The prevalence and correlation of cardiovascular dysfunction in pre-diabetes in adults of different ethnic groups in South African population: a systematic review and meta-analysis protocol.

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Submitted to: JMIR Research Protocols
on: February 16, 2024

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The prevalence and correlation of cardiovascular dysfunction in pre-diabetes in adults of different ethnic groups in South African population: a systematic review and meta-analysis protocol.

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is the most common serious metabolic-endocrine disorder affecting adults worldwide posing a significant global burden on public health [10]. The prevalence of diabetes has drastically increased in developing and other developed countries in recent decades [10]. According to the International Diabetes Federation (IDF), 9.3% (463 million) of adults worldwide have diabetes in 2019. The number is predicted to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The International Diabetes Federation in 2019, recorded the number of diabetic adults (20-65) in Africa was 19 million and South Africa being the highest with 4.6 million diabetic adults [8]. The prevalence of diabetes is rapidly increasing in South Africa [7]. Several risk factors for T2DM include increased age, physical inactivity, obesity, insulin resistance, race, family history and development of cardiovascular complications have contributed to the increase of diabetes prevalence. T2DM is an established risk factor for the development of cardiovascular diseases [1].

One of the identified causes of T2DM is chronic consumption of a high calorie diet as well as a sedentary lifestyle [3]. The resultant insulin resistance leads to the generation of oxidative stress and the release of inflammatory cytokines such as sensitive C-reactive protein (CRP), interleukin 6 (IL-6) and tumour necrotic alpha (TNF-?) [4]. An increase of inflammatory cytokines causes endothelial dysfunction, hypertension, coronary heart disease and atherosclerosis. Endothelial cells continuously produce nitric oxide (NO) and prostacyclin thereby promoting a relaxed vascular state [6]. However, IR decreases the production of NO by inhibiting the endothelial nitric oxide synthase (eNOS) by impairing the phosphatidylinositol 3 kinase (PI3K) – AKT (protein kinase B) pathway [4] [6]. A decrease in NO causes an imbalance triggering vasoconstriction in the endothelial vascular. The excessive bioactivity of endothelin-1 (ET-1) plays a crucial role in the development of endothelial dysfunction resulting in hypertension, impaired vascular function and increased risk of cardiovascular diseases. T2DM is well documented to be a strong risk factor for the development of microvascular and macrovascular complications [11]. However, before the onset of T2DM and its complications prediabetes plays a crucial role in the development of this metabolic disorder.

Pre-diabetes is metabolic health condition characterised by elevated blood glucose levels higher than normal but not high enough to diagnose as type two diabetes mellitus (T2DM) [2]. The prevalence of pre-diabetes is increasing worldwide and reports have predicted that more than 470 million people will have pre-diabetes by the year 2030 [2]. Pre-diabetes is confirmed in patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and elevated glycosylated haemoglobin (HbA1c). The international Diabetes Federation indicates that South Africa has a high prevalence of T2D but also has a high prevalence of undiagnosed pre-diabetes. It is often asymptomatic making it difficult to document the prevalence.

South Africa is a rapidly urbanizing country with cultural and ethnic diversity. With an increase of rapid urbanization characterized by the consumption of high fat diet and physical inactivity have contributed to obesity with 69% of women and 39% of men in South Africa being obese or overweight [7]. Thus, increases the risk of developing of metabolic disorders such as

pre-diabetes and T2DM which contributes immensely to the development of cardiovascular diseases.

However, there has been limited research on the co-existence of pre-diabetes and cardiovascular complications in the South African population. The aim is to synthesise the best available evidence exploring the prevalence of cardiovascular dysfunction and changes in cardiac biomarkers in persons with pre-diabetes

Objective: 1.To determine the prevalence and correlates of cardiovascular dysfunction of pre-diabetes in adults living in South Africa.
2.To assess and determine the changes in cardiac biomarkers in pre-diabetic patients in South Africa.

