TYPE 2 DIABETES, CARDIOVASCULAR RISK FACTORS AND OFFSPRING OVERWEIGHT AND OBESITY 5 TO 6 YEARS AFTER HYPERGLYCAEMIA FIRST DETECTED IN PREGNANCY IN CAPE TOWN, SOUTH AFRICA

Tawanda Chivese

Student Number: CHVTAW001

A thesis submitted to the Department of Medicine

Faculty of Health Sciences

University of Cape Town

in fulfilment of the requirements of the degree of Doctor of Philosophy

Supervisors

Professor Naomi S. Levitt

Professor Shane A. Norris

Cape Town, South Africa

2020

PLAGIARISM DECLARATION

I, Tawanda Chivese, confirm that this thesis is my original work, is not copied from any other person's work (published or unpublished) and has not previously been submitted for assessment either at the University of Cape Town or elsewhere.

Tawanda Chivese

Date: 26 August 2020

DEDICATION

The PRO2D Study is dedicated to the memory of Professor Krisela Steyn, who I was fortunate to work with and learn from. Her hard work and contributions to the study of chronic disease and improving the health of South Africans in this regard will forever be cast in stone. I know she would have been happy about the work we did in the PRO2D study and its contribution to understanding the outcomes of hyperglycaemia first detected in pregnancy in women and their offspring in Africa. May her departed soul rest in peace.

This thesis is being submitted at a time when the world is facing one of the greatest threats to human health of the 21st century, the COVID-19 pandemic. May those who have lost lives to the pandemic rest in peace. It is my sincere hope that nations will build stronger, resilient health systems where everyone benefits equitably.

ACKNOWLEDGEMENTS

I will forever remain thankful to my supervisors Professor Shane Norris and Professor Naomi Levitt for the opportunity to study for my PhD under their supervision. Their patient guidance throughout my studies taught me to grow as a scholar. When I commenced my PhD, I acquired a family at the Chronic Disease Initiative for Africa (CDIA) which includes the staff and fellow students, who become an important part of my PhD journey. Particularly, I would like to thank Ms Chantal Stuart and Ms Siphokazi Konkwane, two people who invested their all into making the PRO2D study a success and sometimes sacrificing their weekends to help. My heartfelt thanks go to my mother, my wife, Faith, my children, and my family who are an integral part of my life. My PhD journey was shared with my children, Ano and Lulu, who had to endure many weekends in the office while I worked and sometimes spent countless hours in the car while travelling to some remote part of the West Coast of the Western Cape province with me, visiting research participants. To our new-born son, Nenyasha, may the Grace of our Lord be your portion for all your life!

FUNDING

I would like to thank the Chronic Disease Initiative for Africa (CDIA) for providing institutional support for this thesis. The CDIA provided a home for me to study for my PhD and funded the research costs of the PRO2D study. I am also grateful to the South African Medical Research Council (SAMRC)/ Wits Developmental Pathways for Health Research Unit (DPHRU) for the institutional support and support for the laboratory analyses for samples of the PRO2D study. I acknowledge funding from the International Development Research Centre (IDRC) (fund number: 411592) who provided a PhD bursary for my studies (under the IINDIAGO project).

COPYRIGHT

STATEMENT OF CONTRIBUTORSHIP

I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications.

Chivese, T., Mahmoud, W., Magodoro, I., Kengne, A. P., Norris, S. A., & Levitt, N. S. (2016). Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000-2016: Protocol of a systematic review and meta-analysis. BMJ Open, *6* (12), e012255-012016-012255. doi:10.1136/bmjopen-2016-012255

Chivese, T., Werfalli, M. M., Magodoro, I., Chinhoyi, R. L., Kengne, A. P., Norris, S. A., & Levitt, N. S. (2019). Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: A systematic review and meta-analysis. BMJ Open. 2019;9(5), e024345. doi:10.1136/bmjopen-2018-024345

Chivese, T., Norris, S. A., & Levitt, N. S. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLoS Med. 2019; 16(9).). e1002865. doi: 10.1371/journal.pmed.1002865

Chivese T, Norris SA, Levitt NS. High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy in Town, South Africa. BMJ Open Diabetes Res Care. 2019 Nov 7;7(1).

Tawanda Chivese, Magret C Haynes, Hetta van Zyl, Una Kyriacos, Naomi S Levitt, Shane A Norris. The influence of maternal blood glucose during pregnancy on weight outcomes at birth and preschool age in offspring exposed to hyperglycaemia first detected during pregnancy, in a South African cohort.

Journal submitted to: BMJ Open Diabetes Res Care.

There were also two conference presentations:

1. Chivese T, Norris A S, Levitt S N. High rate of progression to type 2 diabetes mellitus after hyperglycaemia first detected in pregnancy and associated risk factors, in the Western Cape, South Africa. Oral Presentation. Public Health Association of South Africa (PHASA) Annual Conference, Parys, South Africa, 9th – 12th September 2018.
2. Chivese T, Norris A S, Levitt S N. Hyperglycaemia first detected in pregnancy in South Africa – the need for intervention has never been greater. Oral Presentation. Non-Communicable Disease (NCD) Research Symposium, Cape Town, South Africa, 4 March 2020.

TABLE OF CONTENTS

TABLES

FIGURES

ABBREVIATIONS

95%CI	95% confidence interval
AGA	Appropriate for gestational age
ARV	Anti-retroviral therapy
AUC	Area under the receiving operating characteristics curve
BMI	Body mass index
CVD	Cardiovascular disease
DIP	Diabetes mellitus in pregnancy
DPP	Diabetes prevention programmes
FBG	Fasting plasma glucose
GCP	Good clinical practice
GDM	Gestational diabetes mellitus
GPAQ	Global physical activity questionnaire
HAPO	Hyperglycaemia and Adverse Pregnancy Outcomes
HbA1C	Glycated haemoglobin A1C
HDL Cholesterol	High-density lipoprotein cholesterol
HFDP	Hyperglycaemia first detected in pregnancy
HIC	High-income country
HIP	Hyperglycaemia in pregnancy
HOMA-IR	Homeostatic model assessment of insulin resistance
HRQoL	Health-related quality of life

IADPSG	International Association of Diabetes and Pregnancy Study Group
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IQR	Interquartile range
LDL Cholesterol	Low-density lipoprotein cholesterol
LGA	Large for gestational age
LMIC	Low-to-middle-income country
NCD	Non-communicable diseases
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-
SDG	Sustainable development goal
SGA	Small for gestational age
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T2DM	Type 2 diabetes mellitus
VIF	Variance inflation factor
WHO	World Health Organization

ABSTRACT

Background

The number of people with type 2 diabetes mellitus (T2DM) is increasing rapidly in Africa, straining already overstretched health systems. The association between hyperglycaemia first detected in pregnancy (HFDP), which includes both diabetes mellitus in pregnancy (DIP) and gestational diabetes mellitus (GDM), and the later development of T2DM and cardiovascular disease risk in the mothers and possibly overweight in their children is well recognised. This thesis contributes to the largely unexplored body of work on the prevalence of T2DM and CVD risk factors in African women after HFDP and the relationship between HFDP and childhood overweight and obesity. The thesis investigated: 1) the prevalence of T2DM and impaired glucose metabolism in African women of childbearing age; 2) the prevalence of T2DM and cardiovascular disease risk factors in women within 6 years after HFDP, and 3) the influence of maternal blood glucose levels during pregnancy and overweight and obesity in the offspring at the preschool age.

Methods

A systematic review and meta-analysis of all studies published from January 2000 to 2017 was carried out to estimate the prevalence of T2DM and impaired glucose regulation states. In the PROgression to Diabetes study (PRO2D), women diagnosed with GDM using the 2008 National Institute for Health and Care Excellence (NICE) criteria during 2010 and 2011 at a major referral hospital and their offspring were reviewed up to 6 years later. Relevant maternal and foetal/neonatal data were routinely collected during pregnancy and birth. The women were recalled for an assessment of T2DM (OGTT and HbA1C) and other cardiovascular risk factors (insulin resistance, dysglycaemia, dyslipidaemia and obesity) and their offspring for overweight/obesity. The women were reclassified into DIP and GDM using the WHO 2013 criteria for the diagnosis of HFDP.

Results

The pooled prevalence of T2DM was; 7.2% (95% CI 5.6% to 8.9%), impaired fasting glycaemia, 6.0% (95% CI 4.2% to 8.2%) IGT, 0.9% to 37.0% from 39 studies in 27 African countries, and 53 075 participants. The response rate for the PRO2D was 44.2% (final sample n=220). At follow up, almost half of the women, [48% (95% CI 41.2–54.4)], had T2DM, 83% in the DIP subtype and 31% with GDM had T2DM. The type of treatment [insulin (OR 25.8, 95% CI 3.9–171.4, p = 0.001), oral antidiabetic drugs (OR 4.1, 95% CI 1.3–12.9, p = 0.018)], fasting glucose(OR 2.7, 95% CI 1.5–4.8, p = 0.001), OGTT 2-hour glucose (OR 4.3, 95% CI 2.4–7.7, p < 0.001), during pregnancy; current anthropometry [waist circumference (OR 1.1, 95% CI 1.0–1.1, p = 0.007), hip circumference (OR 0.9, 95% CI 0.8–1.0, p = 0.001), BMI (OR 1.1, 95% CI 1.0–1.3, p = 0.001)]) were associated with T2DM. The prevalence of CVD risk factors was: insulin resistance 75% (95%CI 65.9-82.3), dyslipidaemia 74.6% (95%CI 68.3-79.9), dysglycaemia 62.3% (95%CI 55.6-68.5), and raised blood pressure 41.4% (95%CI 35.0-48.0) and metabolic syndrome 60.9% (95%CI 54.3- 67.2). Of the 443 neonates exposed to HFDP during pregnancy, almost one-third [29.6% (95%CI 25.5 – 34.0)] were large-for-gestational-age (LGA) at birth and just over a fifth [21% (95%CI 15.4 – 27.8)] were either overweight or obese at preschool age. A strong association was found between maternal fasting glucose at HFDP diagnosis and birth weight z-score (OR 1.11, 95%CI 1 -1.22, p=0.046), maternal postprandial 2-hour glucose during the third trimester and weight z-score at birth (OR 1.23, 95%CI: 1.07 - 1.42, p = 0.005) and at preschool age (OR 1.37, 95%CI: 1.03 - 1.81, p = 0.031).

Conclusion

The high prevalence of T2DM and CVD risk factors in relatively young women and overweight and obesity in their offspring within 6 years of the index pregnancy demonstrates the need for context-specific interventions to prevent HFDP, to optimise screening for HFDP and to reduce cardiometabolic disease risk in the postpartum period.

PREFACE

This PhD thesis is the culmination of a dream that I had after graduating with my Master's degree in Clinical Epidemiology at Stellenbosch University. I was aware that the prevalence of non-communicable diseases was on the rise and I wanted my doctoral studies to contribute to a better understanding of cardiometabolic diseases, particularly diabetes, on the African continent.

After some enquiries, I was invited for an interview with Professors Naomi Levitt and Krisela Steyn at the Chronic Disease Initiative for Africa (CDIA). During the interview, I spoke about my passion for epidemiology and the need to focus on the growing burden of non-communicable diseases (NCDs) which were already competing for health resources in Africa. Unbeknown to me, they already had a project on gestational diabetes which required a PhD student; that was the beginning of my doctoral studies.

The diabetes tsunami is sweeping across the world at an alarming pace. The numbers of people with diabetes each year outstrip all previous projections made by the International Diabetes Federation. In low-to-middle-income-countries (LMIC), which includes African countries, the increase in diabetes prevalence is steeper and is being driven by a combination of nutrition and demographic transitions. Premature deaths from diabetes are also higher in the LMICs, compared to high-income countries (HIC). Yet, most of the people with diabetes have type 2 diabetes, which is preventable.

Gestational diabetes (GDM) not only offers us a window of opportunity to prevent type 2 diabetes in one individual but also offers us a chance to prevent diabetes and cardiovascular disease in future generations. If we manage to understand the epidemiology of GDM, we may be able to slow down the seemingly unstoppable tide of ever-increasing numbers of people with diabetes in the LMICs. In Africa, however, the unknowns far outstrip the knowns. We still have not answered basic epidemiology questions. How many women are affected by GDM? What are the risk factors of GDM

in Africa? How do we best detect women with GDM? How do we encourage women to continue the lifestyle change that they do successfully during pregnancy, into the postpartum era.? How many women progress to type 2 diabetes after GDM? Are the women with GDM more vulnerable to CVD compared to those without GDM? The project that my thesis became a part of, at the CDIA, the IINDIAGO project, focused on reducing the risk of type 2 diabetes and CVD in women after gestational diabetes. This thesis would subsequently contribute to the formative work for the IINDIAGO project.

One of the biggest problems we currently have is that there are varied diagnostic criteria for GDM in different regions and countries, to the extent that a woman with GDM will be classified as not having GDMby simply flying from one country to another, and vice versa. As will become apparent later, this issue also affected how my PhD studies progressed. In brief, the women who we included in our study were diagnosed using one criterion and by the time we finished following them up, the new criteria now used in South Africa classified them somewhat differently! This is one of the reasons why the title of the thesis changed from ‘Type 2 diabetes and cardiovascular risk factors in women 5 to 6 years and offspring overweight and obesity after gestational diabetes, in Cape Town, South Africa’ to ‘Type 2 diabetes, cardiovascular risk factors and offspring overweight and obesity after hyperglycaemia first detected in pregnancy, in Cape Town, South Africa”.

This thesis is organised as follows:

Part A. Introduction

This section comprises of chapters 1, 2 and 3 and includes the rationale, background of the study, literature review, aims and objectives and the methods used in the studies. Chapter 1 gives the rationale and a brief background of the thesis. A review of the literature relevant to the body of work of the thesis is in Chapter 2. The aims and objectives of the thesis are presented in Chapter 3, followed by an overview of the methods in the specific chapters that follow.

Part B. Empirical chapters

Chapter 4 contains a systematic review and meta-analysis of the prevalence of T2DM in African women of childbearing age, using studies published during the period 2000 to 2016. Data which may be used for monitoring and studying trends in the prevalence of diabetes in this critical demographic are presented. Chapters 5, 6 and 7 are the result of studies undertaken in women with HFDP in Cape Town, South Africa. In Chapter 5, the medium-term progression to T2DM after HFDP and risk factors associated with postpartum T2DM are investigated. In chapter 6 the prevalence of CVD risk factors and insulin resistance in the same women after 6 years is described. This is the only published paper at present that quantifies the burden of CVD risk factors in these women, who are still young, with a mean age of37 years, in Africa. Chapter 7 is a paper which describes the link between HFDP and the developmental origins of cardiometabolic disease (in this case, the proxy outcomes are overweight and obese) in the offspring.

Chapter 4: Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: A systematic review and meta-analysis.

Chapter 5: Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa.

Chapter 6: Chivese T, Norris SA, Levitt NS. High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy in Cape Town, South Africa. BMJ Open Diabetes Res Care. 2019 Nov 1;7(1).

Chapter 7: The influence in a South African cohort of maternal blood glucose during pregnancy on weight outcomes at birth and preschool age in offspring exposed to hyperglycaemia first detected during pregnancy.

Part C. Integrated discussion and conclusion

This chapter (chapter 8) contains a discussion that brings together all the findings from the thesis. Also discussed in this section are implications for policy and clinical practice and implications for research. Finally, the limitations and strengths of this research are discussed.

KEYWORDS

Hyperglycaemia first detected in pregnancy (HFDP), Type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), diabetes mellitus in pregnancy (DIP), cardiovascular disease (CVD), overweight, obesity, children, women of childbearing age, South Africa.

PART A INTRODUCTION

Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under thy observation in life.

Marcus Aurelius

CHAPTER 1. BACKGROUND

1.1. Rationale and problem statement

Diabetes is a growing problem in sub-Saharan Africa, yet there are many areas where knowledge is limited. These areas include the prevalence, risk factors and outcomes of diabetes in women of childbearing age, who are uniquely affected by diabetes in several ways. Firstly, diabetes in women during pregnancy increases the risk of transmission of diabetes and other cardiometabolic diseases to their offspring and possibly to the offspring's future children. Further, apart from childbearing and childrearing, women assume multiple and increasingly complex roles in both their families and their communities. These include being unpaid caregivers for members of the family when they get sick, as well as breadwinners and housekeepers. Therefore, a diagnosis of diabetes does not affect the woman only but has wide-ranging consequences on her family and society. Apart from preventing diabetes in women of childbearing age, it is important to plan for the provision of and prioritisation of resources for diabetes care. To do that, there is a need to establish the extent of the burden of diabetes in African women of childbearing age. This includes information about the prevalence of diabetes and impaired glucose regulation. Estimates of diabetes prevalence in women of childbearing age will also enable an assessment of trends of the disease in this demographic and progress in meeting targets for the reduction of the prevalence of diabetes.

Hyperglycaemia first detected in pregnancy (HFDP) is one of the strongest risk factors for type 2 diabetes mellitus (T2DM) in the postnatal period. Further, HFDP may also contribute to an increased risk of cardiovascular disease (CVD) and in the offspring exposed during pregnancy, a higher risk of cardiovascular disease in adulthood. The risk for T2DM and CVD after HFDP varies widely across populations and differs with the different criteria that are used to diagnose HFDP in different contexts. This pattern has also been observed in the risk for cardiometabolic disease, including overweight and obesity, in offspring from HFDP complicated pregnancies. In Africa, there are limited data on either T2DM and CVD outcomes in women after HFDP or cardiometabolic outcomes in the offspring. However, many studies have shown that the

prevalence of HFDP is high – and in many cases underdiagnosed – due to the limitations within health systems. This thesis aims to contribute to the understudied areas of the prevalence of T2DM in women in Africa of childbearing age and the cardiometabolic outcomes of HFDP in them and their offspring.

1.2. Background

Non-communicable diseases (NCDs) have become the main causes of illness and death worldwide, accounting for up to 72% of all deaths (1). The number of people affected by diabetes mellitus (diabetes), one of the four major NCDs, has quadrupled from 108 million in 1980 to 463 million in 2019 and is projected to reach 700 million by 2040 (2). The prevalence of diabetes globally is expected to increase from 8.8% in 2017 to 9.9% in 2045 (2). Diabetes is attributable for at least 5% of all premature deaths (death before the age of 70 years) (2). This may well be an underestimate, as diabetes is a major cause of CVD and, to a lesser extent, kidney failure and infectious diseases, and some of the deaths in these categories are attributable to diabetes (1). Therefore, the expected increase in the numbers of people with diabetes will also translate into a consequent increase in CVD and other diseases.

Although there are different types of diabetes, 90% of people who have it have type 2 diabetes (T2DM) (3) which is preventable. If the sustainable development goal (SDG) number 3.4 (4) which aims to reduce premature death from NCDs is to be achieved, more efforts need to be put towards prevention as the treatment costs are already beyond many nations. One way of doing this is by preventing diabetes in those groups of people who are at high risk of developing it. Various diabetes prevention programmes (DPPs) (5) in countries such as India (6) and China (7) have demonstrated a reduced risk of developing T2DM in people with intermediate states of carbohydrate intolerance. However, in Africa, the absence of quality research evidence on the most cost-effective interventions hampers efforts in reducing the diabetes epidemic (8).

The true burden of diabetes in Africa and its related complications is not known because of the lack of quality data from many countries and thus estimates are based on data from relatively few countries (9). Even though the prevalence of diabetes in

Africa is lowest amongst the IDF regions, the number of adults with diabetes, compared to other regions, is expected to increase the most, by 143% from 19.4 million in 2019 to 47 million by the year 2045 (2). Besides, the IDF estimates that Africa has the highest prevalence of undiagnosed diabetes, of 69%, compared to other IDF regions (2), partly because of fewer resources committed to screening and diagnostic services in health systems which are already overburdened by infectious diseases such as malaria, HIV and TB (10). A consequence of the high prevalence of undiagnosed diabetes is a higher incidence of complications as people with undiagnosed diabetes may seek healthcare only when diabetes-related complications have appeared (11). It is perhaps not surprising that the proportion of premature death attributable to diabetes is highest in Africa (77%), with several southern African countries registering proportions of more than 80% (2).

In a continent where resources for diabetes treatment are limited, prevention should be prioritised. There are presently sparse data from trials that have investigated diabetes prevention in Africa. Quality research is required from Africa to inform policy about interventions that are cost-effective in reducing the risk for diabetes in the population as a whole and in groups that are at high risk.

Diabetes affects women differently compared with men. In many African communities, women are expected to be caregivers to their families and assume the burden of care if other family members are ill (12). Further, apart from pregnancy and immediate postnatal complications, if a woman develops diabetes before or during pregnancy there is a high risk of transgenerational transmission of diabetes to her offspring (12). There is mounting evidence showing that intrauterine exposure to hyperglycaemia increases the offspring's risk for overweight and obesity, diabetes and other cardiometabolic diseases (13, 14). Further, research shows that this risk can be transmitted to other generations after the initial exposed generation (12, 15). It is, therefore, possible that health trajectories of future generations can be influenced in a positive direction by optimising the cardiometabolic health of women before, during, and after the pregnancy. The WHO, in its current efforts against NCDs and in recognition of the unique position in which women of childbearing age are placed, recommended a gender-specific approach to the prevention, treatment and

management of NCDs such as diabetes in its Montevideo Declaration in 2017 (16). Quality data about the extent of the T2DM burden in African women of childbearing age are, however, lacking (2) and this makes evidence-based policymaking difficult.

HFDP is a known risk factor for the development of T2DM and includes diabetes mellitus first detected in pregnancy (DIP) and gestational diabetes mellitus (GDM) (17). The WHO adopted the 2010 recommendations of the International Association of Diabetes and Pregnancy Study Group (IADPSG) (18) in its 2013 guidelines (17) and subdivided HFDP as either GDM or DIP. These changes came as a result of the findings of the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, a multi-country study with 25 505 participants from nine countries, which found that even the milder maternal blood glucose levels during pregnancy were associated with adverse foetal outcomes (19). The HAPO study, however, did not include an African cohort and this may limit the application of these guidelines to the African context.

The IDF estimates that the worldwide prevalence of HFDP was 15.8% during 2019, with the highest prevalence reported in South East Asia (2). In Africa, 10.4% of an estimated 3.4 million live births are affected by HDFP every year, although data are missing from most African countries (2). Data from one recent meta-analysis estimated that the prevalence of HFDP was 13.6% (20). There is, however, wide heterogeneity in HFDP estimates across African countries from a low of 2.3% in semi-rural Kenya (21) to a high 32% in urban Cameroon in 2017 (22). Recent epidemiological surveys in South Africa's Gauteng province suggest that HFDP prevalence could be as high as 26% in Johannesburg (23). These data imply that as many as one in every four pregnancies are affected by hyperglycaemia that is only discovered during the pregnancy. Because most provinces in South Africa use risk-factor-based screening for HFDP, it is estimated that this may miss more than half of HFDP cases (23). This means that many women with HFDP are untreated, with the consequent raised risk for T2DM and CVD after the pregnancy for the mother and her offspring.

Systematic reviews, primarily based on data from high-income countries, have reported that women with previous HFDP have a seven-fold risk of developing T2DM (24, 25), double the risk of CVD (24) compared to women with normal glucose metabolism in pregnancy and their offspring have a raised risk of future overweight and

obesity (26). Most of the studies included in these systematic reviews used criteria which did not differentiate between women with DIP and GDM, thus more research evidence is required to investigate the effects of the different HFDP types on both maternal and offspring outcomes. As far as it is known, no published studies in Africa to date have investigated these outcomes. Unlike the high-income countries, Africa is affected by high rates of food insecurity and both under and over-nutrition tend to co-exist in many communities, and even in the same households (27-29). This makes it difficult to compare research findings from other continents to Africa.

1.3. Chapter summary

The rationale for this thesis and the description of the background to the major areas covered in it is provided in this chapter, as is a description of the diabetes problem in women of childbearing age and how they are uniquely affected by diabetes. Also discussed are gaps in research on HFDP in African women and some of the research that was carried out in addressing some of these gaps. The literature on the areas covered in this thesis is comprehensively discussed in the next chapter.

1.4. References

1. Wou C, Unwin N, Huang Y, Roglic G. Implications of the growing burden of diabetes for premature cardiovascular disease mortality and the attainment of the Sustainable Development Goal target 3.4. Cardiovasc Diagn Ther. 2019; 9(2):140.
2. International Diabetes Federation. IDF diabetes atlas 9th Edition. Brussels: International Diabetes Federation, 2019 [cited 2020 13 January]. 9: [Available from: http://www.diabetesatlas.org.]
3. World Health Organization. Classification of diabetes mellitus 2019.Available from: https://apps.who.int/iris/bitstream/handle/10665/325182/9789241515702-eng.pdf.

4. World Health Organization. SDG 3: Ensure healthy lives and promote wellbeing for all at all ages: The goals within a goal: Health targets for SDG 3: World Health Organization; 2016 [cited 2019 10 October]. Available from: https://www.who.int/sdg/targets/en/.
5. Roberts S, Barry E, Craig D, Airoldi M, Bevan G, Greenhalgh T. Preventing type 2 diabetes: Systematic review of studies of cost-effectiveness of lifestyle programmes and metformin, with and without screening, for pre-diabetes. BMJ Open. 2017;7(11): e017184.
6. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 2006;49(2):289-97.
7. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: A 20-year follow-up study. Lancet. 2008;371(9626):1783-9.
8. Pastakia SD, Pekny CR, Manyara SM, Fischer L. Diabetes in sub-Saharan Africa - from policy to practice to progress: Targeting the existing gaps for future care for diabetes.Diabetes Metab Syndr Obes. 2017; 10:247-63.
9. Atun R, Davies JI, Gale EA, Bärnighausen T, Beran D, Kengne AP, et al. Diabetes in sub-Saharan Africa: From clinical care to health policy. Lancet Diabetes Endocrinol. 2017; 5(8):622-67.
10. Mayosi BM, Lawn JE, Van Niekerk A, Bradshaw D, Karim SSA, Coovadia HM, et al. Health in South Africa: Changes and challenges since 2009. Lancet. 2012;380(9858):2029-43.
11. Dall T. Undiagnosed diabetes has high economic burden in USA.PharmacoEcon Outcomes New. 2019; 826:32-20.
12. Jimenez-Chillaron JC, Ramon-Krauel M, Ribo S, Diaz R. Transgenerational epigenetic inheritance of diabetes risk as a consequence of early nutritional imbalances. Proceedings of the Nutrition Society. 2016;75(1):78-89.

13. Schulz LC. The Dutch Hunger Winter and the developmental origins of health and disease. Proceedings of the National Academy of Sciences. 2010;107(39):16757-8.
14. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008 Jul 3; 359(1): 61–73.
15. Kaati G, Bygren LO, Edvinsson S. Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Eur J Hum Genet. 2002;10(11):682.
16. World Health Organization. Montevideo roadmap 2018-2030 on NCDS as a sustainable development priority: WHO; 2017 [Available from: http://www.who.int/ncds/governance/montevideo-roadmap.pdf?ua=1.
17. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy 2013 [Available from: https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=48ABC998E153A412E00E1CD62B90C1EC?sequence=1.
18. International Association of Diabetes Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
19. HAPO Study Cooperative Research Group. Hyperglycaemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002.
20. Muche AA, Olayemi OO, Gete YK. Prevalence and determinants of gestational diabetes mellitus in Africa based on the updated international diagnostic criteria: A systematic review and meta-analysis. Arch Public Health2019;77(1):36.
21. Pastakia SD, Njuguna B, Onyango BA, Washington S, Christoffersen-Deb A, Kosgei WK, et al. Prevalence of gestational diabetes mellitus based on various

screening strategies in western Kenya: A prospective comparison of point of care diagnostic methods. BMC Pregnancy Childbirth. 2017;17(1):226.

22. Munang YN, Noubiap JJ, Danwang C, Sama JD, Azabji-Kenfack M, Mbanya JC, et al. Reproducibility of the 75 g oral glucose tolerance test for the diagnosis of gestational diabetes mellitus in a sub-Saharan African population. BMC Res Notes. 2017;10(1).

23. Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. S Afr Med J. 2017;107(6):523-7.

24. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. Lancet. 2009;373(9677):1773-9.

25. Rayanagoudar G, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: A systematic review and meta-analysis of 95,750 women. Diabetologia. 2016;59(7):1403-11.

26. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: A systematic review. Exp Diabetes Res. 2011; 2011.

27. Brown JC. Socioeconomic status (SES), food insecurity and the double burden of malnutrition within South African households: University of Cape Town; 2018.

28. Kimani-Murage EW, Muthuri SK, Oti SO, Mutua MK, van de Vijver S, Kyobutungi C. Evidence of a double burden of malnutrition in urban poor settings in Nairobi, Kenya. PloS One. 2015;10(6): e0129943.

29. Senbanjo IO, Senbanjo CO, Afolabi W, Olayiwola IO. Co-existence of maternal overweight and obesity with childhood undernutrition in rural and urban communities of Lagos State, Nigeria.Acta Biomed. 2019;90(3)

CHAPTER 2. LITERATURE REVIEW

2.1. Chapter introduction

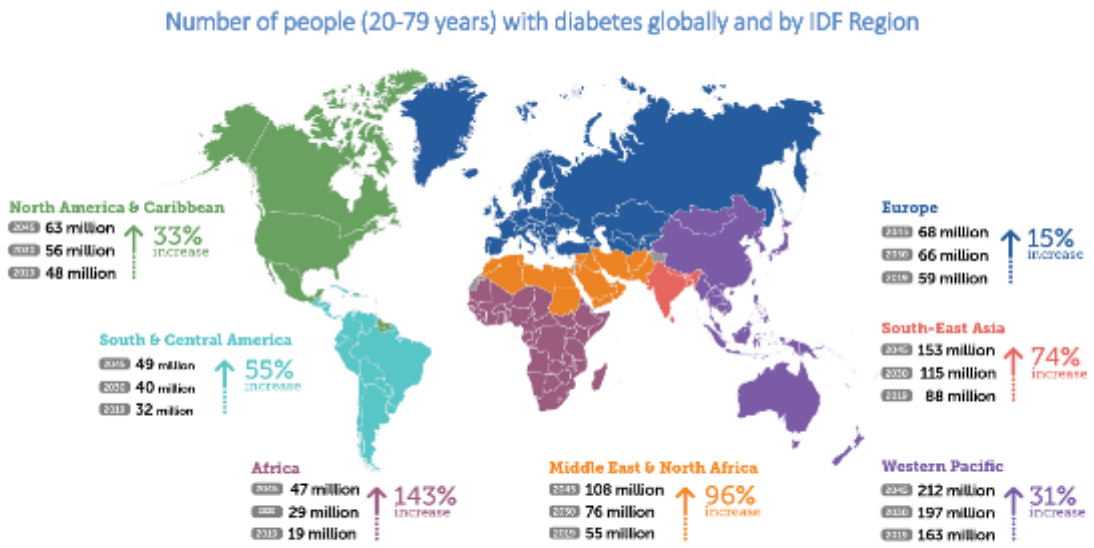
In this chapter, a comprehensive review of research on diabetes in women of childbearing age, the burden of T2DM and CVD due to hyperglycaemia first detected in pregnancy (HFDP), and the effect of HFDP on childhood overweight and obesity in their exposed offspring is discussed. The chapter explores the topic of diabetes mellitus in women of childbearing age and HFDP in the context of Africa, particularly in South Africa. The chapter ends with a brief discussion on T2DM and CVD outcomes in women after HFDP and on the cardiometabolic risk in their exposed offspring. The empirical chapters 4, 5, 6 and 7 also contain discussions on the relevant literature, so care has been taken not to repeat some of those in this literature review. The chapter is based on comprehensive searches for studies, published mainly during the period 2000 to 2019, in all major electronic databases including Scopus, MEDLINE and EMBASE through Pubmed, ISI World of Science, Scopus, the Cochrane Library and Google Scholar.

2.2. Diabetes mellitus

Diabetes is one of the greatest threats to human health around the world, with an estimated global prevalence of 9% in 2019 (1) and 1.5 million deaths directly related to diabetes in 2012 (2). Globally, diabetes prevalence has more than doubled from 4.6% in the year 2000 to 9.3% in 2019 (1). If current trends continue, without successful interventions, the total number of people with diabetes is expected to increase from 463 million in 2019 to 700 million by 2045 (1). This implies an absolute increase of 51% in the number of people living with diabetes and will require significant investment in health resources being availed for the treatment of diabetes. Unsurprisingly, the greatest expected increases in both diabetes prevalence and the numbers of people living with diabetes are in the low-to-middle-income countries, as shown in Fig 2.1, which are at various stages of epidemiological transitions. The IDF African region, for

example, is expected to undergo a 143% increase in the number of people living with diabetes, from 19.4 million in 2019 to 47 million in 2045 (2).

Fig 2.1. Number of people (20 to 70 years) with diabetes globally and IDF region



Reproduced with permission from the International Diabetes Federation Atlas, 9th Edition (1)

Diabetes mellitus is a group of metabolic conditions characterised by raised blood glucose and either a malfunction of or damage to pancreatic β-cells (3). Diabetes has several causes which include genetic defects, autoimmunity, inflammation, insulin resistance, epigenetic and environmental factors (3). In 2019, the WHO introduced a new classification, based on aetiology, which grouped diabetes mellitus as type 1 diabetes (T1DM), type 2 diabetes (T2DM), hybrid forms of diabetes, specific forms of diabetes, unclassified diabetes and hyperglycaemia first detected in pregnancy (HFDP) (3). Hyperglycaemia first detected in pregnancy (HFDP) is categorised into either diabetes in pregnancy (DIP) or gestational diabetes mellitus (GDM) and has a

worldwide prevalence of around 16% (1, 4). T1DM is one of the most severe forms of diabetes, accounts for about 5% of all diabetes cases, usually requires insulin for survival, and results in decreased life expectancy by around 11 to13 years in the high-income countries (HICs) (5, 6). The outcomes for T1DM are worse for people living in the LMICs, for example, sub-Saharan Africa, where diagnostic and treatment services, including insulin availability, are still not adequate (7). In 70-90% of people, T1DM is characterised by autoantibodies against insulin-producing pancreatic β-cells and the exocrine pancreas itself (8, 9) in genetically susceptible individuals and is diagnosed in individuals between the ages of 5-15 years (8).

The majority (more than 90%) of all people with diabetes have T2DM (10), which is caused, in most people, by obesity driven β-cell dysfunction which can either be insulin resistance or deficiencies in insulin secretion (3). T2DM occurs mostly in adults and was previously rare in children and young adults, but prevalence is increasing in parallel with the rising prevalence of obesity in children and young adults (11). Although data are lacking from many countries, Australia recorded a 27% increase in the prevalence of childhood T2DM during the period 1990-2002 (12) while in India 25% of people with T2DM during the period 2000-2006 were below the age of 25 years (13).

The WHO 2019 classification of diabetes (3) introduced a new category: hybrid forms of diabetes in which clinical features found in both T1DM and T2DM exist. This new category includes the groups formerly classified as ketosis-prone T2DM and latent autoimmune diabetes in adults (LADA), now being referred to as “slowly evolving auto-immune mediated diabetes”. Ketosis-prone diabetes is usually diagnosed when a patient presents with ketosis and severe insulin deficiency but usually the patient recovers and does not require insulin (14). Slowly evolving auto-immune mediated diabetes is the second most common form of diabetes with a prevalence between 5 to 10% worldwide (15). Patients with slowly evolving immune-mediated diabetes present with symptoms of T2DM but have Glutamic Acid Decarboxylase autoantibodies, typically observed in patients with T1DM (16). This form of diabetes usually slowly evolves into an insulin-requiring form, hence the name ‘slowly evolving auto-immune mediated diabetes’. The fourth category of diabetes consists of different specific forms of diabetes. These include monogenic diabetes, caused by defects in specific genes,

diseases of the exocrine pancreas, endocrine disorders from hormones that antagonise insulin secretion, drug-induced and infection-related diabetes (3).

2.3. Consequences of diabetes

Diabetes results in damage to both small (17) and large blood vessels (18) and leads to a high risk of damage to organs that are vulnerable to both microvascular (kidneys, eyes and nerves) and macrovascular dysfunction (the brain and the heart) (18).

Diabetic retinopathy is the most common microvascular complication of diabetes and is attributable for 64% of impaired visual acuity and 27% of blindness prevalence, worldwide (17). Diabetic nephropathy prevalence increases with diabetes severity and leads to end-stage kidney disease and kidney death (19). The risk for nephropathy also increases with the duration of diabetes, for example, the United Kingdom Prospective Diabetes Study found a prevalence of microalbuminuria of 7.3% at the time of diabetes diagnosis, which increased to 28% at 15 years follow-up (20). Cardiovascular autonomic neuropathies affect both autonomic and somatic nervous systems and affect between 31% to 73% of people with diabetes (21). Although these neuropathies are classified under microvascular complications, they may lead to myocardial infarction, coronary heart disease, cardiac arrhythmias and sudden death (21).

Diabetes is the strongest risk factor for cardiovascular disease (CVD), with an odds ratio of 4.4, when compared to individuals without diabetes (22). Macrovascular complications such as coronary heart disease, carotid artery disease and peripheral vascular disease are more prevalent in people with diabetes, compared to the general population with coronary heart disease being the most prevalent (prevalence of 21%) complication (23). Findings from several Mendelian randomisation studies have demonstrated that diabetes has a causal association with coronary heart disease (24). In keeping with the higher prevalence of CVD in people with diabetes, mortality from CVD is almost double in people with diabetes, compared to those without (22). Although diabetes prevalence does not differ between the genders, women with diabetes, compared to men with diabetes, have a higher risk for myocardial infarction

and stroke (25), heart failure, peripheral artery disease, overall CVD and double the mortality from CVD (26).

Diabetes is a major cause of mortality and accounts for approximately 11% of global mortality (2). This is partly due to diabetes complications and their strong association with CVD. Data from a meta-analysis of 57 studies showed that half of the people with diabetes, 50.3% (95%CI 37.0 – 63.7), die of CVD (23). Although recent data show a steady decrease in mortality from vascular diseases among people with diabetes in high-income countries (HIC) (27, 28), the opposite is happening in the low-to-middle-income countries (LMIC) (29). Further, estimates from the International Diabetes Federation (IDF) show that more than 60% of diabetes-related-deaths in LMICs are premature deaths, i.e., among people aged 20 to 70 years (2).

Diabetes affects the functioning of communities in many other ways, apart from the increased burden of disease, complications, and death. The high rate of undiagnosed diabetes in the LMICs results in higher rates of complications and increased disability leading to significant impairment of quality of life (30). While diabetes-related health expenditure for adults varies widely between regions and countries, overall, expenditure rose from just over USD200 million in 2006 to over USD750 million in 2019 (1). The high disparities in spending may impact outcomes for affected people, with the average expenditure per person almost 40 times higher in the HICs compared to the low-income countries (USD5 339 vs USD138 per person per year) (1). Health systems in the LMICs may not be well equipped to provide for the diagnosis and treatment needs for the exponential increase in the number of people with diabetes, over and above the existing challenges in their health systems (31). Although data are sparse, out of pocket expenses for diagnosis and treatment may add a significant lifetime economic burden on individuals living in LMICs.

2.4. Diabetes mellitus in Africa

In Africa, the raw prevalence of diabetes is 6% and the distribution of diabetes phenotypes appears to be similar to other regions with up to 90% of all people with diabetes having T2DM (2). Compared to other IDF regions, Africa has the lowest age-

adjusted diabetes prevalence of diabetes, perhaps due to lower urbanisation, a population still dominated by the younger age groups and relatively lower levels of obesity (1). However, African countries are undergoing epidemiological transitions, driven by the combined effects of rapid urbanisation, a demographic transition towards older populations and a nutrition transition (32). During the period 1980 to 2014, the prevalence of diabetes more than doubled in both men (from 3.4% to 8.5%) and women (from 4.1% to 8.9%) (33), and the IDF expects Africa to have the greatest increase in the number of people living with diabetes from 19 million in 2019 to 47 million in 2045 (2). The African region also had the highest estimated prevalence of undiagnosed diabetes (69%) during 2019 (1). Late diagnosis of diabetes increases the risk of complications and, ultimately, the cost of treating diabetes. Of concern is that, compared to other regions, spending on diabetes in Africa is estimated to be around 20 times lower (1), which may result in poor diagnostic and screening services and poor quality of care.

Rigorous population-based data are still lacking from many African countries but the available data show that the distribution of diabetes varies by region, with the highest prevalence reported from North Africa (1). A systematic review of studies conducted during the period 1999 to 2011 showed that the prevalence of T2DM in North Africa ranged from 2.6% in rural Sudan to 20% in urban Egypt (13). A separate systematic review of sub-Saharan African studies found that T2DM prevalence ranged from 1% in rural Uganda to 12% in urban Kenya during the same period (14). In 2019, South Africa had both the highest age-standardised prevalence (12.7%) and the highest number of people living with diabetes (4.6 million) in sub-Saharan Africa (1). Notably, prevalence estimates vary considerably between and within countries depending on the screening method used, rural/urban location and diagnostic criteria used.

Diabetes was estimated to account for 6% of overall mortality in Africa in 2017(34). However, 77% of all diabetes-related deaths in Africa were in people below the age of 60 years, the highest proportion of premature deaths due to diabetes in the world (34). The burden of disease due to diabetes, when assessed using disability-adjusted life years (DALYs), is highest in sub-Saharan Africa compared to other regions (35). Sub-Saharan Africa also experienced the greatest increase (126%) in DALYs due to

diabetes during the period 1990 to 2017 (35). This increase in DALYs is largely explained by population growth and the demographic transition into older populations (35). A closer look at sub-Saharan Africa shows that southern Africa has a higher burden of diabetes, compared to other regions of sub-Saharan Africa, with a crude rate of 1927 DALYs (compared to Central– 1233, Western – 887 and Eastern – 915) (35). Preventive interventions are urgently needed to reduce the effect of the increase in both prevalence and numbers of people in need of diabetes treatment on already overstretched health systems.

Africa has several challenges that may worsen the prevalence of T2DM (36). The prevalence of overweight and obesity, the strongest known risk factor for T2DM, has increased greatly across many African countries, with the average BMI in women increasing from 22kg/m2 in 1980 to 25kg/m2 in 2014 (33). At a population level, data from Africa for the period 1980 and 2014 show a strong correlation between both mean BMI and diabetes prevalence and absolute BMI change and change in diabetes prevalence (33). The prevalence of obesity and overweight is not uniform across the African countries, but data from a cross-sectional survey of four countries showed high prevalence ranging from 46% in adults in rural Uganda to 85% in teachers in South Africa (37).

Data from meta-analyses of observational studies and Mendelian randomisation studies have shown that the association between various proxies of adiposity such as body mass index (BMI), weight gain, waist and hip circumference and T2DM is causal (38). At a mechanistic level, increased adiposity, especially central adiposity, leads to increased intra-abdominal visceral fat which has a disruptive effect on insulin metabolism and consequently leads to T2DM (39). Many African countries already have high levels of obesity and overweight and indications are that this will translate into a higher prevalence of T2DM in the future.

Undernutrition has also been associated with diabetes, albeit before the 1970s in some parts of Africa and Asia, but it is now rare. Also named fibocalculous diabetes, starvation-related diabetes was found in individuals with a history of undernutrition. This type of diabetes was characterised by calcification of the pancreas, chronic pancreatitis and malfunction of the exocrine pancreas (36). Apart from starvation, exposure to

disease such as malaria was also thought to contribute to fibocalculous diabetes through impairment of beta-cell function (40).

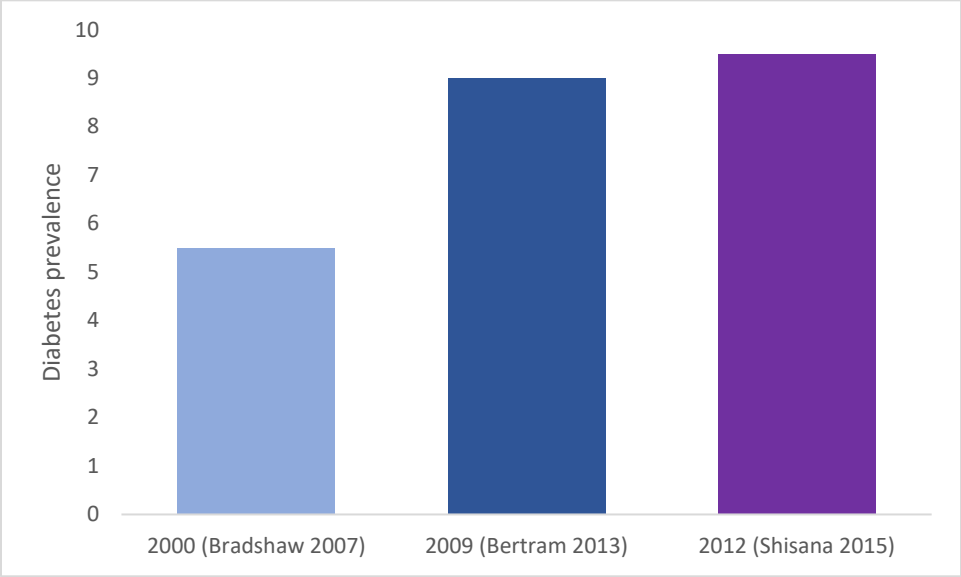
In addition to adiposity, and other known risk factors such as genetic susceptibility (41), family history (42), unhealthy diets, low levels of physical activity, increased sedentary time, smoking and HFDP (38), other risk factors may be driving the diabetes pandemic in Africa. Sub-Saharan Africa is host to more than two-thirds of all people living with HIV, of which around 60% are on antiretroviral therapy (ART) (43). While the wide coverage of ART has increased the life expectancy of people living with HIV to nearly the same as that of people without HIV (44), higher prevalence of diabetes has been reported in people on HIV ART (45, 46). The increased prevalence of diabetes in people on ART may be partly explained by the combination of ART-related body fat redistribution (47) and HIV-related chronic inflammation (48), although data are not conclusive and more rigorous research is needed. Although the incidence of HIV appears to be slowing down in many sub-Saharan African countries, HIV prevalence will continue rising due to the increased life expectancy in people living with the virus. More research evidence is required to investigate the effect of ART on diabetes and CVD risk, and on the best interventions to reduce the risk for these conditions in people living with HIV.

2.5. Diabetes in South Africa

South Africa had the highest age-adjusted prevalence of diabetes, 12.7%, and the highest number of people living with diabetes, 4.7 million, in sub-Saharan Africa during 2019 (1). Similar to other African nations, diabetes prevalence is higher in urban settings compared to rural areas and more than half of people with diabetes in South Africa are not aware of their status (1). The burden of diabetes has increased significantly in South Africa during the past few decades as can seen in Fig. 2.2. Previous estimates showed a crude prevalence of diabetes of 5.5% in the year 2000 (49) which increased to approximately 9% in adults South Africans in 2009 (50). Data from the South African National Health and Nutrition Examination Survey (SANHANES) showed a crude prevalence of 9.5% during 2012 (51). Notably, the prevalence of

diabetes is higher in people of older age (52), and varies with ethnicity and rural/urban locations, with the highest prevalence reported in urban areas. The crude prevalence of diabetes was highest in South Africans of Indian descent in urban KwaZulu Natal, 32%, in a study in 2016 (53), followed by a prevalence of 24% in South Africans of mixed ancestry during 2012, and lowest (12% to 13%) in black South Africans during 2012 and 2016, respectively, (54, 55) and 4.6% in rural KwaZulu Natal in 2008 (56). Data from the other provinces show a similar distribution in terms of prevalence, and ethnic and rural/urban differences (51).

Fig 2.2. Change in the prevalence of diabetes mellitus in South Africa during the period 2000 – 2012

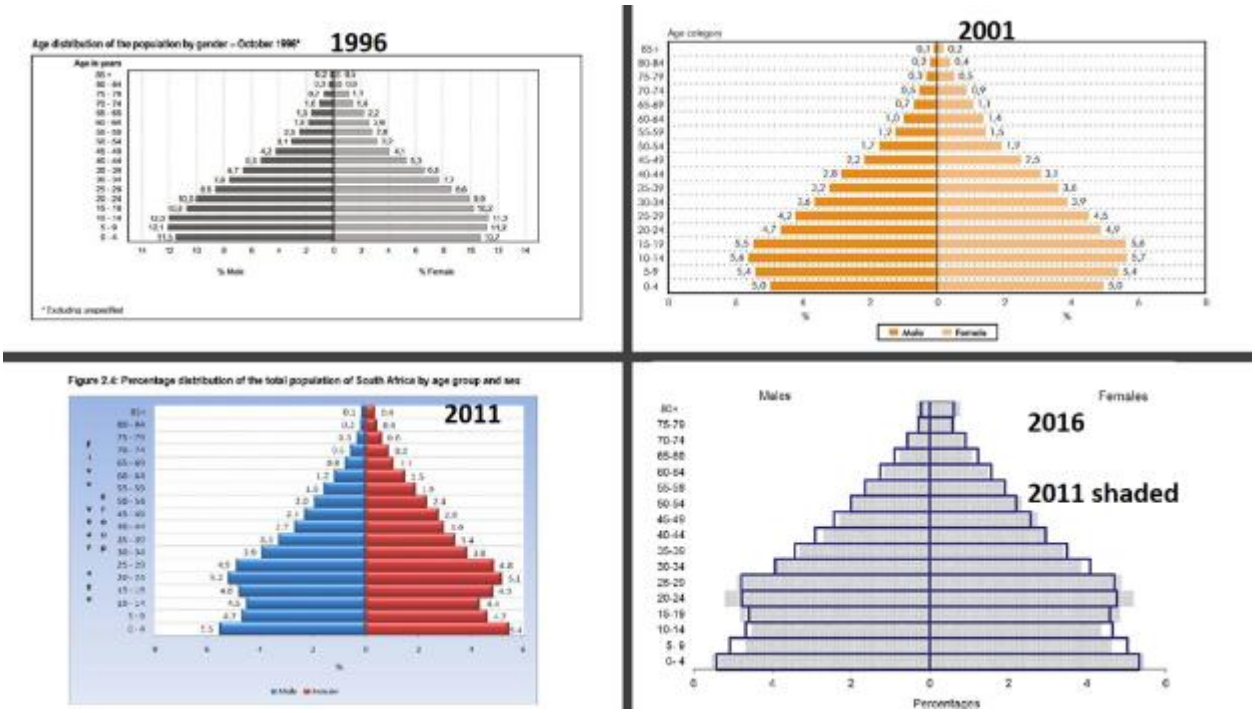


Bradshaw 2007 (49) - a meta-analysis of 5 studies, diagnosis criteria not clear.
Bertram 2013 (50) - a meta-analysis of 4 studies published between 2008-2012. Diabetes diagnosed using WHO 1998 criteria.
Shisana 2015 (51) – nationwide representative sample (South Africa National Health and Nutrition Examination Survey). Diabetes diagnosed using HbA1c≥6.5%.

