Mortality associated with depression:
a systematic review and meta-analysis protocol

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Aims and hypothesis:
The key questions are:
- Does the diagnosis of depression have an impact on cause-specific and all-cause mortality when compared to the general population?
- Does anti-depressant treatment change that risk?

Background:
Depression is a high prevalence, chronic and recurring condition[1]. It is associated with excess all-cause and cause-specific mortality[2]. This includes mortality from myocardial infarction (MI)[3], stroke[4], as well as cancer[5] (Figure 1). Complexity is introduced by some evidence of increased mortality with pharmacological antidepressant treatment[6], though this could be confounded by indication. Patients with difficult to treat unipolar depression have significantly higher all-cause mortality than other depressed patients[7]. This could be related to baseline severity, differences in underlying pathophysiology and/or evidence that effective treatment reduces mortality risks. In late life depression, increased mortality rates have been associated with antidepressants, even though the strength of that evidence varies by drug class and mostly comes from observational studies[8].

Methods:
Medline, Embase, Scopus, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews will be used to conduct the search. Grey literature will also be considered for cross-checking of references.
Cohorts, case-control studies, and randomized controlled trials will be included. Additional inclusion criteria will include studies of adult patients with depression (unipolar or bipolar), prescribed anti-depressant treatment (medication and/or neurostimulation) or not, with measures of mortality and follow-up duration ≥ 1 year. No restrictions on date or language of publication.

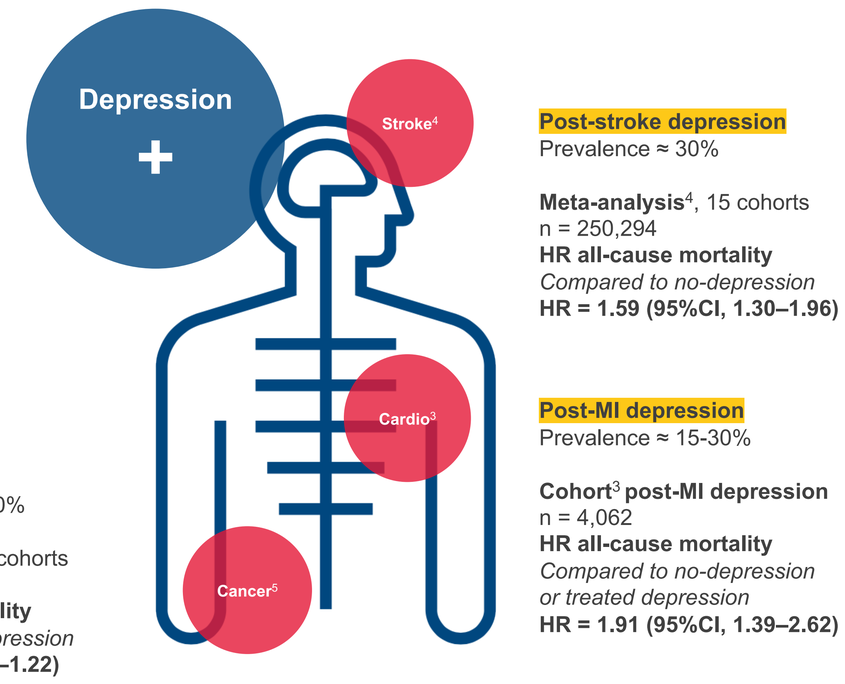

Figure 1: Relative risks of mortality with co-morbid depression.

Ethics approval will not be needed because the data used in this systematic review will be extracted from published studies.

Results:
The risk of bias for the studies included in the meta-analysis will be assessed by the ROBINS-I for observational studies and the RoB 2 for randomised trials. The primary outcome of interest is mortality. It is expected that the most commonly reporting metric for this will be a mortality risk estimate, including a ratio and the associated measure of uncertainty. Where possible, pooled estimates of the risk ratio of mortality for the included studies will be assessed using a random effects meta-analysis, conducted in MetaEssentials.

Conclusions and Next Steps:
This systematic review and meta-analysis protocol has been published in the PROSPERO international prospective register of systematic reviews, with the registration number CRD42020200812. Results will be disseminated by publication in a peer-reviewed journal.

References:
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2 - Machado, MO, et al., The association of depression and all-cause and cause-specific mortality: an umbrella review of systematic reviews and meta-analyses. BMC Med, 2018.16(1): 112.
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4 - Cai, W, et al., Post stroke depression and risk of stroke recurrence and mortality: A systematic review and meta-analysis. Ageing Res Rev, 2019. 50: 102-109.
5 - Pinquart, M and Duberstein, PR, Depression and cancer mortality: a meta-analysis. Psychol Med, 2010. 40(11): 1797-810.
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7 - Li, G, et al., All-cause mortality in patients with treatment-resistant depression: a cohort study in the US population. Ann Gen Psychiatry, 2019. 18: 23
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