		
Total number of participants with T2D		
How was T2D defined or measured in this population?		
How was the study population recruited?		
What were the sampling methods? Explain		
Inclusion criteria for study population		
Exclusion criteria for study population		
COMPARATOR		
Was there data on people with T2D with no other chronic condition (only T2D)?	☐Yes ☐No	If yes, please fill in both columns of table 1. If no only fill in the left column.
Total number of participants with T2D		

with no other chronic condition		

Table 1: Characteristics of those with and without type 2 diabetes

Characteristics	**T2D population n =**	**T2D Only (T2D with no other conditions – control group) n =**
Age, mean (SD)		
Female sex, N (%)		
Ethnicity, N (%) - Caucasian - Etc.		
Social economic status -		
Occupation -		
Education -		
Diabetes duration, mean (SD)		
HbA1c, mean (SD)		
Body mass index, kg/m^2, mean (SD)		
Insulin treated, N (%)		
Oral anti-diabetes drugs, N(%) - None - One - Two or more - Etc.		

EXPOSURE

	Response	Notes
How was multimorbidity count defined in this population?		
List the conditions included for multimorbidity count		

Table 2: Multimorbidity characteristics of those with type 2 diabetes
Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**Number of people with MM characteristic recorded n =**
Multimorbidity count	
0 comorbidity, N (%)	
1 comorbidity, N (%)	
2 comorbidities, N (%)	
3 comorbidities, N (%)	
4 comorbidities, N (%)	
5 comorbidities, N (%)	
6+ comorbidities, N (%)	
Comorbid conditions	
e.g. Hypertension, N(%)	
e.g. Cardiovascular disease, N(%)	
Add additional columns and rows if needed	

OUTCOMES

MORTALITY OUTCOME:

	Response	Notes
Is all-cause mortality an outcome?	☐Yes ☐No	
How was all-cause mortality measured?		
Statistical analysis; How was the relationship between multimorbidity count and all-cause mortality explored?		
Length of follow up		

Table 3: Hazard ratios and 95% Confidence Interval (reword if MM count and mortality relationship explored differently) for effect of MM count on Mortality in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

Multimorbidity Characteristics	**HR (95% CI)**
Multimorbidity count	
0 comorbidity	
1 comorbidity	
2 comorbidities	
3 comorbidities	
4 comorbidities	
5 comorbidities	
6+ comorbidities	
Comorbid conditions	
e.g. Hypertension	
e.g. Cardiovascular disease	

What variables were adjusted in the statistical analysis?: ___

GLYCAEMIC OUTCOME:

	Response	Notes
Are any measures of glycaemia an outcome?	☐Yes ☐No	
How was glycaemia measured?	☐HbA1c ☐Fasting plasma glucose ☐Hypoglycaemic event ☐Hyperglycaemic event ☐Any measure of glycaemic variability Explain:	
Statistical analysis; How was the relationship between multimorbidity count and glycaemia explored?		
What was glycaemic outcome treated as	☐Continuous outcome ☐Categorical outcome ☐Both Explain:	
Length of follow up		this may not be applicable as we are only looking at cross sectional data

If glycaemic outcome is measured as a continuous variable use this: ☐Yes ☐No

Table 4: Estimated mean change, β1 and 95% Confidence Interval, in HbA1c (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (measured in HbA1c) in people with T2D

Or

If glycaemic outcome is measured as a categorical variable use this: ☐Yes ☐No

Table 4: Odds ratios and 95% Confidence Interval (reword if MM count and glycaemia relationship measured differently) for effect of MM count on glycaemia (if measured in OR, glycaemia most likely measured in hypoglycaemic/hyperglycaemic events) in people with T2D

Adjust table where necessary, i.e. if multimorbidity is measured in terms of Charlson Comorbidity Index (CCI) – adjust table to show different CCI scores.

	Reviewer uses 1 of the columns below depending on whether glycaemic outcome is measured as continuous or categorical			
Multimorbidity Characteristics	**Continuous: Estimated mean change, β1 (95% CI)**	**p-value**	**Categorical: OR (95% CI)**	**p-value**
Multimorbidity count				
0 comorbidity, N (%)				
1 comorbidity, N (%)				
2 comorbidities, N (%)				
3 comorbidities, N (%)				
4 comorbidities, N (%)				
5 comorbidities, N (%)				

6+ comorbidities, N (%)				
Comorbid conditions				
e.g. Hypertension, N(%)				
e.g. Cardiovascular disease, N(%)				

What variables were adjusted in the statistical analysis?: ___

OTHER

	Response	Notes
Was there missing data? Explanation	☐Yes, explain: ☐No	
Attrition? Explanation:	☐Yes, explain: ☐No	
Authors' conclusion		
Miscellaneous comments		
Funding source		
Other		
Additional notes		

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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	13
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	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	13
Sponsor	5b	Provide name for the review funder and/or sponsor	13
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	13
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
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
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	7
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such	7

		that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
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)	8
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	8
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	9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	10
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	10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	10
	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)	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (see 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.**

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