Although current data show an already high burden of diabetes in South Africa, the prevalence of diabetes may increase more, in tandem with the demographic transition and an epidemiologic transition driven by the increase in the prevalence of obesity. South Africa is undergoing a demographic transition towards a population structure with

increasing proportions of older people, who are at greater risk of diabetes, compared to children and young adults (57). The population age structure of South Africa has changed gradually, towards smaller proportions of young children while proportions of young and older adults have increased during the period 1996 to 2016 as can be seen in Fig 2.3.

Fig. 2.3. Demographic transition in South Africa during the period 1996-2016

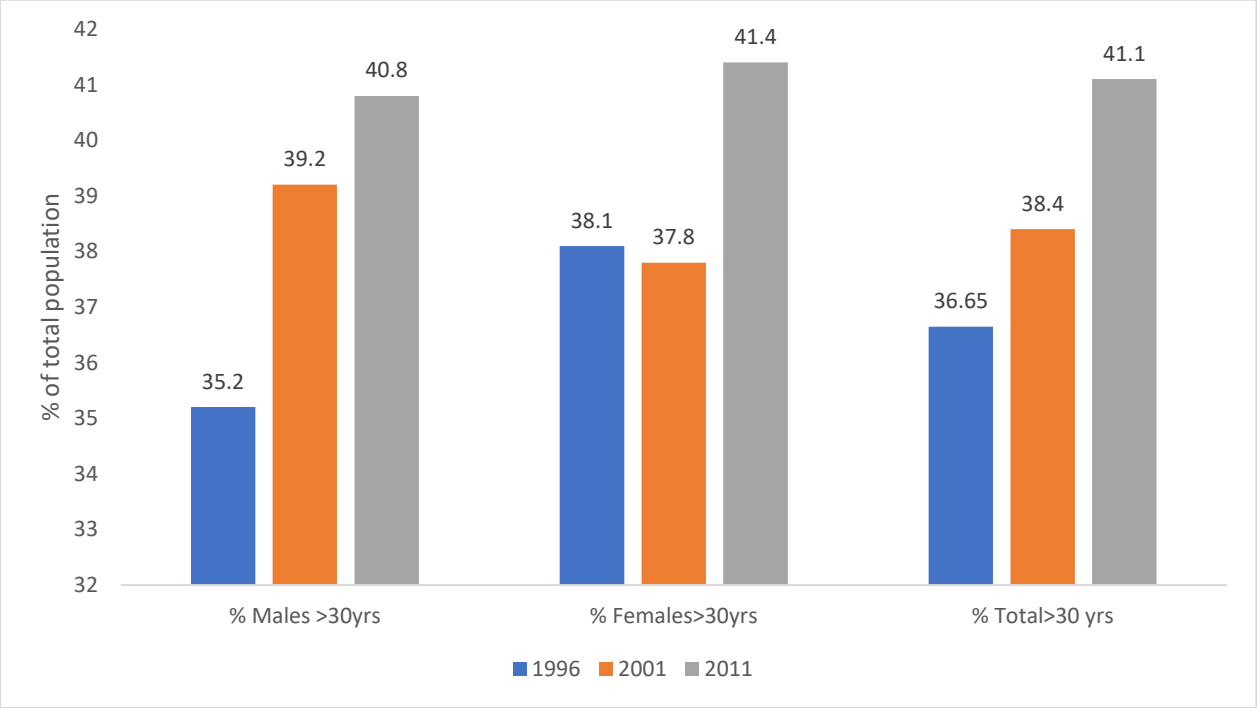


Data are from Statistics South Africa national censuses from 1996- 2011 and the 2016 community survey. For 1996, the percentage in each gender adds up to 100%, for the years 2001, 2011 and 2016, the total percentage is 50% for each of the genders.

While the next census will be during the year 2021, data from the Statistics South Africa's *Community Survey of 2016* show a gradual transition towards higher proportions of young adults and older people in the population structure (Fig 2.2 last frame). Besides, Fig 2.4 below shows that the proportions of adults with age ≥ 30 years (adults at high risk of diabetes) have increased steadily from 36.65% to 41.1% during the 15 years from 1996 to 2011. If this trend continues, the prevalence of diabetes in

South Africa will most likely increase as the proportion of the population that is vulnerable to diabetes increases.

Fig. 2.4. Change in the proportion of the population≥30 years of age in South Africa during 1996-2011

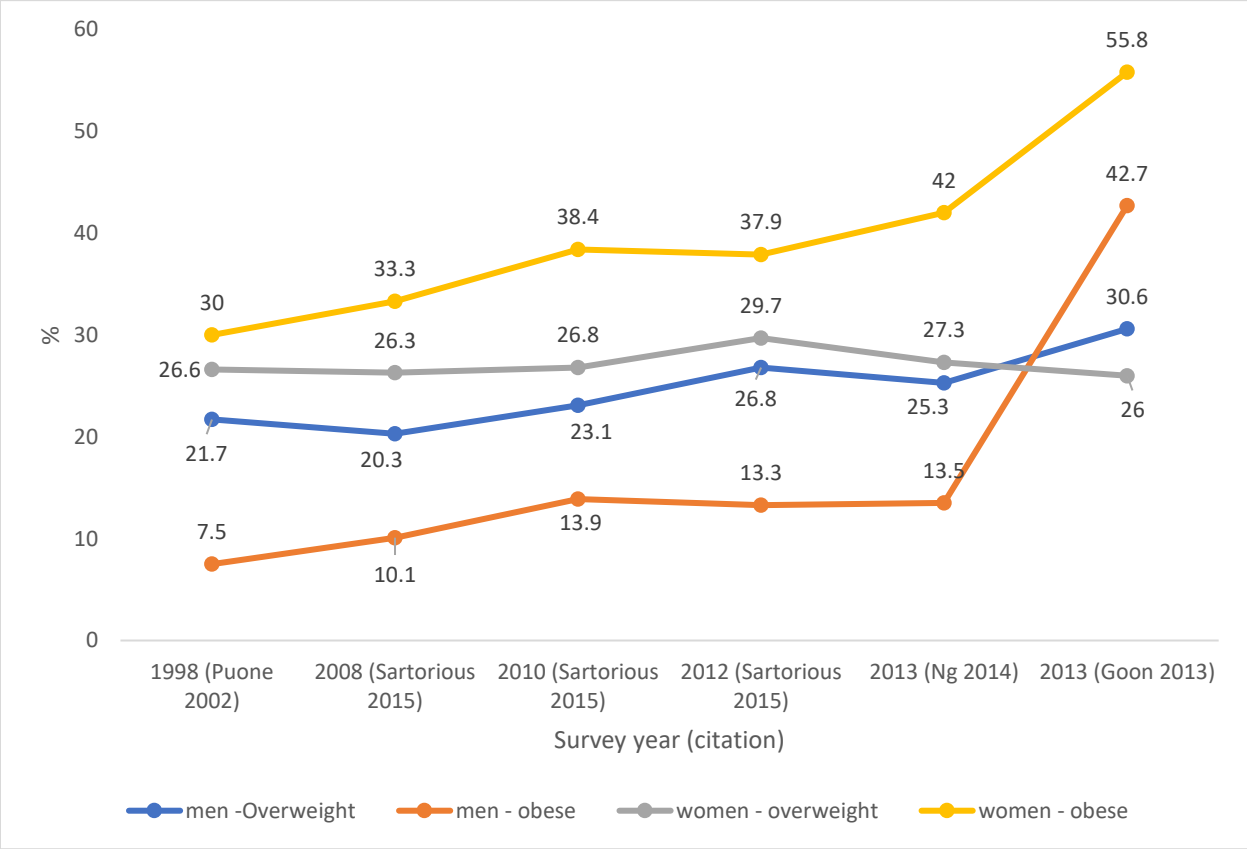


Data were calculated from the Statistics South Africa national censuses of 1996, 2001 and 2011.

South Africa is among the leading the Africa countries with high prevalence of adults who are either overweight or obese (58). The prevalence of overweight and obesity has increased in both males and females during the last 2 decades. Data from successive national representative samples (59-61) show a steady increase in the proportion of men and woman who are either overweight or obese during the period 1998 - 2013. Perhaps more worrying is that while the prevalence of overweight has risen steadily, but slowly, during the period, the prevalence of obesity has risen more steeply (Fig 2.5). As of 2013, 69% of South African women over the age of 15 years were either overweight or obese, with 42% being obese (58), the highest in sub-Saharan Africa.

One study of nurses in Limpopo province (61) found an even higher prevalence of overweight and obesity in both genders, although these data may not be nationally representative. The strong association between obesity and diabetes may mean that South Africa is yet to reach the peak of the diabetes epidemic.

Fig. 2.5. Changes in overweight and obesity prevalence in males and females in South Africa during the years 1998 to 2013



Data from Puone 2002, Sartorius 2015, Ng 2014 and Goon 2013 (57-60). Data are from nationally representative studies, except Goon 2013 (60), a study of male and female nurses in Limpopo province, South Africa.

The diabetes epidemic in South Africa adds to a health system that already has multiple challenges which are well described in literature (31). South Africa has relatively poor health outcomes, evidenced by maternal and child mortality rates that are still unacceptably high, given the country's level of economic development (62). The poor health outcomes have been attributed to several reasons, including persistent

inequality from the long-term effects of colonialism and apartheid policies, an inefficient health system and the crippling effect of the HIV and TB epidemics (63). This is compounded by the related high prevalence of poverty, persisting lack of access to clean water and sanitation and high levels of unemployment (63). Although, in general, access to health services has improved over the last two decades, formerly disadvantaged ethnic groups are still the worst affected by poverty, unemployment, and lack of access to clean water and sanitation (63). The structural weaknesses in the health system are further exacerbated by a lopsided healthcare financing system where public and medical-schemes-dominated- private-healthcare systems coexist (64). Even though South Africa spends over 8% of its gross domestic product on healthcare, higher than the global average, the health financing model is inefficient. In this fragmented two-tiered healthcare financing system, 80% of the population is dependent on a free public healthcare system that has only half a share of the human and financial resources. For people living with chronic diseases such as diabetes, this system may lead to long term impoverishment. For the poor, recent data show that the incidence of catastrophic health spending on diabetes is as high as 25%, with more women being disproportionately affected (65). Even though diabetes treatment is free in the public healthcare system, individuals still must pay for transport costs and may lose days of work. It remains to be seen how the proposed National Health Insurance (64) will improve the healthcare funding and ultimately, health outcomes for people with diabetes.

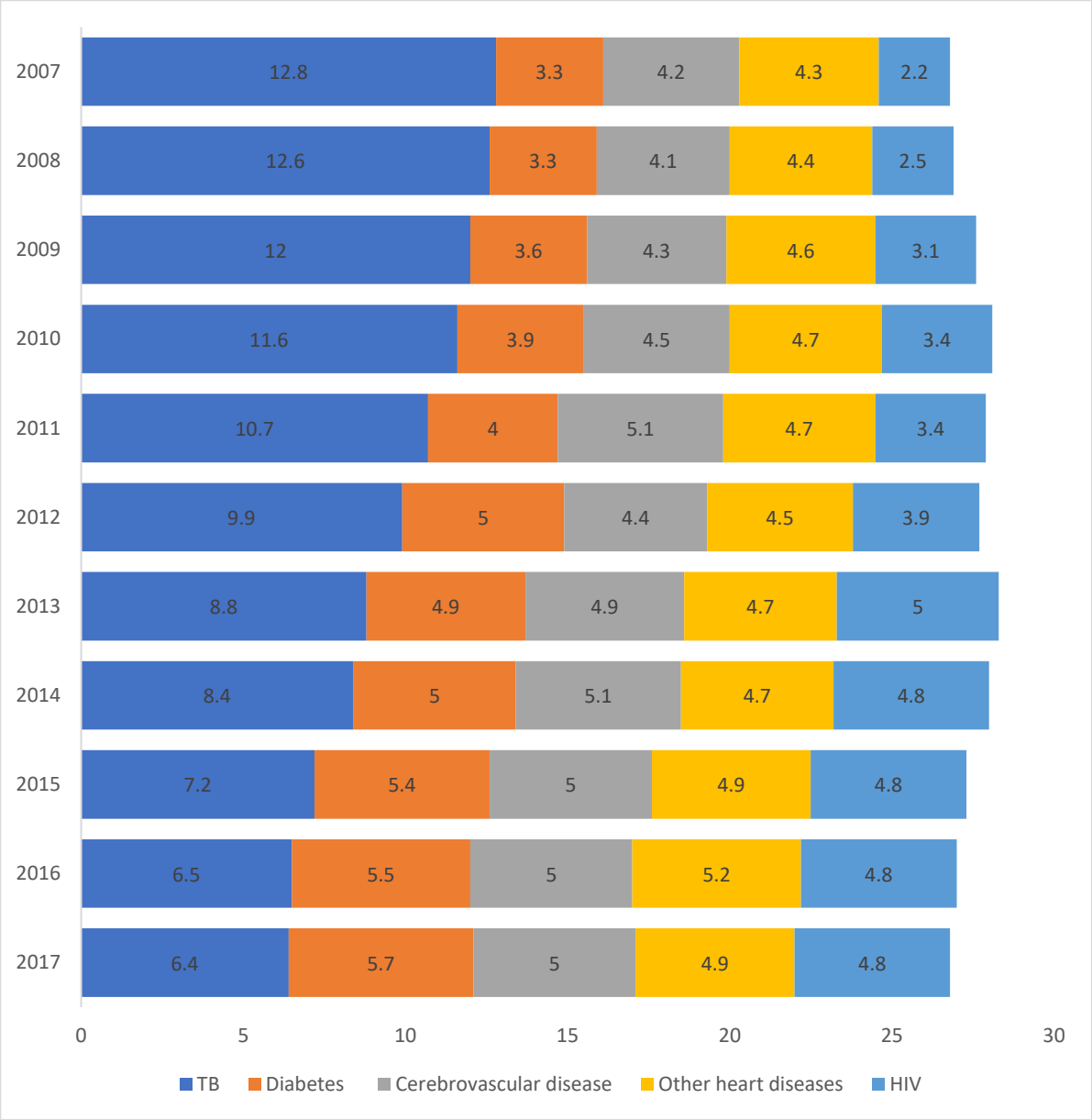
Apart from structural challenges, South Africa is undergoing a complex epidemiological transition characterised by multiple burdens of disease. This multiple disease burden includes persisting infectious diseases, mainly HIV and TB, rising prevalence of non-communicable diseases such as diabetes and CVD, co-existence of under-and-over nutrition, persisting high burdens of maternal and child mortality and high levels of injury and violence (63). The country is host to the largest number of people living with HIV, globally, 7.9 million people in 2017, with an estimated prevalence of 14%, of which 62% are on ART (66). Notably, the high coverage of ART has reduced mortality due to HIV and increased life expectancy which also influences the demographic transition, while ART may result in increased diabetes risk as

discussed earlier. South Africa is also one of the world's high-burden-TB countries with an estimated TB incidence of 520 per 100 000 during 2018 and a high TB case fatality ratio of 22% (67). In addition to a high burden of infectious diseases and maternal and child mortality, South Africa also has one of the highest burdens of trauma in Africa due to interpersonal violence (31). Diabetes imposes an additional burden on this already overstrained health system and prevention may play crucial role in managing the diabetes epidemic in South Africa.

The burden of disease and mortality due to diabetes has increased with the increasing diabetes prevalence in South Africa during the past few decades, although data from national surveys are sparse. During the year 2000 diabetes was directly responsible for 2.6% of all deaths (68) and 1.6% of the total DALYs (49). In 2009, an estimated 73 000 DALYs were due to diabetes and its non-fatal complications while there were 2000 amputations and 8000 cases due to diabetes (50). Data on these non-fatal complications during the other years is lacking, although it may be assumed that the complications have increased due to the increase in the prevalence of diabetes.

Data from Statistics South Africa (69–72) show that the proportion of deaths due to diabetes has doubled from 3.3% to 5.7% during the decade 2007-2017 (Fig 2.5). Diabetes was the tenth leading underlying cause of death in South Africa in the year 2000 (49) but has become the second leading cause of death after TB since 2012 (Fig 2.6). Notably, data from death notifications do not show the excess mortality from CVD and renal failure that may be due to diabetes. If the excess mortality is considered, the true mortality and morbidity burden due to diabetes are likely to be higher than suggested by the data from the death notifications. Up-to-date epidemiological data are needed to estimate the true mortality burden due to diabetes.

Fig 2.6. The proportion of deaths due to diabetes– findings from death notifications from 2007 to 2017



Data are from the Statistics South Africa Mortality and causes of death: Findings from death notifications, Statistical releases from 2008 (68), 2012 (69), 2015 (70) and 2020 (71)

2.6. Diabetes in African women of childbearing age in Sub-Saharan Africa and South Africa

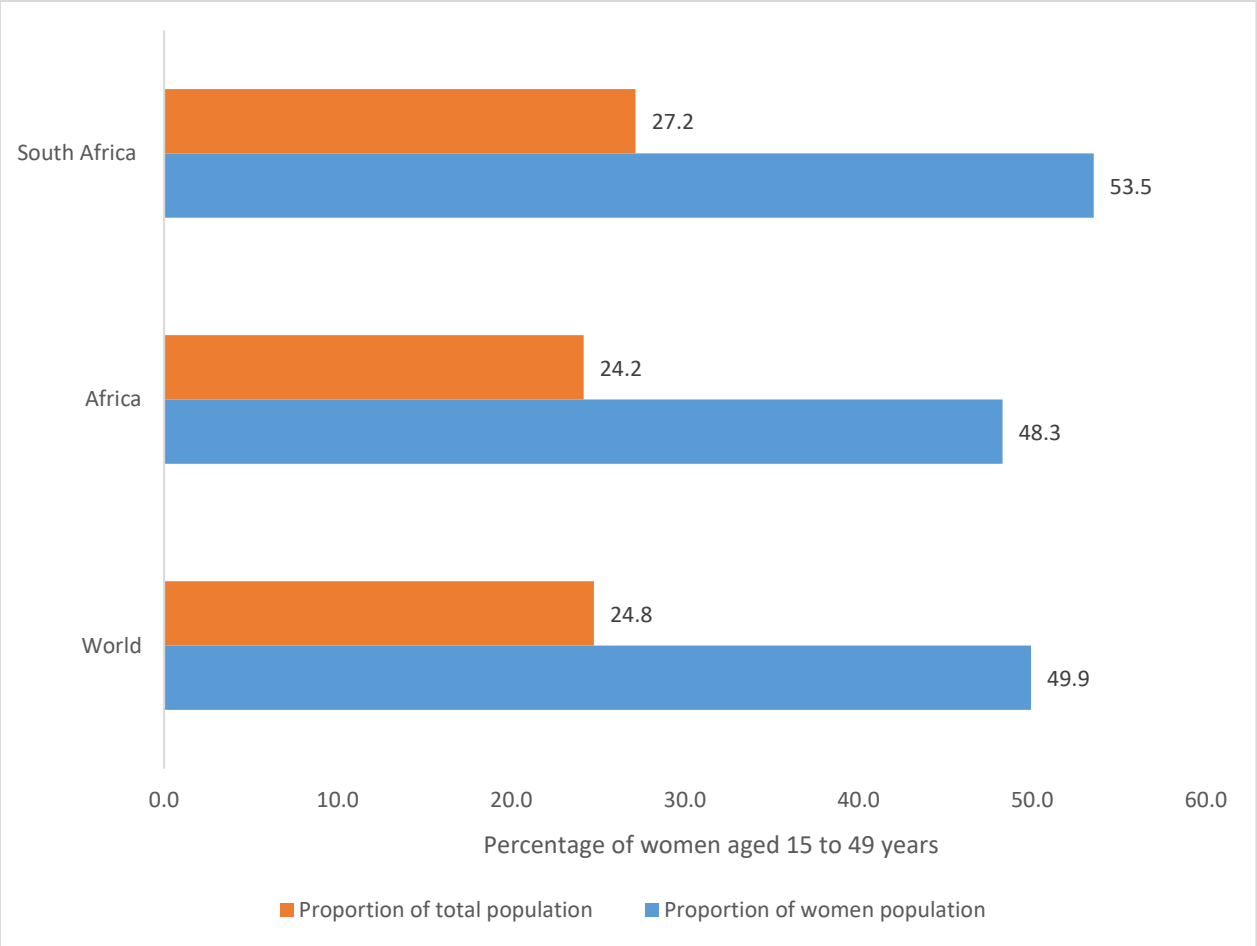
According to the WHO, the childbearing age in women is between the ages of 15 and 49 years (73). Women of childbearing age contribute substantial proportions to both the total populations and the total population of women (Fig. 2.6) (74). Out of the total world population of 7.7 billion in 2019, women aged 15 to 49 years numbered 1.9 billion, contributing half (49.9%) of the total population of women and a quarter (24.8%) of the global population. In Africa, out of a population of 1.3 billion, the proportion of women aged 15-49 years mirrored the global pattern (Fig. 2.7), although slightly lower (48.3% of the total population of women and 24.2% of the total African population). I

Compared to the global population distribution, in South Africa, women of childbearing age contribute higher proportions to both the total population of women (53.5%) and the overall population (27.2%). In the Western Cape and the Cape metropole, the population distribution mirrored that of the country (75). South Africa has nine provinces and the Western Cape province (estimated population of 6.3 million during the 2016 community survey) is the fourth most populous after Gauteng, KwaZulu Natal and the Eastern Cape (75). The province is made up of five main districts, including the Cape Town City Metropole, where 63.8% of the people live (75). Most of the people in the province are of mixed ancestry, a term used to describe a heterogeneous group of people who have diverse Khoisan, Bantu-speaking African, Asian and European ancestry. Similar to black South African women, women of mixed race are also affected by poverty and inequality as they were also discriminated against during colonialism and, later, apartheid. There is still no consensus about the best socially acceptable term to describe people of mixed-race ancestry without the racial implications engendered during apartheid.

Although women of childbearing age have seen their participation in the economy and education increase drastically since the advent of democracy in South Africa in 1994 (76), they are still greatly disadvantaged. Most South African women of childbearing age are of black ethnicity, in line with the general population distribution, and are more likely to be poor and either unemployed or employed in poorly paying jobs (76). For example, in 2015, 42% of black women were in low skilled jobs

compared to 1.4% of white women (71). The ethnic imbalance is also reflected with other formally marginalised groups, such as people of mixed ancestry who are predominant in the Western Cape province (71). Women, unlike their male compatriots, work predominantly in pink-collar jobs and tend to earn less than men (71). Despite improvements in gender equality, most women are still expected to play multiple roles in their families, including childbearing, child-rearing, caregiving to ill members of the family, housekeeping and being breadwinners (76).

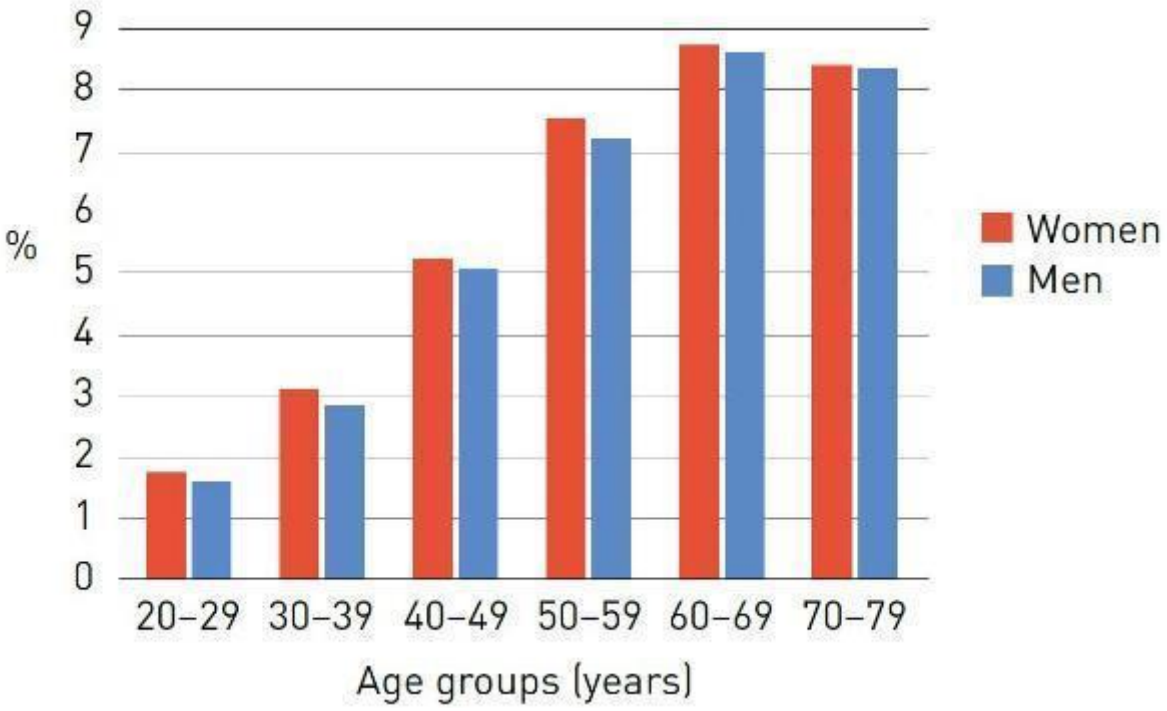
Fig 2.7. Proportions of women of childbearing age compared to the total population of women (brown colour) and the total population (blue)



Graph constructed using data from https://www.populationpyramid.net (73).

The prevalence of diabetes in women of childbearing age in Africa is not known, partly due to the unavailability of quality data from many countries. Data from the IDF show that the prevalence of diabetes across all age groups during 2019 was slightly higher in women in general compared to men in Africa, (Fig 2.8) (1). In South Africa, the prevalence of diabetes in women is slightly higher than that in males and follows the same age and ethnic distributions seen in the general population (51).

Fig 2.8. Diabetes prevalence by age and gender in Africa during 2019



Reproduced with permission from the International Diabetes Federation Atlas, 9th Edition (1)

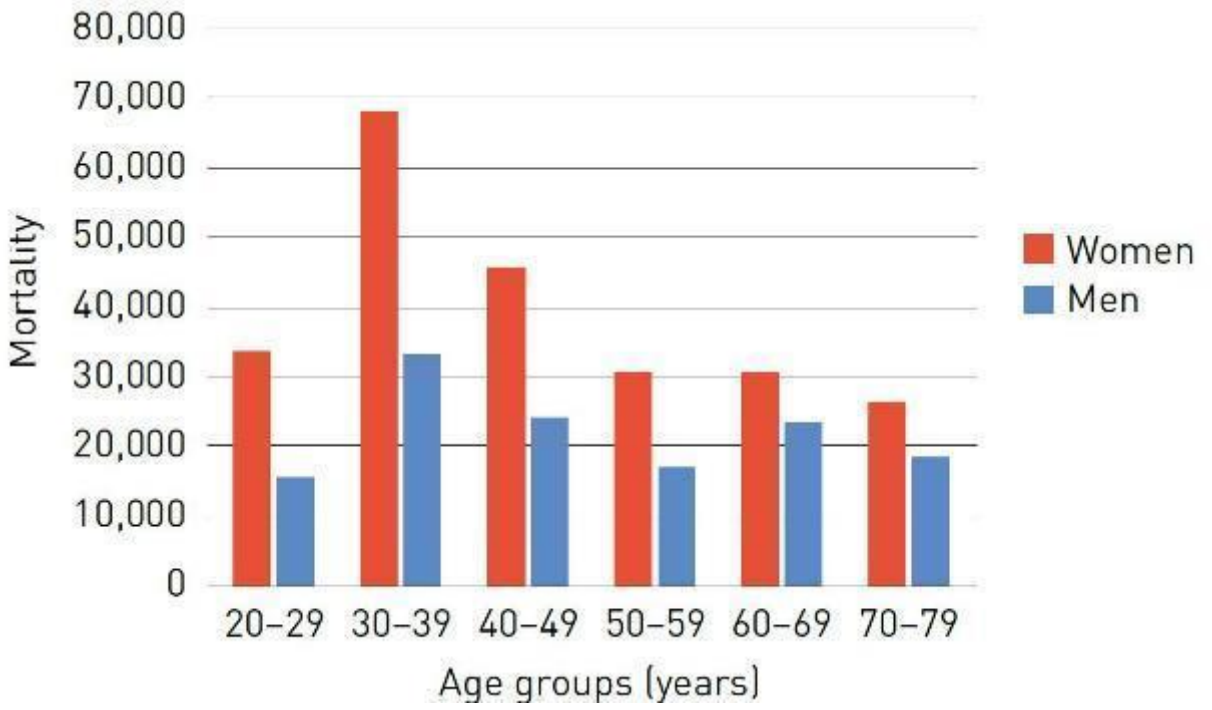
Across most of sub-Saharan Africa, the prevalence of overweight and obesity among women of childbearing age, the strongest known risk factor for T2DM, increased greatly, in fact, tripled in some cases, in many African countries during the period 1993-2014 (77). Cultural perceptions of overweight and obesity as symbols of wealth may worsen the prevalence of obesity and hinder preventive measures. In South African women the prevalence of obesity increased drastically during the decade 2002 to 2012, as was previously shown in Fig 2.5 (58-61). Data from the SANHANES showed that 69% of women were either overweight or obese, and more than two-fifths (42%) of

women were obese in 2012 (51). This may mean women may have a higher prevalence of diabetes in the future, driven by the higher prevalence of obesity (33, 78). Apart from the direct effects of the disease, women with diabetes are affected by psychosocial factors, including psychosocial stress (79). Factors such as low education status, low socioeconomic status, low income and poorly paying jobs, psychosocial stress, occupational stress and sleep disturbances are associated with both diabetes and obesity in women (79-81). In many studies the associations are often bidirectional, i.e., psychosocial factors leading to a high risk of diabetes and vice versa (79, 82). Psychosocial stress may be exacerbated by gender imbalances in many societies and greater demands and responsibilities during childbearing and childrearing. In many African communities, apart from expected housekeeping roles, childbearing and being primary caregivers for children, women tend to assume complex roles which include being breadwinners and unpaid caregiver for unwell family members (83, 84). Non-communicable disease (NCDs) in general and diabetes in particular, impose a burden on women and their families, as the care is long term and requires a change in lifestyle, apart from treatment. Thus, if a woman of childbearing age is diagnosed with diabetes or other NCDs, the effects are not limited to the woman alone, but her family is also affected. One study in Tehran found that the total, physical and mental health-related quality of life (HRQoL), decreased significantly after the diagnosis of diabetes, not only for the woman but for her partner and children (82). In sub-Saharan Africa, the role of psychosocial factors in the risk of diabetes and the prognosis after diagnosis with diabetes in women of childbearing age remains understudied.

In terms of clinical outcomes, women seem to have worse outcomes than men. Women with diabetes have a higher risk for CVD (85), myocardial infarction and stroke (34). Overall mortality from diabetes is almost twice for women compared to men, and the ratio is highest during the reproductive age groups of 20 to 49 years (Fig 2.9) (1). Again, the higher mortality could be partly attributable to a higher risk of CVD in women with diabetes. The higher risk for CVD and mortality in women with diabetes is in sharp contrast to the well-established lower risk for CVD in women compared to men during the childbearing age (86). In Central Europe, women with diabetes were found to have higher levels of LDL-cholesterol and higher levels of both systolic and diastolic blood

pressure (87). There are limited data on the distribution of CVD risk factors between the genders from Africa, except prevalence of obesity, a common risk factor for T2DM and CVD, which is higher in women of childbearing age compared to their male counterparts (78). Besides, hyperglycaemia in pregnancy increases the risk for both diabetes and CVD and may contribute to the higher mortality in women during childbearing age.

Fig 2.9. Mortality from diabetes by gender in Africa during 2019

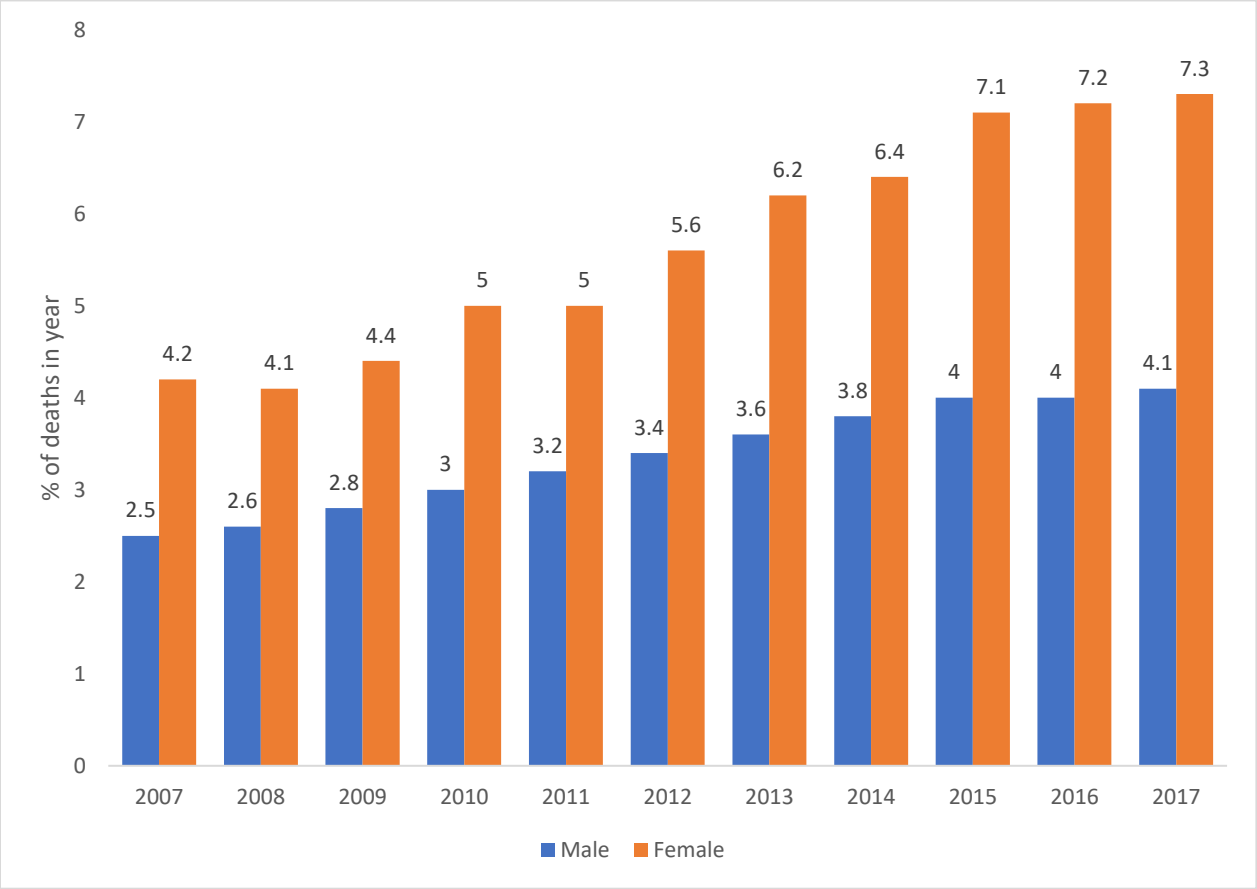


Reproduced with permission from the International Diabetes Federation Atlas, 9th Edition (1)

Data from death notifications in South Africa during the decade 2007 to 2017 (69-72), show a similar pattern to world data (Fig 2.10), with female proportions of deaths due to diabetes ranging between 1.6 to 1.8 times the male proportions (Table 2.1). In South African women, diabetes-related mortality has risen sharply during the last decade. Diabetes was the second leading cause of death during 2013 and 2014 and has been the leading cause of death in South African women since the year 2015 (Table 2.1).

Diabetes-related deaths occur mostly in the older age groups, (50 to 64 years and over 65 years), although the data on proportions of deaths in women of childbearing age are not available.

Fig 2.10. Percentage of deaths attributable to diabetes, by gender, in South Africa during the period 2007 to 2017



Data are from the Statistics South Africa Mortality and causes of death: Findings from death notifications, Statistical releases from 2008 (68), 2012 (69), 2015 (70) and 2020 (71)

Table 2.1. The proportion of mortality due to diabetes in South Africa by gender during the period 2007-2017

Year	Male (% of deaths)	Rank -male causes of death	Female (% of deaths)	Rank -female causes of death	Ratio of Female%: Male%
2007	2.5	7	4.2	6	1.68
2008	2.6	7	4.1	6	1.58
2009	2.8	8	4.4	6	1.57
2010	3	7	5	6	1.67
2011	3.2	7	5	5	1.56
2012	3.4	6	5.6	4	1.65
2013	3.6	6	6.2	2	1.72
2014	3.8	6	6.4	2	1.68
2015	4	6	7.1	1	1.78
2016	4	5	7.2	1	1.8
2017	4.1	4	7.3	1	1.78

Data are from the Statistics South Africa Mortality and causes of death: Findings from death notifications: Statistical releases from 2008 *(68), 2012 (69), 2015 (70) and 2020 (71)*

2.7. Hyperglycaemia in pregnancy and hyperglycaemia first detected in pregnancy

Hyperglycaemia in pregnancy (HIP) consists of all forms of raised blood glucose occurring during pregnancy. This may include already existing type 1, type 2 diabetes and hyperglycaemia first detected in pregnancy (HFDP) and, according to the IDF (1), affected 15.8% of pregnancies worldwide during 2019.

HFDP contributes to most of the cases of HIP in pregnancy (about 83% IN 2019) (1) and is defined as any glucose intolerance diagnosed during pregnancy for the first time after ruling out other forms of diabetes (4). HFDP is further categorised as gestational diabetes (GDM) and diabetes in pregnancy (DIP). Women with HFDP may

fail to adjust to the metabolic demands of pregnancy which increase after the second trimester and coupled with pre-existing chronic insulin resistance, develop hyperglycaemia as a symptom of altered glucose metabolism (88).

The term HFDP was introduced by the WHO in its 2013 guidelines to distinguish between women with GDM and those with more severe forms of glycaemia, similar to diabetes outside pregnancy (4). The previous WHO criteria of 1999 defined GDM in a way that included all women with various degrees of hyperglycaemia. There was a lot of heterogeneity in the diagnosis of gestational diabetes mellitus (GDM), before this, with some definitions including women with diabetes and women with intermediate dysglycaemia as defined outside of pregnancy. Most of the studies that investigated GDM before the IADPSG recommendations used definitions that would have included women with both GDM and DIP. In this thesis, the term HFDP is applied in studies which GDM definitions are used that may have included women with DIP. Notably, the guidelines and the criteria for the diagnosis of GDM are still heterogeneous as can be seen in Table 2.2.

GDM was first described in the literature in the early 1950s but the controversy on how to diagnose it and which criteria to use has still not been completely resolved. In 1949, Priscilla White described 439 pregnancies where she classified the degree of glycaemia using the letters A to E (89). Her classification took account of the age of diabetes onset, duration of diabetes and whether a woman had diabetes complications.

> *"Class A, with highest chance for foetal survival, includes patients in whom the diagnosis of diabetes was made upon a glucose tolerance test which deviates but slightly from the normal. Such patients require no insulin and little dietary regulation."*

"Class A", in Priscilla White's classification would later become known as GDM. In 1954, a French paper by J. P. Hoet which was translated into English also described GDM (90). Although there was increasing awareness of the negative effects of hyperglycaemia on pregnancies, the diagnosis criteria for GDM were hotly debated. During the mid-1950s, Carrington, Schurman and Reardon in the USA presented data from 92 'prediabetic pregnant women' who they described as having gestational diabetes (91). They used a 2-hour post-load glucose of 170mg/dL (9.4 mmol/L) to classify

‘prediabetic pregnant women’. However, in 1957, O’ Sullivan, based on Hoet’s study and a large cohort of women whom they followed up, proposed the 3-hour OGTT for women with risk factors for GDM. These risk factors were a family history of diabetes, foetal overgrowth and glycosuria during the pregnancy. They also proposed a 2-step process, starting with a 1-hour 50gm OGTT, and a follow-up 3-hour OGTT for women with abnormal 1-hour OGTT (130mg/L). Later, O’ Sullivan and Mahan (a statistician) performed 752 OGTTs in women in their second and third trimesters and determined cut-offs for the diagnosis of GDM using mean plus 2 standard deviations (92). These criteria (fasting glucose 5.0mmol/L, 1-hour 9.2mmol/L, 2-hour 8.1mmol/L and 3-hour 6.9mmol/L) were based on future risk of diabetes and were subsequently widely used for decades. The National Diabetes Data Group (93) modified the 2-step 3-hour OGTT in 1979 and further modifications were suggested by Carpenter and Coustan in 1982 (94) (fasting glucose 5.3mmol/L, 1-hour 10.0mmol/L, 2-hour 8.6mmol/L and 3-hour 7.8mmol/L). In 1985, the WHO (95) recommended a 1-step 2-hour OGTT with criteria similar to non-pregnant individuals of fasting blood glucose of at least 7.8mmol/L and/or 2-hour glucose of 11.1mmol/L. The WHO modified its criteria in 1999 (96), while the American Diabetes Association (1998) used criteria similar to the Carpenter and Coustan criteria (97).

Although Pederson (98) and White (89) highlighted the need for diagnostic criteria that were based on preventing adverse foetal outcomes, it took six decades to have these criteria. The WHO guidelines of 2013 (4) were the result of a consideration of evidence from several studies and the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommendations on the diagnosis and classification of hyperglycaemia in pregnancy (99). Both the WHO guidelines and the IADPSG recommendations were based largely on the findings of the Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study, which showed a graded continuous relationship between maternal blood glucose levels and several adverse pregnancy outcomes (100). The HAPO study followed up 25 505 women with fasting blood glucose ≤5.8 mmol/L and/or OGTT 2-hour blood glucose ≤11.1 mmol/L measured during the 24-32 weeks of gestation. Maternal blood glucose at 24 to 32 weeks gestational age was associated with birthweight>90th percentile, cord blood C-peptide >90th percentile, primary caesarean section and neonatal hypothermia. The

HAPO study also showed that maternal blood glucose levels which had previously been thought of as 'normal'. were associated with the risk of adverse pregnancy outcomes. Notably, the HAPO study did not establish maternal blood glucose cut-offs at which adverse events occurred, and this has complicated the search for diagnostic cut-offs for GDM, which are still debated. Further, although the HAPO study had cohorts from 10 countries in North America, Europe, Asia and Australasia, there were no participants from Africa (101). Data from the continent are needed to provide insights on the role of maternal hyperglycaemia on adverse pregnancy short- and long-term outcomes in both the mother and the foetus in a continent with multiple challenges. In many African communities, overnutrition and undernutrition frequently co-exist, together with the multiple burdens of infectious diseases such as HIV, malaria and TB, high maternal and child mortality and the prevalence of non-communicable diseases is on the rise.

While many regional bodies have adopted the WHO 2013 guidelines, there is still no consensus on diagnostic criteria for HFDP (102, 103), as can be seen in Table 2.2. Debate is still ongoing about when to screen for HFDP, what screening methods to use, how to classify women with blood glucose values in the ranges of diabetes outside of pregnancy, and the advantages and disadvantages of using lower blood glucose criteria for GDM diagnosis (103). There are still no conclusive findings of the costs compared to benefits of using lower fasting glucose criteria recommended by the IAPDSG which will most likely result in higher numbers of women being diagnosed with GDM, and the consequent need for more health resources in pregnancy. One difference between the WHO 2013 guidelines and the IADPSG recommendations is on the issue of women with blood glucose within the ranges of diabetes outside pregnancy. The IADPSG defines these women as having overt diabetes while the WHO defines them as diabetes mellitus in pregnancy (DIP). Regardless of the terminology used, women with more severe forms of hyperglycaemia in pregnancy are at higher risk of adverse pregnancy and have a higher chance of their blood glucose not returning to normality after the pregnancy. The Australasian Diabetes in Pregnancy Society (ADIPS) (104) adopted the WHO 2013 criteria, while the American Diabetes Association (ADA) (105) adopted the IADPSG recommendations. The National Institute

for Health and Care Excellence (NICE) maintained its 2008 guidelines in their revised guidelines of 2015 (106). In South Africa, the Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) (57) adopted the WHO 2013 criteria in 2017, although the terms overt 'diabetes' and 'DIP' are used interchangeably in the guideline. The differences in the criteria used for HFDP also result in heterogeneity in estimates of HFDP prevalence across different regions and countries.

Table 2.2. Some of the criteria for the diagnosis of HFDP in pregnancy

Criteria	HFDP type	Timing of testing (weeks)	Test	Fasting glucose	OGTT 2-hr glucose
IADSPG 2010	GDM	24-28	One step 75gm OGTT	5.1-6.9mmol/L	8.5-11.0 mmol/L
	Overt diabetes	Anytime during the pregnancy	One step 75gm OGTT	≥7.0mmol/L	≥11.1mmol/L
WHO 2013	GDM	24-28	One step 75gm OGTT	5.1-6.9 mmol/L	8.5-11.0 mmol/L
	DIP	Anytime during the pregnancy	One step 75gm OGTT	≥7.0 mmol/L	≥11.1mmol/L
ADA 2018	GDM	24-28	One step 75gm OGTT or 2-step test (50gm OGTT 1-hr followed by 100gm OGTT 3 hrs if first step abnormal	For the 75gm OGTT 5.3-6.9mmol/L	8.6-11.0 mmol/L
	Overt diabetes	Anytime during the pregnancy	One step 75gm OGTT or 2-step test	≥7.0mmol/L	≥11.1mmol/L
Diabetes Canada 2018	GDM	24-28	One step 75gm OGTT	≥5.3 mmol/L	≥9.0 mmol/L
ADIPS 2014	GDM	24-28	One step 75gm OGTT	5.1-6.9 mmol/L	8.5-11.0 mmol/L
DIPSI 2014			NONE	NONE	7.8 mmol/L
FIGO 2015	GDM	24-28	One step 75gm OGTT	≥5.1 mmol/L	8.5 mmol/L
SEMDSA 2017	GDM	24-28	One step 75gm OGTT	5.1-6.9 mmol/L	8.5-11.0 mmol/L
	DIP/overt diabetes	Anytime during the pregnancy	One step 75gm OGTT	≥7.0mmol/L	≥11.1mmol/L
NICE 2014	GDM	24-28	One step 75gm OGTT	>5.5mml/L	7.8mmol/L

ADA: American Diabetes Association; ACOG: American College of Obstetricians and Gynaecologists; DIPSI: Diabetes Canada Clinical Practice Guidelines Diabetes in Pregnancy Society Group India; EASD: European Association for the Study of Diabetes; FIGO: International Federation of Gynaecology and Obstetrics; ADIPS: Australasian Diabetes in pregnancy Society; WHO: World Health Organization; IADPSG: International Association of the diabetes and Pregnancy Study Groups; NICE: National Institute for Health and Care Excellence.

In the WHO HFDP diagnosis guidelines of 2013 (4), the distinction between the two forms of HFDP is mainly through blood glucose levels at diagnosis. GDM is diagnosed when the maternal fasting blood glucose is above 5.1 mmol/L but less than 7.0mmol/L and/or OGTT 2-hour blood glucose above 8.5 mmol/L but less than 11.1 mmol/L. DIP is diagnosed when a woman without a previous diagnosis of diabetes has either fasting blood glucose ≥7.0 mmol/L and/or 11.1 mmol/L (4). Women with DIP may have a higher risk for adverse pregnancy outcomes, compared to those with GDM, including a higher risk of post-partum progression to T2DM, but the lack of studies in this area makes it difficult to evaluate the strength of the evidence (4).

2.8. Risk factors for hyperglycaemia first detected in pregnancy

Research evidence suggests that the risk factors for HFDP are largely similar to those for T2DM although the contribution of each risk factor to the overall risk of HFDP may differ (107, 108). Many observational studies have established various risk factors for HFDP which include non-modifiable such as family history and advanced age, intermediate such as overweight and obesity and modifiable such as smoking, diet and physical activity (109). Genetic and other novel risk factors such as biomarkers have also been described recently (109). Most of the studies that investigated risk factors for GDM, used definitions that would have encompassed women with DIP, hence this review uses the term ‘HFDP’ unless the GDM definition in the study excluded women with DIP. Due to the paucity of research, it is not clear whether risk factors for GDM are different or differ in their magnitude compared to those for DIP.

