

BMJ Open Epidemiology of diabetes mellitus in Pakistan: a systematic review protocol

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ABSTRACT

Introduction Diabetes mellitus (DM) is a chronic metabolic disorder characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. As a major global health concern, its prevalence has been steadily increasing. Pakistan, is no exception to this trend, facing a growing burden of non-communicable diseases including DM. This research aims to comprehensively assess the prevalence of DM, and disparities between rural and urban populations as well as between men and women in Pakistan.

Methods and analysis The systematic review will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and will aim to assess DM prevalence in Pakistan. A comprehensive search strategy will be applied to databases like PubMed, Scopus, Cochrane, PakMediNet and CINAHL from inception up to 1st April 2024. We will include studies that focus on diabetes prevalence in the general population, employing WHO or American Diabetes Association criteria for diagnosis of DM. Cross-sectional studies, cohort studies and population-based surveys with a sample size ≥ 500 , in English will be considered. Data extraction will be done as per a predefined proforma which will include study details such as demographics, prevalence data and methodology. A meta-analysis will be performed using a random effect model with an inverse variance weighted method.^{1,2} statistics will be used to examine heterogeneity, and subgroup analyses will be performed.

Ethics and dissemination The findings from the systematic review will be shared by publishing them in a peer-reviewed journal and showcasing them at pertinent conferences. Our analysis will be based on aggregated data and will not involve individual patient information, thus eliminating the need for ethical clearance.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.¹ It is a major global health concern, with prevalence steadily increasing in both developed and developing countries.² Pakistan, as a populous South Asian nation, is no exception to this trend. The country is facing a growing burden of non-communicable diseases (NCDs), and DM has emerged as a significant public health challenge over the past few decades.³

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for systematic reviews and implements a meticulous systematic data extraction process, contributing to the overall comprehensiveness of the review.
- ⇒ Conducts a comprehensive literature search covering studies published until 1st April 2024, bolstering the review's reliability.
- ⇒ Encompasses a wide range of studies by employing both the WHO and American Diabetes Association criteria for diagnosing diabetes mellitus, thus enhancing the review's external validity.
- ⇒ Potential for publication bias due to reliance on published studies, which may favour positive or statistically significant results.
- ⇒ Variations in prevalence estimates across included studies due to differences in study methodologies, studied populations and diagnostic criteria used.

Pakistani context

Epidemiological overview

Pakistan, as the world's fifth most populous country, faces numerous health challenges, including the rise of NCDs.⁴ Among these NCDs, DM stands out as a significant health concern due to its increasing prevalence and associated health and economic burdens. According to estimates, Pakistan had approximately 5.2 million adults living with diabetes in 2000,² and this number amplified to approximately 33 million in 2021.⁵ The WHO estimated that in 2016 NCDs accounted for 58% of all deaths in Pakistan.⁶ The four most prevalent NCDs in Pakistan in 2016 were cardiovascular diseases, cancers, chronic respiratory diseases and diabetes.⁶ In 2016, it was reported that the total number of deaths directly caused by diabetes was estimated to be 3%.⁶ However, diabetes also played a significant role in mortality as a risk factor for other NCDs such as cardiovascular diseases and hypertension.

Factors contributing to the diabetes burden

Rapid urbanisation and shifts in lifestyle patterns have transformed dietary habits, physical activity levels and overall health



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behaviours in Pakistan.⁷ Traditional diets have been replaced by more calorie-dense and processed food options, leading to an increase in obesity rates and other risk factors associated with diabetes.^{8–9} Additionally, sedentary occupations, increased usage of technology and reduced physical activity levels have become prevalent, especially in urban areas. This lifestyle shift has contributed to an increased risk of obesity and diabetes. Pakistan's healthcare system faces several challenges, including limited resources, inadequate healthcare infrastructure and uneven distribution of medical facilities.¹⁰ This can impact the early detection, diagnosis and management of diabetes, particularly in rural and underserved areas. Lack of awareness and education about diabetes and its risk factors can lead to delayed diagnosis and poor management.¹¹ Promoting diabetes awareness campaigns and educational programmes is crucial to encourage early detection and effective management of the disease. The prevalence of diabetes in Pakistan exhibits variations across different age groups and genders.¹² Age is a well-established risk factor for diabetes, and the disease tends to increase with advancing age.¹² Moreover, studies have shown that women in Pakistan may face additional challenges related to diabetes, such as limited access to healthcare, cultural norms impacting their dietary choices and lack of autonomy in healthcare decisions.^{13–14} Lastly, diabetes poses a substantial health burden in Pakistan, with complications such as cardiovascular diseases, kidney failure, blindness and lower limb amputations being common.¹⁵ These complications not only affect the quality of life of individuals but also exert significant economic pressure on families and the healthcare system.

