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Prevalence and correlates of pre-diabetes in adults of mixed ethnicities in the South African population: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Pre-diabetes is a metabolic condition characterised by moderate glycaemic dysregulation and is a front-line risk factor to multiple metabolic complications such as overt diabetes. To the best of our knowledge, this will be the first systematic review and meta-analysis that focuses on generating a comprehensive pooling of studies that report on the pre-diabetes prevalence in South Africa. Therefore, the review's purpose will be to screen and elect reports that can be used to synthesise and provide the best estimate prevalence and correlate of pre-diabetes in the South African population.

Methods and analysis To determine the prevalence and correlates of pre-diabetes in South African, we will search PubMed, Embase and African Journal online for published or unpublished studies reporting the prevalence of pre-diabetes in South Africa starting from the year 2000 to 2020. Studies will be assessed for eligibility by checking if they meet the inclusion criteria. Eligible studies will undergo data extraction and risk of bias assessment. We will perform a subgroup analysis to detect probable causes of heterogeneity.

Ethics and dissemination The review will not require ethics clearance because non-identifiable data will be used. The review outcomes will give more insight into the current burden that pre-diabetes has in South Africa.

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INTRODUCTION

Pre-diabetes (or intermediate hyperglycaemia) is a serious health condition characterised by blood glucose concentration that is higher than normal but not high enough to diagnose with overt type 2 diabetes (T2D).[1 2] The onset of pre-diabetes is preceded by moderate insulin resistance or pancreatic β cell dysfunction, which, in turn, causes a gradual increase in glucose levels.[1 3] The diagnosis of pre-diabetes is confirmed in individuals with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or elevated glycosylated haemoglobin (HbA1c) using

Strengths and limitations of this study

► This will be the first comprehensive systematic review and meta-analysis based on the primary outcome of determining the total pre-diabetes prevalence in South Africa.
► The appraisal for the quality of study and strength of evidence will be done using the established Grading of Recommendations Assessment, Development and Evaluation method.
► Since the criteria for diagnosing pre-diabetes differs, the heterogeneity may be affected by the pre-diabetes diagnostic criteria utilised by each eligible study.

either WHO or American Diabetes Association (ADA).[4] Therefore, when measuring pre-diabetes prevalence, the WHO and ADA criteria are generally used.

The International Diabetes Federation (IDF) estimated that the 2019 pre-diabetes global prevalence was 7.5% (373.9 million people). By 2045, the projected prevalence will increase to 8.6% (548.4 million).[5] In all the seven regions of the IDF, predictions state that the African region will have the most significant increase in pre-diabetes prevalence. The projection is that the 2019 prevalence of 45.3 million will rise by 143.3% to 110.2 million.[5] However, studies conducted in populations with various ethnic groups reported that pre-diabetes prevalence in certain ethnic groups is disproportionally high.[6] In the UK, the observations showed that minority ethnic groups have a higher prevalence of pre-diabetes.[7] Furthermore, another report revealed that 15.3% of adults of the 88 million estimated to have pre-diabetes did not know, which indicates that most people remain with this condition undiagnosed.[5]

This is concerning because the pre-diabetes condition can be very harmful.

Researchers have shown that pre-diabetes can be a toxic environment that instigates multiple metabolic complications, such as T2D.[1] The literature indicates that pre-diabetes promotes severe chronic microvascular and macrovascular complications, blood pressure changes, fatty liver disease conditions and T2D.[3 4] A prevention study spanning over 20 years displayed a greater than 90% cumulative incidence of progression to T2D from IGT.[8] This development rate is a concern because we know that diabetes causes the death of approximately 1.3 million people annually.[9] In addition, the literature reveals that there is an increased risk of heart failure and all-cause mortality in people with pre-diabetes.[10 11] Therefore, the synthesis of available prevalence data for pre-diabetes in a population may prove crucial in many ways.

The pooling of studies with pre-diabetes prevalence data will help determine the current burden that pre-diabetes has on a specific community and assist in mitigating the future prevalence of pre-diabetes and its associated metabolic complications. Subsequently, the findings have the potential to appraise social and healthcare professionals better. Notably, the prevalence of pre-diabetes is shown to vary among different populations.[5] Therefore, populations must have their own summarised prevalence data so that relevant and empirical evidence can be at the policymakers' disposal, which will result in better-informed decisions.

Hence, the review will focus on the population in South Africa, which could also be a representative of Southern Africa. Various studies have reported on the prevalence of pre-diabetes in South Africa.[12–14] However, non of the studies can independently give us an overall prevalence of pre-diabetes and account for all the ethnic groups. Moreover, there is no systematic review that focuses on the primary outcome of determining the total pre-diabetes prevalence in South Africa. Therefore, this led us to generate the following research questions and objectives.

RESEARCH QUESTIONS
1. What is the overall prevalence of pre-diabetes, and is there a fair representation of all the ethnic groups living in South Africa?
2. What are the common correlates of pre-diabetes?

OBJECTIVES
1. To determine the prevalence of pre-diabetes in the adult population of mixed ethnicities.
2. To determine the common correlates of pre-diabetes.

METHODS AND ANALYSIS
Study design
This systemic review protocol has been prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols 2015 guidelines.