Non-modifiable risk factors in HFDP that have been consistently identified in the literature include a history of previous HFDP, ethnicity, family history of diabetes (110), advanced maternal age (111) and polycystic ovary syndrome (112). Previous

pregnancy outcomes such as having a baby with macrosomia, having a stillbirth and having a previous HFDP are also strongly associated with an increased risk of HFDP (113). HFDP is also associated with several pregnancy-related complications such as gestational dyslipidaemia (114), gestational hypertension (115) and pre-eclampsia (116), although these associations are frequently bidirectional and not necessarily causal.

Excess weight in the form of overweight and obesity is perhaps the strongest and most consistently identified intermediate risk factor for HFDP (109, 117). Increased central adiposity may contribute to the development of HFDP as it is associated with chronic insulin resistance which may then be exacerbated during the second and third trimesters of pregnancy (117). Excess weight has been measured using various proxies in epidemiological studies, including BMI, waist-hip circumference, and mid-upper arm circumference. BMI, either as a continuous variable or as various categories compared to normal BMI (e.g., ≥25kg/m2, ≥30kg/m2 or ≥40kg/m2) is one of the most frequently described risk factors for HFDP in the literature (118). The other measures of adiposity, i.e., waist circumference (119), waist-hip ratio (119) and mid-upper arm circumference (120), have also shown strong associations with the development of HFDP and measures of excess weight are frequently used as targets and intermediate outcomes in many HFD prevention trials (121). Biomarkers may also be regarded as intermediate factors and those associated with increased risk of HFDP are elevated chemerin levels during the second trimester (122), elevated mean platelet volume (123), low levels of iron and haemoglobin (124) and low vitamin D levels (125). Notably, these findings from observational studies have either not been tested by randomised controlled trials or have not resulted in therapeutic effect when tested in clinical trials. The latter is the case with vitamin D which has been tested in several trials and failed to result in either reduced risk for HFDP (126) or reduce risk of adverse pregnancy outcomes (127). More research is needed in this area.

The main modifiable risk factors described in literature, diet and physical activity, are also associated with risk of HFDP and although there is wide heterogeneity between studies and, frequently, the associations are not independent of overweight

and obesity. Some research has shown that the Mediterranean diet is beneficial (128) while diets rich in saturated fats, heme iron intake, sugar-sweetened drinks, high amounts of refined carbohydrates, and sweets are harmful (129). Lower physical activity and sedentary activity have been associated with a higher risk for HFDP (130). However, it is worth noting that many lifestyle-change interventions targeting healthy diets (131) or those promoting physical activity during pregnancy have failed to reduce risk of HFDP (131), except when the intervention was performed throughout the pregnancy (132).

2.9. Prevalence of hyperglycaemia first detected in pregnancy in Africa

Results from several meta-analyses suggest that HFDP is prevalent in Africa, with meta-analysis estimates of pooled prevalence ranging from 9% (133) to 14% (134) although quality data are only available from less than a quarter of the 54 countries. As of 2019, data were only available from 33 studies from 12 African countries (133). Most of the primary studies have been published from two countries: Nigeria (11 studies) and South Africa (8 studies) (133). Four systematic reviews and meta-analysis have been published to date, three of which included a mix of women with GDM and DIP (133, 135, 136) (Table 2.4). The largest and latest of these meta-analyses reported a pooled HFDP prevalence of 9% from 33 studies with 31 821 participants. The remaining meta-analysis, which used strict inclusion criteria of studies using either the WHO 2013, the ADA 2015 or the IADPSG 2010 criteria, reported a pooled HFDP prevalence of 13.6% from 23 studies with a total of 11 702 participants. The prevalence of GDM appears highest in sub-Saharan Africa (14.8%) compared to other regions, particularly in Cameroon (137) where one study reported a prevalence of 31% and South Africa (138) (25.8%).

Table 2.3. Summary of systematic reviews and meta-analyses on the prevalence of hyperglycaemia first detected in pregnancy in Africa

Author (year)	Country	Countries	Study design	Criteria	Sample size	Prevalence of

						HFDP/GDM
Natamba 2019 (133)	Sub-Saharan Africa	Ethiopia, DR Congo, Cameroon, Djibouti, Rwanda, South Africa, Nigeria, Mozambique, Morocco, Ethiopia, Tanzania, Zimbabwe	Systematic review and meta-analysis (1969 – 2018)	Any	33 studies (31 821 participants in meta-analysis)	HFDP 9%
Muche 2019 (139)	Africa (North and Sub-Saharan)	Benin, Uganda, Cameroon, Djibouti, Rwanda, South Africa, Nigeria, Kenya, Tanzania, Zimbabwe, Ghana, Egypt	Systematic review and meta-analysis (2013-2018)	WHO 2013 ADA 2015 IADPSG 2010	23 studies (11 702 participants in meta-analysis)	GDM 13.6% - Overall 14.28% - Sub-Saharan Africa 7.57% - North Africa
Macaulay 2014 (135)	Africa (North and Sub-Saharan)	South Africa, Nigeria, Mozambique, Morocco, Ethiopia, Tanzania	Systematic review (1979-2013)	Any	13 studies + 1 abstract	HFDP range 0-13.9%
Mwanri 2015 (136)	Africa (North and Sub-Saharan)	South Africa, Nigeria, Mozambique, Morocco, Ethiopia, Tanzania	Systematic and metaregression of studies (1969 – 2014)	Any	22 studies	HFDP Before 2000 – 3.2% After 2000 – 5.1% 14% in high-risk women

ADA: American Diabetes Association; WHO: World Health Organization; IADPSG: International Association of the Diabetes and Pregnancy Study Groups

2.10. Prevalence of hyperglycaemia first detected in pregnancy in South Africa

The prevalence of HFDP in South Africa is estimated to be between 9% and 25.8%, based on data from two cross-sectional studies published in 2018 (138, 140). A total of eight studies have examined the prevalence of HFDP in South Africa, to date (Table 2.5). Most of the studies (n= 3) (138, 140, 141) have been carried out in the Gauteng province. Data from other provinces are sparse and dated. The first study was published in 1969 (142) and reported a prevalence of HFDP of 8.3% in women without risk factors and of Indian descent in Durban, although the criteria used were not very clear. Since then, a total of seven studies have been published, at a rate of roughly one study per decade. Different screening criteria, diagnosis methods and diagnostic criteria were used in these studies and this makes it difficult to compare prevalence or describe possible trends. Only one study (143) was carried out in a rural setting and reported a prevalence of 8.8% in Limpopo province in 2007 and the rest from urban settings. The lowest prevalence (1.8%) was reported in a study in 2010 (141), a retrospective review of women who were overweight or obese in urban Johannesburg. The low prevalence could be partly explained by the high blood glucose cut-offs the authors used; a fasting blood glucose of ≥8.0 mmol/L and/or random blood glucose ≥11.1mmol/L. The highest reported GDM prevalence of 25.8% in Johannesburg in 2017 (138) is from a study that used universal screening and the IADPSG 2010 criteria. It is not clear why this estimate differed widely from the GDM estimate of 9.1% (140) in Soweto at roughly the same period. This difference could be partly explained by the inclusion of women with DIP as some of fasting glucose values reported by the study were above 7.0mmol/L.

Table 2.4 Summary of studies on the prevalence of hyperglycaemia first detected in pregnancy in South Africa

Author (year)	Region /location	Study design	Criteria for diagnosis	Sample size	Gestational age at assessment	Diagnosis method	Prevalence of HFDP/GDM, %

Notelovitz 1969 (142)	Durban – urban	Cross-sectional	Not clear. Fasting glucose ≥6.4mmol/L in the third trimester. Not clear what other criteria were used	566 (301 without risk factors, 265 with risk factors)	All trimesters	Urinalysis and 100gm OGTT used	HFDP 8.3%
Jackson 1979 (144)	Cape Town - Urban	Cohort	GDM - FBG≥5.5mmol/L AND OGTT 1-hr ≥10.0mmol/L AND OGTT 2-hr≥6.7 Borderline – only one criterion above is positive	558 high-risk women *	All trimesters, GGT repeated in 3rd trimester	50gm OGTT	GDM – 3.1% Borderline – 5.0% Combined – 8.1%
Ranchod 1991 (145)	Pietermaritzburg – urban	Cross-sectional	WHO 1985	1717	All trimesters	75gm OGTT	HFDP 3.8%
Mamabolo 2007 (143)	Limpopo – rural	Cross-sectional	WHO 1999	262	28-36 weeks	75 gm OGTT	HFDP 8.8%
Basu 2010 (141)	Johannesburg -urban	Retrospective review	FBG≥8.0mmol/L Random blood glucose ≥11.1 mmol/L	767 overweight and obese	23-32 weeks	Fasting and random glucose	DIP 1.8%
Macaulay 2018 (140)	Soweto - urban	Cohort	IADPSG 2010	1906 – universal screening	24-28 weeks	75 gm OGTT	GDM 9.1%
Adams 2018 (138)	Johannesburg – urban	Cohort	IADPSG 2010	554 – universal screening	24-28 weeks	75 gm OGTT	GDM 25.8%

**Family history, history of miscarriage, obesity, previous macrosomia, glycosuria, previous congenital anomaly, Indian ethnicity, age≥35 years*

2.11. Management of HFDP in South Africa – from screening to delivery

As with other areas of study concerning HFDP, data from Africa are scarce concerning how women are screened for HFDP and managed thereafter. In South

Africa, most provinces use a risk factor-based screening, which may leave up to 50% with HFDP undiagnosed (138, 146). In the Western Cape, women with any of the following risk factors, i.e., family history of diabetes, BMI≥30kg/m2, polycystic ovarian syndrome, previous GDM, glycosuria and age≥40 years are screened for HFDP (147). It is not clear, however, whether there is consistent screening for all women meeting these criteria (147). Between and within provinces, different diagnostic criteria are still widely used, with the most widely used being the WHO 1999, the NICE 2008, the American College of Obstetricians and Gynaecologists (ACOG) and the IADPSG 2010 (148). Although the SEMDSA recommended the IADPSG 2010 criteria and the use of universal criteria, uptake has been debatable as some clinicians perceive them as increasing an already high workload (148).

The limited available data show that women with HFDP receive adequate care during pregnancy, in line with international standards (147, 149). In the Western Cape province, all women with HFDP are managed at referral hospitals where they receive care from a multidisciplinary team that includes physicians, dieticians and nurses (147). The women receive care at dedicated diabetes clinics and are seen and their blood glucose checked every fortnight until 32 weeks gestations and every week thereafter (149). The management includes individual and group counselling on diet and physical activity from the doctor, nurse and dieticians, oral hypoglycaemic agents and insulin where necessary (147). Despite the good management during the pregnancy, there are gaps in the care for the women after delivery (147). While the current recommendations are that the woman must be assessed for diabetes 6 weeks after delivery, available data suggest that the proportion of women who go for the 6-week visit is less than 30% in South Africa (150). This may be partly because of the fragmentation of postpartum care, as care is provided separately, at different health facilities for the mother and her offspring (147).

2.12. Type 2 diabetes mellitus and cardiovascular disease after hyperglycaemia first detected in pregnancy

Data, primarily from mostly high-income countries, show that women with HFDP have a high risk of T2DM and cardiovascular disease after HFDP (108, 151, 152). Only

a few studies have been published in LMICs, and these were mostly from China, Brazil and India (108). Several systematic reviews and meta-analysis have compared women with GDM to women without GDM concerning the risk of T2DM. Again, the definition of GDM used in many of above-mentioned studies has included women with DIP. As can be seen in Table 6, the risk of progression to T2DM varies considerably between and within countries. In a review by Zhu et al. (108), the relative risk for T2DM after HFDP ranged from a low of 1.3 in Brazil in 2007 to a high of 47.3 in the USA. Within countries, there is also great heterogeneity in risk estimates. For example, in Sweden, the relative risk ranged from 3.2 in 1991 (153) to 38.4 (154), in the USA from 3.9 in 2007 (155) to 47.3 (156) and in Canada, from 10.5 in 2012 (157) to 15.3 (158). The heterogeneity may partly be due to different criteria used for diagnosis of GDM and different lengths of follow-up used in different studies, with follow-up periods ranging from 1 year to 15 years. Even when studies with similar lengths of follow-up are compared, the risk of progression is different between many of the studies. There are no studies in Africa that have investigated the risk of T2DM after HFDP, to date.

Table 2.5. Systematic reviews and meta-analyses on the risk of type 2 diabetes and cardiovascular after hyperglycaemia first detected in pregnancy

Author (year)	Country	Outcomes	Study design	Criteria	Sample size	T2DM or CVD after HFDP
Bellamy 2009(151)	High-income countries	Risk of T2DM	Systematic review and meta-analysis of cohort studies (1960 – 2009)	Any	20 studies (675 455 participants in meta-analysis)	RR for T2DM 7.43
Zhu 2016 (159)	High-income countries (22 studies), 5	Progression to T2DM	Literature review of studies from 1960 - 2015	Any	27 studies, including the 20 studies in Bellamy 2009	RR range 1.3 in Brazil in 2007 – 47.3 in the USA in 1994.

	studies from China (2), Brazil (2) and India)					Risk of progression to T2DM heterogeneous across and within countries
Song 2018 (152)	16 countries	Risk of T2DM by duration after GDM	Systematic and meta-analysis of cohort studies (1969 – 2014)	Any	30 studies (2 626 905 participants)	Overall risk of T2DM RR 7.76, <3yrs RR 5.37, 3-6 yrs RR 16.55, 6-10yrs RR 8.20
Archambault 2014 (160)	USA (3), Canada (2), Sweden (1),	Risk of CVD	Scoping review (1991-2008)	Any	11 studies (6 primary studies, 4 narrative reviews and 1 editorial)	Odds ratios Angina 2.9 Arrhythmia 2.4 CAD 1.6 Heart failure 0.7
Li 2018 (161)	Israel (1), Canada (3), France (1), USA (2)	1. Risk of CVD 2. Risk of CAD 3. Risk of stroke	Systematic review and meta-analysis of cohort studies (2006-2017)	Any	7 studies (3 417 020 participants)	Overall CVD risk RR 1.74 CAD RR 2.09 Stroke RR 1.25
Kramer 2019 (162)	Israel (1), Sweden (1), USA (2), Canada (3), UK (1)	1. Overall risk of CVD 2. Risk of CVD in women without T2DM 3. Risk of CVD within 10 yrs after GDM	Systematic review and meta-analysis (2013-2019)	Any	9 studies (5 390 591 participants)	Overall RR 1.98 Non-T2DM – RR 1.56 First decade RR 2.31

ADA: American Diabetes Association; WHO: World Health Organization; IADPSG: International Association of the Diabetes and Pregnancy Study Groups

Similar to the risk of T2DM after HFDP, the prevalence of T2DM in women after HFDP varies widely from 3.6% in Finland (163) to 52% in India (164) as can be seen in Table 2.7. Again, the length of follow-up and HFDP diagnosis criteria vary widely and

may be partly responsible for the heterogeneity in prevalence estimates between studies. Only one study in Africa (150) has investigated the progression to T2DM to date, at 6-weeks postpartum, in Cape Town in 2018. In this study of 78 participants, the authors found that 27% had diabetes six weeks after the pregnancy. The small sample size and the short follow-up period limit the conclusions that can be drawn from this study.

Table 2.6. Studies on the prevalence of T2DM after hyperglycaemia first detected in pregnancy from 2000-2019

Study	Sample Size	Response Rate	Country	Design	GDM Diagnosis	Follow-up period	T2DM	Prediabetes
Lowe 2018 (165)	4697 (GDM =663)	69.10%	Australia	Cohort	IADPSG 2010	11.4 yrs	10.7%	41.50%
Huvinen 2018 (163)	333	95.70%	Finland	Prospective cohort	WHO 1999	5 yrs	3.60%	15%
Inoue 2018 (166)	77	22.30%	Japan	Retrospective cohort	IADPSG 2010	2 yrs	22%	44.10%
Simmons 2017 (167)	2786 (50 previous GDM)	Not reported	Maori New Zealand	Cross sectional	Self-reported past GDM	lifetime GDM history	20%	Not reported
chamberlain 2016 (168)	578	Not reported	Australia indigenous	Retrospective cohort	Australian DA, FPG ≥5.5, 2-hour ≥8	3, 5, 7 yrs	21.9% 3 yrs, 25.5% 5 yrs, 42.4% 7 yrs	Not reported
	332		Australia non-indigenous				4.2% 3 yrs, 5.7% 5 yrs, 13.5% 7 yrs	
Gupta 2016 (169)	366	37%	India	Cohort	Carpenter and Coustan, IASDPSG 2010	14 months	40%	32%
Tam 2012 (170)	139 (45 GDM)	68.4	China	Prospective cohort	WHO 1999	15 yrs	24.40 %	9.80%
Wang 2012 (171)	19998 (GDM =1142)	Not reported	USA	Cohort	WHO 1999 ADA 2003	8.6 yrs	28.70 %	Not reported

Madaraz 2009 (172)	68 GDM 39NGT	52.50%	Hungary	Follow up cohort	WHO 1985	4 yrs	21%	15%
Lee 2008 (173)	868 GDM 868 controls	Not reported	Korea	Casecontrol	National Diabetes Data Group	2 yrs	11.50 %	Not reported
Rivero 2008 (174)	109	85.8%	Brazil	Prospective cohort	ADA 1997 Working Force on DM and Pregnancy1985	32 months	17.40 %	39.40%
Tam 2007 (175)	203 (63 GDM)	92.6%	China	Prospective cohort	WHO 1999	8 yrs	9%	30.2%
Krishnaveni 2007 (176)	555, gdm = 35	88%	India	Cohort	Carpenter and Coustan	5 yrs	37%	31%
Kale 2004 (177)	126	69.20%	India	Follow up cohort	WHO 1985	4.5 yrs	52%	19%

The high heterogeneity seen in studies examining the risk of T2DM after HFDP is also seen with studies that investigated CVD risk after HFDP as can be seen in Table 2.6. Three meta-analyses have analysed the association between prior HFDP and risk of CVD or its components. Interestingly, the risk for CVD in women after HFDP is almost similar to that for women with diabetes, with odds ratios of 1.74 (161) and 1.98 (162) in separate meta-analyses. In women who did not progress to T2DM, the risk for CVD still appears to be high (OR = 1.56), compared to women without a history of HFDP (162). Currently, there are no studies which have investigated the association between GDM and cardiovascular risk factors in Africa.

2.13. Hyperglycaemia first detected in pregnancy and childhood overweight and obesity in the offspring

There is considerable evidence that both higher maternal blood glucose levels at the diagnosis of HFDP and the level of glucose control during pregnancy are associated with higher foetal birth weight and other measures of adiposity at birth (100). Several possible explanations have been put forward to explain the link between exposure to hyperglycaemia in pregnancy and offspring adiposity. In the 1950s Pederson (98) hypothesised that maternal hyperglycaemia exposure led to foetal

overproduction of insulin and, thereafter, overgrowth. This was later refined into the fuel mediated teratogenesis hypothesis which proposes that excess fuels lead to permanent changes in the foetus (178). Although maternal glucose crosses the placenta to the foetus, insulin particles are too large to cross the placental barrier. Therefore, the foetal pancreas, which is still developing, is forced to produce more insulin than normal. Foetal insulin, apart from regulating blood glucose, also promotes foetal growth and adipose tissue production, resulting in overgrowth during pregnancy and a higher risk of overweight at birth (178). Apart from excess foetal growth *in-utero*, increased insulin production, increased leptin production in the children exposed to hyperglycaemia in pregnancy has also been reported, with children exposed to hyperglycaemia having three times cord blood leptin levels compared to the controls (179). It is hypothesised that the foetal pancreas is exposed to maternal hyperglycaemia at a critical time of its development and that this causes permanent impairment of insulin secretion (foetal hyperinsulinemia) (179). Foetal hyperinsulinemia continues into childhood hyperinsulinemia which may lead to childhood overweight and obesity as shown by data from the Pima Indians, where the 5 to 9-year-old offspring of diabetic mothers had higher fasting insulin levels (180) and were heavier at every age (181) compared to the offspring of non-diabetic mothers.

There is increasing evidence linking exposure to maternal hyperglycaemia and long-term cardiometabolic disease risk in the offspring (165, 182, 183). Besides, higher birth weights have been associated with a high risk of adult hypertension (184), dyslipidaemia (185), insulin resistance (186), and cardiovascular disease (187). Foetal programming for overweight and obesity is another way in which maternal hyperglycaemia is thought to exert long-term effects. Maternal hyperglycaemia may cause permanent adaptive changes in the foetal genome which, in turn, affects the child throughout their life course (188). These adaptive changes in the foetal genome may permanently change the physiology and metabolism of the foetus and, consequently, induce changes in postnatal metabolism where the offspring will have a higher tendency to accumulate fat (189).

Despite the scientific plausibility for the association between maternal blood glucose and childhood overweight and obesity, data from observational studies are not

conclusive about the association between GDM and childhood overweight and obesity. The HAPO follow-up study (165) did not find a significant association between a GDM diagnosis and child BMI at a median age of 11.4 years. An earlier systematic review of 12 studies, in 2011 (190), found that the odds ratios for the association between a GDM diagnosis and risk of childhood and overweight ranged from 0.7 to 6.3. The authors noted that most of the studies that found a significant association between GDM and childhood overweight and obesity may not have adjusted for maternal BMI. A later systematic review and meta-analysis of 25 studies and 308 455 infants (191), published in 2020, similarly found no differences in BMI in infants at ages 1 to -6 months, 7 to 12months and 13 to 24 months. It is also possible that treatment for GDM may be the reason why the expected association is often not seen. In Africa, there are no data on medium- and long-term weight outcomes of children exposed to HFDP.

2.14. Summary

In this chapter, the epidemiology of diabetes mellitus and HFDP in Africa and South Africa has been reviewed. Women of childbearing age constitute about 27% of the population of South Africa, play several important roles in their societies, and are uniquely affected by diabetes. Diabetes in women of childbearing age increases the risk of intergenerational transmission of cardiometabolic disease to the offspring. For women with T2DM, the prognosis is worse than in similarly aged males. Available data suggest that up to a quarter of South African women are affected by HFDP, which increases the risk of T2DM and CVD in the women and may increase long term cardiometabolic risk in their offspring. Even data from other regions suggests that women with HFDP have a higher risk of T2DM and CVD after the pregnancy the risk estimates are heterogeneous between and within countries. In Africa, again, there are no data at present on either risk of T2DM and CVD or their prevalence after HFDP. This chapter has highlighted several areas that have not been investigated in Africa, particularly the medium- and long-term effects of HFDP on the mother and child. The next chapter discusses the methods used in this research.

2.15. References

1. International Diabetes Federation. IDF diabetes atlas 9th Edition. Brussels: International Diabetes Federation; 2019 [cited 2020 13 January]. 9: Available from: http://www.diabetesatlas.org.]
2. Cho N, Shaw J, Karuranga S, Huang Y, da Rocha Fernandes J, Ohlrogge A. et al. IDF Diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045.Diabetes Res Clin Pract. 2018; 138:271-81.
3. World Health Organization. Classification of diabetes mellitus 2019. Available from: https://apps.who.int/iris/bitstream/handle/10665/325182/9789241515702-eng.pdf.
4. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy 2013. Available from: https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=48ABC998E153A412E00E1CD62B90C1EC?sequence=1.
5. Livingstone SJ, Levin D, Looker HC, Lindsay RS, Wild SH, Joss N, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008-2010. JAMA.2015; 313(1):37-44.
6. Huo L, Harding JL, Peeters A, Shaw JE, Magliano DJ. Life expectancy of type 1 diabetic patients during 1997–2010: A national Australian registry-based cohort study. Diabetologia. 2016;59(6):1177-85.
7. Beran D, Yudkin JS. Diabetes care in sub-Saharan Africa. Lancet. 2006;368(9548):1689-95.
8. Fousteri G, Ippolito E, Ahmed R, Hamad ARA. Beta-cell specific autoantibodies: Are they just an indicator of type 1 diabetes?Curr Diabetes Rev . 2017;13(3):322-9.
9. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J, von Herrath MG. Increased immune cell infiltration of the exocrine pancreas: A possible contribution to the pathogenesis of type 1 diabetes. Diabetes. 2014;63(11):3880-90.

10. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol . 2018;14(2):88.
11. Kao K-T, Sabin MA. Type 2 diabetes mellitus in children and adolescents.Aust Fam Physician. 2016;45(6):401.
12. McMahon SK, Haynes A, Ratnam N, Grant MT, Carne CL, Jones TW, et al. Increase in type 2 diabetes in children and adolescents in Western Australia. Med J Aust. 2004;180(9):459-61.
13. Praveen PA, Madhu SV, Mohan V, Das S, Kakati S, Shah N, et al. Registry of Youth Onset Diabetes in India (YDR) Rationale, Recruitment, and Current Status. J Diabetes Sci Technol. 2016;10(5):1034-41.
14. Sjöholm Å. Ketosis-prone type 2 diabetes: A case series. Front. Endocrinol. y. 2019; 10:684.
15. Kumar A, Alberto De Leiva M. prevalence and characteristics of Latent Autoimmune Diabetes in Adults (LADA) in a region of India.Endocr Pract. 2017; 23:48.
16. Grill V. LADA: A type of diabetes in its own right? Curr Diabetes Rev. 2019;15(3):174-7.
17. Avogaro A, Fadini GP. Microvascular complications in diabetes: A growing concern for cardiologists. Int J Cardiol. 2019.
18. Kosiborod M, Gomes MB, Nicolucci A, Pocock S, Rathmann W, Shestakova MV, et al. Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the DISCOVER study program). Cardiovasc Diabetol.2018;17(1):150.
19. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019;26(2_suppl):25-32.
20. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int. 2003;63(1):225-32.

21. Fisher VL, Tahrani AA. Cardiac autonomic neuropathy in patients with diabetes mellitus: Current perspectives. Diabetes Metab Syndr Obes. 2017 Oct 6; 10:419-434.
22. Glovaci D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease.Curr Cardiol Rep . 2019;21(4):21.
23. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17(1):83.
24. Ross S, Gerstein HC, Eikelboom J, Anand SS, Yusuf S, Paré G. Mendelian randomization analysis supports the causal role of dysglycaemia and diabetes in the risk of coronary artery disease.Eur Heart J . 2015;36(23):1454-62.
25. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: A systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet. 2014;383(9933):1973-80.
26. Fox CS. Cardiovascular disease risk factors, type 2 diabetes mellitus, and the Framingham Heart Study. Trends Cardiovasc Med. 2010;20(3):90-5.
27. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: An epidemiological analysis of linked national survey and vital statistics data. Lancet. 2018;391(10138):2430-40.
28. Kim D, Li AA, Cholankeril G, Kim SH, Ingelsson E, Knowles JW, et al. Trends in overall, cardiovascular and cancer-related mortality among individuals with diabetes reported on death certificates in the United States between 2007 and 2017. Diabetologia. 2019;62(7):1185-94.
29. Tandon N, Anjana RM, Mohan V, Kaur T, Afshin A, Ong K, et al. The increasing burden of diabetes and variations among the states of India: The Global Burden of Disease Study 1990–2016. Lancet Glob Health. 2018;6(12): e1352-e62.
30. Rigato M, Pizzol D, Tiago A, Putoto G, Avogaro A, Fadini GP. Characteristics, prevalence, and outcomes of diabetic foot ulcers in Africa. A systemic review and meta-analysis.Diabetes Res Clin Prac . 2018; 142:63-73.

31. Mayosi BM, Lawn JE, Van Niekerk A, Bradshaw D, Karim SSA, Coovadia HM, et al. Health in South Africa: Changes and challenges since 2009. Lancet. 2012;380(9858):2029-43.
32. Mbogori T, Mucherah W. Nutrition transition in Africa: Consequences and opportunities. Global Journal of Transformative Education. 2019;1(1):5-10.
33. Group NRFCAW. Trends in obesity and diabetes across Africa from 1980 to 2014: An analysis of pooled population-based studies. Int J Epidemiol. 2017;46(5):1421-32.
34. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Res Clin Pract. 2019; 157:107843.
35. Gouda HN, Charlson F, Sorsdahl K, Ahmadzada S, Ferrari AJ, Erskine H, et al. Burden of non-communicable diseases in sub-Saharan Africa, 1990–2017: Results from the Global Burden of Disease Study 2017. Lancet GlobHealth. 2019;7(10): e1375-e87.
36. Levitt NS. Diabetes in Africa: Epidemiology, management and healthcare challenges. Heart. 2008;94(11):1376-82.
37. Ajayi IO, Adebamowo C, Adami H-O, Dalal S, Diamond MB, Bajunirwe F, et al. Urban–rural and geographic differences in overweight and obesity in four sub-Saharan African adult populations: A multi-country cross-sectional study. BMC Public Health. 2016;16(1):1126.
38. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PloS One. 2018;13(3).
39. Liu T, Sun Y-C, Cheng P, Shao H-G. Adipose tissue macrophage-derived exosomal miR-29a regulates obesity-associated insulin resistance. Biochem Biophys Res Commun. 2019;515(2):352-8.
40. McLarty D, Pollitt C, Swai A. Diabetes in Africa.Diabet Med. 1990;7(8):670-84.

41. Chen J, Sun M, Adeyemo A, Pirie F, Carstensen T, Pomilla C, et al. Genome-wide association study of type 2 diabetes in Africa. Diabetologia. 2019;62(7):1204-11.
42. K Papazafiropoulou A, Papanas N, Melidonis A, Maltezos E. Family history of type 2 diabetes: Does having a diabetic parent increase the risk? Curr Diabetes Rev. 2017;13(1):19-25.
43. Frank TD, Carter A, Jahagirdar D, Biehl MH, Douwes-Schultz D, Larson SL, et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2017, and forecasts to 2030, for 195 countries and territories: A systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors Study 2017. Lancet HIV. 2019;6(12): e831-e59.
44. Nansseu JRN, Bigna JJR. Antiretroviral therapy related adverse effects: Can sub-Saharan Africa cope with the new “test and treat” policy of the World Health Organization?Infect Dis Poverty . 2017;6(1):24.
45. Levitt NS, Peer N, Steyn K, Lombard C, Maartens G, Lambert EV, et al. Increased risk of dysglycaemia in South Africans with HIV; especially those on protease inhibitors. Diabetes Res Clin Pract 2016; 119:41-7.
46. Nansseu JR, Bigna JJ, Kaze AD, Noubiap JJ. Incidence and risk factors for prediabetes and diabetes mellitus among HIV-infected adults on antiretroviral therapy. Epidemiology. 2018;29(3):431-41.
47. Domingo P, Espinet J, Vidal F. ART regimes and fat: The healing hand wielding the sword. Lancet HIV. 2017;4(1): e2-e3.
48. Dooko CBA, De Wit S, Neuhaus J, Palfreeman A, Pepe R, Pankow JS, et al. Interleukin-6, high sensitivity C-reactive protein, and the development of type 2 diabetes among HIV positive patients taking antiretroviral therapy. J Acquir Immune Defic Syndr (1999). 2014;67(5):538.
49. Bradshaw D, Norman R, Pieterse D, Levitt NS. Estimating the burden of disease attributable to diabetes South Africa in 2000. S Afr Med J. 2007;97(8):700-6.
50. Bertram MY, Jaswal AV, Van Wyk VP, Levitt NS, Hofman KJ. The non-fatal disease burden caused by type 2 diabetes in South Africa, 2009. Glob Health Action. 2013;6(1):19244.

51. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, et al. The South African National Health and Nutrition Examination Survey, 2012: SANHANES-1: The health and nutritional status of the nation. Cape Town: HSRC Press, 2015.
52. Werfalli M, Engel ME, Musekiwa A, Kengne AP, Levitt NS. The prevalence of type 2 diabetes among older people in Africa: A systematic review. Lancet Diabetes Endocrinol. 2016;4(1):72-84.
53. Prakaschandra DR, Esterhuizen TM, Motala AA, Gathiram P, Naidoo DP. High prevalence of cardiovascular risk factors in Durban South African Indians: The Phoenix Lifestyle Project.S Afr Med J. 2016;106(3):284-9.
54. Hird TR, Pirie FJ, Esterhuizen TM, O'Leary B, McCarthy MI, Young EH, et al. Burden of diabetes and first evidence for the utility of HbA1c for diagnosis and detection of diabetes in urban black South Africans: The Durban Diabetes Study. PLoS One. 2016;11(8).
55. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS. Rising diabetes prevalence among urban-dwelling black South Africans. PloS One. 2012;7(9).
56. Motala AA, Esterhuizen T, Gouws E, Pirie FJ, Omar MA. Diabetes and other disorders of glycemia in a rural South African community: Prevalence and associated risk factors. Diabetes care. 2008;31(9):1783-8.
57. SEMDSA Type 2 Diabetes Guidelines Expert Committee. SEMDSA 2017 guidelines for the management of type 2 diabetes mellitus. J Endocr Metab Diabetes S Afr. 2017;22(1 Suppl 1): S1-196.
58. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: A systematic analysis for the Global Burden of Disease Study 2013.Lancet. 2014;384(9945):766-81.
59. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, et al. Obesity in South Africa: The South African demographic and health survey. Obes Res. 2002;10(10):1038-48.

60. Sartorius B, Veerman LJ, Manyema M, Chola L, Hofman K. Determinants of obesity and associated population attributability, South Africa: Empirical evidence from a national panel survey, 2008-2012. PloS One. 2015;10(6).
61. Goon DT, Maputle M, Olukoga A, Lebese R, Khoza LB, Ayanwu F. Overweight, obesity and underweight in nurses in Vhembe and Capricorn districts, Limpopo.South Afr J Clin Nutr. 2013;26(3):147-9.
62. Damian DJ, Njau B, Lisasi E, Msuya SE, Boulle A. Trends in maternal and neonatal mortality in South Africa: A systematic review.Syst Rev. 2019;8(1):76.
63. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934-47.
64. Armstrong P, Erasmus M, Rich E. Benefit Incidence, Financing Incidence and Need of Healthcare Services in South Africa. 2017. Available from: https://econex.co.za/wp-content/uploads/2017/07/ECONEX_researchnote_45.pdf.
65. Mutyambizi C, Pavlova M, Hongoro C, Booysen F, Groot W. Incidence, socio-economic inequalities and determinants of catastrophic health expenditure and impoverishment for diabetes care in South Africa: A study at two public hospitals in Tshwane. Int J Equity Health. 2019;18(1):73.
66. Simbayi L, Zuma K, Moyo S, Marinda E, Mabaso M, Ramlagan S, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. 2019.
67. World Health Organisation. Global tuberculosis report 2019 2019.Available from: https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1.
68. Norman R, Bradshaw D, Schneider M, Pieterse D, Groenewald P. Revised burden of disease estimates for the comparative risk factor assessment, South Africa 2000. Cape Town: Medical Research Council. 2006.
69. Statistics South Africa. Mortality and causes of death in South Africa, 2008: Findings from death notification 2009.Available from: http://www.statssa.gov.za/publications/P03093/P030932008.pdf.

70. Statistics South Africa. Mortality and causes of death in South Africa, 2011: Findings from death notification 2012. Available from: http://www.statssa.gov.za/publications/P03093/P030932011.pdf.
71. Statistics South Africa. Mortality and causes of death in South Africa, 2014: Findings from death notification 2015. Available from: http://www.statssa.gov.za/publications/P03093/P030932014.pdf.
72. Statistics South Africa. Mortality and causes of death in South Africa, 2017: Findings from death notification 2020. Available from: http://www.statssa.gov.za/publications/P03093/P030932017.pdf.
73. World Health Organisation. Sexual and reproductive health 2020. Available from: https://www.who.int/reproductivehealth/topics/infertility/definitions/en/.
74. PopulationPyramid.net. Population Pyramids of the World from 1950 to 2100 2020.Available from: https://www.populationpyramid.net/.
75. Statistics South Africa. Community Survey 2016 Provincial profile: Western Cape, 2016 2018.Available from: http://cs2016.statssa.gov.za/wp-content/uploads/2018/07/WesternCape.pdf.
76. Jaga A, Arabandi B, Bagraim J, Mdlongwa S. Doing the ‘gender dance’: Black women professionals negotiating gender, race, work and family in post-apartheid South Africa.Community Work Fam. 2018;21(4):429-44.
77. Amugsi DA, Dimbuene ZT, Mberu B, Muthuri S, Ezeh AC. Prevalence and time trends in overweight and obesity among urban women: An analysis of demographic and health surveys data from 24 African countries, 1991–2014. BMJ Open. 2017;7(10): e017344.
78. Goedecke JH, Mtintsilana A, Dlamini SN, Kengne AP. Type 2 diabetes mellitus in African women.Diabetes Res Clin Pract . 2017; 123:87-96.
79. Kautzky-Willer A, Harreiter J, Pacini G. Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. Endocrine Reviews. 2016;37(3):278-316.
80. Butler JZ, Slopen N, Moorthy MV, Williams DR, Powell-Wiley TM, Pradhan A, et al. Cumulative psychosocial stress and incident type II diabetes in older women

participating in the Women's Health Study. Circulation. 2018;138(Suppl_1): A16428-A.

81. Peters T, Pelletier R, Behlouli H, Rossi A, Pilote L. Excess psychosocial burden in women with diabetes and premature acute coronary syndrome. Diabet Med. 2017;34(11):1568-74.
82. Moeineslam M, Amiri P, Karimi M, Jalali-Farahani S, Shiva N, Azizi F. Diabetes in women and health-related quality of life in the whole family: A structural equation modeling.Health Qual Life Outcomes . 2019;17(1):178.
83. Musingarabwi S. Time-use and wellbeing in Onesi, Namibia: Cape Town: University of Cape Town; 2016.
84. Van der Heijden I, Harries J, Abrahams N. In pursuit of intimacy: Disability stigma, womanhood and intimate partnerships in South Africa. Health Qual Life Outcomes. 2019;21(3):338-51.
85. Ballotari P, Ranieri SC, Luberto F, Caroli S, Greci M, Giorgi Rossi P, et al. Sex differences in cardiovascular mortality in diabetics and nondiabetic subjects: A population-based study (Italy). Int J Endocrinol. 2015;2015.
86. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: The Framingham study. Ann Intern Med. 1976;85(4):447-52.
87. Maric C. Risk factors for cardiovascular disease in women with diabetes. Gend Med. 2010;7(6):551-6.
88. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational Diabetes. Diabetes Care. 2007;30(Supplement 2): S112.
89. White P. Pregnancy complicating diabetes of more than twenty years' duration.Med Clin North Am . 1947;31(2):395-405.
90. Hoet JP. Carbohydrate metabolism during pregnancy. Diabetes. 1954;3(1):1-12.
91. Carrington ER, Shuman CR, Reardon HS. Evaluation of the prediabetic state during pregnancy.Obstet Gynecol. 1957;9(6):664-9.
92. O'Sullivan JB. Criteria for the oral glucose tolerance test in pregnancy. Diabetes. 1964; 13:278-85.

93. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979;28(12):1039.
94. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes.Am J Obstet Gynecol . 1982;144(7):768-73.
95. . WHO Study Group on Diabetes Mellitus & World Health Organization Diabetes mellitus: Report of a WHO Study Group. Geneva: WHO 1985. WHO Technical Report Series. 1985(727).
96. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization; 1999.
97. American Diabetics Association. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1998;21(Supplement 1): S5.
98. Pedersen J. Weight and length at birth of infants of diabetic mothers. Eur J Endocrinol. 1954;16(4):330-42.
99. International Association of Diabetes Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
100. HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes.N Engl J Med . 2008;358(19):1991-2002.
101. . HAPO Study Cooperative Research Group The hyperglycemia and adverse pregnancy outcome (HAPO) study. Int J Gynaecol Obstet. 2002;78(1):69-77.
102. Hadar E, Hod M, Metzger BE. Lesson from the Hyperglycemia and Adverse Pregnancy Outcome Study: New diagnostic criteria for gestational diabetes mellitus.In Lapolla A, Metzger, BE. Gestational diabetes. Basel:Karger ; 2020. p. 35-49.
103. Agarwal R, Baid R. Gestational diabetes mellitus: A diagnostic dilemma. CHRISMED Journal of Health and Research. 2017;4(3):161.
104. Nankervis A, McIntyre H, Moses R, Ross G, Callaway L, Porter C, et al. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes

mellitus in Australia. Modified June. 2014.Available from: https://www.adips.org/downloads/2014ADIPSGDMGuidelinesV18.11.2014.pdf

105. Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37(Supplement 1): S81-S90.
106. National Institute for Health Care and Excellence (NICE). Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. Clinical guideline NG3 (2015). 2015. Available from: www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-and-itscomplications-from-preconception-to-the-postnatal-period-51038446021
107. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with type 2 diabetes. Diabet Med. 2004;21(2):103-13.
108. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: A global perspective.Curr Diab Rep . 2016;16(1):7.
109. Giannakou K, Evangelou E, Yiallouros P, Christophi CA, Middleton N, Papatheodorou E, et al. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. PloS One. 2019;14(4).
110. Moosazadeh M, Asemi Z, Lankarani KB, Tabrizi R, Maharlouei N, Naghibzadeh-Tahami A, et al. Family history of diabetes and the risk of gestational diabetes mellitus in Iran: A systematic review and meta-analysis. Diabetes Metab Syndr. 2017;11: S99-S104
111. Lean SC, Derricott H, Jones RL, Heazell AE. Advanced maternal age and adverse pregnancy outcomes: A systematic review and meta-analysis. PloS One. 2017;12(10).
112. Kjerulff LE, Sanchez-Ramos L, Duffy D. Pregnancy outcomes in women with polycystic ovary syndrome: A metaanalysis.Am J Obstet Gynecol . 2011;204(6):558. e1-. e6.
113. Kiani F, Naz MSG, Sayehmiri F, Sayehmiri K, Zali H. The risk factors of gestational diabetes mellitus: A systematic review and meta-analysis study. Diabetes. 2017; 10:17.

114. Paredes S, Fernandes A, Pereira ML, editors. Gestational diabetes-association of lipid profile in pregnancy with post-partum dysglycemia. 20th European Congress of Endocrinology; 2018: BioScientifica.
115. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis.BMC Pregnancy Childbirth. 2018;18(1):494.
116. Wu P, Kwok CS, Haththotuwa R, Kotronias RA, Babu A, Fryer AA, et al. Pre-eclampsia is associated with a twofold increase in diabetes: A systematic review and meta-analysis. Diabetologia. 2016;59(12):2518-26.
117. Kennelly M, McAuliffe F. Prediction and prevention of Gestational Diabetes: An update of recent literature. Eur J Obstet Gynecol Reprod Biol.2016; 202:92-8.
118. Giannakou K, Evangelou E, Yiallouros P, Christophi CA, Middleton N, Papatheodorou E, et al. Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. PloS One. 2019;14(4): e0215372.
119. Zhu Y, Hedderson MM, Queensberry CP, Feng J, Ferrara A. Central obesity increases the risk of gestational diabetes partially through increasing insulin resistance. Obesity. 2019;27(1):152-60.
120. Nombo AP, Mwanri AW, Brouwer-Brolsma EM, Ramaiya KL, Feskens EJ. Gestational diabetes mellitus risk score: A practical tool to predict gestational diabetes mellitus risk in Tanzania.Diabetes Res Clin Pract . 2018; 145:130-7.
121. Goveia P, Cañon-Montañez W, Santos DdP, Lopes GW, Ma RC, Duncan BB, et al. Lifestyle intervention for the prevention of diabetes in women with previous gestational diabetes mellitus: A systematic review and meta-analysis. Front Endocrinol. 2018; 9:583.
122. Zhou Z, Chen H, Ju H, Sun M. Circulating chemerin levels and gestational diabetes mellitus: A systematic review and meta-analysis. Lipids Health Dis 2018;17(1):169.
123. Zhou Z, Chen H, Sun M, Ju H. Mean platelet volume and gestational diabetes mellitus: A systematic review and meta-analysis. J Diabetes Res. 2018;2018.
124. Kataria Y, Wu Y, Horskjær PdH, Mandrup-Poulsen T, Ellervik C. Iron status and gestational diabetes—a meta-analysis. Nutrients. 2018;10(5):621.

125. Amraei M, Mohamadpour S, Sayehmiri K, Mousavi SF, Shirzadpour E, Moayeri A. Effects of vitamin D deficiency on incidence risk of gestational diabetes mellitus: A systematic review and meta-analysis.Front Endocrinol . 2018; 9:7.
126. Yap C, Cheung NW, Gunton JE, Athayde N, Munns CF, Duke A, et al. Vitamin D supplementation and the effects on glucose metabolism during pregnancy: A randomized controlled trial. Diabetes Care. 2014;37(7):1837-44.
127. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: A systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2015;103(5):1278-88. e4.
128. Kibret KT, Chojenta C, Gresham E, Tegegne TK, Loxton D. Maternal dietary patterns and risk of adverse pregnancy (hypertensive disorders of pregnancy and gestational diabetes mellitus) and birth (preterm birth and low birth weight) outcomes: A systematic review and meta-analysis.Public Health Nutr. 2019;22(3):506-20.
129. Donazar-Ezcurra M, López-del Burgo C, Bes-Rastrollo M. Primary prevention of gestational diabetes mellitus through nutritional factors: A systematic review. BMC Pregnancy Childbirth. 2017;17(1):30.
130. Tobias DK, Zhang C, Van Dam RM, Bowers K, Hu FB. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: A meta-analysis. Diabetes Care. 2011;34(1):223-9.
131. Zhang C, Rawal S, Chong YS. Risk factors for gestational diabetes: Is prevention possible? Diabetologia. 2016;59(7):1385-90.
132. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, Álvarez-Bueno C, Sánchez-López M, Martínez-Vizcaíno V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: A meta-analysis. BJOG. 2015;122(9):1167-74.
133. Natamba BK, Namara AA, Nyirenda MJ. Burden, risk factors and maternal and offspring outcomes of gestational diabet es mellitus (GDM) in sub-Saharan Africa (SSA): A systematic review and meta-analysis.BMC Pregnancy Childbirth. 2019;19(1):450.

134. Muche AA, Olayemi OO, Gete YK. Prevalence and determinants of gestational diabetes mellitus in Africa based on the updated international diagnostic criteria: A systematic review and meta-analysis. Arch Public Health 2019;77(1).
135. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: A systematic review. PloS One. 2014;9(6): e97871-e.
136. Mwanri AW, Kinabo J, Ramaiya K, Feskens EJ. Gestational diabetes mellitus in sub-Saharan Africa: systematic review and metaregression on prevalence and risk factors.Trop Med Int Health . 2015;20(8):983-1002.
137. Djomhou M, Sobngwi E, Noubiap JJN, Essouma M, Nana P, Fomulu NJ. Maternal hyperglycemia during labor and related immediate post-partum maternal and perinatal outcomes at the Yaoundé Central Hospital, Cameroon. J Health Popul Nutr. 2016;35(1):28.
138. Adams S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors.S Afr Med J . 2017;107(6):523-7.
139. Muche AA, Olayemi OO, Gete YK. Prevalence and determinants of gestational diabetes mellitus in Africa based on the updated international diagnostic criteria: A systematic review and meta-analysis. Arch Public Health. 2019;77(1):36.
140. Macaulay S, Ngobeni M, Dunger DB, Norris SA. The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. Diabetes Res Clin Pract. 2018; 139:278-87.
141. Basu JK, Jeketera CM, Basu D. Obesity and its outcomes among pregnant South African women. Int.J. Gynecol.Obstet.. 2010;110(2):101-4.
142. Notelovitz M. Carbohydrate tolerance in the pregnant Natal Indian. S Afr Med J. 1969;43(3).
143. Mamabolo RL, Alberts M, Levitt NS, Delemarre-van de Waal HA, Steyn NP. Prevalence of gestational diabetes mellitus and the effect of weight on measures of insulin secretion and insulin resistance in third-trimester pregnant rural women residing in the Central Region of Limpopo Province, South Africa. Diabetic Medicine. 2007;24(3):233-9.

144. Jackson E. Glycosuria as an indication for glucose tolerance testing during pregnancy. S Afr Med J. 1969;43(3). 1979;56(22):921-3.
145. Ranchod H, Vaughan J, Jarvis P. Incidence of gestational diabetes at Northdale Hospital, Pietermaritzburg. S Afr Med J. 1991;80(1):14-6.
146. Dias S, Adam S, Rheeder P, Pheiffer C. Prevalence of and risk factors for gestational diabetes mellitus in South Africa. S Afr Med J. 2019;109(7):463-7.
147. Muhwava LS, Murphy K, Zarowsky C, Levitt N. Policies and clinical practices relating to the management of gestational diabetes mellitus in the public health sector, South Africa: A qualitative study. BMC Health Serv. 2018;18(1).
148. Dias S, Pheiffer C, Rheeder P, Adam S. Screening and diagnosis of gestational diabetes mellitus in South Africa: What we know so far. S Afr Med J. 2019;109 (7):457-62.
149. Van Zyl H, Levitt N. Pregnancy outcome in patients with pregestational and gestational diabetes attending Groote Schuur Hospital, Cape Town, South Africa. S Afr Med JSAMJ. 2018;108(9).
150. Coetzee A, Mason D, Hall DR, Conradie M. Prevalence and predictive factors of early postpartum diabetes among women with gestational diabetes in a single-center cohort.Int. J.of Gynecol. & Obstet.. 2018.
151. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: A systematic review and meta-analysis. Lancet. 2009;373(9677):1773-9.
152. Song C, Lyu Y, Li C, Liu P, Li J, Ma R, et al. Long-term risk of diabetes in women at varying durations after gestational diabetes: A systematic review and meta-analysis with more than 2 million women. Obes Rev. 2018;19(3):421-9.
153. Persson B, Hanson U, Hartling SG, Binder C. Follow-up of women with previous GDM: Insulin, C-peptide, and proinsulin responses to oral glucose load. Diabetes. 1991;40(Supplement 2):136-41.
154. Linné Y, Barkeling B, Rössner S. Natural course of gestational diabetes mellitus: Long term follow up of women in the SPAWN study. 2002;109(11):1227-31.
155. Gunderson EP, Lewis CE, Tsai A-L, Chiang V, Carnethon M, Queensberry CP, et al. A 20-year prospective study of childbearing and incidence of diabetes in

young women, controlling for glycemia before conception: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Diabetes. 2007;56(12):2990-6.