Rural versus urban population

Pakistan's population is characterised by a diverse mix of urban and rural inhabitants. While urban centres experience higher levels of industrialisation, better access to healthcare facilities and potentially greater exposure to risk factors associated with DM, the rural population often faces unique challenges in terms of access to healthcare, education and awareness about NCDs. These disparities between rural and urban areas could influence the prevalence and management of DM across different regions in Pakistan.^{9–16}

Understanding the potential differences in DM prevalence between rural and urban populations is crucial for designing targeted interventions that consider the specific needs and challenges faced by each group. It can also inform healthcare policymakers and practitioners about the allocation of resources and the implementation of preventive measures tailored to the characteristics of distinct population segments.

Objectives

The primary objective of this systematic review is to provide a comprehensive assessment of the prevalence of DM in Pakistan. Specifically, the review aims to:

- ▶ Determine the overall prevalence of DM in the general population of Pakistan.
- ▶ Explore variations in DM prevalence based on factors such as age, gender and geographical location (eg, provinces, urban vs rural areas).
- ▶ Identify potential temporal trends in DM prevalence over the study period if sufficient data are available.
- ▶ Assess the quality of the studies included in the review to ensure the robustness and reliability of the findings.

By synthesising existing data from diverse sources, this systematic review will contribute to the current understanding of the burden of DM in Pakistan. The findings will be valuable for policymakers, healthcare professionals and stakeholders in shaping evidence-based strategies for the prevention, management and control of DM in the country. Furthermore, the review will help identify research gaps and areas requiring further investigation, ultimately supporting evidence-informed decision-making in public health and healthcare policies related to DM in Pakistan.

The seminal work by Akhtar *et al*¹⁷ diligently outlined the prevalence of diabetes and pre-diabetes across Pakistan. However, the landscape of diabetes epidemiology is dynamic, marked by evolving trends and nuanced demographic variations that necessitate a comprehensive re-evaluation. This current study seeks to diverge from Akhtar *et al*'s¹⁷ singular focus on prevalence by undertaking a longitudinal exploration of the shifting prevalence rates of diabetes over time. Moreover, it aims to dissect gender-based and regional-based disparities by meticulously analysing the prevalence of diabetes and pre-diabetes in both men and women, dissecting potential variations that might exist between these cohorts.

METHODS AND ANALYSIS

Study design

This is a protocol paper designed for a systematic review that is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Protocol papers.¹⁸ The systematic review that follows will also adhere to the PRISMA guidelines.¹⁹ The review will be conducted using a rigorous and transparent methodology to ensure the systematic and unbiased synthesis of evidence related to the prevalence of DM in Pakistan. The study is registered with PROSPERO.²⁰

Selection criteria

Inclusion criteria

The systematic review will encompass studies published from inception up to 1st April 2024. The primary population of interest will comprise individuals residing in Pakistan, with no restrictions based on age, gender or ethnicity. Studies conducted in various centres, both regional and national, to ensure a comprehensive representation of the prevalence of DM in Pakistan. The review will encompass research that features both patients previously diagnosed with DM as well as those newly diagnosed. The criteria

for new cases in these studies should adhere to either the WHO guidelines or the American Diabetes Association (ADA) criteria for diagnosing DM.^{1 21} The study designs to be included are cross-sectional studies, cohort studies and population-based surveys. To ensure language homogeneity and accessibility of data, only studies published in the English language will be considered for inclusion in the systematic review.