Methods: 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 (MMC and AMS) will conduct a comprehensive search of databases to find all related articles published on diabetes mellitus and pre-diabetes in South Africa from January 2002 to December 2022 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," "Inflammatiom", "Cardiovascular disease," "Atherosclerosis," "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 cardiovascular function in 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 years of age) 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%. Any study lacking a clear diagnosis criteria description will be excluded if, after contacting authors twice, the information is not provided. Additionally, diagnosis of cardiovascular dysfunction will be done according to the WHO diagnostic criteria.

Inclusion and exclusion criteria
The inclusion criteria in this study were the following:
• Studies reported between the years 2002 and 2022 will be included.
• Studies that reported on pre-diabetes or type 2 diabetes mellitus will be considered eligible.
• Studies reported on cardiovascular dysfunction and inflammation in pre-diabetes will be considered eligible.
• Studies that reported on pre-diabetes prevalence in South Africa will be eligible.

The exclusion criteria in this study were the following:
• Studies that fall outside the 20 year range between 2002 and 2022 will be excluded.
• Animals studies will be excluded
• Studies not adhering to the participants' requirement will be excluded.

Results: •Prevalence and correlates of cardiovascular dysfunction of pre-diabetes in adults living in South Africa.
•Predominant cardiac biomarkers during pre-diabetes.

Conclusions: Pending

(JMIR Preprints 16/02/2024:57409)

DOI: https://doi.org/10.2196/preprints.57409

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The prevalence and correlation of cardiovascular dysfunction in pre-diabetes in adults of different ethnic groups in South African population: a systematic review and meta-analysis protocol.

INTRODUCTION

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adults worldwide posing a significant global burden on public health [10]. The prevalence of diabetes has drastically increased in developing and other developed countries in recent decades [10]. According to the International Diabetes Federation (IDF), 9.3% (463 million) of adults worldwide have diabetes in 2019. The number is predicted to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The International Diabetes Federation in 2019, recorded the number of diabetic adults (20-65) in Africa was 19 million and South Africa being the highest with 4.6 million diabetic adults [8]. The prevalence of diabetes is rapidly increasing in South Africa [7]. Several risk factors for T2DM include increased age, physical inactivity, obesity, insulin resistance, race, family history and development of cardiovascular complications have contributed to the increase of diabetes prevalence. T2DM is an established risk factor for the development of cardiovascular diseases [1].

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Pre-diabetes is metabolic health condition characterised by elevated blood glucose levels higher than normal but not high enough to diagnose as type two diabetes mellitus (T2DM) [2]. The prevalence of pre-diabetes is increasing worldwide and reports have predicted that more than 470 million people will have pre-diabetes by the year 2030 [2]. Pre-diabetes is confirmed in patients with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and elevated glycosylated haemoglobin (HbA1c). The international Diabetes Federation indicates that South Africa has a high prevalence of T2D but also has a high prevalence of undiagnosed pre-diabetes. It is often asymptomatic making it

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RESEARCH QUESTIONS

1. What is the overall prevalence and correlates of cardiovascular dysfunction of pre-diabetes in adults living in South Africa?
2. What are the changes in cardiac biomarkers during pre-diabetes?

OBJECTIVES

1. To determine the prevalence and correlates of cardiovascular dysfunction of pre-diabetes in adults living in South Africa.
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Africa.

METHODS AND ANALYSIS

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The exclusion criteria in this study were the following:

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- Animals studies will be excluded
- Studies not adhering to the participants' requirement will be excluded.

Primary outcomes

- Prevalence and correlates of cardiovascular dysfunction of pre-diabetes in adults living in South Africa.
- Predominant cardiac biomarkers during pre-diabetes.

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. The mean and standard deviation of cardiac biomarkers will be extracted. 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 (MMC and AMS) will independently assess the methodological quality of comprised studies using the risk of bias tool for prevalence studies developed by Hoy and colleagues. 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 (AK) will resolve disagreements between the two investigators by consensus or arbitration.

Data synthesis of the quality of included studies

The MetaXL and RevMan (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 selected 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. Suppose the I^2 value is higher than 75%.

In that case, the heterogeneity between studies will be deemed high. 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 (i.e. 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: risk of bias, geographical location and 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. 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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