156. Osei K, Gaillard TR, Schuster DP. History of gestational diabetes leads to distinct metabolic alterations in nondiabetic African American women with a parental history of type 2 diabetes. Diabetes Care. 1998;21(8):1250-7.

157. Mukerji G, Chiu M, Shah B. Impact of gestational diabetes on the risk of diabetes following pregnancy among Chinese and South Asian women. Diabetologia. 2012;55(8):2148-53.

158. Cormier H, Vigneault J, Garneau V, Tchernof A, Vohl MC, Weisnagel S, et al. An explained variance-based genetic risk score associated with gestational diabetes antecedent and with progression to pre-diabetes and type 2 diabetes: A cohort study. BJOG: 2015;122(3):411-9.

159. Zhao P, Liu E, Qiao Y, Katzmarzyk PT, Chaput JP, Fogelholm M, et al. Maternal gestational diabetes and childhood obesity at age 9-11: Results of a multinational study. Diabetologia. 2016;59(11):2339-48.

160. Archambault C, Arel R, Filion KB. Gestational diabetes and risk of cardiovascular disease: A scoping review. Open Medicine. 2014;8(1): e1-9.

161. Li J, Song C, Li C, Liu P, Sun Z, Yang X. Increased risk of cardiovascular disease in women with prior gestational diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2018; 140:324-38.

162. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: A systematic review and meta-analysis. Diabetologia. 2019.

163. Huvinen E, Eriksson JG, Koivusalo SB, Grotenfelt N, Tiitinen A, Stach-Lempinen B, et al. Heterogeneity of gestational diabetes (GDM) and long-term risk of diabetes and metabolic syndrome: Findings from the RADIEL study follow-up. Acta Diabetol. 2018;55(5):493-501.

164. Kale SD, Yajnik CS, Kulkarni SR, Meenakumari K, Joglekar AA, Khorsand N, et al. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. Diabet Med. 2004;21(11):1257-8.

165. Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, et al. Association of Gestational Diabetes with Maternal Disorders of Glucose Metabolism and Childhood Adiposity. JAMA. 2018;320(10):1005-16.
166. Inoue H, Ishikawa K, Takeda K, Kobayashi A, Kurita K, Kumagai J, et al. Postpartum risk of diabetes and predictive factors for glucose intolerance in East Asian women with gestational diabetes.Diabetes Res Clin Pract . 2018; 140:1-8.
167. Simmons D, Kumar S, Crook N, Rush E. Diabetes among Maori women with self-reported past gestational diabetes mellitus in a New Zealand Maori community. Aust N Z J Obstet Gynaecol. 2017;57(6):599-603.
168. Chamberlain CR, Oldenburg B, Wilson AN, Eades SJ, O'Dea K, Oats JJ, et al. Type 2 diabetes after gestational diabetes: Greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. Diabetes Metab Res Rev. 2016;32(2):217-27.
169. Gupta Y, Kapoor D, Desai A, Praveen D, Joshi R, Rozati R, et al. Conversion of gestational diabetes mellitus to future Type 2 diabetes mellitus and the predictive value of HbA1c in an Indian cohort. Diabet Med. 2017;34(1):37-43.
170. Tam W-H, Ma RC-W, Yang X, Ko GT-C, Lao TT-H, Chan MH-M, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: A 15-year follow-up study.Gynecol Obstet Invest . 2012;73(2):168-76.
171. Wang Y, Chen L, Horswell R, Xiao K, Besse J, Johnson J, et al. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. J Womens Health (2002). 2012;21(6):628-33.
172. Madarász E, Tamás G, Tabák ÁG, Kerényi Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes.Diabetes Res Clin Pract . 2009;85(2):197-202.
173. Lee H, Jang HC, Park HK, Metzger BE, Cho NH. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. Diabetes Res Clin Pract. 2008;81(1):124-9.
174. Rivero K, Portal VL, Vieira M, Behle I. Prevalence of the impaired glucose metabolism and its association with risk factors for coronary artery disease in women with gestational diabetes. Diabetes Res Clin Pract .2008;79(3):433-7.

175. Tam W, Yang X, Chan J, Ko G, Tong P, Ma R, et al. Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes.Diabetes Metab Res Rev . 2007;23(6):485-9.
176. Krishnaveni GV, Hill JC, Veena SR, Geetha S, Jayakumar MN, Karat CLS, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes Res Clin Pract. 2007;78(3):398-404.
177. Kale S, Yajnik C, Kulkarni S, Meenakumari K, Joglekar A, Khorsand N, et al. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. Diabet Med 2004;21(11):1257-8.
178. Freinkel N. Banting Lecture 1980: Of pregnancy and progeny. Diabetes. 1980;29(12):1023-35.
179. Dabelea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care. 2007;30(Supplement 2): S169-S74.
180. Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC. Abnormal glucose tolerance during pregnancy in Pima Indian women: Long-term effects on offspring. Diabetes. 1991;40(Supplement 2):126-30.
181. Pettitt DJ, Nelson RG, Saad MF, Bennett PH, Knowler WC. Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. Diabetes Care. 1993;16(1):310-4.
182. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM: Role of intrauterine environment. Diabetes. 1988;37(5):622-8.
183. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med. 1983;308(5):242-5.
184. Barker D, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. BMJ. 1990;301(6746):259-62.
185. Barker D, Martyn C, Osmond C, Hales C, Fall C. Growth in utero and serum cholesterol concentrations in adult life. BMJ. 1993;307(6918):1524-7.
186. Phillips D, Barker D, Hales C, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. Diabetologia. 1994;37(2):150-4.

187. Barker DJ, Osmond C, Winter P, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;334(8663):577-80.
188. Wang J, Wu Z, Li D, Li N, Dindot SV, Satterfield MC, et al. Nutrition, epigenetics, and metabolic syndrome. Antioxid Redox Signal 2012;17(2):282-301.
189. Barker DJ. The origins of the developmental origins theory. J Intern Med. 2007;261(5):412-7.
190. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: A systematic review. Exp Diabetes Res. 2011;2011.
191. Manerkar K, Harding J, Conlon C, McKinlay C. Maternal gestational diabetes and infant feeding, nutrition and growth: A systematic review and meta-analysis. Br J Nutr. 2020;123(11):1201-15.

CHAPTER 3. AIMS, OBJECTIVES AND OVERVIEW OF METHODS

3.0. Chapter Outline

This chapter starts with a description of the aims and objectives of the thesis, followed by an overview of the methods for the two components of the body of work of this thesis: a systematic review and meta-analysis and a primary study. The manuscripts in the chapters that follow give additional detailed descriptions of the methods used in each specific study.

3.1.1. Aim

The study aims to add to the body of knowledge on the prevalence of T2DM in African women of childbearing age, and the medium-term cardiometabolic outcomes of HFDP in both the mother and her exposed offspring.

3.1.2. Specific Objectives

1. To estimate the prevalence of T2DM and impaired glucose metabolism in women of childbearing age in Africa as reported in studies published during the period January 2000 to December 2016, using a systematic review and meta-analysis.
2. To estimate the proportion of women who progress to T2DM within 6 years of HFDP, and factors associated with risk of postpartum T2DM, in Cape Town, South Africa.
3. To investigate the prevalence of and factors associated with CVD risk factors in women 6 years after HFDP, in Cape Town, South Africa.
4. To investigate the association between maternal blood glucose concentrations during HFDP and offspring weight at birth and preschool age and overweight and obesity in the same offspring.

3.2. Overview of methods of the systematic review and meta-analysis

The systematic review was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis guideline (PRISMA) (1). The study protocol for the systematic review (Appendix 3.1), with full details of the methods used, was registered online on PROSPERO, the International prospective register of systematic reviews (http:www.crd.york.ac.uk/PROSPERO, registration number: CRD42015027635) on 6 November 2015 and published in a peer-reviewed international journal (2). Since the methods are well described in Appendix 1, this chapter provide a brief description.

The systematic review and meta-analysis was performed according to this protocol except that the age range inclusion of women was changed to 15-54 years. The reason for this change was that many studies used starting from 15 – 24, 25 – 34, 35 – 44 and 45 – 54 years. Comprehensive searches for published and unpublished studies of all the major electronic databases, and the World Health Organization STEPWise country reports for STEP 3 was carried out. Eligible studies were published from 2000 to 2016, included women of African women of childbearing age and should have used the World Health Organization (WHO) guidelines of 1999 (3) or equivalent criteria for the diagnosis of type 2 diabetes.

The analysis of the primary outcome (prevalent diabetes) was done in two steps: (a) identification of data sources and documenting estimates and (b) application of the random-effects meta-analysis model to aggregate prevalence estimates and account for between-study variability in calculating the overall pooled estimates and 95% CI for diabetes prevalence. Heterogeneity, systematic biases and publication bias were assessed using established methods.

3.3. Overview of the PRO2D Study

The PROgression to type 2 Diabetes study (PRO2D Study) is a study whose main purpose was to study maternal and offspring cardiometabolic outcomes 5-6 years after HFDP. During the study women who were diagnosed with GDM at one of the 3 major

tertiary hospitals in the Western Cape were recalled, together with their offspring, 5-6 years later. Notably, the women were originally diagnosed using the NICE 2008 criteria (4), which included both women with DIP and GDM, when assessed using the WHO 2013 criteria (5). Therefore, a decision was made to refer to them as women with HFDP instead of GDM only. During the pregnancy, clinical data were collected routinely from the women and at birth. At the time of follow-up, the women were assessed for T2DM, insulin resistance and CVD risk and the children were assessed for overweight and obesity. Since the women were still young (mean age 37 years), CVD was not assessed directly but we assessed them for the following risk factors; obesity, central obesity, raised blood pressure, dysglycaemia and dyslipidaemia.

The methods for the PRO2D are described in each of the manuscripts in Chapters 5, 6 and 7, the first two are published already (6, 7). In this chapter, an overview of the PRO2D study and its context will be discussed as well as aspects that may not have been discussed fully in chapters 5, 6 and 7.

3.3.1. The PRO2D Study Setting

The PRO2D Study was carried out at Groote Schuur hospital, one of the three main tertiary hospitals in the Western Cape province of South Africa. The Western Cape province, the fourth biggest province of South Africa in terms of population size, is in the southernmost part of the Africa continent (8). The province consists of a mixture of several towns, some semi-rural settlements and many farming areas. The economy of the Western Cape is diverse, from agriculture, tourism, finance, technology and manufacturing. The province is a big tourist attraction with one of the 8 wonders of the world, Table Mountain, situated a few kilometres from the Cape Town central business district.

Fig 3.3.1. The Western Cape province geographical position in Africa

Map from www.westerncape.gov.za

The estimated population of the Western Cape was 6.3 million people in 2019, with almost two-thirds (4 million) of the population residing in the Cape Town metropole (9). People of mixed ancestry, controversially referred to as “Colored”, a legacy of apartheid, form the majority (42.4%) of the population followed by people of Black ethnicity (38.6%) and people of White ethnicity (15.7%) (9). Similar to other South African provinces, the legacy of apartheid is still evident in the towns and cities of the Western Cape. This can be seen in the way residential areas are predominantly occupied by people of each of the major ethnicities, even though the restriction on inter-racial mixing is over. Just over half (51%) of the population of the province are women and the most common language is Afrikaans (46%, followed by isiXhosa (31% and lastly English (19%) (9). Most of the residents of the Western Cape belong in the low-income group. The average annual household income in 2016 was R29 400.00, roughly equal to USD2000.00 (9). An estimated 16.6% of households live in informal housing and 38% of households had women as the head during 2016 (9). During 2016, 96% of households had access to tap water, 89% had reliable refuse removal, 98% had access to electricity and 95% had access to flush toilets (9). During 2016, the employment rate was 50% with 78% employed in the formal sector (9).

Apart from the Cape Town metropole, there are 5 other main districts in the province and a total of over 25 district hospitals (8). The West Coast district has an economy based on a mixture of farming, including rooibos tea, manufacturing and the Port of Saldanha Bay and includes the towns of Saldanha Bay, Malmesbury,

Clanwilliam, Vredenburg and Mooresburg. The Cape Winelands district produces about 70% of South Africa's wines and includes the towns of Paarl, Wellington, Franschoek and Stellenbosch. The Overberg district is on the Southernmost tip of the African content and consists of the towns of Cape Agulhas, Swellendam, Hermanus, Bredasdorp and Caledon. The Garden Route district is an important tourist attraction and consists of the towns of Plettenberg Bay, Mossel Bay, Oudtshoorn, George, Calitzdorp and Knysna. The Central Karoo is the largest district in the province by land mass but has the smallest population, and consists of the towns of Prince Albert, Beaufort West and Laingsburg. Patients from these districts are referred to any of the three tertiary hospitals (Groote Schuur, Tygerberg and Red Cross Memorial Children's Hospital) when they require specialized or complicated care (8). The Red Cross Memorial Children's hospital is the only tertiary level specialist paediatric hospital in South Africa (8). Women with complicated pregnancies from the Southern suburbs of the Cape Town metropole are referred to Mowbray Maternity hospital, a secondary level referral facility (8).

During the period 1 September 2010 to 31 August 2011, women with GDM, as it was diagnosed at that time, in the Cape Town metropole were treated at the Mowbray, Groote Schuur and Tygerberg hospitals, depending on their location. The Groote Schuur hospital is situated about 5km from the Cape Town city central business district and has a colourful history, including being the hospital where the first human transplant was done (8). The name "Groote Schuur" means "The Great Barn" in Dutch. Officially opened in 1938, the hospital is a teaching hospital of the University of Cape Town, is part of the public health sector and serves most people from low-income settings (10). The hospital is the second biggest in the Western Cape province, after the Tygerberg, with roughly 900 beds. The hospital has a dedicated diabetes clinic in the department of obstetrics and gynaecology, where pregnant women with all forms of hyperglycaemia in pregnancy (HIP) are treated.

Fig 3.3.2. The Groote Schuur hospital

3.3.2. The PRO2D Study Methods

Routine data were collected during the pregnancy, on all women who had different forms of diabetes in pregnancy during the period 1 September 2010 to 31 August 2011, as part of separate research (11) and a database created. From this database, all the women who were categorized as having gestational diabetes mellitus (GDM) at the time of diagnosis, were selected for a follow-up cross-sectional study, together with their offspring from the HFDP complicated pregnancy. The follow-up study was carried out during the period 1 January 2016 to 31st January 2017. This cross-sectional study was used to answer the objectives 2,3 and 4 in the thesis. Data from both the pregnancy period and the follow-up measurements were used to assess the association between

maternal blood glucose during the pregnancy and foetal weight outcomes at birth and preschool age (ages 5-6 years).

3.4. Summary of the chapter

In this chapter, the aims and objectives and the methods used in this research were discussed. The methods are also described well in manuscripts which are part of this thesis (Appendix 1, Chapter 5, 6 and 7). Therefore, an overview of the methods used in the systematic review and meta-analysis and the PRO2D study is given, together with the context of the PRO2D Study. In the next chapter, the results of the systematic review and meta-analysis are presented.

3.5. References

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339: b2535.
2. Chivese T, Mahmoud W, Magodoro I, Kengne AP, Norris SA, Levitt NS. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000-2016: protocol of a systematic review and meta-analysis. BMJ Open. 2016;6(12): e012255-2016-.
3. World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation Geneva: World Health Org. 1999.
4. Guideline Development Group. Guidelines: management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ: British Medical Journal. 2008;336(7646):714.
5. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy 2013 [Available from: https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=48ABC998E153A412E00E1CD62B90C1EC?sequence=1.]

6. Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLOS Medicine. 2019;16(9): e1002865.
7. Chivese T, Norris SA, Levitt NS. High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy in Cape Town, South Africa. BMJ Open Diabetes Research and Care. 2019;7(1).
8. Western Cape Government. Western Cape Government: Overview 2020 [Available from: https://www.westerncape.gov.za/your_gov/70#overview].
9. Statistics South Africa. Community Survey 2016 Provincial profile: Western Cape, 2016 2018 [Available from: http://cs2016.statssa.gov.za/wp-content/uploads/2018/07/WesternCape.pdf.]
10. South Africa History Online. Groote Schuur Hospital 2019 [Available from: https://www.sahistory.org.za/place/groote-schuur-hospital.
11. Van Zyl H, Levitt N. Pregnancy outcome in patients with pregestational and gestational diabetes attending Groote Schuur Hospital, Cape Town, South Africa. South African Medical Journal. 2018;108(9).

PART B. EMPIRICAL CHAPTERS

"To acquire knowledge, one must study; but to acquire wisdom, one must observe." ~ Marilyn vos Savant

CHAPTER 4. PAPER 1

The prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000-2016: A systematic review and meta-analysis

Roles of the candidate and co-authors

The candidate, together with Professors Norris, Levitt and Kengne conceptualized the study and the study protocol. The candidate drafted the study protocol and registered it on PROSPERO and led its publication. The candidate, with the help of a librarian, searched for the studies. The candidate extracted data and carried out risk of bias analysis with the help of Dr Mahmoud Werfalli, Dr Itai Magodoro and Mr Rekayi Chinhoyi. The candidate carried out the data analysis with the help of Professor Andre Kengne and the 2 supervisors. The candidate drafted the initial, revisions and final manuscript with the help of Professors Kengne, Shane Norris and Naomi Levitt. The candidate led the publication and was the corresponding author.

Publication status

The study protocol (Appendix 1) is published at https://bmjopen.bmj.com/content/bmjopen/6/12/e012255.full.pdf, with the following citation:

Chivese T, Mahmoud W, Magodoro I, Kengne AP, Norris SA, Levitt NS. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000-2016: protocol of a systematic review and meta-analysis. BMJ Open. 2016;6(12): e012255-2016.

The systematic review and meta-analysis is published at https://bmjopen.bmj.com/content/bmjopen/9/5/e024345.full.pdf with the following citation:

Chivese T, Werfalli M, Magodoro I, et al. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: a systematic review and meta-analysis. BMJ Open 2019;0: e024345. doi:10.1136/bmjopen-2018-024345

4.1. Abstract

4.1.1. Objectives

This research aimed to estimate the prevalence of T2DM, impaired fasting glucose and impaired glucose tolerance, in African women of childbearing age.

4.1.2. Study design

Systematic review and meta-analysis of relevant African studies published from January 2000 to December 2016.

4.1.3. Data sources

We searched several databases, including EMBASE, MEDLINE, CINAHL, grey literature and references of included studies.

4.1.4. Setting

Studies carried out in African communities or any population-based studies were included.

4.1.5. Participants

We included studies, carried out in Africa, with non-pregnant women of childbearing age. Studies must have been published between the years 2000 and 2016.

4.1.6 Outcomes

The primary outcome was prevalent T2DM. The secondary outcomes were impaired fasting glucose and impaired glucose tolerance.

4.1.7. Data extraction and synthesis

Two reviewers independently extracted data and, using the adapted Hoy risk of bias tool, independently assessed for risk of bias. We used random-effects meta-analysis models to pool prevalence estimates across studies. We used Cochran's Q statistic and the I2 statistic to assess heterogeneity.

4.1.8. Results

A total of 39 studies from 27 countries were included, totalling 52 075 participants, of which 3813 had T2DM. The pooled prevalence of T2DM was 7.2% (95%CI 5.6-8.9%)

overall and increased with age. The pooled prevalence was 6.0% (95%CI 4.2% - 8.2%) for impaired fasting glycemia while the prevalence of impaired glucose tolerance ranged from 0.9% to 37.0% in women aged 15-24 years and 45-54 years respectively. Substantial heterogeneity across studies was not explained by major studies characteristics such as period of publication, rural/urban setting or whether a study was nationally representative or not.

4.1.9. Conclusion

This review highlights the need for interventions to prevent and control diabetes in African women of childbearing age, given the significant prevalence of T2DM and prediabetes.

PROSPERO registration number: CRD4201502763

4.2. Strengths and limitations of this study

This research has included many population-based surveys from a broad range of African countries than previous systematic reviews has been carried out rigorously and transparently. This is one of the first reviews to investigate the prevalence of T2DM, IFG and IGT in African women of childbearing age, a key population in the fight against the rise of noncommunicable diseases in Africa. One limitation of the research is that gender stratified data are not reported in many studies of T2DM prevalence, making them unusable in the current meta-analysis. Further, this review has limitations in that the methods of screening for dysglycaemia and representativeness of the data in some of the included studies were not very satisfactory. There was substantial heterogeneity in prevalent T2DM, IFG and IGT which could not be explained by the major study characteristics.

4.3. Introduction

Worldwide, the estimated number of people with diabetes has quadrupled from 108 million people in 1980 to 422 million in 2014 [1] and is projected to reach 640 million by 2040 [2]. It is predicted that the greatest increase in numbers will occur in Africa, where in 2014, 14.2 million adults aged 20 to 79 years had diabetes, with over two thirds unaware of their diabetic status [3]. In African women in general, T2DM prevalence more than doubled, from 4.1% in 1980 to 8.9% in 2014 [4]. The rapid increase in diabetes has led to calls by the International Diabetes Federation (IDF) for the establishment of national diabetes programs to better deliver prevention and control solutions [5]. In line with the United Nations Sustainable Development Goal (SDG) 3.4, aiming to reduce premature mortality from NCDs by one third by the year 2030 [6], identifying special at-risk populations and delivering context-appropriate interventions is one of the most important strategies in combating the T2DM epidemic. Up to 70% of people with intermediate states of impaired glucose metabolism [impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)] progress to T2DM within a decade [3]. To date, most diabetes prevention programs have focused on people with IGT although some have intervened in another group at risk i.e. women with previous gestational diabetes (GDM). However, data on intermediate states of impaired glucose metabolism such as GDM, IFG and IGT are scarce in Africa. Overweight and obesity, the biggest single attributable risk factor for T2DM, is increasing in all African women, with the age-standardized BMI having increased from 21.9kg/m2 in 1980 to 24.9kg/m2 in 2014, possibly implying future obesity-driven T2DM increases in women [4]. In 2017, the WHO, recognizing the differential effects of non-communicable diseases (T2DM included) on gender, recommended a gender-based approach in prevention and treatment policies, in the Montevideo Roadmap 2018-2030 [7].

African women are affected by diabetes in more ways than their male counterparts, often assuming unpaid caregiver roles for affected family members in addition to taking care of their own diabetes/themselves [7]. Further, if a woman with diabetes becomes pregnant, her unborn child is at an increased risk of developing T2DM in adulthood [9], thereby accelerating the intergenerational risk of T2DM. Mapping the prevalence of

T2DM in this population is important as it has implications for future trends and monitoring of the T2DM burden in Africa.

The World Health Organization [WHO] defines women of childbearing age as women aged between 15 and 49 years [8]. Apart from the IDF estimates, several systematic reviews have investigated the prevalence of T2DM in Africa [1,10,11], but none have examined the T2DM prevalence in women of childbearing age, nor the prevalence of IFG and IGT in women of this age-group despite their contribution to the risk of both GDM and T2DM. While two systematic reviews [12,13] have examined GDM prevalence on the continent, reporting a prevalence ranging from 0% to 14%, the reviews highlighted the sparse data on GDM prevalence and the absence of active GDM screening programs in most African countries. As T2DM and impaired glucose metabolism affect both maternal and child health, it is important to understand the prevalence of T2DM and its distribution in African women of childbearing age to inform better planning of preventive interventions and treatment and monitoring strategies.

This systematic review aimed to address the research question: what is the respective prevalence of T2DM, impaired fasting glucose, and impaired glucose tolerance in African women of childbearing age between 2000 and 2016? The T2DM estimates from this systematic review will complement those of the IDF to enable assessment of progress towards reaching the Global Action Plan for NCDs and SDG 3.4 [14] in women of childbearing age.

4.4. Methods

The study protocol of this review is registered on PROSPERO (CRD42015027635) and published in a peer-reviewed journal [15]. We searched for eligible studies, published during the period 1 January 2000 to 31 December 2016, with the aid of an expert librarian, from the following databases; MEDLINE via PubMed, EMBASE via OVID, ISI Web of Science, Cochrane Central, Global Health, Scopus, CINAHAL, POPLINE, AfricaWide, Google scholar as well as grey literature databases such as OpenSigle. All the databases were searched using an African search filter. Besides, we hand-searched the reference lists of included studies and asked experts for any studies they knew of. We wrote to authors requesting non-reported data. The search strategy is shown in Appendix 4.1.

4.4.1. Eligibility criteria

We included population-based cross-sectional studies, published since the year 2000 as older studies would not have used the WHO 1998 T2DM diagnosis guidelines, that assessed the prevalence of T2DM in at least 100 African women of childbearing age, in any language. We excluded case-control studies, hospital-based studies and studies on migrant Africans. For the meta-analysis, we included only studies that reported age and gender-specific prevalence.

4.4.2. Study selection, quality assessment and data extraction

After the retrieval of articles and sorting duplicates, three reviewers (TC, IM and MW) independently screened the titles, abstracts and, if necessary, full articles for inclusion. The reviewers resolved any differences by discussion and consulted the fourth reviewer in the case of disagreement. The three reviewers assessed each included study for risk of bias and internal and external validity using the tool by Hoy et al. [16] as adapted by Werfalli et al. [10]; Supplementary Table 4.1.

Four reviewers (TC, MW, IM and LC) independently extracted from the selected articles, two reviewers per study. The investigators compared their findings and any differences were resolved through discussion. We extracted data on study characteristics including the first author's name, date of publication, country where the study was conducted, the number of participants included and proportion of participants who were women of childbearing age, diagnostic method and diagnostic criteria, sampling method, response rate, and unadjusted T2DM prevalence estimates.

4.4.3. Primary and secondary outcomes

The primary outcome was T2DM, defined as; fasting plasma glucose of at least 7.0 mmol/L, fasting blood glucose of at least 6.1 mmol/l, 2-hour Oral Glucose Tolerance Test (OGTT) plasma glucose of 11.1 mmol/L, or an existing T2DM diagnosis [17]. The secondary outcomes were IGT (fasting blood glucose less than 6.1 mmol/L and 2-hour

OGTT blood glucose of at least 7.8 mmol/L but less than 11.1 mmol/L and IFG (fasting blood glucose greater than 6.1 mmol/L but less than 7.0 mmol/L).

4.4.4. Data synthesis and analysis

We compiled a summary of extracted data in a table and a narrative synthesis of all the 80 included studies. We then conducted a meta-analysis with the studies that provided age and gender specific diabetes prevalence. Our population of women of childbearing age was defined as African women between the ages of 15 – 49 years, per WHO definition. However, in this review, we used the upper cut-off of 54 years as most studies used age groups starting from 15 – 24, 25 – 34, 35 – 44 and 45 – 54 years.

We pooled the T2DM prevalence using the statistical software STATA 15 [18], and metaprop package [19]. We applied the random effects meta-analysis framework as we expected variability in the prevalence estimates from different studies. The package first models the prevalence estimates using the exact binomial distribution and then applies the Freeman-Turkey double arcsine variance stabilising transformations, normalising the estimates before pooling and then back transforming the estimates. The pooled estimates are then computed using the procedure described by Dersimonian and Laird [20].

We assessed heterogeneity between studies using Cochran's Q statistic [21] and estimated the percentage of total variation across studies due to true between-study differences rather than chance, using the I2 statistic [22]. We explored sources of heterogeneity through subgroup analysis using study-level characteristics. Besides, we assessed the presence of publication bias by examining the funnel plots, supplemented with formal statistical testing using the Egger test [23], and the Begg's test [24] for publication bias.

4.4.5. Patient involvement

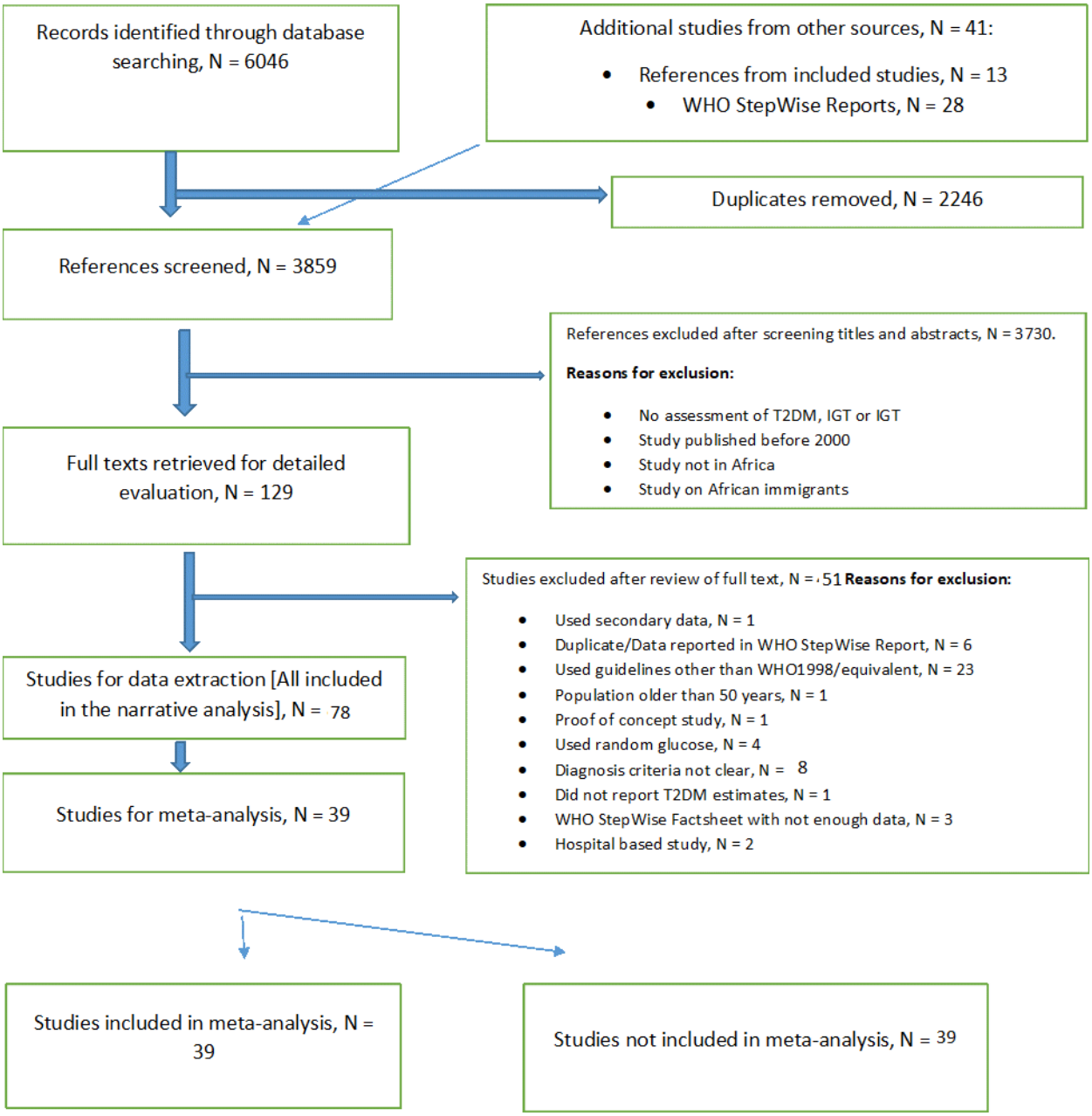
We did not involve patients in the development of the research question, development of the study outcomes, design of the study or the conduct of the study.

4.5. Results

4.5.1. Search results

The flow chart of the search is shown in Figure 4.1. Out of a total of 6046 studies identified via searches, 129 remained after removing irrelevant studies and duplicates. A further 41 studies were identified through screening of references of included studies (13 studies) and from the WHO STEPWise country reports on the WHO website (28 studies). The final number of studies included was 80, of which only 39 studies were included in the meta-analysis as they reported age-group and gender-specific diabetes outcomes. Forty-one studies were included in the narrative description only because either they did not report age group-specific data (38 studies) or reported only the percentage of participants with T2DM but did not report the raw frequencies (3 studies). There were two major age groups systems used by authors, 25 studies (64%) used the format: 15-24, 25-34, 35-44 and 44-54 years, 7 (18%) used the format: 20-29, 30-39 and 40-49 years. We merged some age groups into either of the two systems depending on which systems they were most related to, for example, the age group 18-25 was merged with 15-24 while the age group 20-29 was merged with the 18-29 years. The remaining 7 studies (18%) used other age groups which were very different from the two main systems described above [15-29, 30-44 years (4 studies), 25-44 years (2 studies) and <50 years (1 study)] and we did not attempt to merge them into either of the systems.

Fig 4.1. Flow chart showing search, selection of and final included studies



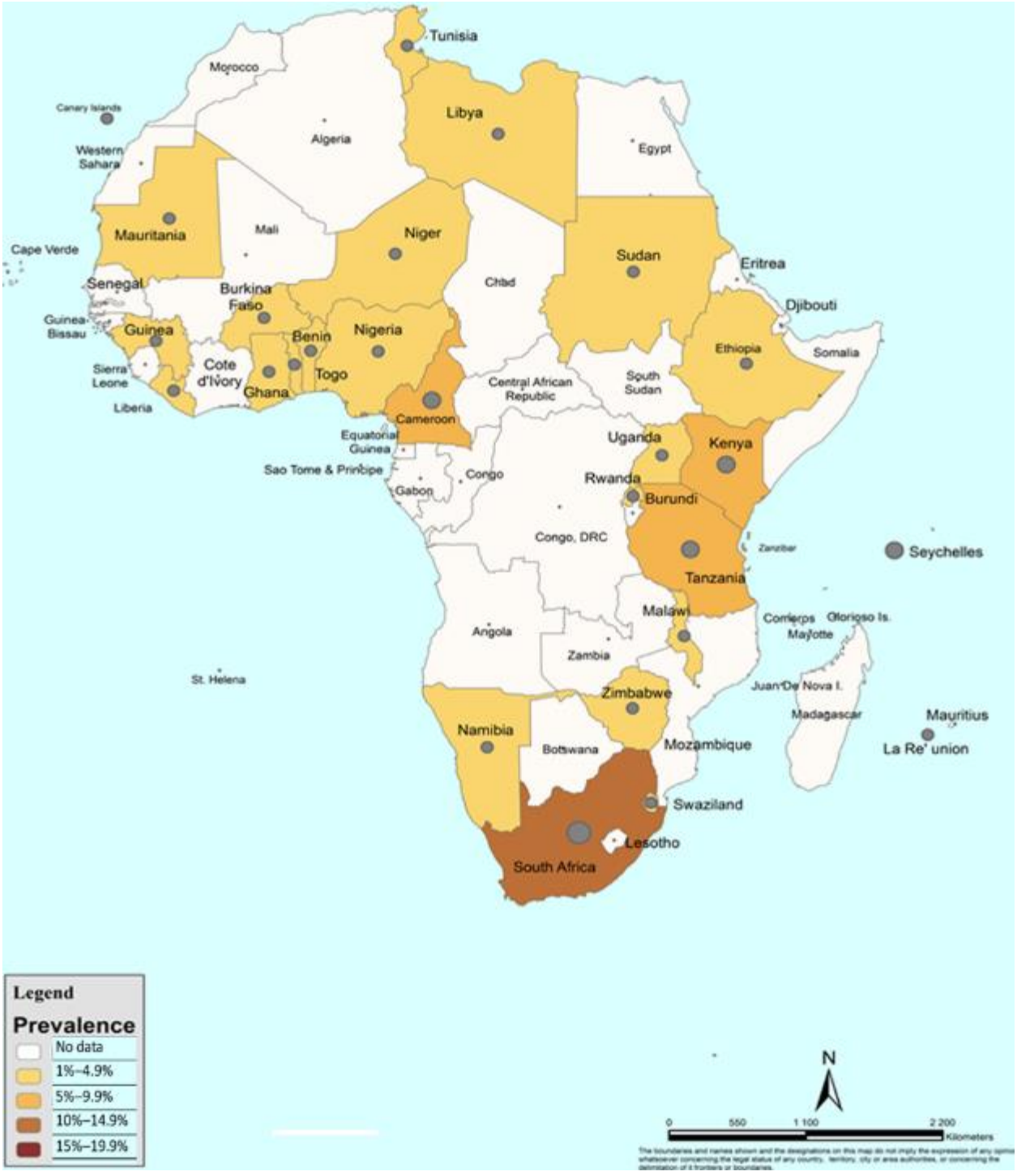
4.5.2. Characteristics of included studies

Appendix 4.2 shows the list and characteristics of all the 80 included studies from 39 countries. Most of the studies were from Nigeria, 14 (18%), South Africa, 8 (10%), Tanzania, 5 (6%), Cameroon, 4 (5%) Kenya, 4 (5%), Tunisia, 3 (4%); 10 countries contributed 2 eligible studies while the remaining 23 countries each

contributed a single study. Most studies were published during the years 2014, 12 (15%), 2013, 11(14%) and the year 2015, 9 (11%) and 2016, 7 (9%). Forty-five studies, i.e., 56%, were conducted in both urban and rural populations, 19 (23%) in urban settings only, 14 (17%) in rural settings only and one study [25] did not clearly state the setting. The reported response rate ranged from 40% [26] to 100% [27]. Of the 81 studies, 31 (38%) were nationally representative studies, with 28 of these being WHO STEPWise surveys and one national demographic and health survey from Namibia [28]. Appendix 4.2 contains the characteristics of the included studies.

Almost three-quarters of the studies, (n = 59 (74%) used fasting plasma glucose, 20 (25%) used the 2-hour OGTT, while 2 studies used the HbA1C for the diagnosis of T2DM. There were a total of 197 848 participants in the included studies of which the proportion of all women included ranged from 21% [29] to 100% [27]. The prevalence of T2DM in both sexes in the included studies ranged from 0.8% [30] to 33% [31], while the T2DM prevalence in all women in the studies ranged from 0.5% [30] to 36% [31]. Figure 4.2 shows the map of pooled T2DM prevalence for each country, in women of age 15-54 years. Regarding the risk of bias, 74 92.5%of the included studies scored a low risk, 3.8% scored moderate risk and the remaining 3.8% scored high risk of bias (Appendix 4.3).

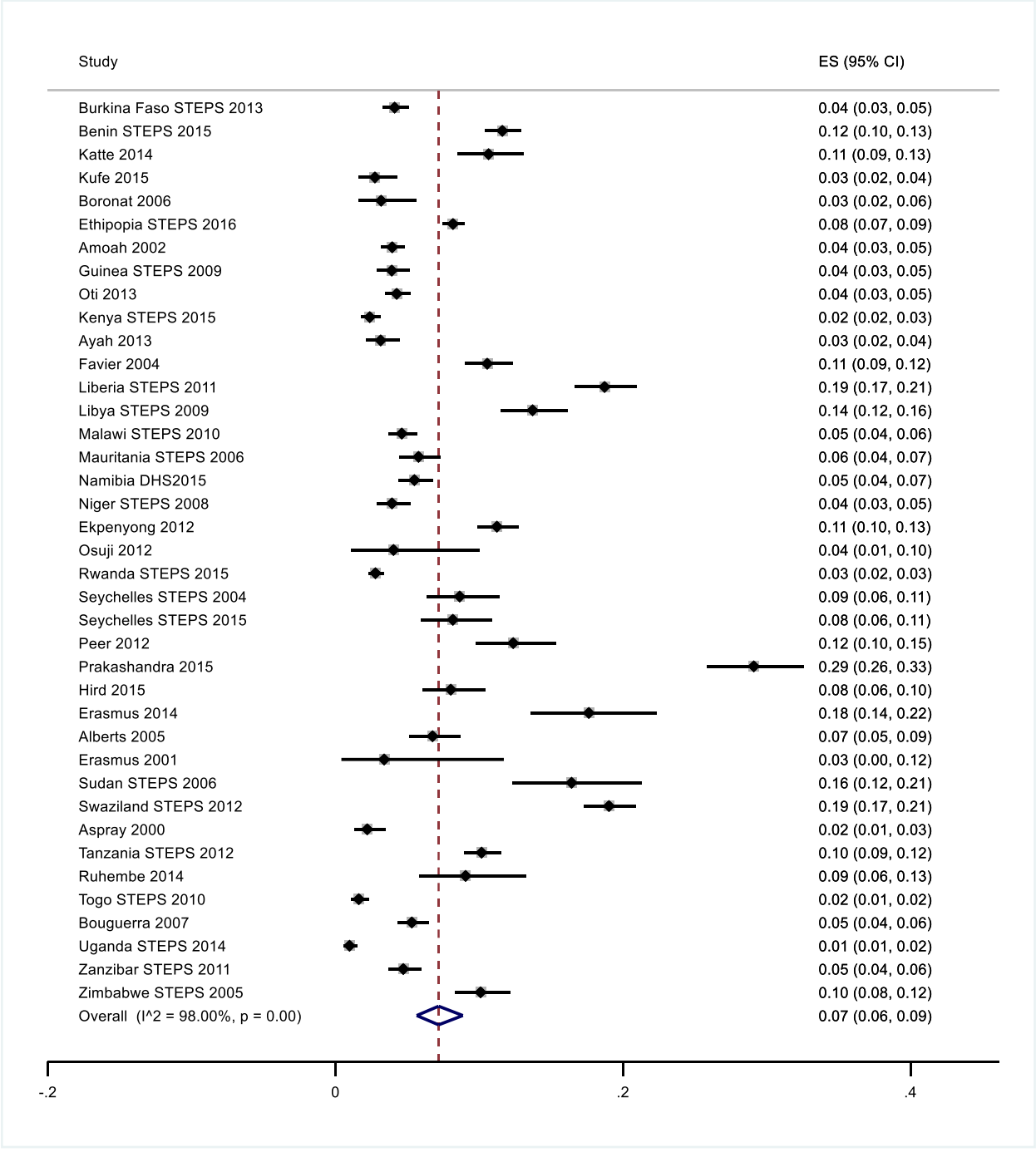
Fig 4.2. Map showing pooled T2DM prevalence in African women aged 15-54 years in each country



4.5.3. T2DM prevalence in women aged 15 – 54 years

A total of 39 studies, from 27 countries, with 52 075 women of childbearing age, of which 3 813 had T2DM were included in the meta-analysis. The T2DM prevalence in women aged between 15-54 years ranged from 1% in Uganda (Uganda STEPS 2011) to 29% in South Africa (31). The pooled prevalence was 7.2% (95%CI 5.6% – 8.9%, n = 39 studies), with significant heterogeneity (I2 = 98%, p< 0.001), Figure 4.3.

Fig 4.3. Forest plot of T2DM prevalence in African women aged 15-54 years, from studies published during the period 2000-2016.



NB: Studies must have used WHO 1999 or equivalent guidelines for the diagnosis of T2DM

4.5.4. Prevalence of T2DM by age group

The lowest pooled T2DM prevalence was found in the 15 - 24 years age group (2.0% 95%CI 1.0% - 3.4%, n = 11 studies, I2 83.2%, p < 0.001) and the 25 – 34 years age group (3.0%, 95%CI 1.7-4.5%, n = 24 studies, I2 90.0%, p < 0.001). The highest pooled T2DM prevalence was observed in the 45 – 54 years age group (13.1% 95%CI 9.8-16.8%, n = 23 studies, I2 94.3%, p < 0.001) (Table 4.1 and Table. 4.A). T2DM prevalence significantly increased with age, compared to the 15 – 24 years age group, with a higher prevalence observed in the following age groups; 30 – 44 years 35 – 44 years, 40 – 49 years and 45 – 54 years (p < 0.001) (Table 1).