Search strategy
With a librarian's aid, two independent reviewers will conduct a comprehensive search of databases to find all related articles published on diabetes mellitus and pre-diabetes in South Africa from January 2000 to May 2020 regardless of the language of publication. The databases that will be screened will include MEDLINE through PubMed, Google Scholar, Embase and African Journals Online. They will use some of the following Medical Subject Heading in our search strategy: "Pre-diabetes," "South Africa," "Prevalence," "Type 2 diabetes mellitus," "Impaired fasting glucose," and "Impaired glucose tolerance." A detailed method shown in online supplemental table 1 will be used to search PubMed. We will use the Mendeley referencing manager (V.1.19.10) to remove duplicates. Moreover, they will perform a hand searching to identify other eligible studies not indexed in the databases, especially in the included studies' bibliography and relevant literature reviews. We will also request and screen unpublished manuscripts and thesis from the University of KwaZulu-Natal registry and contact researchers.

Types of study eligible
The studies that we will consider for this review consist of prospective or retrospective cross-sectional population based and cohort studies reporting pre-diabetes prevalence in South Africa. The study must have a minimum of 100 participants for it to pass eligibility. There will be no language restriction for the eligibility of studies. Furthermore, the most up-to-date and comprehensive version will be selected for studies that will report the same results in multiple articles.

Types of participants
The participants in the studies included will need to be adults (≥18) located in South Africa, registered citizens who are black, coloured, Indian/Asian or white. The participants used in the studies will need to be clinically diagnosed with pre-diabetes using the ADA or WHO diagnosis criteria. The diagnosis criteria defined by the ADA and the WHO will be considered. Accordingly, the diagnosis is determined by observing IFG, IGT and elevated HbA1c.[15] IFG is defined as fasting plasma glucose of 5.6–6.9 mmol/L. IGT is defined as the 2-hour plasma glucose of 7.8–11.0 mmol/L after a 2-hour interval following the ingestion of 75 g of an oral glucose load or a combination of both the IGT and the IFG recorded during the oral glucose tolerance test. Also, pre-diabetes diagnosis with HbA1c will be accepted for any value between 5.7% and 6.5%.[15 16] Any study lacking a clear diagnosis criteria description will be excluded if, after contacting authors twice, the information is not provided.

Inclusion and exclusion criteria
The two independent reviewers will be responsible for choosing eligible studies that meet the type of study and participant requirements. The articles or thesis included will have to be studies done between the years 2000 and

2020. Therefore, all studies not adhering to the eligible type of study, participant requirements, and that fall outside the 20 year range between 2000 and 2020 will be excluded. Studies with insufficient data to calculate the primary outcome will face exclusion if the requested data is not provided after contacting the corresponding author twice.

Primary outcomes
► Prevalence of pre-diabetes.
► Prevalence of pre-diabetes across different ethnic groups.

Secondary outcome
► Determine the most conventional risk factors associated with pre-diabetes.

Data extraction
Using a predesigned excel form, the reviewer will extract the applicable data. To ensure the quality of extracted data, another reviewer will independently check all data. If there are any disagreements, they will be deliberated and solved with the assistance of a third reviewer. The data to be extracted will include the population sampled, crude pre-diabetes prevalence estimates, and any prevalence estimates reported stratified by age, sex or location (within South Africa). Data on parameters such as weight, hypertension and family history of diabetes will be pulled to appraise the most conventional risk factors associated with pre-diabetes. Prevalence figures and 95% CIs will be extracted or calculated, provided that all necessary data is made available. Where data are insufficient or presented graphically, we will contact the article's first author to request more data or calculate from the available data using Wilson's method. Given that all essential data will be provided, we will pull all correlates for pre-diabetes present in the clinically diagnosed participants.

Assessment of the quality of included studies
Two investigators (AMS and AK) will independently assess the methodological quality of comprised studies using the risk of bias tool for prevalence studies developed by Hoy and colleagues.[17] A score of 0–4, 5–7 or 8–10 rated the risk of bias as high, moderate or low, respectively. A third review author (NCM) will resolve disagreements between the two investigators by consensus or arbitration.

Data synthesis and analysis
The MetaXL (www.epigear.com) add-in for Microsoft Excel will be utilised for the synthesis and analysis. The point estimate for each study will be transformed with the Freeman-Tukey double arcsine method to stabilise the variance. The normal distribution of data will be validated using the D'Agostino & Pearson omnibus normality test. The study-specific estimates with 95% CI will be pooled to generate an overall summary prevalence figure across the elected studies. After that, the heterogeneity between estimates will be assessed using the I^2 statistics.

The I^2 value describes the percentage of variation not because of chance or sampling error across studies.[18] Suppose the I^2 value is higher than 75%. In that case, the heterogeneity between studies will be deemed high.[19] Any possible influences on prevalence estimates will be investigated using subgroup analyses and meta-regression. Where studies allow, we will descriptively compare prevalence estimates by the following subgroups: sex, race, age, body mass index, lipid profile, family history, exercise and education. After that, we will calculate the regression coefficient to ascertain a linear relationship between the effect estimate (ie, outcome variable) and the explanatory variable or subgroup. We will then assess the influence on estimates of the following study-level variables identified a priori as potential sources of variation in the estimates of prevalence[1]: risk of bias,[2] geographical location and[3] data collection method. Finally, where fitting the outcomes will be displayed in tables or forest plots.

Confidence in cumulative evidence
The Grading of Recommendations Assessment, Development and Evaluation (GRADE) method will assess the strength of evidence.[20] The GRADE method will provide a score of the quality of the studies and the strength of the evidence depending on methodological flaws within the included studies, consistency of results across diverse studies, precision estimates and publication bias.

Patient and public involvement
There was no patient and public involvement.

ETHICS AND DISSEMINATION
The systematic review and meta-analysis do not require ethics clearance since studies with non-identifiable data will be used. The review will give insight on the current burden that pre-diabetes has on specific areas in the country and may assist in predicting and mitigating future prevalence of other associated conditions like T2D.

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