Exclusion criteria

Studies with a sample size of less than 500 will be excluded due to their potential impact on the reliability of prevalence estimates. Studies focusing solely on gestational diabetes or diabetes in specific subpopulations (eg, patients with diabetes with specific comorbidities) will be excluded. Studies that rely solely on self-reported diabetes, that is, where the diagnosis of DM is based on data reported by the patient instead of using an authentic diagnostic method (blood testing as defined by WHO or ADA) will be excluded.

Diagnostic criteria

The ADA criteria for the diagnosis of DM comprise four potential criteria.

- i. Glycated haemoglobin (HbA1c) $\geq 6.5\%$. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program certified and standardised to the Diabetes Control and Complications Trial assay. In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
- ii. Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
- iii. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.
- iv. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

The WHO criteria for the diagnosis of DM comprise five potential criteria.

- i. Fasting (overnight fast of 8–14 hours) venous or capillary plasma glucose ≥ 7.0 mmol/L (126 mg/dL).
- ii. 2-hour post-load venous plasma glucose ≥ 11.1 mmol/L (200 mg/dL).
- iii. 2-hour post-load capillary plasma glucose ≥ 12.2 mmol/L (220 mg/dL).
- iv. Random plasma glucose ≥ 11.1 mmol/L (200 mg/dL). To be used only in the presence of symptoms.

- v. HbA1c $\geq 6.5\%$ (48 mmol/mol).

Outcomes

The primary outcome of interest for this systematic review is the prevalence of DM in Pakistan. The prevalence will be expressed as a proportion expressed as a percentage of the total population assessed in each study. Additionally, the study will also look into potential confounders associated with diabetes (eg, hypertension, family history and obesity) where possible.

Search strategy

The literature review will be carried out by two independent reviewers in the following electronic databases PubMed, Scopus, Cochrane, PakMediNet and CINAHL. The search strategy will combine relevant keywords using the Boolean operators (OR and AND) including ‘diabetes’, ‘diabetics’, ‘DM’, ‘diabetes Mellitus’, ‘T2DM’, ‘prevalence’ and ‘Pakistan’, ‘Sind’, ‘Punjab’, ‘NWFP’, ‘Khyber Pakhtunkhwa’ and ‘Baluchistan’ (online supplemental file 1). The selection process for the articles will follow the PRISMA guidelines.

Data extraction

Data extraction will be conducted independently by two reviewers using a predefined data extraction form. The extracted data will include the following information:

- ▶ Study characteristics: author(s), year of publication, study design and sample size.
- ▶ Population characteristics: age, gender and location of study participants.
- ▶ Risk factors: number of patients with hypertension, family history, overweight, obesity, dyslipidaemia, current cigarette smoking status and cardiovascular disorder.
- ▶ Prevalence data: number of individuals with diabetes, number of patients with pre-diabetes, total sample size and prevalence.
- ▶ Methodological details: diagnostic criteria used for diabetes, data collection methods and study limitations.

Quality assessment

The quality and risk of bias of included studies will be assessed using appropriate tools. Joanna Briggs Institute critical appraisal checklist for studies reporting prevalence data will be used for cohort and cross-sectional studies to evaluate the quality of the selected studies.²² The Grading of Recommendations, Assessment, Development and Evaluation tool will be used to assess the certainty of evidence and this evaluation will be conducted by two independent reviewers.²³

Data analysis

Descriptive analysis

Initially, a descriptive analysis will be conducted to present an overview of the characteristics of the included studies. This analysis will involve summarising the study designs, sample sizes, age groups, gender distribution,

geographical locations and prevalence rates reported in each study. The data will be tabulated and presented in a narrative format to provide a comprehensive understanding of the studies included in the review.