Table 4.1. Summary of sub-group meta-analysis of T2DM, IFG and IGT in women aged 15-54 years

Sub-group		T2DM			IFG		IGT	
		Number of studies	Prevalence [95% CI]	I^2, p value	Prevalence [95% CI]	I^2, p value	Prevalence [95% CI]	I^2, p-value
Overall		39	7.2 [5.6 – 8.9]	98%, p< 0.001	6.0 [4.2 - 8.2]	96%, p <0.001	7.0 [3.5 - 11.2]	95.9%, p < 0.001
Setting	Urban	11	9.2 [5.5 - 13.7]	97.7%, p < 0.001	6.6 [0.8 – 17.3]	99%, p<0.001	6.0 [2.3 – 10.1]	95.9%, p<0.001
	Rural	2	4.2 [3.3 - 5.2]	90.7%, p<0.001	3.8 [2.6 – 5.4]	-	-	-
	Both urban and rural	26	6.6 [4.9 - 8.6]	98.2%, p < 0.001	5.9 [4.1 – 8.0]	98%, p<0.001	6.0 [2.3 – 10.1]	95.9%, p<0.001
Age group	15-24 years	10	2.0 [0.9-3.4]	83.2%, p < 0.001	7.1 [1.3 – 10.4]	99.4%, p<0.001	1.9 [0.5 – 4.1]	-
	15-29 years	7	3.6[1.2-7.4]	98.1, p<0.001	5.3 [3.1 – 8.1]	97.5%, p<0.001	2.1 [1.3 – 3.3]	-
	25-34 years	22	3.0 [1.7-4.5]	90.0%, p < 0.001	5.1 [2.7 – 8.1]	97.0%, p<0.001	0.6 [0.0 -7.3]	92.3%, p<0.001
	25-44 years	2	8.4 [7.2-9.7]	-	-	-	-	-
	30-44 years	4	9.7 [5.0-15.6]	97.2%, p < 0.001	-	-	-	-
	30 – 39 years	5	4.3[3.3-5.5]	36.9%, p = 0.17	-	-	-	-

	35-44 years	2	7.1 [5.3-9.1]	91.5%, p < 0.001	6.5[5.3 – 7.9]	-	10.9 [5.8 – 17.3]	89.6%, p<0.001
	35-54 years	2	2.9[1.2-5.2]	-	-	-	-	-
	40-49 years	6	9.4 [5.4-14.2]	88.0%, p < 0.001	-	-	-	-
	45-54 years	23	13.1 [9.8-16.8]	94.3%, p < 0.001	-	-	16.8 [8.3 – 27.6]	95.1%, p<0.001
	20-40 years	1	4.6 [1.9-9.1]	-	-	-	-	-
	30-49 years	1	1.6[0.9-2.6]	-	-	-	-	-
	<50 years	1	4.0[1.1-10.0]	-	-	-	-	-
	15-34 years	1	1.4 [0.5-2.67]	-	-	-	-	-
	35-54 years	1	2.9[1.2-5.2]	-	-	-	-	-
	20-40 years	1	4.6[1.9-9.1]	-	-	-	-	-
Diagnostic method	FPG	27	6.1 [4.6 - 7.8]	98.2%, p < 0.001	5.3 [3.5 – 7.5]	98.0%, p<0.001	-	-
	OGTT	12	10 [6.2 - 14.5]	97.7%, p < 0.001	7.3 [2.9 – 13.5]	93.7%, p<0.001	-	-
Period of publication	2000-2011	18	6.5 [4.6 - 8.6]	98.5%, p < 0.001	5.8 [3.6 – 8.5]	98.6%, p <0.001	-	-
	2012-2016	21	7.8 [5.6 - 10.4]	97.0%, p < 0.001	6.4 [3.2 – 10.7]	97.9%, p<0.001	-	-
Representativeness	Nationally representative	20	7.4 [5.4 - 9.8]	98.3%, p < 0.001	-	-	-	-
	Local/regional studies	19	6.9 [4.6 - 9.6]	98.3%, p < 0.001	-	-	-	-

Table 4. A. Pooled T2DM prevalence in different age categories in African women aged 15-54 years, from studies published during the period 2000-2016

Study and age group	Prevalence estimate	Lower 95%CI	Upper 95%CI
25-34			
Burkina Faso STEPS 2	3.7	2.7	5.1
Katte 2014	10.3	6.2	15.9
Kufe 2015	0.9	0.2	2.3
Amoah 2002	2.1	1.3	3.3
Guinea STEPS 2009	3.1	1.6	5.4
Ayah 2013	1.8	0.7	3.9
Libya STEPS 2009	10.5	7.4	14.4
Malawi STEPS 2010	3.7	2.5	5.1
Mauritania STEPS 200	3.5	1.8	6.1
Niger STEPS 2008	3.7	1.9	6.4
Ekpenyong 2012	9.7	7	13
Rwanda STEPS 2015	2.3	1.6	3.3
Seychelles STEPS 200	3.8	1.4	8.1
Seychelles STEPS 201	2.5	0.7	6.2
Peer 2012	6	3.3	9.8
Prakashandra 2015	13.1	7.2	21.4
Hird 2015	4.3	1.9	8.4
Erasmus 2014	0	0	97.5
Sudan STEPS 2006	12.2	6.5	20.4
Tanzania STEPS 2012	8.9	7.1	11
Togo STEPS 2010	0.8	0.3	2
Zimbabwe STEPS 2005	9.2	6.4	12.6
Sub-total			
Random pooled ES	3	1.7	4.5
35-44			
Burkina Faso STEPS 2	3.8	2.3	5.8
Katte 2014	9.4	6	13.8
Kufe 2015	2.2	0.6	5.7
Amoah 2002	3.9	2.6	5.5
Guinea STEPS 2009	4.8	2.4	8.5

Ayah 2013	4.1	1.9	7.7
Libya STEPS 2009	10.5	7.5	14.2
Malawi STEPS 2010	4.8	3.1	6.9
Mauritania STEPS 200	8.7	5.6	12.8
Namibia DHS2015	5	3.6	6.7
Niger STEPS 2008	3.7	1.8	6.6
Ekpenyong 2012	13	10.4	16
Rwanda STEPS 2015	3.4	2.4	4.8
Seychelles STEPS 200	6.4	3.3	11.2
Seychelles STEPS 201	7.1	3.7	12
Peer 2012	10.4	6.2	16.2
Prakashandra 2015	29	23.1	35.4
Hird 2015	5.6	2.3	11.3
Erasmus 2014	13.7	8.6	20.4
Alberts 2005	3.9	2.1	6.6
Sudan STEPS 2006	14.3	8	22.8
Tanzania STEPS 2012	11	8.9	13.4
Togo STEPS 2010	1.3	0.4	2.9
Zimbabwe STEPS 2005	11.2	8	15.1
Sub-total			
Random pooled ES	7.1	5.3	9.1
45-54			
Burkina Faso STEPS 2	5.6	3.5	8.4
Katte 2014	14	10	18.9
Kufe 2015	38.5	20.2	59.4
Amoah 2002	7	5	9.4
Guinea STEPS 2009	11.2	6.7	17.3
Ayah 2013	13.4	7.7	21.1
Libya STEPS 2009	24.4	18.7	30.9
Malawi STEPS 2010	6.5	4.3	9.4
Mauritania STEPS 200	9.2	5.7	13.8
Namibia DHS2015	6.1	4.4	8.2
Niger STEPS 2008	4.7	2.4	8.3
Rwanda STEPS 2015	3.6	2.2	5.3
Seychelles STEPS 200	14.9	10.1	21
Seychelles STEPS 201	14.2	9.5	20.1
Peer 2012	23.2	17.1	30.3
Prakashandra 2015	37.5	32.3	42.9
Hird 2015	24.5	17.9	32.2
Erasmus 2014	21.2	15.2	28.2
Alberts 2005	11.6	8.3	15.7
Sudan STEPS 2006	23.8	15.2	34.3
Tanzania STEPS 2012	10.9	8.4	13.9

Togo STEPS 2010	4.5	2.3	7.7
Zimbabwe STEPS 2005	10.1	6.9	14.1
Sub-total			
Random pooled ES	13.1	9.8	16.8
15-29			
Benin STEPS 2015	10.2	8.3	12.2
Ethipopia STEPS 2016	5.6	4.7	6.6
Oti 2013	3.8	2.8	5
Kenya STEPS 2015	0.3	0.1	1
Swaziland STEPS 2012	12.8	10.4	15.6
Bouguerra 2007	0.8	0.3	2
Uganda STEPS 2014	0.3	0.1	1
Sub-total			
Random pooled ES	3.6	1.2	7.4
30-44			
Benin STEPS 2015	10.1	8.4	12
Ethipopia STEPS 2016	12	10.5	13.5
Kenya STEPS 2015	3	2	4.3
Swaziland STEPS 2012	16.2	13.3	19.5
Sub-total			
Random pooled ES	9.7	5	15.6
45-59			
Benin STEPS 2015	17.7	14.5	21.3
Ethipopia STEPS 2016	6.6	5	8.5
Kenya STEPS 2015	6.2	3.8	9.3
Liberia STEPS 2011	24.4	19.8	29.4
Ekpenyong 2012	29.4	23.9	35.3
Swaziland STEPS 2012	28.4	24.9	32.1
Zanzibar STEPS 2011	8.7	6.4	11.4
Sub-total			
Random pooled ES	16.1	9.1	24.6
15-24			
Katte 2014	1.8	0	9.6
Guinea STEPS 2009	1.6	0.7	3.3
Ayah 2013	0	0	1.3
Mauritania STEPS 200	3.2	1.6	5.9
Niger STEPS 2008	3.9	2.1	6.5
Ekpenyong 2012	3.9	2.6	5.7
Rwanda STEPS 2015	2.3	1.4	3.5
Prakashandra 2015	11.6	5.1	21.6

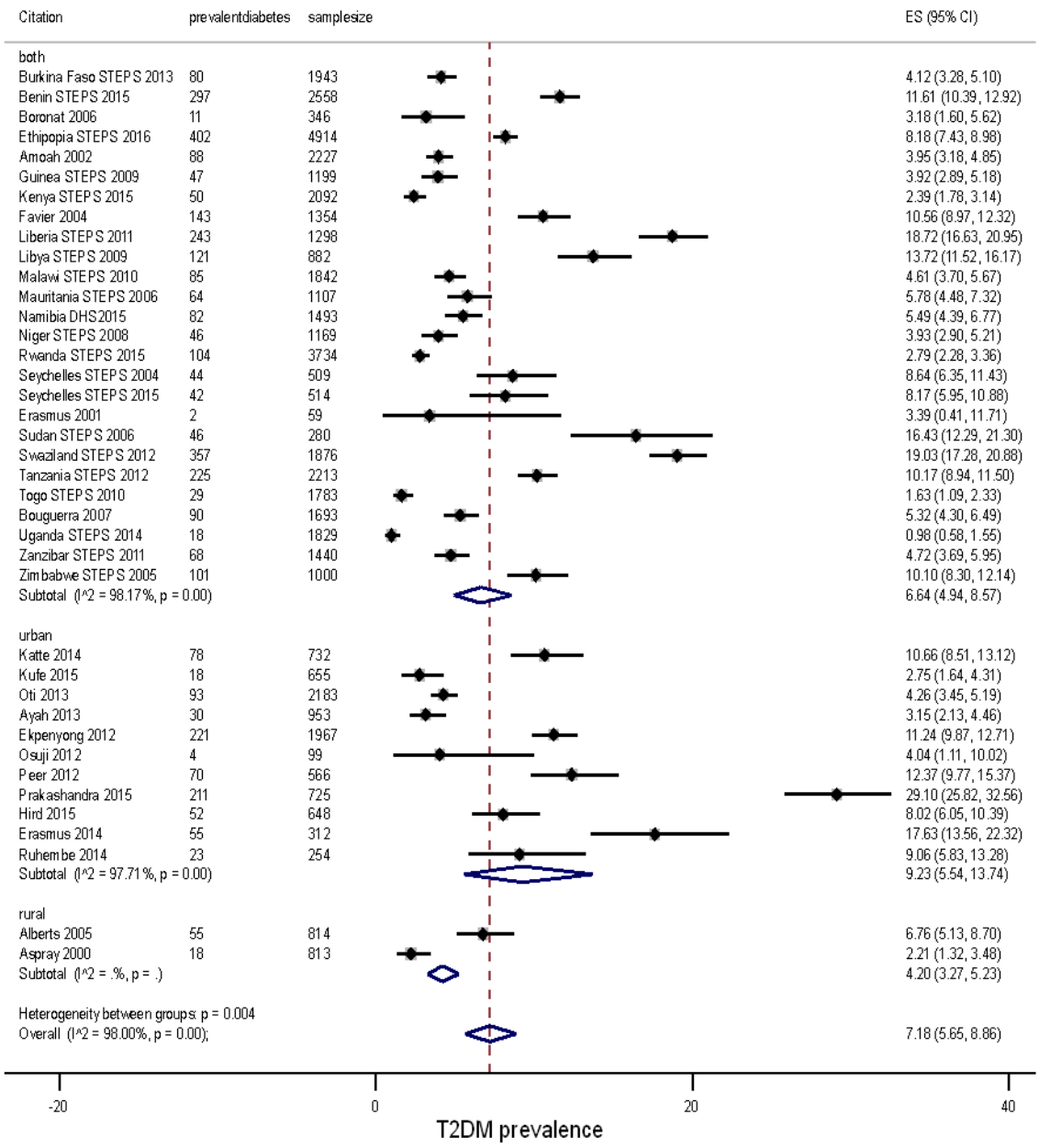
Hird 2015	0	0	1.9
Togo STEPS 2010	1.3	0.5	2.7
Sub-total			
Random pooled ES	2	0.9	3.4
30-39			
Boronat 2006	2.1	0.6	5.4
Oti 2013	4.4	2.9	6.3
Favier 2004	5.9	4.3	7.8
Alberts 2005	3.1	1	7.1
Bouguerra 2007	4.4	2.9	6.3
Sub-total			
Random pooled ES	4.3	3.3	5.5
40-49			
Boronat 2006	4.4	1.8	8.9
Oti 2013	5.8	3.5	9
Favier 2004	16.3	13.4	19.4
Erasmus 2001	3.4	0.4	11.7
Ruhembe 2014	16	9.4	24.7
Bouguerra 2007	12.3	9.5	15.7
Sub-total			
Random pooled ES	9.4	5.4	14.2
25-44			
Liberia STEPS 2011	16.8	14.5	19.3
Zanzibar STEPS 2011	2.4	1.5	3.6
Sub-total			
Random pooled ES	8.4	7.2	9.7
<50			
Osuji 2012	4	1.1	10
15-34			
Aspray 2000	0.5	0	2.7
Aspray 2000	2.2	0.9	4.5
Sub-total			
Random pooled ES	1.4	0.5	2.7
35-54			
Aspray 2000	1.5	0.3	4.3
Aspray 2000	7.9	3.2	15.5
Sub-total			
Random pooled ES	2.9	1.2	5.2

20-40				
Ruhembe 2014		4.5	1.8	9.1
30-49				
Uganda STEPS 2014		1.6	0.9	2.6
Overall				
Random pooled ES	7.2		5.6	8.9

4.5.5. Prevalence of T2DM in urban and rural settings

The highest pooled T2DM prevalence was 9.2% (95%CI 5.5-13.7%, I2 97.7%, p < 0.001) in the 11 studies from urban settings only, 6.6% (4.9-8.6%, I2 98.2%, p < 0.001) in the 26 studies with mixed urban and rural participants, and 4.2% (3.3% - 5.2%, I2 90.7%, p<0.001) in the 2 studies in participants from rural settings only; p=0.1418 (Table 4.1 and Figure 4.5).

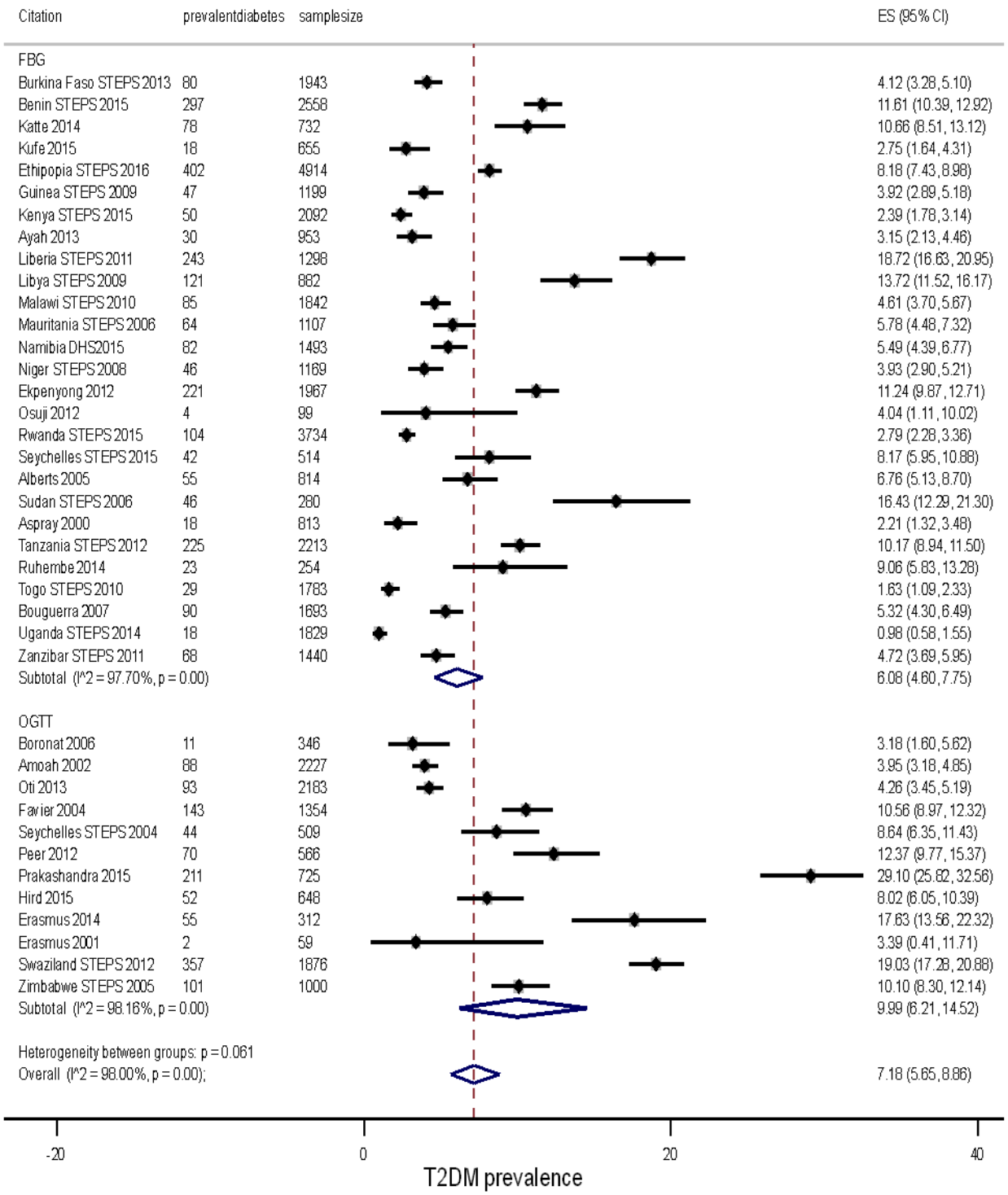
Fig 4.5. Prevalent T2DM in urban and rural settings



4.5.6. Prevalence of T2DM by diagnostic methods

The pooled T2DM prevalence was significantly higher in the 12 studies that used the 2-hour OGTT (10% 95%CI 6.2- 14.5%, I2 97.7%, $p < 0.001$), compared to the pooled T2DM estimate in the 27 studies that used the FPG (6.1% 95%CI 4.6-7.8%, I2 98.2%, $p < 0.001$); ($p = 0.003$) (Table 1 and Figure 4.6).

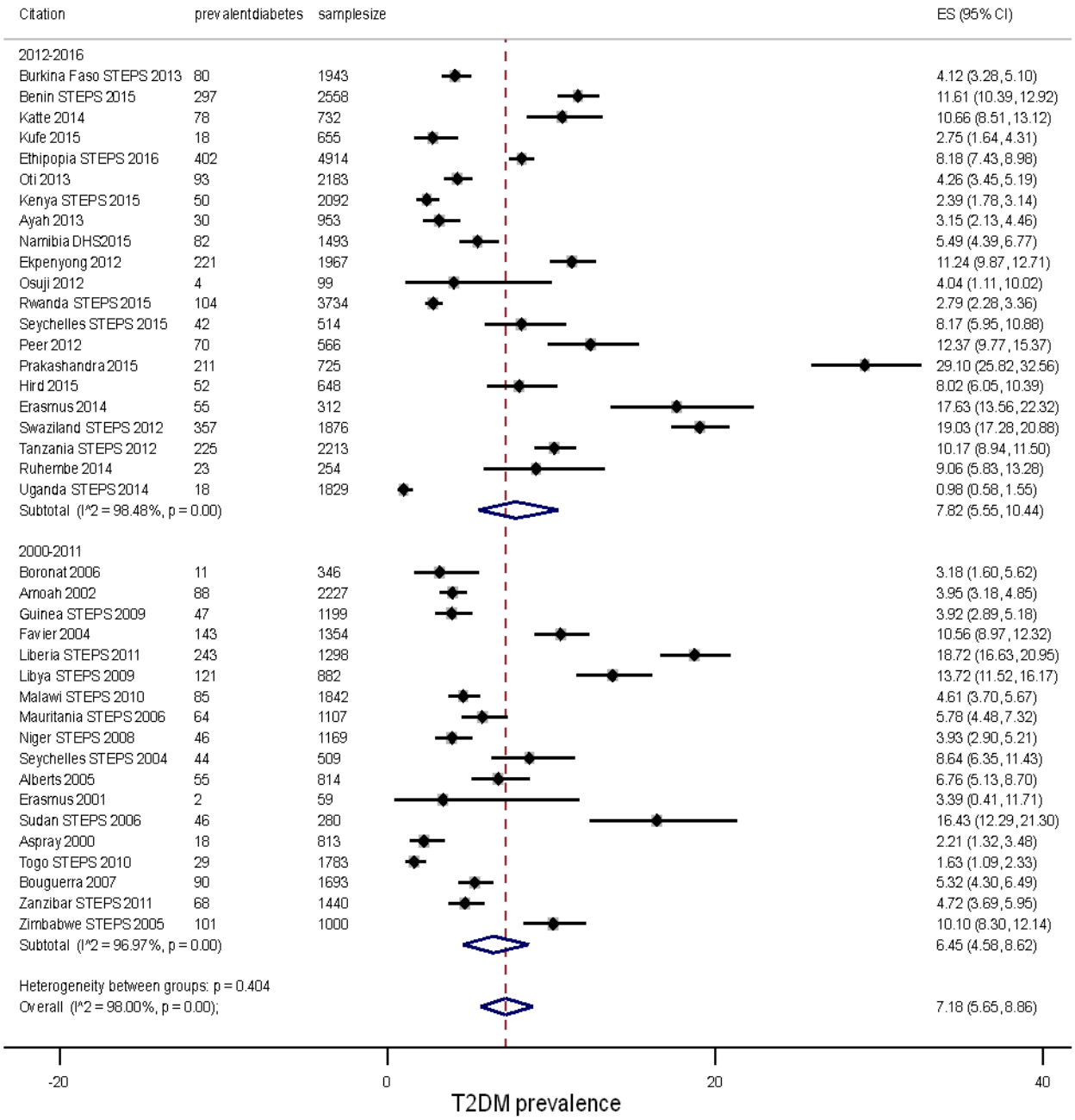
Fig 4.6. Prevalent T2DM comparing OGTT and FPG diagnostic methods



4.5.7. T2DM prevalence by the period of publication

The median year of publishing was 2012. The pooled T2DM prevalence for the 18 studies published during the period 2000 – 2011 was 6.5% (95%CI 4.6-8.6%, I2 98.5%, $p < 0.001$), compared to 7.8% (5.6-10.4%, I2 97.0%, $p < 0.001$) for the 21 studies published during the period 2012 – 2016; $p = 0.175$ (Table 1 and Figure 4.7).

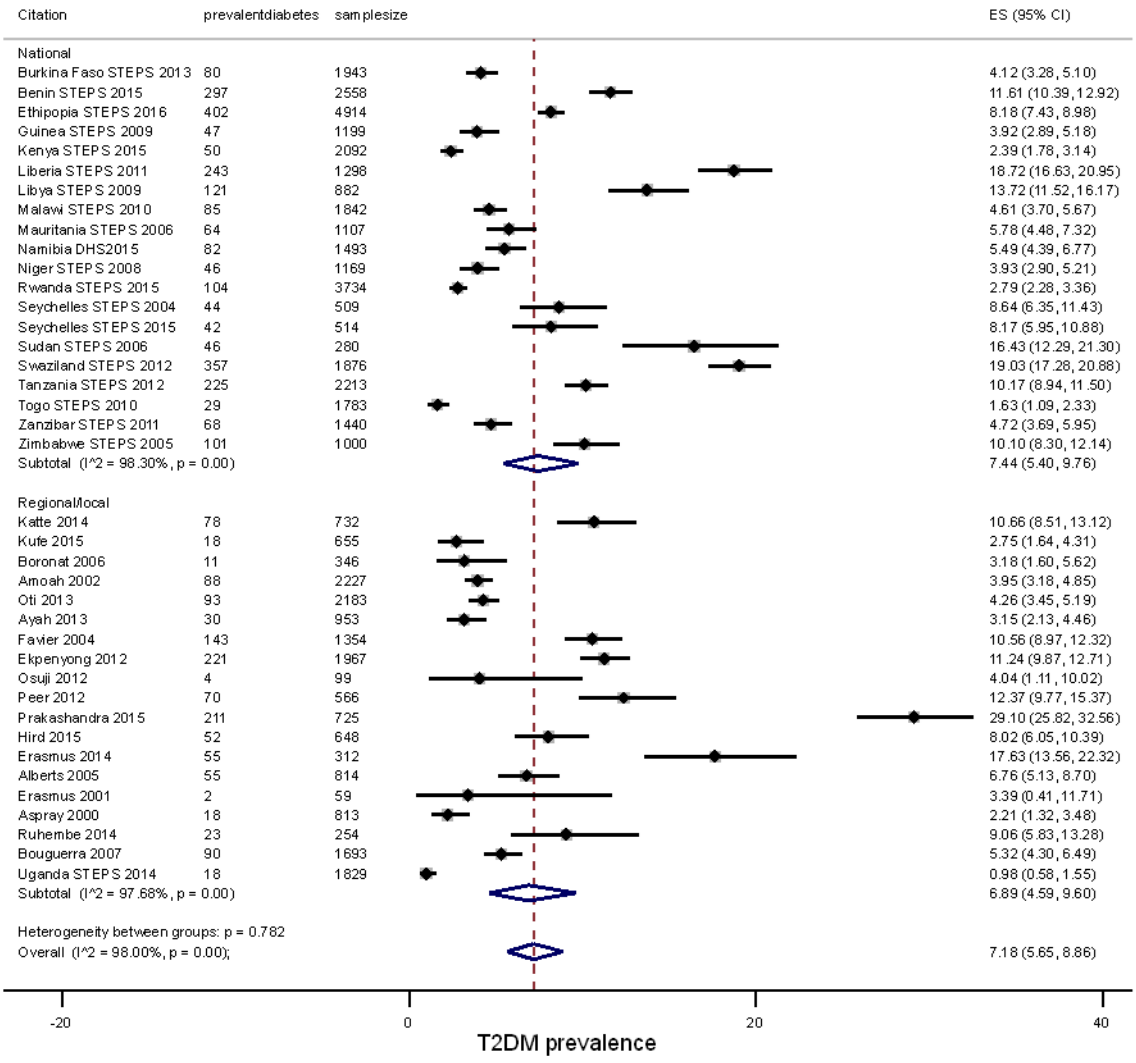
Fig 4.7. Prevalent T2DM comparing studies published during 2000-2011 and studies published during 2012-2016



4.5.8. T2DM prevalence comparing nationally representative and local/regional studies

The prevalence of T2DM was 7.4% (95%CI 5.4- 9.8%, I2 98.3%, p < 0.001) in the nationally representative studies compared to 6.9% (4.6-9.6%, I2 98.3%, p < 0.001) in regional and local studies; p=0.949) (Table 1 and Figure 4.8).

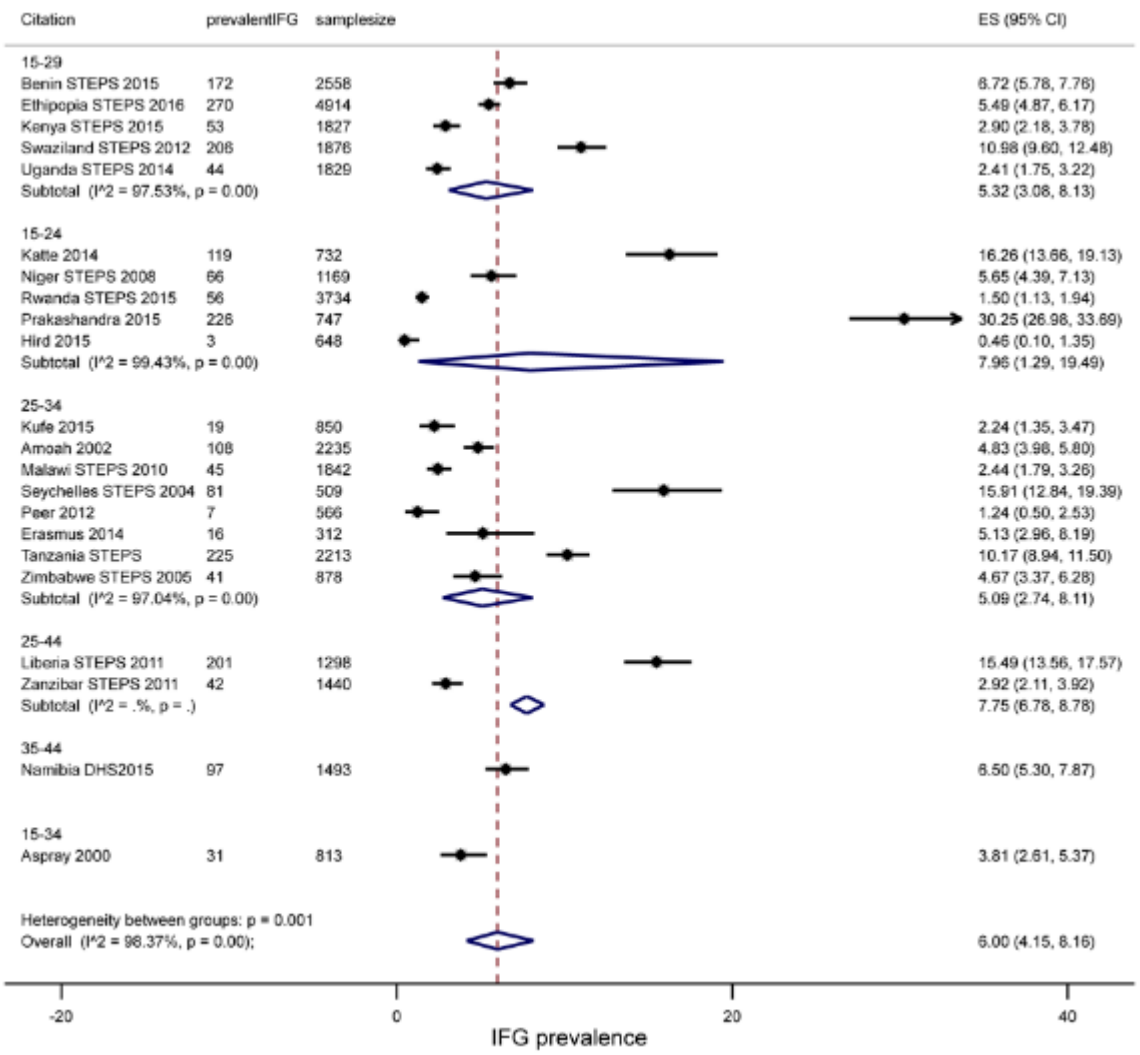
Fig 4.8. Prevalent T2DM comparing nationally representative studies and local/regional studies



4.5.9. IFG prevalence in African women aged 15 – 54 years

There were 22 studies from 17 countries with IFG data; 4 (18%) were South African, 2 (9%) were Cameroonian while the rest were individually from the remaining 15 countries. These studies included 34 483 participants, of which 2128 had IFG. The overall IFG prevalence was 6.0% (95%CI 4.2% - 8.2%) (Figure 4). There was significant heterogeneity in the pooled estimate of IFG ($I^2 = 0.96$, $p < 0.001$). In sub-group analyses, there were no significant differences in the IFG prevalence between different age groups (p=0.870), rural and urban studies (p=0.603) and between the studies published during the period 2000 – 2011 and the studies published during 2012 – 2016 (p=0.998) (Fig 4.7, Figures 4.8& 4.9).

Fig 4.9. Forest plot showing IFG prevalence in African women aged 15-54 years, from studies published during the period 2000-2016



4.5.10. IGT prevalence in African women aged 15 – 54 years

Six studies reported age and gender categorized data on IGT; 5 of the studies were from South Africa and one each from Ghana and Mauritius (Appendix 1). Due to the wide variation in IGT between the studies and the few studies available, a meta-analysis was not performed. The lowest IGT prevalence (0.8%) was in women aged 15-24 years in South Africa in 2008 while the highest prevalence (37%) was in women aged 45-54 years in 2016, both in urban KwaZulu Natal province. In Ghana, IGT

prevalence was 7.3% and 13.0% in women aged 25-34 years and 45-54 years, respectively while in Mauritius, in 2004, IGT prevalence ranged from 5.9% to 15.9% in women aged 20-29 years and 40-49 years, respectively.

4.5.11. Publication bias assessment

We found no evidence of publication bias, as shown in Supplementary Figures 10-12 and using Begg's and Egger tests; for T2DM (Begg's p = 0.07, Egger's p = 0.293) and IFG (Begg's p=0.367, Egger's p=0.202).

4.6. Discussion

The implications of diabetes on the health of both the mother and that of the offspring have been researched in detail elsewhere [9,32-35], and evidence is mounting that this may contribute to the developmental origins of chronic disease in exposed offspring, especially metabolic abnormalities, in later life [36-38]. In this systematic review, we investigated the prevalence of dysglycaemia in African women of childbearing age, as reported in studies published during the period 2000 – 2016. The major findings of this systematic review and meta-analysis of 39 studies are an overall pooled T2DM prevalence of 7%, and overall pooled IFG prevalence of 6% while IGT prevalence ranged from 0.9% to 37%, with substantial heterogeneity in all three outcomes. Subgroup meta-analysis did not explain the heterogeneity observed. Further, we found a significantly higher prevalence of T2DM in studies which used the OGTT compared to studies which used the FPG for the diagnosis of T2DM.

To date, ours is the only systematic review that has assessed the prevalence of T2DM, IFG and IGT in women of childbearing age in Africa, thus limiting our ability to compare our findings with those of existing reviews. Most of the existing reviews have investigated the prevalence of T2DM, IFG and IGT either in both men and women or in all women. In 2015, the IDF used an analytic hierarchical process which included sample representativeness, diagnostic criteria, sample size, and age of study to select studies from which to estimate the T2DM prevalence. Only 13 high-quality data sources from 12 African countries during the years 2000 to 2015 met the stringent criteria for

inclusion [3]. However, there are notable similarities between our data and the IDF data for African women of childbearing age. The T2DM prevalence for African women aged 20 – 54 years from IDF data sources ranged from 0.001% to 32%, compared to our reported data which ranged from 0.5% to 36%. In the IDF data, reported T2DM prevalence in women aged 20-54 years ranged from 0.1% to 23% in Europe, from 1.4% to 43% in the Middle East and North Africa region, 1.3% to 34% in the North American and Caribbean region, 1.5% to 21.5% in the South and Central America region, 1% to 36% in the South East Asia region, while the highest reported T2DM prevalence was reported, as expected, in the Western Pacific region (range 0.1% to 62%).

There are other published systematic reviews which did not investigate the T2DM prevalence in women only but rather in both African men and women [T2DM prevalence ranged from 1% to 12% [39,40]. Hilawe et al. 2013, using a systematic review and meta-analysis of 36 studies, found a T2DM prevalence in African women aged 15 years and above in Sub-Saharan Africa, of 5.9 (95%CI 4.6% – 7.6%), [41] that overlaps with our finding of 7% (95%CI 5.6% – 8.9%). Our review differed from that of Hliawe in several areas. First, in contrast to Hilawe et al, we included only women from 15 to 54 years and not under the age of 15 years or women above 54 years. Second, Hilawe et al. included studies from 1984 until 2011- only 23 studies are common to both reviews. Third, the diagnostic criteria differ: the studies included in the Hilawe et al. review were based on the WHO or American Diabetes Association diagnostic criteria used at the time of the study, while the studies in our review have used a standard WHO 1998 criterion.

More recently, the NCD-Risk Factor Collaboration (NCD-RisC), using more data sources [76 reports], and robust methods, estimated the T2DM in 2014 at 8.9% in all African women [4]. The difference between our prevalence estimate and the NCD-RisC estimate can be partly explained by the inclusion of older women in the later estimate, as T2DM prevalence increases with age. For example, Werfalli et al. 2015 [10], using a systematic review and meta-analysis, found a T2DM prevalence of 15% in African women aged 55 years and above, highlighting the higher prevalence in older women.

We are also limited in comparisons of our IFG and IGT estimates with existing systematic reviews. Very few primary studies have reported IFG and IGT outcomes and, consequently, these are infrequently reported in systematic reviews and meta-analyses. The IDF's 2015 report did not report IFG prevalence in Africa but estimated the IGT prevalence in African men and women at 7.9% (95%CI 4.8 – 21.7), which is in line with our estimate. Bos et al. 2013, [39] in a systematic review of T2DM in North African countries, found an IFG prevalence in all women of 5.1% (n = 1 study) in Tunisia, 2.2% in rural Sudan and 13.1% in urban Egypt (n = 5 studies). The review by Bos et al. included studies published during the period from 1990 to 2012 and included any studies reporting diabetes, regardless of how it was defined.

We identified 22 studies which reported IFG prevalence while only 6 studies reported IGT prevalence. The smaller number of studies reporting IGT reflects that most epidemiological studies use the FPG, instead of the OGTT for the diagnosis of T2DM, IFG and IGT. The time requirement and labour-intensive nature of the OGTT make it an unfavourable tool for diabetes screening in epidemiological studies. However, there is mounting evidence that the two impaired glucose regulation states are distinct entities, with isolated IFG reflecting impaired insulin secretion while isolated IGT reflects impaired insulin sensitivity [42,43]. Furthermore, the use of the FPG only for the identification of impaired glucose regulation states could result in up to 20% of IGT cases being missed [43]. Several studies have shown that disorders in insulin secretion and sensitivity are already present when the FPG is within normal ranges and are more likely to be detected as IGT [44,45]. Although it has been suggested (1) that HbA1c be used for screening for impaired carbohydrate metabolism, as it is more convenient, faster, doesn't require prior fasting and is becoming more affordable, there is no conclusive evidence on the HbA1c cut-off points that correspond to either IFG, IGT or both, in African populations.

Risk factors for T2DM in African women of childbearing age are on the increase, driven by the nutrition transition, urbanization and decreasing physical activity [46]. Several studies have shown that African women are more insulin resistant than their Caucasian counterparts, while antiretroviral therapy for HIV contributes to more fat

deposition in affected women [46]. In Sub-Saharan Africa, HIV positive women are more likely to be young and overweight or obese [46]. Further, evidence suggests that the mean BMI in African women increased from 21.9kg/m^2 in 1980 to 24.9kg/m^2 in 2014 [4]. All these factors suggest that we may see a high future diabetes burden in African women of childbearing age, compared to the present prevalence.

Africa is one of the continents where the IDF expects the greatest increases in the numbers of people with diabetes to occur between the years 2015 and 2035. African health systems are already overburdened by infectious diseases such as HIV, TB and malaria while at the same time catering for people already diagnosed with non-communicable diseases, diabetes included [47]. Prevention of new cases is, therefore, a priority. Prevention of diabetes can be achieved using either a population-wide approach or a “screen and treat” approach or a combination of both. The population-wide approach targets everyone through public health policies, for example, the sugar tax to help reduce overweight and obesity, advocated by the W.H.O. [48], which has already been implemented in several European countries, such as Norway, Ireland and the United Kingdom, while in Africa, the tax was introduced in South Africa in 2017.

On the other hand, the “screen and treat”, used in various Diabetes Prevention Programs, involves identifying at-risk groups, such as people with IFG, IGT or GDM, and offer targeted interventions, which are usually pharmacological, or lifestyle change interventions or a combination of both. Despite the success of various diabetes prevention programs [49], in the USA [50], China [51] and India [52], among other countries, studies investigating the effectiveness of either pharmacological or lifestyle change interventions in delaying or preventing T2DM in African women are scarce. In 2017, the WHO, in the Montevideo RoadMap on non-communicable diseases [NCDs] [7], stressed the double impact of non-communicable diseases such as T2DM, where women may become sufferers and unpaid caregivers to family members with chronic NCDs. In the same policy document, the WHO advocates for gender-based approaches to the prevention of NCDs. The prevention of T2DM in women of childbearing age is one such area where a gender-based approach will be appropriate. Women with IFG, IGT and GDM are special at-risk populations for T2DM. While we did

not investigate the prevalence of GDM in this review, systematic reviews published in 2014 and 2015 found reported GDM prevalence as high as 14% in African women [12,53]. Identifying women with IGT and IFG in Africa is not part of routine care or national programs. On the other hand, many African health settings screen women for GDM, and perhaps this is a group with which “screen and treat” approaches could be used, to prevent or delay future T2DM, particularly in the maternal and child health context. Research is needed to investigate the effectiveness of lifestyle, and even pharmacological, interventions in delaying or preventing T2DM in African women with IFG, IGT and GDM, in the context of limited resources and possibly different modifiable environmental risk factors to those in the higher income countries.

A strength of the current study is that it is based on a larger number of population-based surveys from a broader range of African countries than previous estimates. However, the quality of the included surveys, the inclusion of studies with small sample sizes, methods of screening for dysglycaemia and the representativeness of the data remain of concern. Of the 39 studies included in our meta-analysis, 20 could be described as nationally representative. All the 20 studies, except for the Namibian Demographic and Health Survey [28] were WHO STEPWise surveys. Further, we acknowledge that variations in economic development may explain some of the heterogeneity across the studies and that our estimate may not be representative of the prevalence across the African continent due to this. Included studies rarely report data on the detection, treatment and control of diabetes/dysglycaemia as well as prevalent chronic diabetes complications in the surveyed populations. Therefore, the current review is unable to comment on the performance of health systems in preventing and controlling diabetes in African women of childbearing age.

We planned to use the WHO definition of women aged 15-49 years for this review, but as most studies utilized the 15-24, 25-34, 35-44, 45-54 years age group system for operative reasons, we capped the upper age at 54 years. We likely included a proportion of women who were not of childbearing age in the review, and consequently, that we may have overestimated the T2DM, IFG and IGT prevalence in our analysis.

4.7. Conclusions

Our study demonstrates that T2DM, IFG and IGT prevalence is high in African women of childbearing age. Due to the long and short-term implications, on both the mother and child of any form of diabetes, it is imperative to develop interventions targeted at at-risk women, within the maternal and child health framework.

Funding

There are no funders to report for this project.

Competing interests

The authors declare no competing interests.

Acknowledgements

Dr Jennifer Hirst, Nuffield Department of Primary Care Health Sciences, University of Oxford – for assistance with formatting forest plots

Mr Shakespear Makamanzi & Dr Alfred Musekiwa, CDC Pretoria – for assistance with plotting the map of pooled T2DM prevalence in African women aged 15 – 54 years per country.

Data sharing statement

All data relevant to the study are included in the article or uploaded as supplementary information. This is a systematic review and meta-analysis of published data. The data may be available in the primary studies.

4.8. References

1. NCD Risk Factor Collaboration [NCD-RisC]. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. The Lancet 2016 4/9–15;387[10027]:1513-1530.

2. Ogurtsova K, da Rocha Fernandes J, Huang Y, Linnenkamp U, Guariguata L, Cho N, et al. IDF Diabetes Atlas: Global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract 2017; 128:40-50.
3. Rahelic D. 7th Edition of Idf Diabetes Atlas--Call for Immediate Action. Lijec Vjesn 2016 JanFeb;138[1-2]:57-58.
4. Kengne AP, Bentham J, Zhou B, Peer N, Matsha TE, Bixby H, et al. Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. Int J Epidemiol 2017.
5. International Diabetes Federation. IDF Diabetes Atlas, sixth edn. 2015; Available at: https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/134-idf-diabetes-atlas-8thedition.html Accessed 13/12, 2018.
6. World Health Organisation. Sustainable Development Goal 3 - Ensure healthy lives and promote well-being for all at all ages. 2016; Available at: https://sustainabledevelopment.un.org/SDG3. Accessed 31 October 2017.
7. World Health Organisation. MONTEVIDEO ROADMAP 2018-2030 ON NCDs AS A SUSTAINABLE DEVELOPMENT PRIORITY. 2017; Available at: http://www.who.int/ncds/governance/montevideo-roadmap.pdf?ua=1. Accessed 31 October 2017.
8. World Health Organisation. Sexual and reproductive health. 2015; Available at: http://www.who.int/reproductivehealth/topics/infertility/definitions/en/. Accessed 11/13, 2015.
9. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycaemia. Diabetes Care 2008 Feb;31[2]:340-346.
10. Werfalli M, Engel ME, Musekiwa A, Kengne AP, Levitt NS. The prevalence of type 2 diabetes among older people in Africa: a systematic review. The Lancet Diabetes & Endocrinology 2015.
11. Hall V, Thomsen RW, Henriksen O, Lohse N. Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review. BMC Public Health 2011;11[1]:564.

12. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PloS one 2014;9[6]: e97871.
13. Mwanri AW, Kinabo J, Ramaiya K, Feskens EJ. Gestational diabetes mellitus in subSaharan Africa: systematic review and metaregression on prevalence and risk factors. Tropical Medicine & International Health 2015;20[8]:983-1002.
14. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. 2013.
15. Chivese T, Mahmoud W, Magodoro I, Kengne AP, Norris SA, Levitt NS. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000-2016: protocol of a systematic review and meta-analysis. BMJ Open 2016 Dec 13;6[12]: e012255-2016-012255. [16] Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol 2012;65[9]:934-939.
16. Consultation W. Definition, diagnosis and classification of diabetes mellitus and its complications. 1999.
17. Stata Corporation. College Station [TX]. Stata Press 2016.
18. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Archives of Public Health 2014;72[1]:39.
19. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. Contemporary clinical trials 2007;28[2]:105-114.
20. Borenstein MH, Higgins L, Rothstein J. HR [2009]. Introduction to meta-analysis. Chichester, England: Wiley.doi 2009;10:9780470743386.
21. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343: d5928.
22. Egger M, Smith GD. Meta-Analysis. Potentials and promise. BMJ 1997 Nov 22;315[7119]:1371-1374.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994:1088-1101.

24. Meiloud G, Arfa I, Kefi R, Abdelhamid I, Veten F, Lasram K, et al. Type 2 diabetes in Mauritania: Prevalence of the undiagnosed diabetes, influence of family history and maternal effect. Primary care diabetes 2013;7[1]:19-24.
25. Alberts M, Urdal P, Steyn K, Stensvold I, Tverdal A, Nel JH, et al. Prevalence of cardiovascular diseases and associated risk factors in a rural black population of South Africa. European Journal of Cardiovascular Prevention & Rehabilitation 2005;12[4]:347-354.
26. Osuji CU, Nzerem BA, Dioka CE, Meludu SC, Onwubuya EI. Prevalence of diabetes mellitus in a group of women attending “August meeting” at Naze South East Nigeria. Journal of Diabetes mellitus 2012;2[03]:321.
27. Ndishishi A. Namibia Demographic and Health Survey 2013. Namibia Demographic and Health Survey 2013. 2014.
28. Shikur B, Firdu N, Shimels T, Tesfaye T. Prevalence and factors associated with diabetes mellitus and impaired fasting glucose level among members of federal police commission residing in Addis Ababa, Ethiopia. BMC endocrine disorders 2016;16[1]:68.
29. Sabir A, Ohwovoriole A, Isezuo S, Fasanmade O, Abubakar S, Iwuala S. Type 2 diabetes mellitus and its risk factors among the rural Fulanis of Northern Nigeria. Annals of African medicine 2013;12[4]:217.
30. Prakaschandra DR, Esterhuizen TM, Motala AA, Gathiram P, Naidoo DP. High prevalence of cardiovascular risk factors in Durban South African Indians: The Phoenix Lifestyle Project. South African Medical Journal 2016;106[3]:284-289.
31. Boerschmann H, Pfluger M, Henneberger L, Ziegler AG, Hummel S. Prevalence and predictors of overweight and insulin resistance in offspring of mothers with gestational diabetes mellitus. Diabetes Care 2010 Aug;33[8]:1845-1849.
32. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005 Mar;115[3]: e290-6.
33. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, et al. Overweight and the metabolic syndrome in adult offspring of women with diet-

treated gestational diabetes mellitus or type 1 diabetes. The Journal of Clinical Endocrinology & Metabolism 2009;94[7]:2464-2470.

34. Coustan DR, Lowe LP, Metzger BE, Dyer AR. The Hyperglycaemia and Adverse Pregnancy Outcome [HAPO] study: paving the way for new diagnostic criteria for gestational diabetes mellitus. Obstet Gynecol 2010;202[6]:654. e1-654. e6.
35. Adair LS, Fall CH, Osmond C, Stein AD, Martorell R, Ramirez-Zea M, et al. Associations of linear growth and relative weight gain during early life with adult health and human capital in countries of low and middle income: findings from five birth cohort studies. The Lancet 2013;382[9891]:525-534.
36. Baidal JAW, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 days: a systematic review. Am J Prev Med 2016;50[6]:761-779.
37. Barker DJ. Developmental origins of chronic disease. Public Health 2012;126[3]:185-189. [39] Bos M, Agyemang C. Prevalence and complications of diabetes mellitus in Northern Africa, a systematic review. BMC Public Health 2013 Apr 25; 13:387-2458-13-387.
38. Hall V, Thomsen RW, Henriksen O, Lohse N. Diabetes in Sub Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review. BMC Public Health 2011 Jul 14; 11:564-2458-11-564.
39. Hilawe EH, Yatsuya H, Kawaguchi L, Aoyama A. Differences by sex in the prevalence of diabetes mellitus, impaired fasting glycaemia and impaired glucose tolerance in sub-Saharan Africa: a systematic review and meta-analysis. Bull World Health Organ 2013;91[9]:671-682D.
40. Bartoli E, Fra G, Schianca GC. The oral glucose tolerance test [OGTT] revisited. Eur J Intern Med 2011;22[1]:8-12.
41. Carnevale Schianca GP, Rossi A, Sainaghi PP, Maduli E, Bartoli E. The significance of impaired fasting glucose versus impaired glucose tolerance: importance of insulin secretion and resistance. Diabetes Care 2003 May;26[5]:1333-1337.

42. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo R. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism [SAM] study. Diabetologia 2004;47[1]:31-39.
43. Shyong Tai E, GOH SY, LEE JJ, WONG M, HENG D, HUGHES K, et al. Lowering the criterion for impaired fasting glucose: Impact on disease prevalence and associated risk of diabetes and ischemic heart disease. Diabetes Care 2004;27[7]:1728-1734.
44. Goedecke JH, Mtintsilana A, Dlamini SN, Kengne AP. Type 2 diabetes mellitus in African women. Diabetes Res Clin Pract 2017; 123:87-96.
45. Mayosi BM, Benatar SR. Health and Health Care in South Africa—20 Years after Mandela. N Engl J Med 2014;371[14]:1344-1353.
46. World Health Organization. WHO urges global action to curtail consumption and health impacts of sugary drinks. 2016; Available at: http://www.who.int/mediacentre/news/releases/2016/curtail-sugary-drinks/en/. Accessed 03/29, 2018.
47. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007 Feb 10;334[7588]:299.
48. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: The Diabetes Prevention Program Outcomes Study. The Lancet Diabetes & Endocrinology 2015.
49. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. The Lancet 2008;371[9626]:1783-1789.
50. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar A, Vijay V. The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance [IDPP-1]. Diabetologia 2006;49[2]:289-297.

51. Mwanri AW, Kinabo J, Ramaiya K, Feskens EJ. Gestational diabetes mellitus in subSaharan Africa: systematic review and metaregression on prevalence and risk factors. Tropical Medicine & International Health 2015.
52. Ministry of Health Algeria. Mesure des facteurs de risque des maladies non transmissibles dans deux milayas pilates en Algeria 2003 report. 2005; Available at: http://www.who.int/chp/steps/algeria/en/. Accessed 12/15, 2015.
53. Evaristo-Neto AD, Foss-Freitas MC, Foss MC. Prevalence of diabetes mellitus and impaired glucose tolerance in a rural community of Angola. Diabetology & metabolic syndrome 2010;2[1]:63.
54. Capingana DP, Magalhaes P, Silva AB, Goncalves MA, Baldo MP, Rodrigues SL, et al. Prevalence of cardiovascular risk factors and socioeconomic level among public-sector workers in Angola. BMC Public Health 2013 Aug 7; 13:732-2458-13-732.
55. Ministère de la Santé République du Bénin. Rapport final de l'enquête pour la surveillance des facteurs de risque des maladies non transmissibles par l'approche ''STEPSwise'' de l'OMS ENQUETE ''STEPS 2008'' au Bénin. 2008; Available at: http://www.who.int/chp/steps/2008_STEPS_Report_Benin.pdf?ua=1. Accessed 12/15, 2015.
56. Ministère de la Santé République du Bénin. Rapport final de l'enquête pour la surveillance des facteurs de risque des maladies non transmissibles par l'approche ''STEPSwise'' de l'OMS ENQUETE ''STEPS 2015'' au Bénin. 2017; Available at:
57. http://www.who.int/chp/steps/2008_STEPS_Report_Benin.pdf?ua=1. Accessed 01/17, 2017. [59] Ministere de la Sante Burkina Faso. Rapport de lengquete nationale sur la prevalence des principaux facteurs de risques communs aux maladies non transmissibles au Burkina Faso enquete STEPS 2013. 2014; Available at: http://www.who.int/chp/steps/BurkinaFaso_2013_STEPS_Report.pdf?ua=1. Accessed 12/15, 2015.
58. Sobngwi E, Mbanya JC, Unwin NC, Kengne AP, Fezeu L, Minkoulou EM, et al. Physical activity and its relationship with obesity, hypertension and diabetes in urban and rural Cameroon. Int J Obes Relat Metab Disord 2002 Jul;26[7]:1009-1016.

59. Health of Populations in Transition [HoPiT] Research Group - Cameroon. Cameroon Burden of Diabetes [CamBoD] Project - Baseline Survey Report 2004. 2004; Available at: http://www.who.int/chp/steps/STEPS_Cameroon.pdf?ua=1. Accessed 12/15, 2015.
60. Katte JC, Dzudie A, Sobngwi E, Mbong EN, Fetse GT, Kouam CK, et al. Coincidence of diabetes mellitus and hypertension in a semi-urban Cameroonian population: a cross-sectional study. BMC Public Health 2014 Jul 8; 14:696-2458-14-696.
61. Kufe CN, Klipstein-Grobusch K, Leopold F, Assah F, Ngufor G, Mbeh G, et al. Risk factors of impaired fasting glucose and type 2 diabetes in Yaoundé, Cameroon: a cross sectional study. BMC Public Health 2015;15[1]:59.
62. Ministère de la Santé République Démocratique du Congo, Enquete sur les facteurs des maladies non transmissibles, Selon Lapproche STEPS 2005. 2006; Available at: http://www.who.int/chp/steps/STEPS_DRC_Final.pdf?ua=1. Accessed 12/15, 2015.
63. Katchunga PB, Cikomola J, Tshongo C, Baleke A, Kaishusha D, Mirindi P, et al. Obesity and diabetes mellitus association in rural community of Katana, South Kivu, in Eastern Democratic Republic of Congo: Bukavu Observ Cohort Study Results. BMC endocrine disorders 2016;16[1]:60.
64. Ellabany E, Abel-Nasser M. Community based survey study on noncommunicable diseases and their risk factors, Egypt, 2005-2006. World Health Organization.Report number: STEPS_Report_Egypt_2005-06 2006.
65. Ethiopian Public Health Institute. Ethiopia steps report on risk factors for chronic noncommunicable diseases and prevalence of selected NCDS, 2015. 2016; Available at: http://www.who.int/chp/steps/Ethiopia_2015_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017. [68] Tesfaye T, Shikur B, Shimels T, Firdu N. Prevalence and factors associated with diabetes mellitus and impaired fasting glucose level among members of federal police commission residing in Addis Ababa, Ethiopia. BMC Endocrine Disorders 2016;16.
66. Ministere de la sante publique et de l'hygiene publique Gabon. Enquête sur les facteurs de risque des maladies non transmissibles à Libreville et Owendo 2009.

2009; Available at: http://www.who.int/chp/steps/2009_STEPS_Report_Gabon.pdf?ua=1. Accessed 12/15, 2015.

67. Amoah AG, Owusu SK, Adjei S. Diabetes in Ghana: a community-based prevalence study in Greater Accra. Diabetes Res Clin Pract 2002;56[3]:197-205.
68. Obirikorang C, Osakunor DNM, Anto EO, Amponsah SO, Adarkwa OK. Obesity and Cardio-Metabolic Risk Factors in an Urban and Rural Population in the Ashanti Region-Ghana: A Comparative Cross-Sectional Study. PloS one 2015;10[6]: e0129494.
69. Balde NM, Diallo I, Balde MD, Barry IS, Kaba L, Diallo MM, et al. Diabetes and impaired fasting glucose in rural and urban populations in Futa Jallon [Guinea]: prevalence and associated risk factors. Diabetes Metab 2007 Apr;33[2]:114-120.
70. Ministry of Health Guinea. Guinée [Conakry et Basse Guinée] Enquête STEPS 2009; Available at: http://www.who.int/chp/steps/guinea/en/. Accessed 01/17, 2017.
71. Ministry of Health Kenya. Kenya STEPWise survey for non-communicable diseases risk factors 2015 report. 2016; Available at: http://www.who.int/chp/steps/Kenya_2015_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.
72. Ayah R, Joshi MD, Wanjiru R, Njau EK, Otieno CF, Njeru EK, et al. A population-based survey of prevalence of diabetes and correlates in an urban slum community in Nairobi, Kenya. BMC Public Health 2013;13[1]:371.
73. Christensen DL, Friis H, Mwaniki D, Kilonzo B, Tetens I, Boit M, et al. Prevalence of glucose intolerance and associated risk factors in rural and urban populations of different ethnic groups in Kenya. Diabetes Res Clin Pract 2009;84[3]:303-310.
74. Wanjihia V, Kiplamai FK, Waudo JN, Boit MK. Post-Prandia glucose levels and consumption of Omega 3 fatty acids and saturated fats among two rural populations in Kenya. East Afr Med J 2009;86[6]:259-266.
75. Ministry of Health and Social Welfare Republic of Liberia. Liberia Chronic Disease Risk Factor Surveillance 2011. 2011; Available at: http://www.who.int/chp/steps/Liberia_2011_STEPS_Report.pdf?ua=1. Accessed 12/15, 2015.

76. Ministry of Health Libya, WHO. Libya STEPS Noncommunicable Disease Risk Factors Survey 2009 [in Arabic]. 2009; Available at: http://www.who.int/chp/steps/2009_STEPS_Libya.pdf?ua=1. Accessed 12/15, 2015.
77. Ministry of Malawi, WHO. Malawi National STEPS Survey for Chronic Non-Communicable Diseases and their Risk Factors, WHO Final Report 2009. 2009; Available at: http://www.who.int/chp/steps/Malawi_2009_STEPS_Report.pdf?ua=1. Accessed 12/15, 2015.
78. Ministere De La Sante Republique Islamique De Mauritanie, WHO. Enquête sur les Maladies non Transmissibles selon l'approche STEPwise de l'OMS: étude de l'hypertension arterielle, du diabete et des autres facteurs de risque, rapport d'enquête 2007. 2007; Available at: http://www.who.int/chp/steps/STEPS_Report_Mauritania.pdf?ua=1. Accessed 12/15, 2015.
79. Ministry of Health & Quality of Life, WHO. Mauritius non-communicable diseases survey 2004. 2004; Available at: http://www.who.int/chp/steps/STEPS_Report_Mauritius.pdf?ua=1. Accessed 12/15, 2015.
80. Solet J, Baroux N, Pochet M, Benoit-Cattin T, De Montera A, Sissoko D, et al. Prevalence of type 2 diabetes and other cardiovascular risk factors in Mayotte in 2008: the MAYDIA study. Diabetes Metab 2011;37[3]:201-207.
81. Silva-Matos C, Gomes A, Azevedo A, Damasceno A, Prista A, Lunet N. Diabetes in Mozambique: prevalence, management and healthcare challenges. Diabetes Metab 2011;37[3]:237-244.
82. Tazi MA, Abir-Khalil S, Chaouki N, Cherqaoui S, Lahmouz F, Srairi JE, et al. Prevalence of the main cardiovascular risk factors in Morocco: results of a National Survey, 2000. J Hypertens 2003 May;21[5]:897-903.
83. Ministere De La Sante Republique Du Niger, WHO. Mesure des facteurs de risque des maladies non transmissibles Au Niger [Approche Step"wise" de l'OMS] 2008. 2008; Available at: http://www.who.int/chp/steps/2007_STEPS_Report_Niger.pdf?ua=1. Accessed 12/15, 2015.

84. Nyenwe EA, Odia OJ, Ihekwaba AE, Ojule A, Babatunde S. Type 2 diabetes in adult Nigerians: a study of its prevalence and risk factors in Port Harcourt, Nigeria. Diabetes Res Clin Pract 2003;62[3]:177-185.
85. Oladapo OO, Salako L, Sodiq O, Shoyinka K, Adedapo K, Falase AO. A prevalence of cardiometabolic risk factors among a rural Yoruba south-western Nigerian population: a population-based survey. Cardiovasc J Afr 2010 Jan-Feb;21[1]:26-31.
86. Ejim EC, Okafor CI, Emehel A, Mbah AU, Onyia U, Egwuonwu T, et al. Prevalence of cardiovascular risk factors in the middle-aged and elderly population of a Nigerian rural community. J Trop Med 2011; 2011:308687.
87. Ojewale LY, Adejumo PO. Type 2 diabetes mellitus and impaired fasting blood glucose in urban south western Nigeria. Int J Diabetes Metab 2012; 21:1-9.
88. Ekpenyong CE, Akpan U, Ibu JO, Nyebuk DE. Gender and age specific prevalence and associated risk factors of type 2 diabetes mellitus in Uyo metropolis, South Eastern Nigeria. Diabetologia Croatica 2012;41[1].
89. Okpechi IG, Chukwuonye II, Tiffin N, Madukwe OO, Onyeonoro UU, Umeizudike TI, et al. Blood pressure gradients and cardiovascular risk factors in urban and rural populations in Abia State South Eastern Nigeria using the WHO STEPwise approach. PLoS One 2013;8[9]: e73403.
90. Enang O, Otu A, Essien O, Okpara H, Fasanmade O, Ohwovoriole A, et al. Prevalence of dysglycemia in Calabar: a cross-sectional observational study among residents of Calabar, Nigeria. BMJ Open Diabetes Research and Care 2014;2[1]: e000032.
91. Nwatu C, Ofoegbu E, Unachukwu C, Young E, Okafor C, Okoli C. Prevalence of prediabetes and associated risk factors in a rural Nigerian community. International journal of diabetes in developing countries 2016;36[2]:197-203.
92. Oluyombo R, Olamoyegun MA, Olaifa O, Iwuala SO, Babatunde OA. Cardiovascular risk factors in semi-urban communities in southwest Nigeria: Patterns and prevalence. Journal of epidemiology and global health 2015;5[2]:167-174.

93. Tagurum Y, Okoh E, Inalegwu E, Ozoilo J, Banwat M, Zoakah A. Non-communicable diseases: prevalence and risk factors among adults in a rural community in Plateau State, Nigeria. Int J Biomed Res 2015; 6:228-234.
94. Oguoma VM, Nwose EU, Skinner TC, Digban KA, Onyia IC, Richards RS. Prevalence of cardiovascular disease risk factors among a Nigerian adult population: relationship with income level and accessibility to CVD risks screening. BMC Public Health 2015;15[1]:397.
95. Ejike CE, Uka NK, Nwachukwu SO. Diabetes and pre-diabetes in adult Nigerians: Prevalence, and correlations of blood glucose concentrations with measures of obesity. African Journal of Biochemistry Research 2015;9[3]:55-60.
96. Ministry of health Rwanda, WHO. Rwanda Non-communicable Diseases Risk Factors Report November 2015. 2015; Available at: http://www.who.int/chp/steps/Rwanda_2012_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.
97. Favier F, Jaussent I, Le Moullec N, Debussche X, Boyer M, Schwager J, et al. Prevalence of Type 2 diabetes and central adiposity in La Reunion Island, the REDIA Study. Diabetes Res Clin Pract 2005;67[3]:234-242.
98. Enquête de prévalence des facteurs de risque cardiovasculaire en population générale à Saint-Louis [Sénégal]. Annales de Cardiologie et d'Angéiologie: Elsevier; 2013.
99. Duboz P, Boëtsch G, Gueye L, Macia E. Type 2 diabetes in a Senegalese rural area. World Journal of Diabetes 2017;8[7]:351.
100. Bovet P, William J, Viswanathan B, Madeleine G, Romain S, Yerly P, et al. The Seychelles Heart Study 2004: methods and main findings. Victoria, Republic of Seychelles: Ministry of Health and Social Development 2007.
101. Bovet P, Viswanathan B, Louange M, Gedeon J. National Survey of Noncommunicable Diseases in Seychelles 2013–2014 [Seychelles Heart Study IV]: Methods and main findings. Retrieved from Victoria, Seychelles: http://www.who.int/chp/steps/Seychelles_2013_STEPS_Report.pdf 2015.

102. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS. Rising diabetes prevalence among urban-dwelling black South Africans. PLoS One 2012;7[9]: e43336.
103. Erasmus RT, Soita DJ, Hassan MS, Blanco-Blanco E, Vergotine Z, Kengne AP, et al. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. SAMJ: South African Medical Journal 2012;102[11]:841-844.
104. Motala AA, Esterhuizen T, Gouws E, Pirie FJ, Omar MA. Diabetes and other disorders of glycemia in a rural South African community: prevalence and associated risk factors. Diabetes Care 2008 Sep;31[9]:1783-1788.
105. Alberts M, Urdal P, Steyn K, Stensvold I, Tverdal A, Nel JH, et al. Prevalence of cardiovascular diseases and associated risk factors in a rural black population of South Africa. Eur J Cardiovasc Prev Rehabil 2005 Aug;12[4]:347-354.
106. Erasmus R, Blanco EB, Okesina A, Matsha T, Gqweta Z, Mesa J. Prevalence of diabetes mellitus and impaired glucose tolerance in factory workers from Transkei, South Africa. South African Medical Journal 2001;91[2]:157-160.
107. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, et al. The South African National Health and Nutrition Examination Survey, 2012: SANHANES-1: the health and nutritional status of the nation: HSRC press; 2014.
108. Hird TR, Pirie FJ, Esterhuizen TM, O'Leary B, McCarthy MI, Young EH, et al. Burden of diabetes and first evidence for the utility of HbA1c for diagnosis and detection of diabetes in Urban Black South Africans: the Durban diabetes study. PloS one 2016;11[8]: e0161966.
109. Ministry of Health Sudan, WHO. STEPS noncommunicable disease risk factors survey [Khartoum state] 2005. 2005; Available at: http://www.who.int/chp/steps/STEPS_Report_Sudan2005.pdf?ua=1. Accessed 12/15, 2015.
110. Elmadhoun WM, Noor SK, Ibrahim AAA, Bushara SO, Ahmed MH. Prevalence of diabetes mellitus and its risk factors in urban communities of north Sudan: population-based study. Journal of diabetes 2016;8[6]:839-846.

111. Ministry of Health Swaziland Government, WHO. WHO STEPS Noncommunicable Disease Risk Factor Surveillance Report, Swaziland 2014. 2014; Available at: http://www.who.int/chp/steps/Swaziland_2014_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.
112. Aspray TJ, Mugusi F, Rashid S, Whiting D, Edwards R, Alberti KG, et al. Rural and urban differences in diabetes prevalence in Tanzania: the role of obesity, physical inactivity and urban living. Trans R Soc Trop Med Hyg 2000;94[6]:637-644.
113. Ministry of Health and Social Welfare Tanzania, WHO. Tanzania Steps Survey Report 2012. 2012; Available at: http://www.who.int/chp/steps/UR_Tanzania_2012_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.
114. Miller BJ. Type 2 diabetes mellitus in the AruMeru district of northern Tanzania: Evaluation of the prevalence and associated risk factors in rural communities: Washington State University; 2013.
115. Ruhembe CC, Mosha TC, Nyaruhucha CM. Prevalence and awareness of type 2 diabetes mellitus among adult population in Mwanza city, Tanzania. Tanzania journal of health research 2014;16[2].
116. Ministère de la santé Togo, WHO. Pour citer ce rapport: Rapport final de l'enquête STEPS Togo 2010. 2010; Available at: http://www.who.int/chp/steps/2010STEPS_Report_Togo_FR.pdf?ua=1. Accessed 12/15, 2015.
117. Ben Romdhane H, Ben Ali S, Aissi W, Traissac P, Aounallah-Skhiri H, Bougatef S, et al. Prevalence of diabetes in Northern African countries: the case of Tunisia. BMC Public Health 2014 Jan 28; 14:86-2458-14-86.
118. Bouguerra R, Alberti H, Salem LB, Rayana CB, Atti JE, Gaigi S, et al. The global diabetes pandemic: the Tunisian experience. Eur J Clin Nutr 2007 Feb;61[2]:160-165.
119. Belfki H, Ali SB, Aounallah-Skhiri H, Traissac P, Bougatef S, Maire B, et al. Prevalence and determinants of the metabolic syndrome among Tunisian adults:

results of the Transition and Health Impact in North Africa [TAHINA] project. Public Health Nutr 2013;16[4]:582-590.

120. Mayega RW, Guwatudde D, Makumbi F, Nakwagala FN, Peterson S, Tomson G, et al. Diabetes and pre-diabetes among persons aged 35 to 60 years in eastern Uganda: prevalence and associated factors. PLoS One 2013;8[8]: e72554.

121. Ministry of Health Uganda, WHO. Non-¬-Communicable Disease Risk Factor Baseline Survey UGANDA 2014 REPORT. 2014; Available at: http://www.who.int/chp/steps/Uganda_2014_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.

122. Chiwanga FS, Njelekela MA, Diamond MB, Bajunirwe F, Guwatudde D, Nankya-Mutyoba J, et al. Urban and rural prevalence of diabetes and pre-diabetes and risk factors associated with diabetes in Tanzania and Uganda. Global health action 2016;9[1]:31440.

123. Ministry of Health Zambia, WHO. Prevalence rates of the common noncommunicable diseases and their risk factors in Lusaka district, Zambia 2008. 2008; Available at: http://www.who.int/chp/steps/2008_STEPS_Report_Zambia.pdf?ua=1. Accessed 01/17, 2017.

124. Ministry of Health Zanzibar, WHO. NCD Survey Report, Main findings from the National Non-Communicable Disease Risk Factor Survey 2011. 2011; Available at: http://www.who.int/chp/steps/2011_Zanzibar_STEPS_Report.pdf?ua=1. Accessed 01/17, 2017.

125. Ministry of Health Zimbabwe, WHO. National Survey Zimbabwe Non-Communicable Diseases Risk Factors - [ZiNCoDs], Preliminary report 2005. 2005; Available at: http://www.who.int/chp/steps/STEPS_Zimbabwe_Data.pdf?ua=1. Accessed 12/15/ 2015.

CHAPTER 5. PAPER 2

Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: a cross-sectional study in Cape Town, South Africa

Roles of the candidate and co-authors

The candidate, together with Professors Norris and Levitt conceptualized the study. Professors Norris and Levitt provided overall guidance of the study design, data analysis and writing up. The candidate collected the data and samples for the analysis. The candidate was responsible for data and sample management. The candidate carried out the data analysis with the help of the 2 supervisors. The candidate drafted the initial, revisions and final manuscript with the help of the 2 supervisors. The candidate led the publication and was the corresponding author. All authors contributed to the revision of the manuscript and approved the final manuscript.

Publication status

The study is published at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6733438/pdf/pmed.1002865.pdf with the following citation:

Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLoS medicine. 2019 Sep 9;16(9): e1002865.

5.1. Abstract

5.1.1. Background

Global data indicate that women with a history of hyperglycaemia first detected in pregnancy (HFDP) are at up to seven times risk of progressing to type 2 diabetes mellitus (T2DM), compared to their counterparts who have pregnancies that are not complicated by hyperglycaemia. However, there are no data from the sub-Saharan African region, which has the highest projected rise in diabetes prevalence globally. This study aimed to determine the proportion of women who progress to T2DM and associated risk factors, 5-6 years after HFDP, in Cape Town, South Africa.

5.1.2. Methods and Findings

All women with HFDP at a major referral hospital in Cape Town were followed up 5 to 6 years later using a cross-sectional study. Each participant had a 75gram oral glucose tolerance test, anthropometric measurements and a survey were administered. Two-hundred-and-twenty participants were followed up. At that time, their mean age was 37.2 (SD 6.0) years. Forty-seven percent (95%CI 40.7-53.9) progressed to T2DM, 5.5% (95%CI 3.1 – 9.4) had impaired fasting glucose, and 11% (95%CI 7.4 – 15.8) had impaired glucose tolerance. Of the participants who progressed to T2DM, 47% were unaware of their diabetes status. When HFDP was categorized, post hoc, according to the WHO 2013 guidelines, progression in the DIP group was 81% (95%CI 70.2 – 89.0) and 31.3% (95%CI 24.4 – 39.3) in the GDM category. Factors associated with risk of progression to T2DM were; at follow-up - waist circumference (OR 1.1, 95%CI 1.0 – 1.1, p = 0.007), hip circumference (OR 0.9, 95%CI 0.8 – 1.0, p = 0.001), and BMI (OR 1.1, 95%CI 1.0– 1.3, p = 0.001), and at baseline – insulin (OR 25.8, 95%CI 3.9 – 171.4, p = 0.001) and oral hypoglycaemic treatment during HFDP (OR 4.1, 95%CI 1.3 – 12.9, p = 0.018), fasting (OR 2.7, 95%CI 1.5– 4.8, p = 0.001) and oral glucose tolerance test 2-hour glucose concentration at HFDP diagnosis (OR 4.3, 95%CI 2.4 – 7.7, p < 0.001).

Our findings have limitations in that we did not include a control group of women without a history of HFDP.

5.1.3. Conclusions

The progression to T2DM in women with previous HFDP found in this study highlights the need for interventions to delay or prevent progression to T2DM after HFDP. Besides, interventions to prevent HFDP may also contribute to reducing the risk of T2DM.

5.2. Author Summary

Why Was This Study Done?

International research shows that when a woman has diabetes detected in pregnancy, which may resolve after the pregnancy, she remains at high risk of future diabetes.

However, we do not know what proportion of women progress to type 2 diabetes in Africa, as no research has been done before, despite the rapid increase in the number of people with diabetes.

What Did the Researchers Do and Find?

We recalled 220 women 5-6 years after they had diabetes first detected in pregnancy, and tested them for type 2 diabetes, in Cape Town, South Africa.

We found that almost half of the women, 48%, now had type 2 diabetes. Of the women with type 2 diabetes, 47% did not know that they had type 2 diabetes.

We also found that being obese at follow up and having higher blood sugar concentrations at the time the women were tested for diabetes in pregnancy, increased the chances of progressing to type 2 diabetes 5-6 years after the pregnancy.

What Do These Findings Mean?

A big proportion of South African women who have diabetes first detected in pregnancy may develop type 2 diabetes at an early age and within 6 years after the pregnancy.

It may be necessary to change their lifestyle after pregnancy, so they can reduce the chance of progressing to type 2 diabetes.

Screening for type 2 diabetes after the pregnancy needs to be more often so women who develop diabetes are treated earlier.

Further research is needed, as we did not include women who did not have diabetes first detected in pregnancy in this study.

5.3. Background

Sub-Saharan Africa, compared to other regions, is expected to have the greatest increase in the number of people living with diabetes by the year 2040, with more than half the people affected unaware of their diabetes status [1]. Since 2015, diabetes has already risen to be the second leading cause of death, after tuberculosis, in South Africa [2]. The prevalence of obesity, the strongest known risk factor for type 2 diabetes has increased, across the world, and, more so in African women, with a recent meta-analysis showing that in this group, mean BMI increased from 22kg/m2 in 1980 to 25kg/m2 in 2014 [3]. In South Africa, the combined obesity and overweight prevalence increased from 29% to 40% men and 57% to 70% in women during the period 2002 to 2016 [4,5]. Other drivers of the diabetes epidemic, such as poor nutrition, decreased physical activity has also increased during the last two decades, while HIV antiretroviral therapy-induced lipodystrophy may also increase risk of diabetes, especially in women of childbearing age, who are disproportionally affected by HIV, compared to their male counterparts [6]. Because of the current high burden of diabetes and the expected rise in diabetes prevalence, it is imperative to identify populations at elevated risk and introduce risk-lowering interventions.

Women with a history of hyperglycaemia first detected in pregnancy (HFDP), including gestational diabetes mellitus (GDM), are at high risk of future development

ofT2DM [7]. Initially, GDM was defined based on the risk of developing T2DM, but this may have resulted in the inclusion of women with undiagnosed diabetes in the GDM subgroup. Following the recommendations of the International Association of Diabetes and Pregnancy Study Group (IADPSG) [8] and the publication of the findings from the Hyperglycaemia and Adverse Pregnancy Outcomes Study (HAPO Study) [9], a multicentre study with participants from 10 countries, the WHO [10], in 2013, defined HFDP as either diabetes in pregnancy (DIP) or GDM. According to the WHO, GDM is now diagnosed as glucose intolerance in pregnancy with fasting glucose values between 5.1-6.9mmol/l or/and oral glucose tolerance test (OGTT) 2-hour glucose concentrations between 8.5-11.0mmol/l, while women with blood glucose values diagnostic of type 2 diabetes first discovered in pregnancy are classified as having DIP. The HAPO Study demonstrated associations between fasting glucose concentrations, as low as 5.1mmol/l at HFDP diagnosis and adverse foetal outcomes at birth, while the HAPO follow-up study [11], and others [12], showed a high risk for T2DM in women in the post-partum period as well as long term and adiposity in their offspring. Notably, neither the HAPO study nor the follow-up studies included data from an African cohort. Despite the absence of data from African countries, it is expected that lower fasting glucose concentration cut-offs for HFDP diagnosis, in addition to increased awareness and improved screening as well as increasing calls for universal screening for HFDP, may result in a higher prevalence of HFDP worldwide, especially in transitioning populations, such as South Africa. In China, for example, a four-fold increase in GDM prevalence was noted when universal screening was introduced [13].

Before the introduction of the term HFDP, most studies used the term GDM to describe any hyperglycaemia first detected during pregnancy. In this article we use the term HFDP where the studies may have used the term GDM, using older criteria in which the DIP subgroup was possibly included. The prevalence of HFDP varies in different populations, although this is complicated by the use of different diagnostic criteria as well as different screening methods for hyperglycaemia during pregnancy [14]. HFDP prevalence from a systematic review of the small number of available

studies in Africa ranged from 0 to 14% [15]. Recent studies that used the International Association of Diabetes and Pregnancy Study Groups (IADPSG) [8] criteria for

GDM diagnosis reported prevalence of 8.9% in Nigeria [16], 2.9% in Kenya [17] and, in South Africa; 9.1% in Soweto [18] and 25.8% [19] in Johannesburg. The Johannesburg estimate of 25.8%, may have included women with DIP, and therefore could be an estimate of HFDP. Using the conservative Soweto estimate, if 1 in every 11 pregnancies is complicated by GDM then public health interventions are required to prevent or delay T2DM in these women post the index pregnancy, in South Africa. However, the paucity of data on the prevalence of and associated risk factors for T2DM, in women after GDM, in sub-Saharan Africa and South Africa, may hinder effective development and planning of interventions and policies.

Data from meta-analyses of studies, mostly from high-income countries, show that women with previous GDM have up to seven-fold risk of developing T2DM [7,20], increased risk of long-term cardiovascular disease [7] and, for the offspring, increased risk of immediate adverse perinatal as well as future cardiometabolic disease risk [7], compared to those with non-diabetic pregnancies. Further, the risk of progression to T2DM is highest during the period 3-6 years post GDM [20]. However, the risk may be overestimated as most of the included studies used older GDM criteria which included women with DIP. Besides, there is a great degree of heterogeneity in the risk for T2DM; relative risks ranging from 2.7 in Germany to 38.4 in Sweden [14]. The estimates of risk vary by country and within countries, by ethnicity and region, which may be due to differences in the distribution of risk factors of T2DM in different populations. Different follow-up times and different study designs may also contribute to the differences in the risk estimates.

Progression to T2DM post HFDP varies widely, from a low 6% in Australian non-indigenous women [21] to 42% in Indian women [22], using IADPSG criteria. Risk factors for progression also vary widely, ethnicity, increased BMI, family history of T2DM, increased waist circumference and severity of GDM at diagnosis, being some of the most frequently identified [23]. In Africa, apart from a single study that followed up 77 women up to 12 weeks post HFDP in Cape Town [24], to our knowledge, there are

no data on the progression to T2DM post-HFDP or associated risk factors. This study in women 5-6 years post HFDP, provides the only data, to date, on the proportion of women who progress to T2DM beyond the postpartum period, as well as factors associated with risk of progression, in Africa, specifically in Cape Town, South Africa. We also investigated the proportion of women who progressed to T2DM in the GDM and DIP groups using the modified WHO 2013 criteria, applied retrospectively.

5.4. Methods

5.4.1. Study design, setting and participants

The study was carried according to an ethics approved study protocol (S1 Doc). Data on all women managed for HFDP at Groote Schuur Hospital (GSH) during the period 1 September 2010 to 31 August 2011 were routinely collected during the index pregnancy [25]. During that time, in the Western Cape province of South Africa, GDM screening and diagnosis was based on the provincial guidelines [26]. The screening was based on selective risk factors; maternal age≥40 years, BMI≥40kg/m2, previous GDM, previous foetal birthweight≥4.5kg, previous unexplained miscarriage, acanthosis nigricans and polycystic ovarian syndrome while GDM was diagnosed using the United Kingdom National Institute for Health and Care Excellence (NICE) 2008 criteria (fasting glucose above 5.5mmol/l and OGTT 2-hour glucose over 7.8mmol/l) [27]. A cross-sectional study, of the same participants (n = 498) was undertaken 5-6 years later, during the period 1 January 2016 to 31 Jan 2017. We contacted and invited participants through letters mailed to their last known address, calls to their telephone or cell phone numbers in the hospital record or next of kin and finally, home visits when all other attempts failed. Women who were pregnant at follow-up were excluded from the study.

5.4.2. Study procedures and data collected

On the day of testing, participants underwent a standard 75-gram OGTT after fasting for 8-10 hours. Blood was drawn for glycated haemoglobin A1c (HbA1C), and glucose and insulin at fasting and 120 minutes post OGTT glucose load. The blood samples were kept on ice, aliquoted within 4 hours of collection and stored at -80 degrees until analyzed. All blood samples were analysed after the recruitment of the last participant, at the same time. The time between assay collection and laboratory analysis therefore ranged from a few days to 7 months. However, this would not have influenced the glucose levels as the storage at -80 degrees Celsius would have ensured stability. Participants on treatment for T2DM were not required to do either the OGTT or the HbA1C. A trained fieldworker administered a questionnaire (Appendix 5.1) to obtain sociodemographic, reproductive history, self-reported personal and family medical history and psychosocial health and lifestyle factors such as physical activity (modified W.H.O. Global Physical Activity Questionnaire), smoking and diet using a 2-week food frequency questionnaire.

Height, weight, waist and hip circumference and blood pressure were measured using standardized procedures. Waist-hip ratio was calculated as the ratio of each participant's waist circumference to their hip circumference. BMI was grouped according to WHO criteria for underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2), obese (30-39.9 kg/m2) and morbidly obese (>40 kg/m2) [28]. Outcomes for each participant were T2DM, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) using WHO 2006 criteria [29].

5.4.3. Biochemistry and lab analyses

Plasma glucose was measured using the Randox RX Daytona Chemistry Analyzer. Glycosylated haemoglobin A1C (HbA1C) was measured using turbidimetric inhibition immunoassay (D10TM Haemoglobin A1c Program; Bio Rad Laboratories Inc.,

Hercules, CA, USA). The precision and trueness of the Randox RX Daytona Chemistry Analyzer were verified using the Clinical and Laboratory Standards Institute document EP15. Coefficients of variation calculated from running 40 separate samples at 3 different times were 3.0% for glucose and 1.6% for HbA1c.

5.4.4. Sample size and power

The sample size for this study was based on the main aim, to estimate the proportion of participants who progressed to T2DM by the time of follow-up. Most studies found a prevalence of T2DM during the first 5 years after GDM diagnosis between 20% and 50% [12,30]. Using Open Epi sample size calculator for a proportion (http://www.openepi.com/SampleSize/SS), assuming that 35% of our participants would have progressed to T2DM and using the range 20% to 50% from literature (i.e. 15% either side of our assumed proportion), the minimum sample size required was 154. We anticipated difficulties in following-up women in our setting and therefore decided to include all women who we could contact and who agreed to participate.

5.4.5. Statistical data analysis

All statistical analysis was carried out using Stata 15 statistical software [31]. For all hypothesis testing and comparisons, significance was set at 0.05 while 95% Confidence Intervals (95%CIs) were reported for the prevalence of T2DM as well as all odds ratios (OR). Means and standard deviations were presented for normally distributed measured variables, medians and interquartile ranges (IQR) for variables that were not normally distributed while, for categorical variables, frequencies and proportions were reported.

To compare variables between participants who progressed to T2DM and those who did not, chi-squared test and Fischer's Exact (small frequencies) were used for hypothesis testing for categorical data, while the t-test for independent groups (or

Wilcoxon rank-sum test if data were not normally distributed) were used to compare measured data.

The analysis for factors associated with T2DM at follow up was redone after input from journal reviewers, with the main change being using continuous variables (BMI, age, waist and hip circumference) in their raw, and not categorized forms. We carried out a multiple logistic regression model which included variables which are associated with risk of T2DM. Variables included from data measured at follow-up were; age, anthropometry (BMI, hip and waist circumference), socioeconomic variables (education and employment), comorbidities (self-reported dyslipidaemia and high blood pressure), total physical activity from the GPAQ and family history of diabetes. Variables included from baseline measurements were OGTT glucose concentrations at diagnosis of HFDP and type of treatment for HFDP. Stopping alcohol due to health reasons (n = 58 with responses) was not included in the multivariate regression as there were too many missing or “not applicable” data. We also did not include waist-hip ratio in the model due to the very wide 95% confidence interval. Further OGTT 1-hour glucose at HFDP diagnosis was also not included due to its limited clinical utility and as most health facilities in South Africa do not measure it. For logistic regression model diagnostics, we assessed the following; linearity assumption using the Lowes graph, multicollinearity using variance inflation factors, model specification using the C-statistic, and confirmed the fit of the model using the Hosmer-Lemeshow goodness-of-fit test. We also checked for outliers as well as influential observations.

This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (S3 STROBE Checklist).

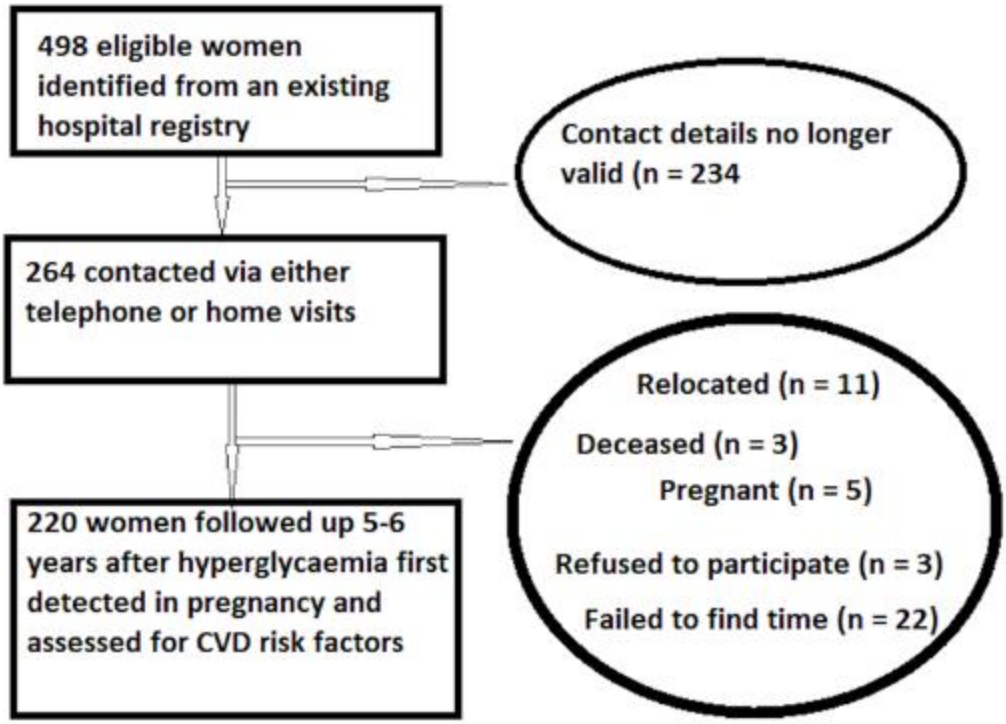
5.4.6. Ethical considerations

The study received ethics clearance from the Human Research Ethics Committees of the University of Cape Town (Ref: 656/2015) (Appendix 5.2) as well as permission to research the GSH. Participants gave written informed consent (Appendix 5.3). If found to have undiagnosed T2DM, participants were referred for treatment.

5.5. Results

Of the 498 eligible women, 220 (44.2%) participated in the follow-up study, 234 (47.0%) could not be contacted and 44 (8.8%) could not participate (Fig 5.1). There were no major differences between participants who were followed up and those lost to follow-up, except that participants followed up had a higher mean BMI at booking and a lower mean OGTT 2-hour glucose concentration at the time of HFDP diagnosis of HFDP (S1 Table).

Fig 5.1. Flow chart of the study



5.5.1. Characteristics of participants

As seen in Table 5.1, at baseline during the index pregnancy, the mean age was 30.8 (SD 5.9) years, most participants, 142 (65.4%) were of mixed ancestry, followed by 68 (31.3%) who self-identified as Black. More than three-quarters had a first-degree family history of diabetes, while most participants were either obese, 96 (44.9%) or morbidly obese, 49 (22.9%). Just under a third of the participants, 27.7%, received oral hypoglycaemic treatment and 23.6% had insulin therapy for HFDP. At HFDP diagnosis, 70 participants had FPG ≥7mmol/l or/and 2-hr blood glucose concentrations 11.1mmol/l and were retrospectively classified as DIP, and the remaining 150 (68.2%) had FPG between 5.6-6.9 mmol/l or/and 2-hr blood glucose concentrations 7.8-11.0mmol/l, retrospectively classified as GDM. Our classification of GDM differed from the WHO 2013 guidelines in that our cohort did not include women with fasting glucose values lower than 5.5mmol/l while we included women with OGTT 2-hour blood glucose between 7.8-8.4 mmol/l.

Table 5.1. Comparison of baseline characteristics of participants with and without T2DM at follow-up

Variable	Level	Overall, n = 220	Progressed to T2DM, N = 105	Did not progress to T2DM, N = 115	P-value
Age, years	Mean (SD)	30.8 (5.9)	31.5 (6.0)	30.3 (5.7)	0.116
Ethnicity, n (%)	Black	68 (31.3)	34 (32.7)	34 (30.1)	0.702
	Mixed ancestry	142 (65.4)	67 (64.4)	75 (66.4)	
	Other	7 (3.2)	3 (2.9)	4 (3.5)	
Family history of diabetes, n (%)	Yes	169 (76.8)	81 (77.1)	88 (76.5)	0.913
BMI at booking (n = 214), kg/m^2	Mean (SD)	34.2 (8.2)	35.2 (7.8)	33.3 (8.5)	0.096
BMI at booking categories, n (%)	Normal	31 (14.5)	10(9.5)	21(18.3)	
	Overweight	44 (20.0) (17.8)	16 (15.2)	22(19.3)	0.134
	Obese	104 (47.3)	56 (53.3)	46 (40.0)	
	Morbidly obese	48 (21.8)	23 (21.9)	26(22.6)	
HFDP type, n (%)	DIP	70 (31.8)	58 (82.9)	12 (17.1)	<0.001
	GDM	150 (68.2)	47 (31.3)	103 (68.7)	

Gestational age at delivery (n = 215)	Weeks, median (IQR)	38 (37 – 39)	38 (37 – 39)	38 (38 – 39)	0.001
HFDP treatment, n (%)	oral hypoglycaemics	61 (27.7)	38 (36.2)	23 (20.0)	0.007
	insulin	52 (23.6)	43 (41.0)	9 (7.8)	<0.001
Glucose metabolism at HFDP diagnosis (mmol/l) (mmol/l) median (IQR)	FPG	5.8 (5.1 – 6.7)	6.4 (5.7 – 7.2)	5.6 (4.9 - 5.9)	<0.001
	OGTT 1-hour	10.4 (9.2 – 11.5)	11.0 (10.0 – 12.2)	9.8 (8.5 – 10.6)	<0.001
	OGTT 2-hours	9.0 (8.3 – 10.4)	10.1 (8.6 – 11.1)	8.6 (8.1 – 9.3)	<0.001

***n is specified for variables with missing data only. All the other variables have complete data

Table 2 shows the characteristics of the participants at follow-up. At follow-up, the mean age of the participants was 37.2 (SD 6.0) years. Most of the participants, 167 (75.9%), had secondary or matric level education. More than two-thirds of the participants were either obese, 96 (44.9%) or morbidly obese, 49 (22.9%).

Table 5. 2. Comparison of characteristics at follow-up of participants with and without T2DM

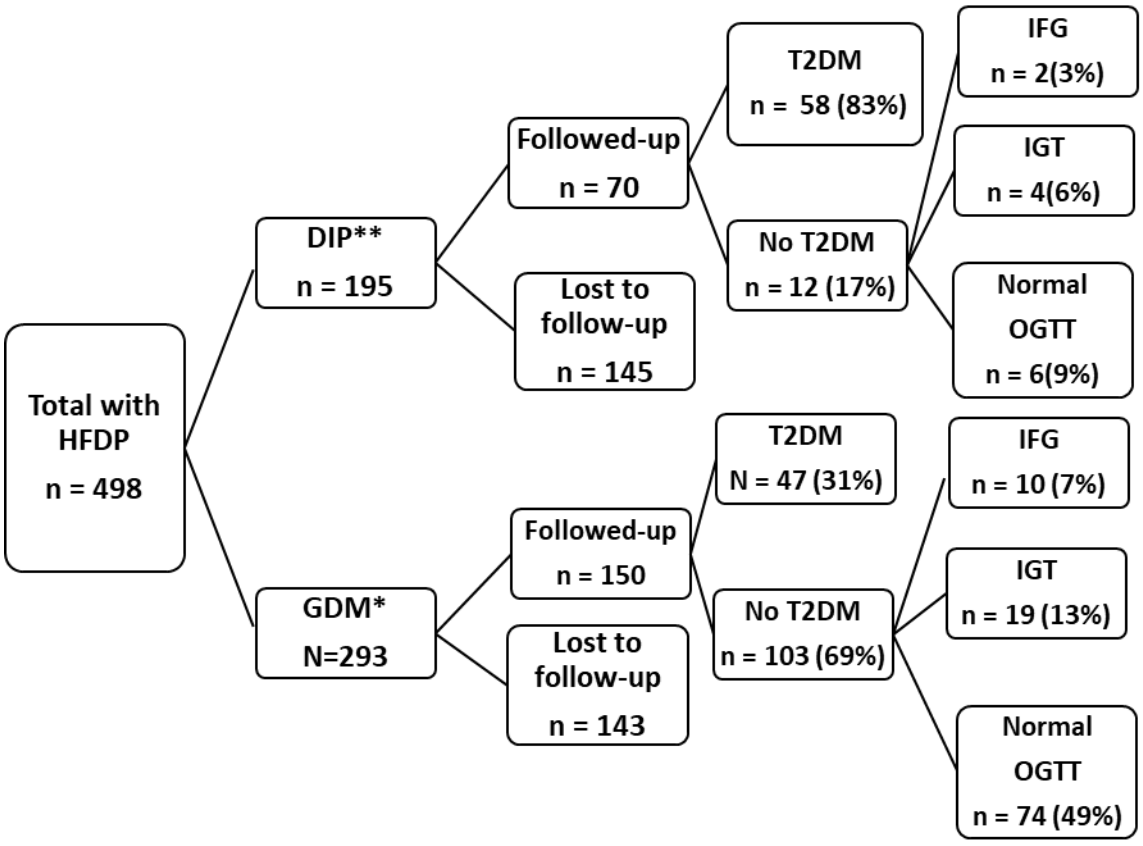
Variable	Level	Overall, n = 220	Progressed to T2DM, N = 104	Did not progress to T2DM, N = 116	P-value
Age (years)	Mean (SD)	37.2 (6.0)	37.1 (6.0)	37.3 (5.9)	0.949
Education, n (%)	Tertiary	30 (13.6)	9 (8.7)	21 (18.3)	
	Secondary and matric	167 (75.9)	80 (76.2)	87 (75.7)	0.017
	Primary	23 (10.5)	15 (14.6)	6 (5.2)	
Employed, n (%)	Yes	108 (49.1)	48 (45.7)	60 (52.2)	0.338
Marital status, n (%)	Married	141 (64.1)	68 (64.8))	73 (63.5)	0.843
Hypertension n (%)	Yes	74 (33.6)	42 (40.0)	32 (27.8)	0.056
On treatment for hypertension, n (%)	Yes	58 (26.4)	35 (33.3)	23 (20.0)	0.025
Dyslipidaemia, n (%)	Yes	29 (13.2)	22 (21.0)	7 (6.1)	0.001
On treatment for high cholesterol	Yes	26 (11.8)	20 (19.1)	6 (5.2)	0.002
On ARV treatment, n (%)	Yes	8 (3.6)	4 (3.8)	4 (3.5)	0.896
Stopped drinking alcohol due to health	Yes	14 (6.4)	9 (8.6)	5 (4.4)	0.038

reasons, n (%) (n = 58)					
GPAQ total physical activity, minutes per week	Median (IQR)	420 (110-1405)	420 (110-1440)	390 (90-1370)	0.890
GPAQ total PA, n (%)	≥150mins/week	158 (71.8)	76 (72.4)	82(71.3)	0.859
Anthropometry					
BMI (kg/m^2)	Mean (SD)	34.9 (8.7)	35.2 (8.9)	34.7 (8.6)	0.705
BMI categories, n (%)	Normal	24 (10.9)	14 (13.3)	10 (8.7)	0.329
	Overweight	44 (20.0)	17 (16.2)	27 (23.5)	
	Obese	104 (47.3)	48 (45.7)	56 (48.7)	
	Morbidly obese	48 (21.8)	26 (24.8)	22 (19.1)	
BMI gain (Follow-up – booking BMI) (kg/m2) (n=214)	Median (IQR)	+0.9 (-1.8-3.4)	0.0 (-3.0-2.8)	+1.6 (1.1-4.0)	0.019
Waist circumference (cm)	Mean (SD)	110.5 (17.6)	111.3 (17.3)	109.7(18.0)	0.491
Hip circumference cm	Mean (SD)	117.3 (16.1)	116.3 (16.5)	118.1 (15.9)	0.416
Waist hip ratio	median (IQR)	0.94 (0.89 – 0.98)	0.95 (0.91 – 1.01)	0.93 (0.88-0.97)	0.006

5.5.2. Progression to T2DM 5-6 years post HFDP

At the time of follow up, n = 105, 47.7% (95%CI 41.2 – 54.4) progressed to T2DM, of these 47.1% were not previously diagnosed, 12 had IFG (5.5%, 95%CI 3.1 – 9.4) and 23 participants (10.5%, 95%CI 7.0 – 15.3) had IGT (Fig 5.2). Using an HbA1c ≥6.5 and an established T2DM diagnosis, the T2DM prevalence was 49.5% (95%CI 42.8 – 56.2). When HFDP was categorized, post hoc, according to the modified WHO 2013 criteria, progression to T2DM in the DIP group was 82.9% (95%CI 72.0 – 90.1), and 31.3% (95%CI 24.4 – 39.3) in the GDM category.

Fig 5.2. Progression to T2DM by the modified WHO 2013 criteria for GDM



**GDM depicts women who would be categorized as GDM under the W.H.O.2013 GDM criteria but in this cohort had slightly different cut-offs (fasting glucose between 5.6 and 6.9mmol/l and/or 2-hour OGTT between 7.8 and 11.0mmol/l)*

***DIP - depicts women who would be diagnosed as DIP under the W.H.O. 2013 GDM criteria (fasting glucose of at least 7mmol/l and 2-hour glucose of at least 11.1mmol/l*

5.5.3. Comparison of participants with and without T2DM at follow-up

Participants who progressed to T2DM, compared to those who did not progress, had significantly higher median glucose concentrations (in mmol/l) at all times of the OGTT at HFDP diagnosis, fasting: 6.4(IQR 5.7 – 7.2 vs 5.6 (IQR 4.9 – 5.9), $p < 0.001$; 1-hour: 11.0 (IQR 10.0 – 12.2) vs 9.8 (IQR 8.5 – 10.6), $p < 0.001$ and 2-hour glucose: 10.1 (8.6 – 11.1) vs 8.6 (8.1 – 9.3), $p < 0.001$), and were more likely to be on either oral

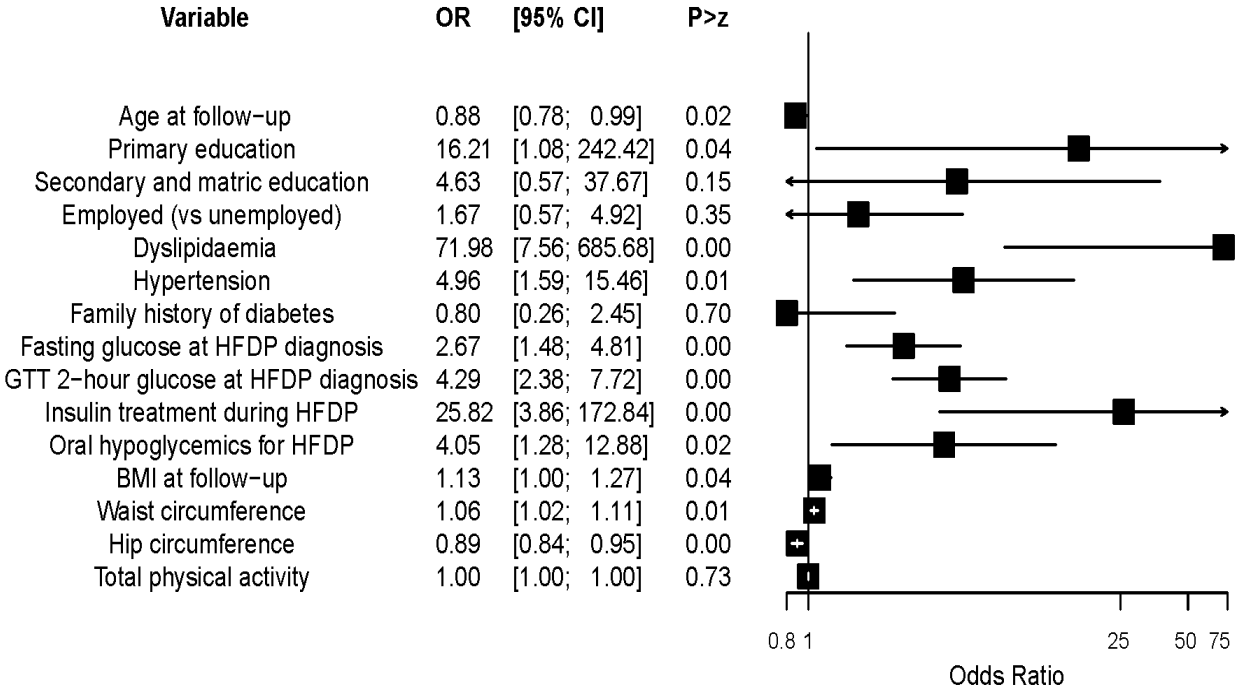
hypoglycaemic (36.2% vs 20.0%, p = 0.007) or insulin therapy (41.0% v 7.8%, p < 0.001) during HFDP (Table 5.1 and 5.2).