Prevalence synthesis

The primary objective of the systematic review is to estimate the prevalence of DM in Pakistan. To achieve this, a meta-analysis will be performed. The meta-analysis aims to pool the prevalence estimates from individual studies to generate an overall summary estimate of diabetes prevalence in the country using the inverse variance-weighted method. Before conducting the meta-analysis, heterogeneity among the included studies will be assessed using the I^2 statistic. Heterogeneity measures the degree of variability in effect sizes (prevalence estimates) across studies. If substantial heterogeneity is identified ($I^2 > 50\%$), a random-effects model will be employed, considering the assumption that the true effect sizes may vary between studies due to differences in study populations, settings and methodologies. The meta-analysis results will be visually represented using a forest plot, where each study's prevalence estimate and its corresponding CI will be plotted. The overall prevalence and the 95% CI will be presented. If a considerable level of heterogeneity is observed, subgroup analyses will be conducted to explore potential sources of variability. Subgroups based on factors such as age groups, gender and geographical locations (eg, provinces, rural vs urban areas) will be considered to assess whether prevalence estimates differ significantly between these subgroups. Additionally, to assess the temporal trends, studies will be divided into different groups based on the year the WHO criteria was updated for the diagnosis of DM. Sensitivity analyses will be performed to examine the robustness of the results. This involves repeating the meta-analysis after excluding studies with a high risk of bias or those with small sample sizes to assess the impact of individual studies on the overall prevalence. Potential publication bias, which refers to the tendency for published studies to be biased toward significant or positive findings, will be assessed using funnel plots.

PATIENT AND PUBLIC INVOLVEMENT

No patient will be involved.

ETHICS AND DISSEMINATION

The findings from the systematic review will be shared by publishing them in a peer-reviewed journal and showcasing them at a pertinent conference. Our analysis will be based on aggregated data and will not involve individual patient information, thus eliminating the need for ethical clearance.

DISCUSSION

The findings of this systematic review will hold significant implications for our understanding of the prevalence of

DM in Pakistan and its multifaceted impact on public health. The comprehensive synthesis of available data will provide insights into the burden of DM across different segments of the population and geographical regions. This discussion section highlights the strengths and limitations of the review, and explores the broader implications for healthcare policies, clinical practice and future research.

The prevalence estimates synthesised in this review will reflect the dynamic nature of DM in Pakistan's population. The documented variations in prevalence based on age, gender and geographical regions align with the complex interplay of genetic, lifestyle and socioeconomic factors. It is noteworthy that the increasing prevalence of DM in Pakistan mirrors global trends in urbanisation, sedentary lifestyles and dietary shifts, indicating the need for targeted interventions.²⁴

Comparing the prevalence rates as a result of this review with previous estimates can offer insights into the temporal trends of DM in Pakistan.^{16 17} Any significant increase in prevalence over time could signal a growing public health concern and emphasise the urgency of addressing DM as a national priority.

The findings of this systematic review will have direct implications for healthcare policy and clinical practice in Pakistan. A clear understanding of DM prevalence is essential for allocating healthcare resources efficiently and designing preventive strategies tailored to specific populations. Identifying high-risk groups, such as older individuals and those residing in urban areas, allows for targeted interventions and early detection efforts.

Furthermore, the prevalence data can inform healthcare providers about the potential patient load and guide clinical decision-making, including risk assessment and management strategies. For policymakers, the findings underscore the importance of a comprehensive national strategy to tackle DM, encompassing awareness campaigns, improved healthcare infrastructure and promoting healthy lifestyles.

This systematic review may help identify several avenues for future research. First, conducting longitudinal studies could provide insights into the changing prevalence of DM over time and help identify potential risk factors contributing to its rise. Second, exploring the socioeconomic determinants of DM prevalence and its disparities across different regions can guide equitable policy formulation. Third, investigating the impact of cultural and lifestyle factors on DM prevalence among specific subgroups could offer nuanced insights into the disease's epidemiology.

Strengths and limitations

One of the notable strengths of this systematic review lies in its adherence to the rigorous PRISMA guidelines.¹⁹ The comprehensive literature search, including studies published up to 1st April 2024, and the systematic data extraction process contribute to the reliability and comprehensiveness of the review. By employing both the

WHO and ADA criteria for diagnosing DM,^{1 21} this review encompasses a broad spectrum of studies, enhancing its external validity.

Despite its strengths, this systematic review is not without limitations. The review's dependency on published studies may introduce publication bias, as studies with positive or statistically significant results are more likely to be published. The inclusion of studies published in the English language may lead to language bias, potentially omitting studies in other languages. Furthermore, the prevalence estimates reported in the included studies may be subject to variations due to differences in study methodologies, populations studied and diagnostic criteria used.

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