At follow-up, compared to participants without T2DM, participants who progressed to T2DM were significantly less likely to have a tertiary level education but more likely to have primary school level education (tertiary: 8.7% vs 18.3%, primary: 14.6% vs 5.2%, respectively, p =0.017), more likely to report having dyslipidaemia (21.0% vs 6.1%, p = 0.001) and to have stopped drinking alcohol for health reasons (8.6% vs 4.4%, p = 0.038) and more likely to have gained less BMI, in kg/m2, [median 0.0 (IQR -3.0 – 2.8) vs 1.6 (-1.1- 4.0) respectively, p = 0.019]. Box plots comparing fasting and OGTT 2-hour glucose levels at HFDP diagnosis, waist, hip circumference and waist-hip ratio at follow-up, by T2DM status at follow up, are shown in S1 Fig, S2 Fig, S3 Fig, S4 Fig and S5 Fig, respectively.

5.5.4. Factors associated with progression to T2DM

Fig 3 shows the results of multiple logistic regression for variables independently associated with T2DM. Baseline variables significantly associated with risk of progression T2DM were; fasting glucose at HFDP diagnosis (OR 2.7, 95%CI 1.5– 4.8, p = 0.001) and OGTT 2-hour glucose concentration at HFDP diagnosis (OR 4.3, 95%CI 2.4 – 7.7, p < 0.001), oral hypoglycaemic treatment for HFDP (OR 4.1, 95%CI 1.3 – 12.9, p = 0.018) and insulin treatment during HFDP, (OR 25.8, 95%CI 3.9 – 171.4, p = 0.001). The following variables measured at the time of follow-up were significantly associated with progression to T2DM; having primary school education only, compared to tertiary education (OR 16.2, 95%CI 1.1 – 244.3, p = 0.044), self-reported dyslipidaemia diagnosis (OR 72.0, 95%CI 7.6 – 682.6, p < 0.001), self-reported hypertension diagnosis (OR 5.0, 95%CI 1.6 – 15.6, p = 0.006), BMI (OR 1.1, 95%CI 1.0– 1.3, p = 0.001), waist circumference (OR 1.1, 95%CI 1.0 – 1.1, p = 0.007) and hip circumference (OR 0.9, 95%CI 0.8 – 1.0, p = 0.001).

Fig 5.3. Multiple variable logistic regression of factors associated with T2DM



Model statistics (observations – 200, LR Chi2 – 167.4, p-value – 0.000, Pseudo R2 – 0.54.6 and log likelihood – 54.6)

5.5.5. Logistic regression model diagnostics

The model consisted of 200 observations after the removal of outliers (n = 17) and the omission of participants with missing data (n = 3). In the final model, the p-values for the C-statistic (_hatsq) and the Hosmer-Lemeshow statistic were 0.123 and 0.809, respectively, confirming good fit for the model. There was no significant collinearity since pairwise correlations resulted in variance inflation factors between 1.04 and 1.82. The Lowes graph confirmed the linear model assumption.

5.6. Discussion

Our major findings are that in women 5-6 years post HFDP, only 36.4% had normal glucose tolerance; 47.7% had progressed to T2DM, of whom 47% were previously undiagnosed, 5.5% had IFG and 10.9% IGT. When we further categorized the HFDP post hoc using modified WHO 2013 GDM criteria, progression to T2DM was 83% and 31% in the DIP and GDM categories, respectively. Factors associated with risk of T2DM were fasting and OGTT 2-hour glucose concentration at HFDP diagnosis, oral hypoglycaemic and insulin treatment during HFDP and primary school education, BMI, waist and hip circumference at follow-up.

A key consideration for this study is the impact of GDM definition changes on the progression to type 2 diabetes. Recommendations of the IADPSG [8], based on findings from the HAPO study were adopted by the WHO in 2013 [10], and since then, most regional bodies have moved towards adopting the WHO guidelines. Consequently, most studies published before 2013 used GDM definitions, such as 1999 WHO guidelines on the diagnosis of GDM, which included both women with GDM and women with DIP and may, therefore, have overestimated the progression to T2DM proportion. In S2 Table, we have listed studies that investigated progression to T2DM, in the medium to long term post-partum period, published during the period 2000-2019, and the proportion of women who progressed to T2DM from each study. Most of these studies [32-46] used either the WHO 1999 guidelines or other criteria while only 4 studies used the IADPSG or equivalent criteria [11,21,22,47], for the diagnosis of GDM. Therefore, any comparisons of our findings with published data will need consideration of the heterogeneity of HFDP and GDM definitions.

In the South African context, the T2DM prevalence in our study population is 4 times higher than that of South African women overall, 11% [48], and higher than the T2DM prevalence in black women aged between 25-74 years, 13.8% [49] or women of mixed ancestry aged over 30 years, (28.2%) [50] in Cape Town. South African women with a history of HFDP are a vulnerable population and require intervention to delay or prevent progression to T2DM. The high proportion of women who progressed to T2DM (48%)

could be explained partly by the possibility that, for some of the women, their glucose never returned to normality as they were not evaluated 6 weeks post the index pregnancy. This highlights the need for postpartum screening in these women. Global data indicates that postpartum screening is between 24% and 58% [51] while, in South Africa, less than 30% attend the recommended 6 weeks postpartum OGTT [24]. Several barriers from both the health system and patient perspectives hinder the 6-week postpartum screening. The South African health system is overburdened [52] and postpartum screening for diabetes at 6 weeks using the recommended 2-hour OGTT would add significantly to the burden. While there are no South African data on barriers to postpartum screening, other studies have shown that the inconvenience of the OGTT and lack of time are the main reasons women do not attend the postpartum screening [51]. There is an ongoing debate on the utility of either fasting glucose only or the HbA1c for the postpartum screening [51]. Research is required to establish the optimum method to replace the OGTT, and for the HbA1C, both optimum timing for screening as well as cut-offs for the diagnosis of type 2 diabetes in African women. In the Western Cape, after delivery, the women must attend diabetes screening at a separate clinic while taking their offspring to a well-baby clinic for vaccination and follow-up, which may result in most women prioritizing the baby's care over theirs. Studies investigating the barriers to postpartum screening as well as optimum screening methods in South African women are needed.

We found very different proportions of women who progressed to T2DM between the GDM and DIP groups. The proportion of women who progressed to T2DM in the GDM group was 31% when we recategorized the women using modified WHO 2013 criteria. The high proportion of women who progressed to T2DM in the DIP group (83% on OGTT alone but 96% on both HBA1c and OGTT), suggests that they may possibly have had T2DM before the pregnancy. However, they clearly had more severe glucose intolerance during the pregnancy, compared to the GDM group. When HbA1c assessment was added, only 3 (4%) of women in the DIP group did not progress to T2DM. Further analysis of the DIP group showed discordance between the OGTT results and HbA1c; 2 of the 7 participants with either impaired glucose intolerance or

impaired fasting glucose had HbA1C levels above 6.5% (7.2% and 8.6%) while 3 out of 6 participants with normal GTT had HbA1C levels of at least 6.5% (6.5%, 6.5%, and 6.6%). The remaining 3 participants with normal GTT had HbA1c levels below 6.5%. Further, the small proportions of IFG and IGT in our sample at follow up suggests that most of the women who will have converted to T2DM had already converted, further proof that most of the conversion to T2DM occurs during the first half decade after HFDP. Our data, although in a small sample of women with DIP, suggests the need for more structured follow-up for assessment for T2DM after the pregnancy.

Comparisons of our findings with other studies that have investigated progression to T2DM is complicated by several issues. Firstly, there are no African studies that have investigated progression to T2DM post HFDP, the HAPO studies did not include an African cohort. Secondly, and more importantly, the heterogeneous definitions used for HFDP and GDM in the published studies (S2 Table) make it difficult to compare proportions of women who progressed to T2DM. Lastly, comparisons with published data are further complicated by the different study designs and different lengths of follow-up from the different studies. The proportion of women who progressed to T2DM of 31% in our GDM group, classified according to a modified WHO 2013 criteria, is somewhat high, compared to the four studies [11, 21, 22, 47] that used either the IADPSG or other criteria almost similar to it. This may be due to the cut-offs we used for GDM. Our study population is slightly different in that we did not include women with fasting glucose values between 5.1-5.5mmol/l, while we included women with OGTT 2-hour glucose values between 7.8-8.4mmol/l The women in our study population, in terms of diagnostic glucose values, would have been almost similar to those included by Chamberlain et al. 2016 [21], where widely different proportions of progression to T2DM for indigenous (25.5%) and nonindigenous women (5.7%), at 5 years post-partum, were reported. The proportion of women who progressed in the indigenous women was fairly similar to our study. A study from India, by Gupta et al. [22], in women diagnosed using the IADPSG GDM criteria, found that 25% and 42% of women aged 20-29 years and 30-39 years, respectively, progressed to T2DM in 5 years. The remaining two prospective cohort studies that used the IADPSG criteria for the

diagnosis of GDM, had follow-up periods which are very different from ours. In Japan, Inoue et al [47] found that 22% progressed to T2DM, 2 years post GDM, while 7.9% progression was observed in the HAPO study [11] after a median follow-up of 11.4 years. It seems that progression to T2DM is heterogeneous, even when similar criteria for GDM diagnosis are used.

Identifying risk factors for the risk of progression to T2DM is a necessary step when designing interventions to delay or prevent T2DM. The risk factors for progression in our study are largely similar to findings from previous studies; fasting [53] and 2-hour OGTT glucose concentration [47,54] at HFDP diagnosis, and, at follow-up, BMI, waist- and hip circumference [39,54,55]. Insulin and oral hypoglycaemic treatment during HFDP are an indicator of the severity of HFDP and, in our study, 77% of women who had insulin treatment were classified as DIP. Of the women with dyslipidaemia, 66% were already on treatment for diabetes at the time of follow-up, and it is well known that uncontrolled diabetes is associated with higher triglyceride and lower HDL levels [56], and the participants with an established diabetes diagnosis were more likely to have been screened for dyslipidaemia as part of standard care [57]. While no other long-term follow-up studies have shown a similar association between T2DM and education to ours, Gante [58], found an association between lower education and persistent post-partum glucose disorders in Portuguese woman at 6 weeks follow-up. In our study and our setting, education is a good indicator of socioeconomic status, and therefore may be associated with an inability to access healthier lifestyle options such as better diets. Women with lower education may also not be able to access information on reducing T2DM risk after HFDP, therefore special interventions may be required for this group.

Women who progressed to T2DM had lower BMI gain compared to those who did not progress to T2DM. A possible explanation for the lower BMI gain in women who progressed to T2DM could be that half of these women were already on treatment for T2DM. Typically this involves both lifestyle change and pharmacotherapy. On the other hand, in the absence of an intervention, women who did not progress to T2DM would not likely have taken lifestyle modifications.

Preventing T2DM can be achieved through either population-wide approaches such as the sugar tax, or interventions targeted at high-risk populations. The latter requires the screening and identification of high-risk individuals and offering interventions. Various diabetes prevention programs in both high income and low-to-medium income countries [46-49] have shown that lifestyle interventions can reduce the risk of T2DM in high-risk populations such as people with impaired glucose tolerance, although screening for impaired glucose tolerance in a population can be expensive and difficult. Our study highlights the notion that women with a history of GDM are an obvious and easily accessible target for prevention, diagnosed as part of routine care in the health system. An added benefit of this approach is that by targeting these women, there is a real chance of decreasing the risk of intergenerational transmission of T2DM to the offspring. In South Africa, there are increasing calls for universal screening for GDM [18,19], which is costly and adds to the workload of health workers compared to the risk factor-based screening which leaves a substantial proportion of women with GDM unscreened. Regardless of the screening approach used, research on the efficacy or effectiveness of lifestyle interventions in preventing or delaying progression to T2DM in women post HFDP, in South Africa, would provide much-needed data.

Our study has several limitations. We were only able to follow-up 44.2% of women after 5-6 years, comparable to other studies [46,47,53] and partly explained by a highly mobile population in the Western Cape, where in-and-out migration is common [59]. The women who participated were more likely to book 2 weeks early (15 vs 17 weeks), had a higher BMI at booking by 2 units (34.6 vs 32.7kgm2), and had lower 2-hour OGTT blood glucose at HFDP diagnosis (9.0 vs 12.0 mmol/l), compared to the women who were lost to follow-up and therefore not completely representative of our study population. Given that we followed up only 31% of women with DIP compared to 40% at baseline, it is possible that the conversion to T2DM would have been higher in the whole group of 498 women. Due to the design, our study did not follow women up until diabetes developed, and therefore we do not have time to development of diabetes as well as being unable to establish temporality for any of the risk factors we identified. The lack of a control group of women with normoglycemic pregnancies at the same

time as our sample is a further limitation. However, when compared to recent T2DM prevalence in similar-aged women in the Western Cape, our data indicate a high T2DM prevalence in women with a history of HFDP. More robust studies, with control groups, may be needed to further investigate our findings.

5.7. Conclusion

Almost half of the women with a history of HFDP progress to T2DM within 5-6 years, with almost half of them undiagnosed, in Cape Town, South Africa. There is a need for postpartum screening and interventions to reduce the risk of progression.

Acknowledgements

We thank Ms Chantal Stuart (logistics and administration) and Ms Siphokhazi Khonkwane (data collection) at the Chronic Disease Initiative for Africa, for their support during the conduct of the study.

5.8. References

1. Rahelic D. 7th Edition of Idf Diabetes Atlas--Call for Immediate Action. Lijecnicki vjesnik. 2016;138(1-2):57-8.
2. Statistics South Africa. P0309.3 - Mortality and causes of death in South Africa: Findings from death notification, 2016. 2018.
3. Kengne AP, Bentham J, Zhou B, Peer N, Matsha TE, Bixby H, et al. Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. International journal of epidemiology. 2017.
4. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, et al. Obesity in South Africa: The South African demographic and health survey. Obesity research. 2002;10(10):1038-48.
5. Department of Health South Africa. World Obesity Day 2016 2016 [Available from: http://www.health.gov.za/index.php/gf-tb-program/323-world-obesity-day-2016.
6. Goedecke JH, Mtintsilana A, Dlamini SN, Kengne AP. Type 2 diabetes mellitus in African women. Diabetes research and clinical practice. 2017; 123:87-96.

7. Bellamy L, Casas J-P, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. The Lancet. 2009;373(9677):1773-9.
8. International Association of Diabetes Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes care. 2010;33(3):676-82.
9. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Pregnancy Outcome (HAPO) Study Cooperative Research Group. N Engl J Med. 2008; 358:991-2002.
10. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. 2013.
11. Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, et al. Association of Gestational Diabetes with Maternal Disorders of Glucose Metabolism and Childhood Adiposity. JAMA. 2018;320(10):1005-16.
12. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: A Global Perspective. Current diabetes reports. 2016;16(1):7.
13. Ma RCW, Tsoi KY, Tam WH, Wong CKC. Developmental origins of type 2 diabetes: a perspective from China. European journal of clinical nutrition. 2017;71(7):870-80.
14. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Current diabetes reports. 2016;16(1):7-015-0699-x.
15. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PLoS One. 2014;9(6): e97871.
16. Olagbuji BN, Atiba AS, Olofinbiyi BA, Akintayo AA, Awoleke JO, Ade-Ojo IP, et al. Prevalence of and risk factors for gestational diabetes using 1999, 2013 WHO and IADPSG criteria upon implementation of a universal one-step screening and diagnostic strategy in a subSaharan African population. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015; 189:27-32.
17. Pastakia SD, Njuguna B, Ajwang'Onyango B, Washington S, Christoffersen-Deb A, Kosgei WK, et al. Prevalence of gestational diabetes mellitus based on various

screening strategies in western Kenya: a prospective comparison of point of care diagnostic methods. BMC pregnancy and childbirth. 2017;17(1):226.

18. Macaulay S, Ngobeni M, Dunger DB, Norris SA. The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. Diabetes research and clinical practice. 2018; 139:278-87.
19. Adams S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: prevalence, comparison of diagnostic criteria and the role of risk factors. South African Medical Journal. 2017;107(6):523-7.
20. Song C, Lyu Y, Li C, Liu P, Li J, Ma R, et al. Long-term risk of diabetes in women at varying durations after gestational diabetes: a systematic review and meta-analysis with more than 2 million women. Obesity reviews. 2018;19(3):421-9.
21. Chamberlain CR, Oldenburg B, Wilson AN, Eades SJ, O'Dea K, Oats JJ, et al. Type 2 diabetes after gestational diabetes: greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. Diabetes/metabolism research and reviews. 2016;32(2):217-27.
22. Gupta Y, Kapoor D, Desai A, Praveen D, Joshi R, Rozati R, et al. Conversion of gestational diabetes mellitus to future Type 2 diabetes mellitus and the predictive value of HbA1c in an Indian cohort. Diabetic medicine: a journal of the British Diabetic Association. 2017;34(1):37-43.
23. Rayanagoudar G, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic review and meta-analysis of 95,750 women. Springer; 2016.
24. Coetzee A, Mason D, Hall DR, Conradie M. Prevalence and predictive factors of early postpartum diabetes among women with gestational diabetes in a single-center cohort. International Journal of Gynecology & Obstetrics. 2018.
25. Van Zyl H, Levitt N. Pregnancy outcome in patients with pregestational and gestational diabetes attending Groote Schuur Hospital, Cape Town, South Africa. South African Medical Journal. 2018;108(9).
26. Maternal Guideline Reference Group and the Subcommittee of the Society for Maternal and Foetal Medicine in South Africa. Diabetes in Pregnancy, Provincial Guideline of the

Western Cape, for the Management of Diabetes and Its Complications from Pre-conception to the Postnatal Period. In: Government WCP, editor. 2010.
27. Guideline Development Group. Guidelines: management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ: British Medical Journal. 2008;336(7646):714.
28. World Health Organization. Obesity and overweight 2015 [cited 2019 30 January]. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.
29. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia - Report of a WHO/IDF consultation 2006 [Available from: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/.
30. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes care. 2002;25(10):1862-8.
31. Stata C. College Station (TX). Stata Press. 2016.
32. Huvinen E, Eriksson JG, Koivusalo SB, Grotenfelt N, Tiitinen A, Stach-Lempinen B, et al. Heterogeneity of gestational diabetes (GDM) and long-term risk of diabetes and metabolic syndrome: findings from the RADIEL study follow-up. Acta Diabetol. 2018;55(5):493-501.
33. Simmons D, Kumar S, Crook N, Rush E. Diabetes among Maori women with selfreported past gestational diabetes mellitus in a New Zealand Maori community. The Australian & New Zealand journal of obstetrics & gynaecology. 2017;57(6):599-603.
34. Chamberlain CR, Oldenburg B, Wilson AN, Eades SJ, O'Dea K, Oats JJ, et al. Type 2 diabetes after gestational diabetes: greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. Diabetes Metab Res Rev. 2016;32(2):217-27.
35. Tam WH, Yang XL, Chan JC, Ko GT, Tong PC, Ma RC, et al. Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes. Diabetes/metabolism research and reviews. 2007;23(6):485-9.
36. Wang Y, Chen L, Horswell R, Xiao K, Besse J, Johnson J, et al. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. Journal of women's health (2002). 2012;21(6):628-33.

37. Madarász E, Tamás G, Tabák ÁG, Kerényi Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes research and clinical practice. 2009;85(2):197-202.
38. Lee H, Jang HC, Park HK, Metzger BE, Cho NH. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. Diabetes research and clinical practice. 2008;81(1):124-9.
39. Lee H, Jang HC, Park HK, Metzger BE, Cho NH. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. Diabetes Res Clin Pract. 2008;81(1):124-9.
40. Rivero K, Portal VL, Vieira M, Behle I. Prevalence of impaired glucose metabolism and its association with risk factors for coronary artery disease in women with gestational diabetes. Diabetes Res Clin Pract. 2008;79(3):433-7.
41. Tam WH, Ma RC, Yang X, Ko GT, Lao TT, Chan MH, et al. Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. Gynecologic and obstetric investigation. 2012;73(2):168-76.
42. Krishnaveni GV, Hill JC, Veena SR, Geetha S, Jayakumar MN, Karat CLS, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes research and clinical practice. 2007;78(3):398-404.
43. Kale S, Yajnik C, Kulkarni S, Meenakumari K, Joglekar A, Khorsand N, et al. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. Diabetic medicine. 2004;21(11):1257-8.
44. Tam WH, Ma RC, Yang X, Ko GT, Tong PC, Cockram CS, et al. Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. Pediatrics. 2008;122(6):1229-34.
45. Simmons D, McElduff A, McIntyre HD, Elrishi M. Gestational diabetes mellitus: NICE for the U.S.? A comparison of the American Diabetes Association and the American College of Obstetricians and Gynecologists guidelines with the U.K. National Institute for Health and Clinical Excellence guidelines. Diabetes Care. 2010;33(1):34-7.

46. Gupta Y, Kapoor D, Desai A, Praveen D, Joshi R, Rozati R, et al. Conversion of gestational diabetes mellitus to future Type 2 diabetes mellitus and the predictive value of HbA1c in an Indian cohort. Diabet Med. 2017;34(1):37-43.
47. Inoue H, Ishikawa K, Takeda K, Kobayashi A, Kurita K, Kumagai J, et al. Postpartum risk of diabetes and predictive factors for glucose intolerance in East Asian women with gestational diabetes. Diabetes research and clinical practice. 2018; 140:1-8.
48. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, et al. The South African National Health and Nutrition Examination Survey, 2012: SANHANES-1: the health and nutritional status of the nation. 2014.
49. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS. Rising diabetes prevalence among urban-dwelling black South Africans. PloS one. 2012;7(9):e43336.
50. Erasmus RT, Soita DJ, Hassan MS, Blanco-Blanco E, Vergotine Z, Kengne AP, et al. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. SAMJ: South African Medical Journal. 2012;102(11):841-4.
51. Venkataraman H, Sattar N, Saravanan P. Postnatal testing following gestational diabetes: time to replace the oral glucose tolerance test? The Lancet Diabetes & Endocrinology. 2015;3(10):754-6.
52. Mayosi BM, Benatar SR. Health and Health Care in South Africa—20 Years after Mandela. New England Journal of Medicine. 2014;371(14):1344-53.
53. Madarasz E, Tamas G, Tabak AG, Kerenyi Z. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. Diabetes Res Clin Pract. 2009;85(2):197-202.
54. Kale SD, Yajnik CS, Kulkarni SR, Meenakumari K, Joglekar AA, Khorsand N, et al. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. Diabet Med. 2004;21(11):1257-8.
55. Krishnaveni GV, Hill JC, Veena SR, Geetha S, Jayakumar MN, Karat CL, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. Diabetes research and clinical practice. 2007;78(3):398-404.

56. Tomkin G, Owens D. Diabetes and dyslipidaemia: characterizing lipoprotein metabolism. Diabetes, metabolic syndrome and obesity: targets and therapy. 2017; 10:333.
57. Association AD. Standards of medical care in diabetes—2016 abridged for primary care providers. Clinical diabetes: a publication of the American Diabetes Association. 2016;34(1):3.
58. Gante I, Ferreira AC, Pestana G, Pires D, Amaral N, Dores J, et al. Maternal educational level and the risk of persistent post-partum glucose metabolism disorders in women with gestational diabetes mellitus. Acta Diabetol. 2018;55(3):243-51.
59. Statistics South Africa. Mid-year population estimates 2018 2018 [cited 2019 1 March 2019]. Available from: http://www.statssa.gov.za/publications/P0302/P03022018.pdf.

Chapter 6. PAPER 3

High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy, in Cape Town, South Africa

Role of the candidate and co-authors

The candidate, together with Professors Norris and Levitt conceptualized the study. Professors Norris and Levitt provided overall guidance of the study design, data analysis and writing up. The candidate collected the data and samples for the analysis. The candidate was responsible for data and sample management. The candidate carried out the data analysis with the help of the 2 supervisors. The candidate drafted the initial, revisions and final manuscript with the help of the 2 supervisors. The candidate led the publication and was the corresponding author. All authors contributed to the revision of the manuscript and approved the final manuscript.

Publication status

The study is published at https://drc.bmj.com/content/bmjdrc/7/1/e000740.full.pdf with the following citation:

Chivese T, Norris SA, Levitt NS. High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy in Cape Town, South Africa. BMJ Open Diabetes Research and Care. 2019 Nov 1;7(1).

6.1. Abstract

6.1.1. Objective

To investigate the prevalence, and associated risk factors for cardiovascular risk factors, 6 years after hyperglycaemia first detected in pregnancy (HFDP), in Cape Town, South Africa.

6.1.2. Research Design and Methods

Data were collected during the index pregnancy from all women diagnosed with HFDP at a major referral hospital in Cape Town. Participants were evaluated 6 years later, using a cross-sectional study. At follow up participants had a 75gram oral glucose tolerance test, fasting lipogram, blood pressure and anthropometric measurements and a field worker administered the questionnaire. We used the ATP III criteria for the diagnosis of metabolic syndrome and individual risk factors. Insulin resistance was assessed using the homeostatic model of insulin resistance.

6.1.3. Results

At follow up 220 women were reviewed. Their mean age at follow up was 37.2 (SD 6.0) years. The prevalence of CVD risk factors was: metabolic syndrome - 60.9% (95%CI 54.3- 67.2), insulin resistance - 75% (95%CI 65.9-82.3), dysglycaemia - 62.3% (95%CI 55.6-68.5), raised blood pressure - 41.4% (95%CI 35.0-48.0), and dyslipidaemia - 74.6% (95%CI 68.3-79.9). Women with diabetes in pregnancy, compared to those with gestational diabetes during the index pregnancy had a higher prevalence of metabolic syndrome (74.3% vs 54.7%, p = 0.010) and dysglycaemia (88.6% vs 50.0%, p<0.001) at follow-up. Lower school education attainment, having a subsequent pregnancy, waist circumference at follow-up, and fasting blood glucose at HFDP diagnosis, were associated with metabolic syndrome.

6.1.4. Conclusion

We found a high prevalence of CVD risk factors found in South African women within 6 years of HFDP, which highlights the need to develop and evaluate interventions optimising the cardiometabolic health of this vulnerable group. The main limitations in our research are the lack of a comparative group of women without HFDP and that we did not assess for CVD risk factors before HFDP.

6.2. Significance of this study

What is already known about this subject?

Women with a history of hyperglycaemia first detected in pregnancy (HFDP), which includes gestational diabetes, may have a higher risk for CVD, although there are no data from Africa.

What are the new findings?

In this study, we found a high prevalence of CVD risk factors 6 years after HFDP, in women, of mean age 37 years, in Cape Town, South Africa.

How might these results change the focus of research or clinical practice?

Given their relatively young age, there is a need for research which investigates innovative interventions for encouraging women to change their lifestyles after HFDP. These women may require frequent screening for CVD risk factors after pregnancy.

6.3. Background

Non-communicable diseases (NCDs) are the leading causes of illness and death worldwide. they account for up to 70% of overall mortality while cardiovascular diseases (CVD) and diabetes are responsible for almost 50% of the NCD burden (1). The majority of premature deaths from NCDs (85%) occur in low to middle-income countries (1) where health systems are struggling to cope with the concurrent problems of infectious diseases and emerging NCDs. In South Africa, the rapidly increasing prevalence of NCDs contributes to the multiple burdens of disease, comprising tuberculosis (TB) and HIV, ongoing malnutrition, and high maternal and child mortality (2, 3). Diabetes and CVD have been the second and third leading causes of death in the country since 2014. (4), highlighting the need to prioritize their prevention. One prevention strategy could be through identification of high-risk populations and offering tailored interventions.

Recent South African epidemiological surveys show that at least a quarter of pregnant women (26%) have hyperglycaemia first detected in pregnancy (HFDP) (5) while almost 10% have gestational diabetes (GDM) (6). This may increase their risk for early CVD. However, as the risk factor-based-screening currently being used in South Africa is sub-optimal, a significant proportion of pregnant women are not screened for HFDP (5, 7). Until recently, GDM was defined as HFDP with a post-partum return to normalcy in many guidelines. Further, the criteria used for the diagnosis of GDM have varied widely in different countries. However, the WHO 2013 guidelines (8) which were largely based on the results of the Hyperglycaemia and Adverse Pregnancy Outcomes Study (HAPO) (9) and recommendations of the International Association of Diabetes and Pregnancy Study Group (IADPSG) (10), have been adopted by many regional and national bodies. These WHO guidelines include the adoption of lower fasting glucose cut-offs and the distinction between GDM and diabetes in pregnancy (DIP), where blood glucose concentrations are diagnostic of type 2 diabetes mellitus (T2DM).

Meta-analyses have shown that women with a history of GDM (although these studies also included women with DIP, according to the WHO 2013 criteria) have double the risk for overall CVD (11, 12) and coronary artery disease in the long term

(12) and four times the risk for metabolic syndrome (13), compared to women with normo-glycaemic pregnancies (13). There may be population differences in the association between GDM and the metabolic syndrome, as the Asian studies did not show the association seen with other populations. Although the metabolic syndrome's utility as a clinical entity is debatable, it represents a constellation of risk factors for CVD, with possible common pathophysiology and common environmental risk factors. Insulin resistance, thought to be central in the development of metabolic syndrome (14), is also associated with beta-cell deterioration during the immediate post-HFDP period (15) and consequent progression to type 2 diabetes (16).

To the best of our knowledge, there are no published studies on the intermediate and long-term burden of CVD in African women post HFDP, despite the increasing understanding of the critical role women of childbearing age play in the possible intergenerational transmission of and prevention of CVD risk. This study aimed to describe the prevalent metabolic syndrome, insulin resistance and individual CVD risk factors (raised blood pressure, dysglycaemia, dyslipidaemia, raised waist circumference and overweight and obesity) and their risk factors in women 6 years post HFDP in Cape Town, South Africa. We also compared the prevalence of metabolic syndrome and individual CVD risk factors between GDM and DIP groups, after re-classifying HFDP, post hoc, using modified WHO 2013 criteria.

6.4. Methods

All women diagnosed and treated for GDM at a major tertiary referral hospital in Cape Town, South Africa, between 1 August 2010 and 30 September 2011, were eligible for a cross-sectional follow-up study 6 years later. At the time of the pregnancy, GDM was defined as any glucose intolerance first detected in pregnancy according to the 2008 NICE guidelines (fasting glucose >5.6mmol/l and oral glucose tolerance test (OGTT) 2-hour glucose ≥7.8mmol/l) (17). We retrospectively classified these women using modified WHO 2013 criteria as HFDP, since the criteria used at the time of the pregnancy included women with GDM and those with DIP, and then grouped the participants into GDM (fasting glucose 5.6-6.9mmol/l and OGTT 2-hour glucose 7.8-

11.0mmol/l) and DIP (fasting glucose≥7.0mmol/l and OGTT 2-hour glucose ≥ 11.1 mmol/l). Between the 1st of May 2016 and the 30th of March 2017, the women were invited for follow up assessment via telephone, postal mail and home visits. Women with known type 1 or type 2 diabetes were excluded during the pregnancy and pregnant women were excluded from the follow-up study.

6.4.1. Study procedures

Pregnancy-related data were collected during the index pregnancy, as part of routine clinical care, but the women, as part of this study, were not assessed for the following CVD risk factors; central obesity, raised blood pressure and dyslipidaemia, as they are affected by the pregnancy. At follow-up, participants were invited to come for assessment at the research unit. Trained fieldworkers administered a questionnaire (adapted from the WHO STEPWise survey questionnaire (18) to collect sociodemographic, breastfeeding and potential risk factor information. The following sections of the core WHO STEPWise questionnaire were used: history of chronic illnesses, physical measurements, alcohol and tobacco use, in addition to questions on reproductive health. Physical activity was assessed using the modified Global Physical Activity Questionnaire (GPAQ). Average breastfeeding length was calculated as the total months a participant breastfed divided by the number of children she breastfed.

The fieldworkers carried out anthropometric measurements (height, weight, waist and hip circumference) using standard methods (18). Each measurement was repeated three times, at least 5 minutes apart, and the average calculated. Height was measured to the nearest 0.1cm, using a wall-mounted stadiometer. Weight was measured to the nearest 0.1kg, with the participant putting on light clothing, without shoes, on a bathroom scale placed on a hard, flat floor. Waist circumference was measured to the nearest 0.1cm using a flexible tape, with the participant having one layer of clothing, at the midpoint between the lower costal margin and the level of the superior iliac crests. Hip circumference was measured to the nearest 0.1cm at the widest part of the hip, with a flexible tape held horizontally. Each participant had 3 blood pressure

measurements 5 minutes apart while seated comfortably, using an Omron automated BP monitor (Omron 711; Omron Health Care, Hamburg, Germany). The average of the last two readings was used in analyses.

Each participant underwent a 75-gram OGTT (unless already diagnosed with diabetes) after fasting for 8 to 10 hours. Fasting blood was drawn for glucose, insulin and lipids. Besides, blood was drawn at 2 hours for glucose. Participants on treatment for high blood pressure raised blood lipids and diabetes were not required to give samples or take measurements for the respective conditions. The samples were kept on ice until centrifugation within 4 hours of collection and the aliquots stored at minus 80 degrees Celsius until biochemical analysis.

6.4.2. Outcomes

Outcomes were the metabolic syndrome (having ≥3 CVD risk factors) and individual CVD risk factors (dysglycaemia, raised blood pressure, dyslipidaemia and central obesity), defined according to a modified National Cholesterol Education Program Adult Treatment Panel (NCEPATP III) (19). Raised blood pressure was defined as either diastolic blood pressure above 85mmHg and/or systolic blood pressure above 130mmHg. Dyslipidaemia was defined as either triglyceride ≥1.7mmol/L and /or HDL-cholesterol ≤1.30mmol/L. Dysglycaemia was defined as fasting plasma glucose ≥5.6mmol/L. BMI was grouped according to WHO criteria for underweight (<18.5 kg/m2), normal weight (18.5–24.9 kg/m2), overweight (25–29.9 kg/m2), obese (30-39.9 kg/m2) and morbidly obese (>40 kg/m2) while a waist circumference cut-off of ≥88cm was used for central obesity (20). We assessed insulin resistance using the homeostatic model assessment of insulin resistance (HOMA-IR) using a cut-off of 1.95 as used in a previous study in obese South African women (21). Participants with known diabetes at the time of follow-up were excluded from insulin resistance assessment.

6.4.3. Biochemistry and laboratory analyses

Plasma glucose was measured using the hexokinase method on a Randox RX Daytona Chemistry Analyzer. Enzymatic colorimetric assays were used to measure triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-cholesterol) using the Roche Modular Auto Analyzer while low-density lipoprotein cholesterol (LDL-cholesterol) was calculated using direct methods. Coefficients of variation calculated from running 40 separate samples in duplicate, were 3.0% for glucose,3.1% for cholesterol, 3.1% for triglycerides and 3.4% for insulin.

6.4.4. Statistical data analysis

Stata 15 (22) statistical software was used for all analyses, with $p<0.05$ for significance and 95% confidence intervals (95%CIs) reported for estimates, where appropriate. Means and standard deviations are presented for normally distributed measured data, medians and interquartile ranges (IQRs) for non-normally distributed data and frequencies and proportions for categorical variables. Comparisons of participants with metabolic syndrome and those without were done using the Chi-squared test for categorical data and independent groups t-test (normally distributed measured data) or Wilcoxon sum rank test (for measured data that were not normally distributed). The prevalence of CVD risk factor was calculated as the proportion of participants with the outcome over the total assessed.

To explore factors associated with metabolic syndrome, multiple variable logistic regression was used. Pregnancy-related variables entered into the logistic regression models were fasting and 2-hour OGTT glucose levels at HFDP diagnosis and type of treatment during HFDP. Variables measured at follow-up included in the logistic regression were: socioeconomic (age, ethnicity, education and employment), anthropometry (waist and hip circumference, BMI), family history of high blood pressure, reproductive health factors (subsequent pregnancy (yes/no) and average breastfeeding length in months), total minutes of physical activity per week from the

modified GPAQ, smoking (current smoker or not). Stopping alcohol due to health reasons and BMI at pregnancy booking was not included in the multiple logistic regression due to missing data.

For each of the following individual CVD risk factors; raised blood pressure, dysglycaemia; dyslipidaemia and insulin resistance, separately, we explored risk factors using multiple variable logistic regression. Bonferroni adjustment was used to compensate for multiple testing by multiplying the individual p-values by the total number of outcomes (four). For insulin resistance, only the 108 participants who had no diabetes at follow-up and had fasting insulin measurements, were included.

Logistic regression model diagnostics included: linearity assumption testing using the Lowes graph, multicollinearity testing using variance inflation factors (VIF), using a cut-off of the square of the VIF above 4, model specification testing using the C-statistic link test (_hatsq), and confirmation of the fit of the model using the Hosmer-Lemeshow goodness-of-fit test. The area under the receiving operating characteristic (ROC) curve and k-fold cross-validation (k=10) were used for model validation. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (23) guidelines.

6.4.5. Ethical considerations

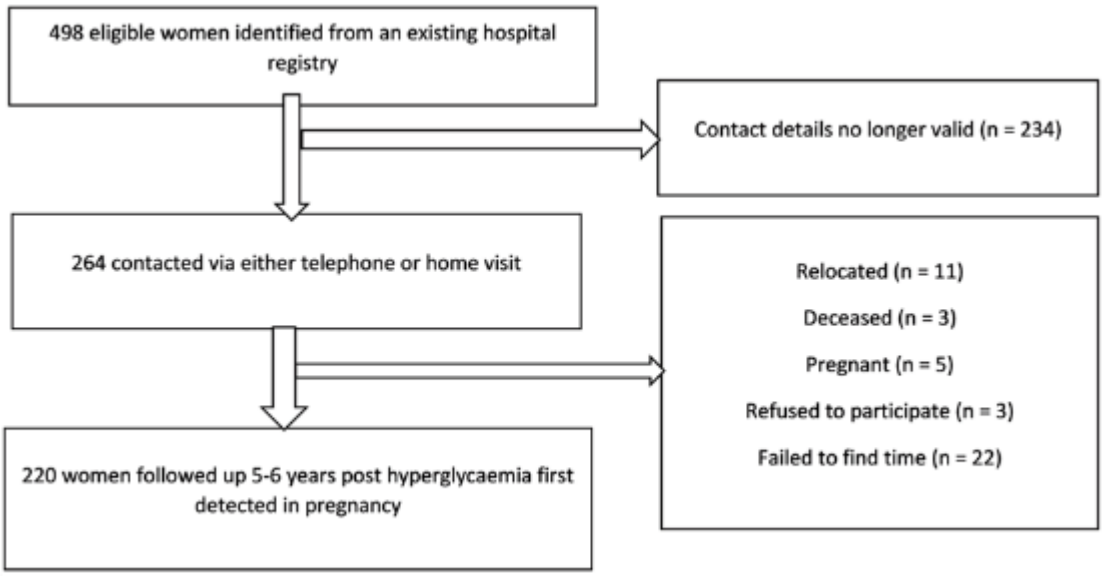
The study was carried out according to the principles of the Helsinki Declaration (24). The study was approved by the Human Research Ethics Committees of the University of Cape Town (Ref: 656/2015). Informed consent was obtained from all participants. Participants who were found to have either hypertension or diabetes were referred for treatment.

6.5. Results

Two hundred and twenty participants (44.2%) were followed up (Fig. 6.1). There were no differences in any socio-demographic characteristics during the index HFDP in those followed up compared to the women lost to follow up. However, compared to

participants lost to follow-up, participants assessed at follow-up had higher median BMI at booking [34.6 (IQR 28.8 – 41.4) vs 32.7 (IQR 27.6-38.4) kg/m2, respectively] but lower median 2-hour OGTT glucose concentrations at HFDP diagnosis [9 (IQR 8.2–10) vs 12 (IQR 11.2-12.8) mmol/l, respectively] (Supplemental Table 6.1).

Fig 6.1. Study flow chart



Tables 6.1 shows the characteristics of the participants during the pregnancy and at follow-up, as well as a comparison by metabolic syndrome status. When the HFDP was classified retrospectively using modified WHO 2013 criteria, 70 of the 220 participants were classified as DIP while the remaining 150 women were classified as GDM.

Table 6.1. Characteristics of participants– by the presence or absence of the metabolic syndrome

	Overall	Metabolic syndrome at follow-up	No Metabolic syndrome at follow-up (<3 CVD risk factors)	p-value
Number of participants	220	134	86	

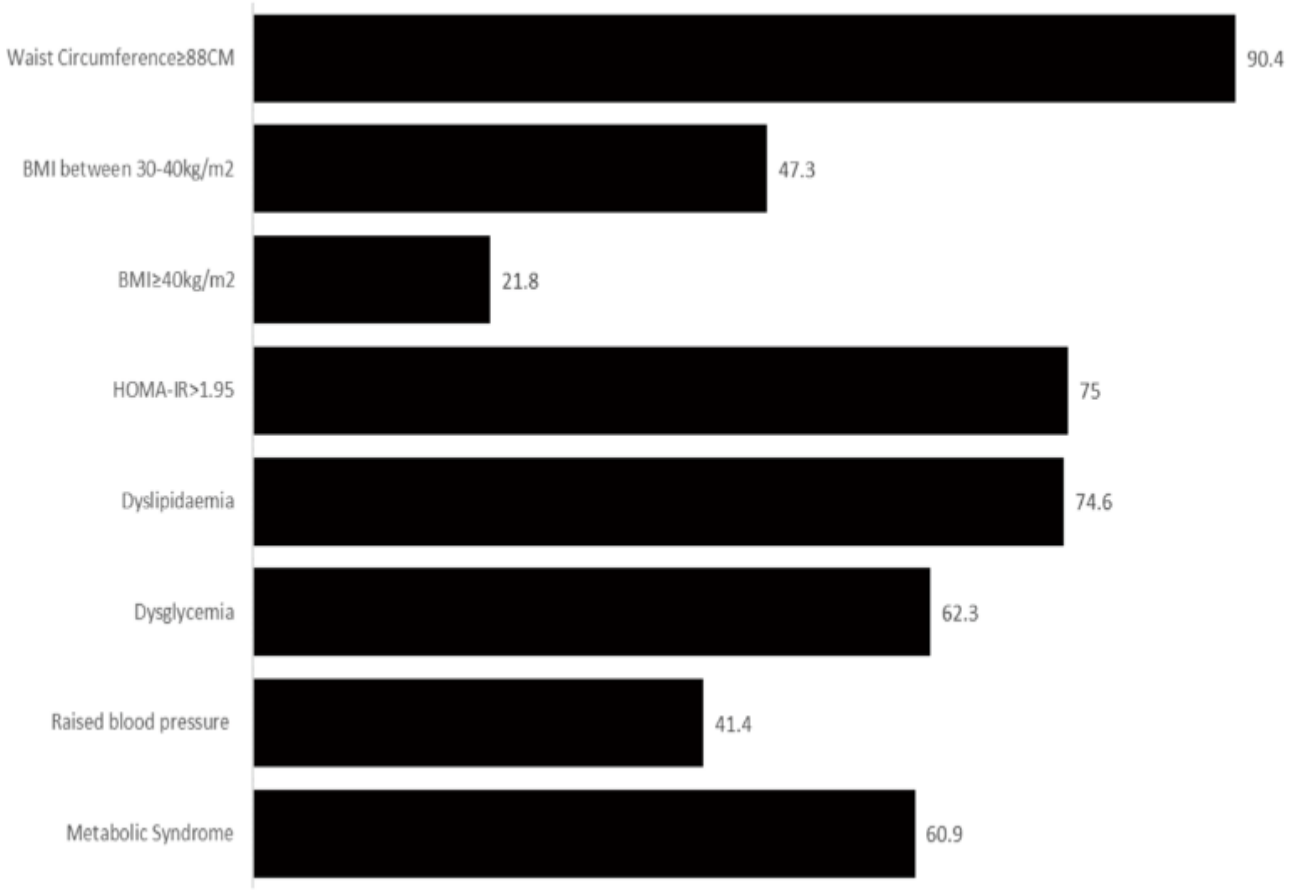
Variables measured at baseline					
Age (years)	Mean (SD)	30.8 (5.9)	32.0 (5.7)	29.0 (5.7)	<0.001
BMI at booking (kg/m^2)	Mean (SD)	34.2 (8.2)	36.2 (7.3)	32.2 (8.5)	<0.001
BMI at booking categories, n (%)	Normal	31 (14.5)	7 (5.2)	24 (27.9)	
	Overweight	38 (17.8)	17 (12.7)	21 (24.4)	
	Obese	96 (44.9)	76 (56.7)	26 (30.2)	<0.001
	Morbidly obese	49 (22.9)	34 (25.4)	15 (17.4)	
HFDP type, n (%)	DIP	70 (31.8)	18 (22.1)	52 (38.8)	
	GDM	150 (68.2)	67 (77.9)	82 (61.2)	0.010
Insulin treatment for HFDP, n (%)	Yes	52 (23.6)	39 (29.1)	13 (15.1)	0.017
OGTT at HFDP diagnosis					
Fasting blood glucose (mmol/l)	Median (IQR)	5.8 (5.1-6.7)	6.1 (5.4-7.1)	5.5 (4.9-6.3)	<0.001
1-hour blood glucose (mmol/l)	Median (IQR)	10.4 (9.2-11.6)	10.6(9.5-11.9)	10.0 (8.7-11.2)	0.006
Insulin treatment for HFDP, n (%)	Yes	52 (23.6)	39 (29.1)	13 (15.1)	0.017
2-hour glucose (mmol/l)	Median (IQR)	9.0 (8.3-10.5)	9.1 (8.4-1.0)	8.8 (8.2-9.6)	0.022
Variables measured at follow-up					
Follow up time (years)	Median (IQR)	6.1 (2.8-11.0)	5.6(1.1–9.5)	6.9 (4.8-12.8)	0.002
Education, n (%)	Tertiary	30 (13.6)	9 (6.7)	21 (24.4)	
	Secondary &matric	167 (75.9)	109 (81.3)	58 (67.4)	0.001
	Primary	23 (10.5)	16 (11.9))	7 (8.1)	
Employed, n (%)	Yes	108 (49.1)	57 (42.5)	51 (59.3)	0.015
Marital status, n (%)	Married	141 (64.1)	86 (64.2)	55 (64.0)	0.832
Family history, n (%)	Diabetes	169 (76.8)	103 (76.9)	66 (76.7)	0.983
	Hypertension	156 (70.9)	98 (73.1)	58 (67.4)	0.364
	Stroke and heart attack	96 (43.6)	59 (44.0)	37 (43.0)	0.883
Stopped drinking alcohol for health reasons, n (%)	Yes	14 (6.4)	10 (7.5))	4 (4.7)	0.486
Current smoker, n (%)	Yes	64 (29.1)	37 (27.6)	27 (31.4)	0.547
GPAQ total physical activity, minutes	Median (IQR)	450(110-1405)	420 (177.5-1502.5)	375 (90-1280)	0.274
Subsequent pregnancy, n (%)	Yes	58 (26.4)	32 (23.9)	26 (30.2)	0.297
Average breastfeeding length (months)	Median (IQR)	6 (1 – 18)	8 (1 – 18)	6 (1 – 12)	0.332
Follow-up BMI (kg/m^2)	Mean (SD)	34.9 (8.7)	36.8 (8.3)	32.0 (8.6)	<0.001
Weight gain (kg)	Median (IQR)	2.0 (-4.6 - 9.0)	1.5 (-7.0–9.0)	3.3 (-3.1 – 7.9)	0.511
Follow-up BMI categories, n (%)	Normal	24 (10.9)	6 (4.5)	18 (20.9)	
	Overweight	44(20.0)	21 (15.7)	23 (26.7)	
	Obese	104(47.3)	70 (52.2)	34 (39.5)	<0.001
	Morbidly obese	48(21.8)	37 (27.6)	11 (12.8)	
Waist circumference (cm)	Mean (SD)	110.5 (17.6)	115.6 (16.9)	102.3 (15.6)	<0.001
Hip circumference (cm)	Mean (SD)	117.3 (16.1)	119.3 (15.7)	113.9 (16.4)	0.008
Self-reported comorbidities, n (%)	Diabetes	55 (25.0)	45 (33.6)	10 (11.6)	<0.001
	Hypertension	44 (20.0)	42 (31.3)	2 (2.3)	<0.001
	Dyslipidaemia	24 (10.9)	22 (16.4)	2 (2.3)	0.001

At booking of the index pregnancy, the participants' mean age was 30.8 (SD 5.9) years, and at follow up; 37.2 (SD 6.0) years. The majority,142 (65.4%), were of mixed ancestry. Participants with the metabolic syndrome at follow-up had significantly higher mean BMI and age at booking of the index pregnancy and higher fasting and OGTT 1-hour and 2-hour blood glucose concentrations at diagnosis of HFDP, compared to those without metabolic syndrome (Table 6.1). One hundred and five (47.7%) participants had diabetes at follow-up and were not assessed for insulin resistance. Compared to participants without metabolic syndrome, those with metabolic syndrome were had a significantly higher BMI and were significantly less likely to have tertiary education (Table 6.1). The anthropometric and biochemical characteristics of the participants at follow-up are shown in Supplemental Table S6.2.

6.5.1. Prevalence of CVD risk factors, metabolic syndrome and insulin resistance at follow up, and comparison between DIP and GDM

The prevalence of the metabolic syndrome was 60.9% (95%CI 54.3-67.2); and the prevalence of the individual CVD risk factors was; insulin resistance - (75.0%, 95%CI 65.9-82.3), waist circumference≥88cm - 90.4% (95%CI 85.6-93.7), dyslipidaemia - 74.6% (95%CI 68.3-79.9), dysglycaemia - 62.3% (95%CI 55.6-68.5), obesity - 47.3% (95%CI 40.7-53.9), morbid obesity - 21.8% (95%CI 16.8-27.8) and raised blood pressure - 41.4% (95%CI 35.0-48.0) (Fig 6.2 & Supplemental Table S6.3). The proportions of participants already diagnosed with the CVD risk factors were as follows; diabetes – 25.0%, hypertension – 20.0% and dyslipidaemia – 10.9% (Table 6.1). Compared to women with GDM, women with DIP had a higher prevalence of both metabolic syndrome (74.3% vs 54%, $p = 0.010$) and dysglycaemia (88.6% vs 50%, $p<0.001$), but the proportions with insulin resistance, and the remaining CVD risk factors, did not differ significantly between the two groups (Supplemental Table S6.3).

Fig 6.2. Prevalence of CVD risk factors and insulin resistance 6 years post hyperglycaemia first detected in pregnancy



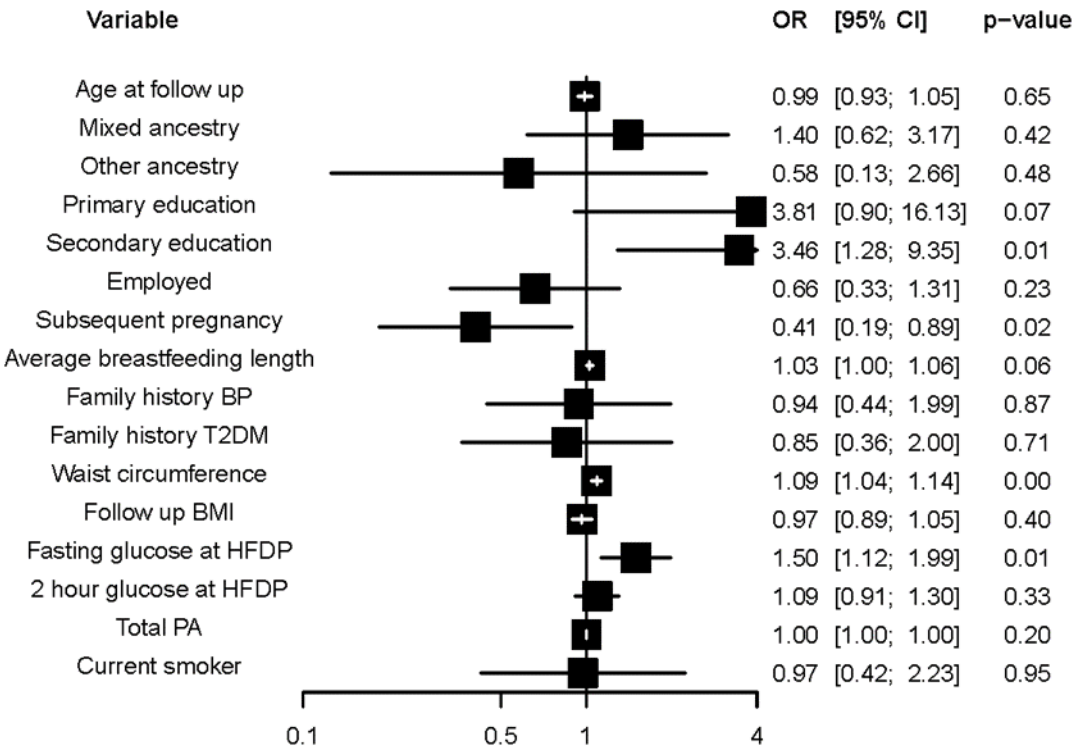
6.5.2. Factors associated with metabolic syndrome and individual CVD risk factors at follow-up – multiple variable logistic regression

After multiple variable logistic regression, fasting blood glucose at HFDP diagnosis (OR 1.5, 95%CI 1.1 – 2.0, p =0.006), having secondary and matric education, compared to tertiary education (OR 2.5, 95%CI 1.3 – 9.4, p = 0.014)), having a subsequent pregnancy (OR 0.4, 95%CI 0.2 – 0.9), and waist circumference (OR 1.1,

95%CI 1.0 – 1.1, p <0.001) were independently associated with the metabolic syndrome (Fig. 6.3).

Supplemental Table 4 shows the multiple variable logistic regression of factors associated with the individual CVD risk factors. Waist circumference was associated with raised blood pressure (OR 1.1, 95%CI 1.0 – 1.1, p =0.036), dyslipidaemia (OR 1.1, 95%CI 1.0 – 1.1, p = 0.32) and dysglycaemia (OR 1.1, 95%CI 1.0 – 1.1, p <0.001), while hip circumference was associated with dyslipidaemia (OR 0.9, 95%CI 0.9 – 1.0, p = 0.032) and dysglycaemia (OR 0.9, 95%CI 0.9 – 1.0, p = 0.044). Being employed was associated with raised blood pressure (OR 0.3, 95%CI 0.2 – 0.7, p = 0.008).

Fig 6.3. Multiple variable logistic regression for factors associated with metabolic syndrome



Legend

Notes: 1. Model statistics (Observations – 218, LR chi2 – 73.5, P-value – 0.000, Pseudo R2 – 0.25)

6.5.3. Logistic regression diagnostics and validation – metabolic syndrome outcome

The Lowess graph indicated an acceptable linear relationship. Hip circumference (VIF 4.39) was removed from the initial model as it was colinear with waist circumference (VIF 3.95) and BMI at follow up (VIF 4.78). The link function was correctly specified (p=0.630) and the Hosmer Lemeshow goodness of fit test showed that the model fit was acceptable (p=0.444). A few influential cases were identified by plotting residual against predicted probabilities, although sensitivity analysis showed no differences in model estimates when these cases were omitted. The model validation was reasonable, the area under the ROC curve was 0.907 and the Crossfield validation with k=10 folds showed pseudo R2 values which ranged from 0.21 to 0.49.

6.6. Discussion

In this study of women with a mean age of 37 years and a 6-year prior history of HFDP, there was a high prevalence of the metabolic syndrome as well as of the individual components, with very low proportions being aware of their disease status. When the HFDP was categorized according to criteria that approximated the WHO 2013 HFDP diagnostic criteria, women with DIP had a higher prevalence of both the metabolic syndrome and dysglycaemia compared to those classified as GDM. A high waist circumference, lower education attainment, having had a subsequent pregnancy at follow-up and fasting blood glucose at HFDP diagnosis were all independently associated with metabolic syndrome at follow up. An increase in waist circumference was associated with risk of raised blood pressure, dyslipidaemia and dysglycaemia.

To our knowledge, this is the first to investigate metabolic syndrome, insulin resistance and individual CVD risk factors prevalence in African women post HFDP. As different study designs, heterogeneous definitions of GDM and different lengths of follow-up complicate comparison of our findings with international data, we have

attempted to compare our findings with studies that used similar criteria for GDM to ours as well as a similar duration of follow up. Our prevalence estimates are similar to data from India, where the reported metabolic syndrome prevalence was 55% (25), dysglycaemia prevalence 68% (26) and dyslipidaemia 71% (25). On the other hand, our prevalence estimates are much higher than those reported from other countries. In China, the prevalence of the metabolic syndrome was 7.5% (27), in Brazil the dysglycaemia prevalence was 39.4% (28) and in Ireland, the prevalence of dyslipidaemia was 25% (29). The single study that assessed insulin resistance (29), found a prevalence of 33.6%, which is less than half of the prevalence in our study.

We were unable to find studies that compared CVD risk factors at follow-up between women with DIP and those with GDM. Given that the DIP group may include undiagnosed type 2 diabetes cases, this group's higher prevalence of dysglycaemia compared to that in the GDM group, is expected. The former's higher metabolic syndrome prevalence could be partly explained by the higher proportion of women with dysglycaemia as well as diabetes-associated dyslipidaemia. Thus, early intervention and screening for CVD risk factors for women in this category are warranted.

Our study has several limitations. A major limitation was the lack of a control group. Despite this, we were able to use prevalence estimate, based on the same criteria for our outcomes of interest in women of childbearing age from population surveys in Cape Town. In these the prevalence of the metabolic syndrome was 9.9% (30) and 43% (31), raised blood pressure 19.9% (30), dysglycaemia 2.2% (32), 17.9% (33) and 32.6% (34), dyslipidaemia 46% and insulin resistance (in obese women) 38% (35). Thus, our data indicate that women with a history of HFDP in our study have a higher prevalence of CVD risk factors than women of childbearing age in Cape Town. Our findings highlight the need to intervene in women post HFDP to reduce risk of CVD risk factors and consequent CVD in South Africa. This has the potential to improve more than the mothers' health, it may also reduce the risk of hyperglycaemia in future pregnancies and subsequently reduce the potential for intergenerational transmission of CVD risk through foetal programming (36).

The first intervention could be integrating CVD risk factor screening with the recommended post-partum screening for diabetes. Currently, the recommended 6 weeks post-partum screening for diabetes has a poor uptake, in keeping with international trends. In our setting, innovative solutions to the various health system and socio-demographic barriers may be required to improve uptake (37). The very low numbers of women who were aware that they had CVD risk factors and on treatment is a cause for concern. There is need for interventions that sensitize women about their higher risk for CVD post HFDP. Social science research about how to effectively communicate risk to the women is needed. Combining the post-partum care of the mother with that of the baby may offer a window to both screen for CVD risk factors and provide an opportunity to engage with the mother to promote change in her modifiable CVD risk factors. This post-partum review may need to be extended to include obese women, as our data showed that high waist circumference was associated with the risk of metabolic syndrome at follow-up. However, this will have health system implications because of the high prevalence of obesity in South African women of childbearing age (38). The high prevalence of obesity has been attributed to changes in diet and physical activity patterns among urban-dwelling South African women (38). Lifestyle change should, therefore, be part of a holistic package to prevent CVD risk in these women and reduce the consequent cardiometabolic risk in future offspring.

A further limitation of our study is that we were only able to assess 44% of women at follow up, due to the population being highly mobile. The rate of follow up is comparable to studies from other low-to-middle income countries (39, 40). As we were able to follow-up fewer women with DIP, we may have underestimated the prevalence of both metabolic syndrome and dysglycaemia. On the other hand, the women who we were able to follow-up had a higher BMI by 2 units compared to those we were not able to follow up. Finally, as we did not assess the presence of the metabolic syndrome during the index pregnancy, it is difficult to ascertain the effect of HFDP on the risk of metabolic syndrome and its components.

6.7. Conclusion

Given the considerable and growing burden of diabetes and CVD in South Africa, the high prevalence of CVD risk factors found in relatively young African women within 6 years of a previous HFDP highlights the urgent need to develop and evaluate interventions optimising the cardiometabolic health of this group.

Acknowledgements

We thank Ms Chantal Stuart (administration and logistics) and Ms Siphokazi Khonkwane (fieldwork) at the Chronic Disease Initiative for Africa for their support during data collection at follow-up. We acknowledge Dr Hetta van Zyl for collecting pregnancy-related data from participants and Professors Krisela Steyn and Christina Zarowsky for help during the conception of the research.

Abbreviations

Non communicable diseases (NCD), Hyperglycaemia first detected in pregnancy (HFDP), gestational diabetes mellitus (GDM), anti-retroviral therapy (ARV), body mass index (BMI), cardiovascular disease (CVD), diabetes in pregnancy (DIP), fasting plasma glucose (FBG), gestational diabetes mellitus (GDM), global physical activity questionnaire (GPAQ), National Cholesterol Education Program Adult Treatment Panel (NCEP-ATP III), Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO), high density lipoprotein cholesterol (HDL), International Association of Diabetes and Pregnancy Study Group (IADPSG), interquartile range (IQR), National Institute for Health and Care Excellence (NICE), oral glucose tolerance test (OGTT), odds ratio (OR), homeostatic model assessment of insulin resistance (HOMA-IR), Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), type 2 diabetes mellitus (T2DM), 95% confidence interval (95%CI), area under the receiving operating characteristic curve (ROC), variance inflation factor (VIF), world health organization (WHO)

Conflict of interest

TC – none declared
SAN – none declared
NSL – none declared

Funding

This research was funded by the Chronic Disease Initiative for Africa. We acknowledge funding from the International Development Research Centre (IDRC) (fund number: 411592) for TC (under the IINDIAGO project). The funders played no role in the conception, the conduct or writing up of or the decision to submit this research for publication.

6.8. References

1. World Health Organization. Noncommunicable diseases 2016 [updated 1 June 2018; cited 2019 27 Jan 2019]. Available from: https://www.who.int/en/news-room/factsheets/detail/noncommunicable-diseases.
2. Kabudula CW, Houle B, Collinson MA, Kahn K, Gómez-Olivé FX, Clark SJ, et al. Progression of the epidemiological transition in a rural South African setting: findings from population surveillance in Agincourt, 1993–2013. BMC public health. 2017;17(1):424.
3. Mayosi BM, Benatar SR. Health and Health Care in South Africa—20 Years after Mandela. New England Journal of Medicine. 2014;371(14):1344-53.
4. Statistics South Africa. P0309.3 - Mortality and causes of death in South Africa: Findings from death notification, 2016. 2018.
5. Adams S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: prevalence, comparison of diagnostic criteria and the role of risk factors. South African Medical Journal. 2017;107(6):523-7.
6. Macaulay S, Ngobeni M, Dunger DB, Norris SA. The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. Diabetes research and clinical practice. 2018; 139:278-87.

7. Coetzee A, Mason D, Hall DR, Conradie M. Prevalence and predictive factors of early postpartum diabetes among women with gestational diabetes in a single-center cohort. International Journal of Gynecology & Obstetrics. 2018.
8. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. 2013.
9. HAPO Study Cooperative Research Group, Metzger B, Lowe L, Dyer A, Trimble E, Chaovarindr U, et al. Pregnancy Outcome (HAPO) Study Cooperative Research Group. N Engl J Med. 2008; 358:991-2002.
10. International Association of Diabetes and Pregnancy Study Group. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes care. 2010;33(3):676-82.
11. Kramer CK, Campbell S, Retnakaran R. Gestational diabetes and the risk of cardiovascular disease in women: a systematic review and meta-analysis. Diabetologia. 2019.
12. Li J, Song C, Li C, Liu P, Sun Z, Yang X. Increased risk of cardiovascular disease in women with prior gestational diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2018; 140:324-38.
13. Xu Y, Shen S, Sun L, Yang H, Jin B, Cao X. Metabolic syndrome risk after gestational diabetes: a systematic review and meta-analysis. PLoS One. 2014;9(1): e87863.
14. Stern MP. Diabetes and cardiovascular disease: the “common soil” hypothesis. Diabetes. 1995;44(4):369-74.
15. Retnakaran R, Qi Y, Ye C, Hanley AJ, Connelly PW, Sermer M, et al. Hepatic insulin resistance is an early determinant of declining β-cell function in the first year postpartum after glucose intolerance in pregnancy. Diabetes Care. 2011;34(11):2431-4.
16. Xiang AH, Kjos SL, Takayanagi M, Trigo E, Buchanan TA. Detailed physiological characterization of the development of type 2 diabetes in Hispanic women with prior gestational diabetes mellitus. Diabetes. 2010;59(10):2625-30.

17. Guidelines Development Group. Guidelines: management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ: British Medical Journal. 2008;336(7646):714.
18. World Health Organization. WHO STEPS surveillance manual: the WHO STEPwise approach to chronic disease risk factor surveillance. 2005.
19. Expert Panel on Detection Evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Jama. 2001;285(19):2486.
20. World Health Organization. Waist Circumference and Waist-Hip Ratio Report of a WHO Expert Consultation, GENEVA, 8–11 DECEMBER 2008, 2008 [Available from: https://apps.who.int/iris/bitstream/handle/10665/44583/9789241501491_eng.pdf?ua=1].
21. Jennings CL, Lambert EV, Collins M, Levitt NS, Goedecke JH. The atypical presentation of the metabolic syndrome components in black African women: the relationship with insulin resistance and the influence of regional adipose tissue distribution. Metabolism. 2009;58(2):149-57.
22. Stata C. College Station (TX). Stata Press. 2016.
23. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. PLoS medicine. 2007;4(10): e296.
24. Helsinki WEU. Do. World medical association declaration of Helsinki. Fortaleza, Brazil. 2013
25. Kale S, Yajnik C, Kulkarni S, Meenakumari K, Joglekar A, Khorsand N, et al. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. Diabetic medicine. 2004;21(11):1257-8.
26. Krishnaveni GV, Hill JC, Veena SR, Geetha S, Jayakumar MN, Karat CL, et al. Gestational diabetes and the incidence of diabetes in the 5 years following the index

pregnancy in South Indian women. Diabetes research and clinical practice. 2007;78(3):398-404.
27. Tam WH, Yang XL, Chan JC, Ko GT, Tong PC, Ma RC, et al. Progression to impaired glucose regulation, diabetes and metabolic syndrome in Chinese women with a past history of gestational diabetes. Diabetes/metabolism research and reviews. 2007;23(6):485-9.
28. Rivero K, Portal VL, Vieira M, Behle I. Prevalence of the impaired glucose metabolism and its association with risk factors for coronary artery disease in women with gestational diabetes. Diabetes Res Clin Pract. 2008;79(3):433-7.
29. Noctor E, Crowe C, Carmody LA, Kirwan B, O'Dea A, Glynn LG, et al. ATLANTIC-DIP: prevalence of metabolic syndrome and insulin resistance in women with previous gestational diabetes mellitus by International Association of Diabetes in Pregnancy Study Groups criteria. Acta Diabetol. 2015;52(1):153-60.
30. Jennings CL, Lambert EV, Collins M, Levitt NS, Goedecke JH. The atypical presentation of the metabolic syndrome components in black African women: the relationship with insulin resistance and the influence of regional adipose tissue distribution. Metabolism: clinical and experimental. 2009;58(2):149-57.
31. Peer N, Lombard C, Steyn K, Levitt N. High prevalence of metabolic syndrome in the Black population of Cape Town: The Cardiovascular Risk in Black South Africans (CRIBSA) study. European Journal of Preventive Cardiology. 2014;22(8):1036-42.
32. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the
33. Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Assocciation for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016; 253:281-344.
34. Peer N, Steyn K, Lombard C, Lambert EV, Vythilingum B, Levitt NS. Rising diabetes prevalence among urban-dwelling black South Africans. PloS one. 2012;7(9):e43336.

35. Erasmus RT, Soita DJ, Hassan MS, Blanco-Blanco E, Vergotine Z, Kengne AP, et al. High prevalence of diabetes mellitus and metabolic syndrome in a South African coloured population: Baseline data of a study in Bellville, Cape Town. SAMJ: South African Medical Journal. 2012;102(11):841-4.
36. Jennings CL, Lambert EV, Collins M, Joffe Y, Levitt NS, Goedecke JH. Determinants of insulin-resistant phenotypes in normal-weight and obese Black African women. Obesity. 2008;16(7):1602-9.
37. Nehring I, Chmitorz A, Reulen H, Von Kries R, Ensenauer R. Gestational diabetes predicts the risk of childhood overweight and abdominal circumference independent of maternal obesity. Diabetic medicine. 2013;30(12):1449-56.
38. Venkataraman H, Sattar N, Saravanan P. Postnatal testing following gestational diabetes: time to replace the oral glucose tolerance test? The Lancet Diabetes & Endocrinology. 2015.
39. Gradidge PJ-L, Crowther NJ. Review: Metabolic Syndrome in Black South African Women. Ethnicity & disease. 2017;27(2):189-200.
40. Gupta Y, Kapoor D, Desai A, Praveen D, Joshi R, Rozati R, et al. Conversion of gestational diabetes mellitus to future Type 2 diabetes mellitus and the predictive value of HbA1c in an Indian cohort. Diabet Med. 2017;34(1):37-43.
41. Liu Z-y, Zhao J-j, Gao L-l, Wang AY. Glucose screening within six months postpartum among Chinese mothers with a history of gestational diabetes mellitus: a prospective cohort study. BMC pregnancy and childbirth. 2019;19(1):134.

Chapter 7. PAPER 4

The influence of maternal blood glucose during pregnancy on weight outcomes at birth and preschool age in offspring exposed to hyperglycaemia first detected during pregnancy, in a South African cohort

Tawanda Chivese, Magret C Haynes, Hetta van Zyl, Una Kyriacos, Naomi S Levitt, Shane A Norris

Role of the candidate and co-authors

The candidate, together with Professors Norris and Levitt conceptualized the study. Professors Norris and Levitt provided overall guidance of the study design, data analysis and writing up. The candidate collected the data, with the help of MCH and HVZ. The candidate was responsible for data and sample management. The candidate carried out the data analysis with the help of the 2 supervisors. The candidate drafted the initial, revisions and final manuscript with the help of all the supervisors and UK. The candidate led the publication and was the corresponding author. All authors contributed to the revision of the manuscript and approved the final manuscript.

Publication status

The manuscript has been submitted to a journal for publication.

7.1. Abstract

7.1.1. Introduction

Little is known about the influence of hyperglycaemia first detected in pregnancy (HFDP) on weight outcomes in exposed offspring in Africa. We investigated the influence of maternal blood glucose concentrations during pregnancy on offspring weight outcomes at birth and preschool age, in offspring exposed to HFDP, in South Africa.

7.1.2. Research design and methods

Women diagnosed with HFDP had data routinely collected during the pregnancy and at delivery, at a referral hospital, and the offspring followed up at preschool age. Maternal fasting, oral glucose tolerance test 1 and 2-hour blood glucose were measured at diagnosis of HFDP and 2-hour postprandial blood glucose during the third trimester. Offspring were classified as either those exposed to diabetes in pregnancy (DIP) or gestational diabetes (GDM). At birth neonates were classified into macrosomia, low birth weight (LBW), large for gestational (LGA)age, appropriate (AGA) and small for gestational age (SGA)] groups. At preschool age, offspring had height and weight measured and Z-scores for weight, height and BMI calculated.

7.1.3. Results

Four hundred and forty-three neonates were included in the study at birth, with 165 exposed to DIP and 278 exposed to GDM. At birth, the prevalence of LGA, macrosomia and LBW were 29.6%, 12.2% and 7.5%, respectively, with a higher prevalence of LGA and macrosomia in neonates exposed to DIP. At pre-school age, the combined prevalence of overweight and obesity was 26.5%. Maternal third trimester 2-hour postprandial blood glucose was significantly associated with z-scores for weight at birth and preschool age, and both SGA and LGA at birth.

7.1.4. Conclusion

In offspring exposed to HFDP, there is a high prevalence of LGA and macrosomia at birth, and overweight and obesity at preschool age, with higher prevalence in those exposed to DIP, compared to GDM. Maternal blood glucose control during the pregnancy influences offspring weight at birth and preschool age.

1. What is already known about this subject?

2.

Hyperglycaemia first detected in pregnancy (HFDP) includes both gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP). Higher maternal blood glucose levels at diagnosis of GDM and during pregnancy are associated with higher birth weight, which may result in adverse birth events such as macrosomia and shoulder dystocia, although there are no data from an African cohort. Whether HFDP still influences weight outcomes during childhood remains inconclusive. Further, little is known about the effect of DIP compared to GDM exposure on offspring weight outcomes at birth and during childhood.

3. What are the new findings?

We found a high prevalence of large for gestational age (LGA) at birth (30%) and overweight and obesity at preschool age (27%) in a South African cohort.

Offspring exposed to DIP had a higher prevalence of LGA at birth and overweight and obesity at preschool age.

Poor maternal blood glucose control during the pregnancy, represented by maternal postprandial 2-hour glucose increased the risk of both LGA and SGA at birth and was associated with weight z-score at preschool age.

3. How might these results change the focus of research or clinical practice?

There is a need for earlier screening for HFDP in this setting, to allow earlier detection of DIP and intervention. Improved management of maternal blood glucose during pregnancy is needed to reduce both LGA and SGA at birth and overweight and obesity at preschool age.

7.2. Introduction

The prevalence of childhood overweight and obesity is a public health concern globally, with 25% of children under the age of 5 years who are overweight or obese being in Africa (1). While childhood overweight and obesity is plateauing in high-income countries, in Africa the prevalence in under-fives doubled to 5% during the period 2000 to 2017 (2) and the prevalence of obesity quadrupled between 1975 to 2016 (3). Children who are overweight and obese, tend to remain so in adulthood, with a consequent earlier and higher risk for cardiovascular risk factors and cardiovascular disease (CVD) (4). As interventions during early life are more effective in reducing the risk of adulthood overweight and obesity than those in childhood (3), it is imperative to identify and intervene in children at risk of overweight and obesity.

Developmental Origins of Health and Disease (DOHaD) has shown that maternal under-and-overnutrition during pregnancy affect the offspring's future risk for overweight and obesity and consequent cardiometabolic disease (5, 6). Offspring of women with hyperglycaemia first discovered in pregnancy (HFDP) may be particularly at risk for being large-for-gestational-age (LGA) at birth and overweight and obese during childhood, due to exposure to a high glucose uterine environment (7). This has led the World Health Organization (WHO) Report of the Commission on Ending Childhood Obesity to emphasize the need to improve the diagnosis and management of HFDP (1), as one of the strategies to reduce risk of childhood overweight and obesity.

The World Health Organization (WHO) guidelines of 2013 define HFDP as either diabetes in pregnancy (DIP) or gestational diabetes (GDM) (8). Many older guidelines and studies have classified both DIP and GDM groups as GDM, although DIP may in some cases, imply that the foetus is likely to be exposed to hyperglycaemia for a longer

period compared to GDM and consequently, untreated hyperglycaemia for a longer period until screening and treatment (9). Data comparing the effect of these two subtypes of HFDP on offspring overweight and obesity during childhood are scarce (7). Maternal glucose levels at diagnosis of HFDP are linked to neonate weight outcomes at birth.

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) Study of 23 216 participants from 10 countries, demonstrated a linear graded relationship between maternal blood glucose at diagnosis of GDM and birth size (10). The major guidelines for the diagnosis of HFDP, including the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and the WHO 2013 criteria, have since adapted their criteria, based on this landmark study. However, the lack of an African cohort in the HAPO study may limit the applicability of the findings to the continent, where a high prevalence of HFDP has been reported in several countries (11-14) and where undernutrition and overnutrition coexistence is prevalent (15). Data from African cohorts are needed to compliment the HAPO findings.

Evidence on whether maternal blood glucose influences overweight and obesity risk during early and later childhood remains inconclusive (7). Findings from the HAPO follow up study (16) showed no significant associations between GDM and childhood overweight and obesity at ages 10-14 years, after adjusting for maternal BMI, but, at the same age, there were significant associations with other measures of adiposity such as body fat percentage, waist circumference and the sum of skinfolds. Three systematic reviews (7, 17, 18) found higher BMI z-scores in children exposed to GDM, compared to those from normoglycemic pregnancies, although in some of the included studies the association was not statistically significant once adjusted for maternal BMI. Arguably, as a child grows older, other factors such as socioeconomic factors, diet and physical activity, contribute to a child's nutrition and the influence of maternal hyperglycaemia may lessen. Nevertheless, more research evidence is needed.

In South Africa, recent epidemiological studies reported prevalence of HDFP and GDM of 26% (14) and 9% (13), respectively, suggesting that at least a quarter of pregnancies may be complicated by HFDP. Since most provinces in the country use a selective risk factor screening approach and consequently may miss up to 50% of

women with HFDP, a substantial proportion of children are likely to be exposed to untreated HFDP (19). This study was undertaken to contribute to the understudied area of the cardiometabolic outcomes of children from HFDP in South Africa and elsewhere in Africa. The main aim was two-fold: (i) to investigate the influence of maternal blood glucose during pregnancy, and offspring weight at birth and preschool age and to investigate the prevalence of overweight and obesity at ages 5-6 years in children exposed to HFDP, and (ii) to compare the prevalence of overweight and obesity at birth and at follow-up, between children exposed to DIP and those exposed to GDM, in an African cohort.

7.3. Research design and methods

A cohort of offspring exposed to HFDP had birthweight measured at birth and was followed up at ages 5-6 years. Routine pregnancy and delivery data were collected on all mothers diagnosed and managed with HFDP at a major tertiary hospital in the Western Cape province of South Africa between 1 September 2010 to 31 August 2011. At that time, the National Institute for Health and Care Excellence (NICE) 2008 guidelines were used to diagnose GDM [fasting blood glucose > 5.5mmol and/or oral glucose tolerance test (OGTT) 2-hour glucose > 7.8mmol/l] (20). Five to six years after the pregnancy, a cross-sectional study (21, 22) was carried out, where each mother was recalled and assessed for diabetes and CVD risk factors. Each mother was asked to bring her offspring 5-6 from the index pregnancy. Neonates who had the following characteristics at birth were excluded from the analysis: children from multiple births, premature, congenital birth disorders, admitted into neonatal intensive care at birth and neonates hospitalized with serious conditions.

7.3.1. Data collected

During the index pregnancy, maternal age, BMI and gestational age at booking, maternal HIV status, treatment for HFDP, type of birth delivery and gestational age at delivery were routinely collected by the attending clinician. Maternal glucose measures

included fasting glucose, OGTT 1-hour and OGTT 2-hour glucose concentrations at HFDP diagnosis, and routine fasting and postprandial glucose measurements during the third trimester. We retrospectively classified the children into 2 groups, using a modified WHO 2013 criteria and maternal blood glucose values at HFDP diagnosis, into DIP-exposed (maternal fasting glucose at HFDP diagnosis of at least 7.0mmol/l and /or OGTT 2-hour glucose of at least 11.1 mmol/l) and GDM-exposed (maternal fasting glucose at HFDP diagnosis of at least 5.5mmol but less than 7.0 mmol/l and/or OGTT 2-hour glucose of at least 7.8 mmol/l but less than 11.1 mmol/l). Maternal fasting blood glucose and 1 and 2-hour postprandial blood glucose were measured weekly during the third trimester, as part of routine clinical monitoring, until delivery, and the mean blood glucose calculated for each woman.

7.3.2. Outcomes

Birthweight was measured by the attending clinician, who was not part of the study. Gestational age at birth was calculated from the first day of the last menstrual period and ultrasound estimation. Birthweight z-scores and birthweight percentiles for gestational age and gender were computed using the International Newborn Size at Birth Standards software (23). Neonates with birthweight percentile<10% were classified as small-for-gestational-age (SGA) while those with birthweight> 90% were classified as large-for-gestational-age (LGA). Additionally, neonates with birthweight<2500 grams were classified as low-birthweight (LBW) and neonates with birthweight>4000 grams as macrosomic. At follow-up, trained study staff measured the children's anthropometry in light clothing and without shoes. Height was measured eight to the nearest 0.1cm, using a wall-mounted stadiometer. Weight was measured to the nearest 0.1kg, using a calibrated digital scale. All measurements were taken in duplicate and the average calculated. Z-scores for weight, height and BMI were calculated using the WHO Child Growth Standards STATA igrowup package for children 5 years old or younger and the WHO Child Growth Standards STATA WHO 2007 package for children above 5 years (24). Children over the age of 5 years with

BMI z-scores above one but less than 2 were classified as overweight while children with BMI z-score of at least 2 were classified as obese. Children with BMI z-scores below -1 were classified as underweight.

7.3.3. Sample size and sampling

The study sample consisted of 443 eligible neonates at birth and these were all included. The same children were eligible for follow-up and thus the sample size at follow up consisted of all children who were able to participate in the study, although there was significant attrition.

7.3.4. Statistical data analysis

We used STATA 15 (25) and R statistical software (26) for all statistical analyses, $p<0.05$ as a cut-off for significance and reported 95% confidence intervals (CI) for prevalence and regression estimates, where applicable. For summarizing data, we reported frequencies and proportions for categorical data, means and standard deviations (SD) for measured data, such as child anthropometry and ages, if normally distributed, and medians and interquartile ranges (IQR) for non-normal data. We calculated the prevalence of neonates who were LGA and the prevalence of overweight and obesity at preschool age as a proportion of the children with the outcome divided by the total assessed.

We compared z-scores, LGA at birth, and overweight and obesity at preschool age between children exposed to DIP and those exposed to GDM during the pregnancy. P-values for group comparisons were computed using the chi-squared test for categorical data and the t-tests for independent groups or Wilcoxon rank-sum test (where data were not normally distributed).

Multiple variable linear regression was used to investigate the association between maternal blood glucose concentrations during pregnancy, and weight z-score at birth and preschool age and BMI at preschool age. A linear mixed-effects model was used to

investigate the effect of maternal blood glucose on longitudinal offspring weight z-score, as there were no data for offspring BMI z-score at birth. Multiple variable multinomial logistic regression was used to examine the association between maternal blood glucose and the categorized outcomes of size at birth (LGA and SGA with AGA as the base outcome) and BMI category at preschool age (Overweight and Obesity with normal BMI as the base outcome). In all the models the following maternal blood glucose variables were included; 1) glucose levels at HFDP diagnosis (fasting blood glucose, OGTT 1-hour, OGTT 2-hours) and third trimester mean 2-hour postprandial blood glucose. In all models, the following variables were adjusted for, maternal age at pregnancy booking, maternal BMI at pregnancy booking, gender and mode of birth delivery. In addition, size at birth (LGA or SGA vs AGA) was adjusted for in all models at preschool age. Maternal HIV was not included in the analysis due to the low prevalence in the study while fasting and 1-hour postprandial blood glucose were omitted as they had too much missing data.

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (1 STROBE Checklist).

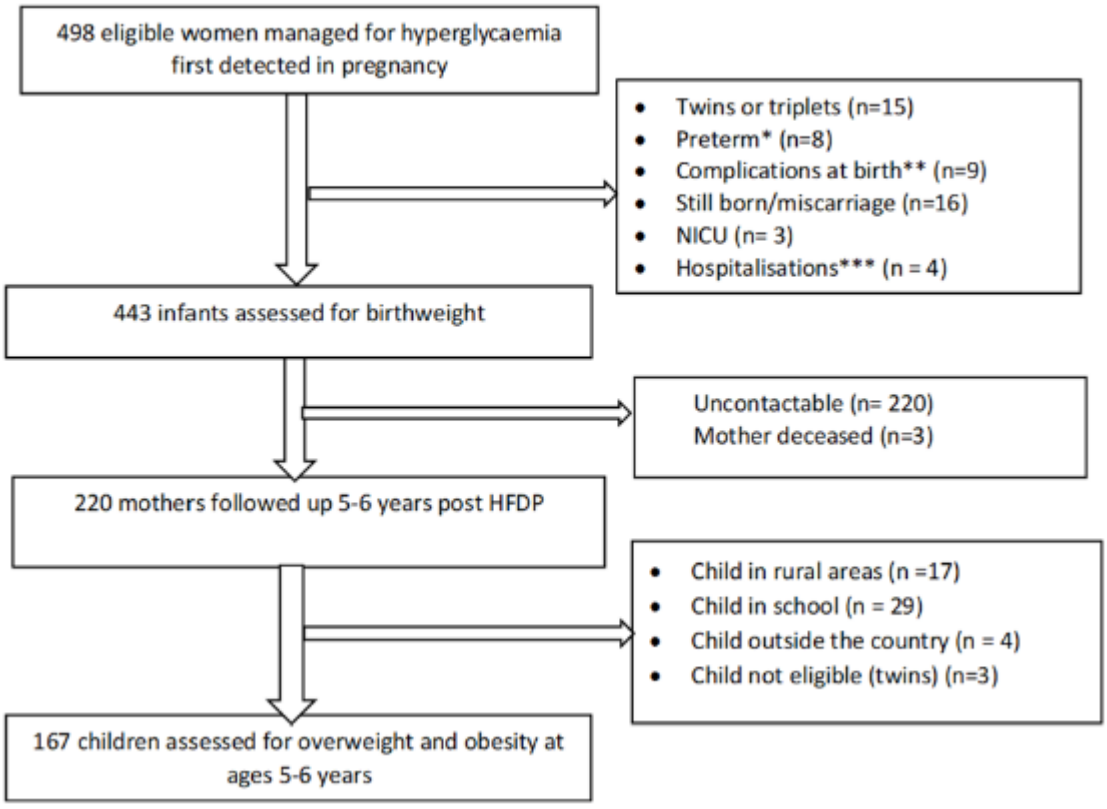
7.3.5. Ethics

This study protocol (S2 Doc) was approved by the Human Research Ethics Committees of the University of Cape Town (Refs: 377/2012 and 656/2015) and permission obtained to conduct research at the tertiary hospital. The study was conducted according to the ethical principles of the Helsinki Declaration (27). At follow up, mothers gave informed consent for their children to participate and each child assented before they had their weight and height measured. All the children who were brought to the research site assented.

7.4. Results

Of the 498 women treated for HFDP, 443 (89.0%) had children who were eligible for the birthweight assessment. Of these 167 (37.7%) were followed up at ages 5-6 years. The remainder were lost to follow-up due to various reasons (Fig 7.1). The only differences in the baseline clinical characteristics of children followed up compared to those lost to follow up (Supplemental Table 1) were: the lower mean gestational age at booking of the pregnancy and smaller proportion of children exposed to DIP in those seen as follow up compared to those not followed up [(15 (IQR 12-21) vs 17(IQR 13-23) weeks, and 29.9% vs 41.7% respectively, p = 0.013].

Fig.7.1. Flow chart of the study



**Preterm – extreme or very preterm: gestational age below 32 weeks (WHO classification), and/or birthweight ≤ 1500 grams*

***Dandy Walker syndrome (n=1), ventriculomegaly (n = 1), Intrauterine growth restriction (n=4), short-long bones (n=2), kyphosis (n = 1)*

****hospitalizations (multiple problems (n=2), hypoglycaemia (n=1), hypothermia and microencephaly(n=1))*

7.4.1. Participant characteristics and comparison between DIP and GDM- exposed infants

Table 7.1 shows maternal and offspring characteristics. At booking of the pregnancy, mean maternal age was 30.5(SD 6.2) years, mean maternal BMI was 34.5(SD 8.6) kg/m2 and median gestational age was 16(IQR 12-22) weeks. Two hundred-and-twenty (49.7%) of the 443 infants were female. At HFDP diagnosis, the median fasting and OGTT 2-hour blood glucose concentrations were 5.8 (IQR 5.2-6.6) mmol/l and 9.1 (IQR 8.3-10.6) mmol/l, respectively, with, as expected, higher concentrations in the mothers with DIP, compared to those with GDM (Table 7.1). The children's mean age at follow up was 5.5 (SD 0.5) years, with only 26 (15.5%) being 5 years old or younger. After classification using modified WHO 2013 criteria, 165 (37.2%) and 50 (29.9%) were classified as DIP at birth and preschool age, respectively. The maternal characteristics at follow up did not differ significantly between the DIP-exposed and GDM-exposed children (Table 7.1).

Table 7.1. Characteristics of, and comparison between infants exposed to GDM and those exposed to DIP

Variable	Level	Overall	DIP	GDM	p-value
Pregnancy-related data		**N = 443**	**N = 165**	**N = 278**	
Maternal age at booking (mean (SD))	Years	30.5 (6.2)	31.2 (6.0)	30.1 (6.2)	0.06
Maternal ethnicity (n (%))	Black	130 (29.4)	57 (34.6)	73 (26.3)	0.064
	Mixed ancestry	313 (70.7)	108 (65.5)	205 (73.7)	
Maternal BMI at booking (kg/m^2) (n =385)	(mean (SD))	34.5 (8.6)	35.1 (8.3)	34.2 (8.7)	0.35
Maternal HIV status (n (%))	Positive	27 (6.1)	16 (9.8)	11 (4.0)	0.024
Maternal CD4 count (cells/dm^3), n= 25	(median [IQR])	453 (364-595)	433.0 [345.8, 465.0]	654.0 [390.0, 874.0]	0.089

Maternal gravida	(median [IQR])	3 (2-4)	3 [2, 4]	3 [2, 4]	0.024
Maternal parity	(median [IQR])	3 (2-4)	2 [1, 3]	1 [0, 2]	0.029
Gestational age at booking (weeks)	(median [IQR])	16 (12-22)	18.0 [12.0, 23.0]	15.5 [13.0, 21.0]	0.179
Fasting glucose (mmol/l) at HFDP diagnosis (n =422)	(median [IQR])	5.8 (5.2-6.6)	7.20 [6.2, 8.5]	5.6 [5.0, 5.9]	<0.001
OGTT 2-hour glucose (mmol/l) at HFDP diagnosis (n=381)	(median [IQR])	9.1 (8.3-10.6)	11.9 [11.1, 13.4]	8.6 [8.1, 9.4]	<0.001
Third trimester postprandial 2-hour blood glucose (n = 440)	(median [IQR])	5.7 [5.1 – 6.3]	5.9 [5.2- 6.6]	5.6 [5.1 – 6.2]	0.031
Insulin treatment for HFDP (n (%))	Yes	111 (25.1)	88 (53.3)	23 (8.3)	<0.001
Oral hypoglycaemics treatment (n (%))	Yes	141 (31.9)	70 (42.4)	71 (25.6)	<0.001
Mode of birth delivery (n (%))	Caesarean section	231 (52.4)	96 (58.2)	135 (48.9)	0.074
	Vaginal	210 (57.6)	69 (41.8)	141 (51.1)	
Gestational age at delivery (weeks)	Median [IQR]	38 [38-39]	38.0 [37.0, 38.0]	38.0 [38.0, 39.0]	<0.001
Infant gender (n (%))	Female	225 (50.8)	88 (53.3)	137 (49.3)	0.467
Follow up data (age 5-6 years), N = 167					
Child gender (n (%))	Female	80 (47.9)	28 (56.0)	52 (44.4)	0.171
Child age (years)	(Mean (SD))	5.5 (0.5)	5.7 (0.5)	5.5 (0.5)	0.014
Maternal education (n (%))	Primary	15 (8.9)	8 (16.0)	7 (6.0)	0.093
	Secondary	129 (77.3)	37 (74.0)	92 (78.6)	
	Tertiary	23 (13.8)	5 (10.0)	18 (15.4)	
Mother employed (n (%))	Yes	80 (47.9)	23 (46.0)	57 (48.7)	0.878
Maternal alcohol (n (%))	Ever consumed	72 (43.9)	22 (44.0)	50 (43.9)	1.000
Maternal smoking (n (%))	Ever smoked	61 (36.5)	17 (34.0)	44 (37.6)	0.789

NB: n is specified where data are missing

Abbreviations: BMI, body mass Index, FBG, fasting blood glucose, HFDP, hyperglycaemia first detected in pregnancy, OGTT, oral glucose tolerance test, DIP, diabetes in pregnancy, GDM, gestational diabetes mellitus

7.4.2. Prevalence of LGA at birth and overweight and obesity at preschool age, and comparison between exposure to DIP and GDM

The median birthweight of the offspring was 3.3 (IQR 3.0-3.6) kg and their mean BMI at preschool age was 16.12 (SD 2.92) kg/m2. The DIP-exposed neonates had a significantly higher mean z-score for birthweight than GDM-exposed infants [0.52 (SD

1.20) vs 0.11 (SD 0.97), respectively, p <0.001] but there were no significant differences in weight, height and BMI, between the two groups of children at preschool age (Table 7.2 and Fig 7.2).

The prevalence of LGA at birth was 29.6% (95%CI 25.5 – 34.0), with a significantly higher prevalence in the neonates exposed to DIP, compared to those exposed to GDM (37.6% vs 24.8%, p =0.018, respectively). The prevalence of macrosomia was 12.2% (95%CI 9.4% - 15.6%), with a higher prevalence in DIP-exposed compared to GDM-exposed, although not significant at a 5% significance level (Table 2). At preschool age, the combined prevalence of overweight and obesity was 26.5% (95%CI 20.1 – 34.0), with no significant differences between DIP-exposed and GDM-exposed infants (Table 7.2).

Table 7.2: Anthropometry at birth and preschool age, and comparison between children exposed to GDM and those exposed to DIP

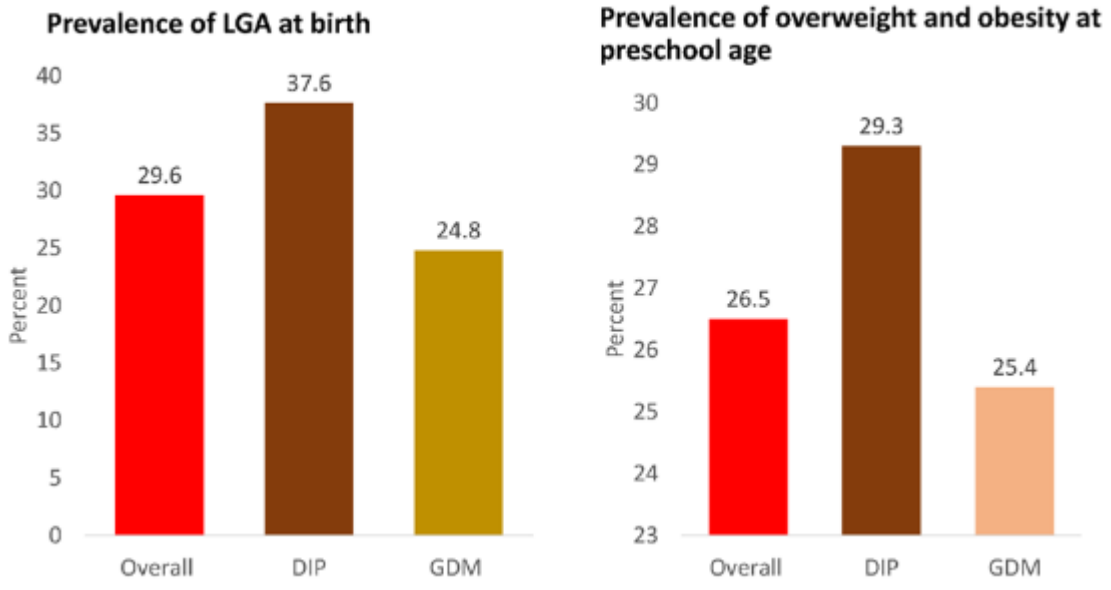
Variable	Level	Overall	DIP	GDM	P
Birth		**N = 443**	**N = 165**	**N = 278**	
Neonate birthweight (kg)	(median [IQR])	3.3 [3.0 – 3.6]	3.3 [3.0, 3.7]	3.3 [3.0, 3.6]	0.474
Neonatal birthweight z-score	(mean (SD))	0.26 (1.1)	0.52 (1.20)	0.11 (0.97)	<0.001
Birthweight percentile for gestational age category (n (%))	AGA	291 (65.69)	96 (58.18)	195 (70.14)	0.018
	SGA	21 (4.74)	7 (4.24)	14 (5.04)	
	LGA	131 (29.57)	62 (37.58)	69 (24.82)	
Birthweight category	Macrosomia (n (%))	54 (12.19)	27 (16.36)	27 (9.71)	0.117
	LBW (n (%))	33 (7.45)	12 (7.27)	21 (7.55)	
Preschool-age					
Height (cm)	(Mean (SD))	112.50 (5.63)	113.80 (6.68)	112.00 (5.12)	0.072
BMI at follow up (kg/m^2)	(Mean (SD))	16.12 (2.92)	16.57 (3.71)	15.95 (2.55)	0.229
Child weight (kg)	(Mean (SD))	20.52 (4.77)	21.59 (5.99)	20.06 (4.09)	0.057
Child height z-score	(Mean (SD))	-0.15 (1.02)	-0.06 (1.09)	-0.18 (0.99)	0.503
Weight z-score	(Mean (SD))	0.14 (1.51)	0.28 (1.77)	0.07 (1.39)	0.409

Child BMI z-score	(Mean (SD))	0.34 (1.54)	0.35 (1.77)	0.33 (1.46)	0.937
BMI category (n (%)), N = 155	Underweight (z-score <-1)	26 (16.8)	7 (17.1)	19 (16.7)	0.935
	Normal (-1≤z-score ≤1)	88 (56.8)	26 (52.0)	78 (66.7)	
	Overweight (1<z-score≤2	24 (15.5)	7 (17.1)	17 (14.9)	
	Obese (z-score>2)	17 (11.0)	5 (12.2)	12 (10.5)	
Combined overweight & obese category (n (%))	BMI z-score>1	41 (26.5)	12(29.3)	29 (25.4)	0.681

NB: Neonates with birthweight percentile<10% were classified as small-for-gestational-age (SGA) while those with birthweight> 90% were classified as large-for-gestational-age (LGA). Neonates with birthweight<2500 grams were classified as low-birthweight (LBW) and neonates with birthweight>4000 grams as macrosomic.

Abbreviations: LGA, large for gestational age, AGA, appropriate for gestational age, SGA, small for gestational age, BMI, body mass Index, FBG, fasting blood glucose, DIP, diabetes in pregnancy, GDM, gestational diabetes mellitus

Fig 7.2. Prevalence of LGA at birth and overweight and obesity at preschool age and comparison between DIP and GDM exposures



Abbreviations: DIP – diabetes in pregnancy, GDM, gestational diabetes, LGA, large for gestational age

7.4.3. Maternal blood glucose during pregnancy and birth size and overweight and obesity at preschool age

All maternal blood glucose values were consistently high for the neonates who were LGA, compared to those who were either AGA or SGA (Table 7.3). Postprandial blood glucose exhibited the strongest association with an increase in birth size, with the highest mean (SD) for LGA, followed by AGA and lastly SGA. Similarly, maternal blood glucose levels were significantly higher for LGA compared to AGA for both fasting and OGTT 2-hour glucose at diagnosis of HFDP but not for OGTT-1hour glucose. At preschool age, all mean maternal blood glucose parameters were high for offspring who were overweight and obese compared to those who had either normal BMI or underweight, although not statistically significant (Table 7.3).

Table 7.3. Maternal blood glucose and weight outcomes at birth and preschool age

Birth size

	LGA, N = 131	AGA, N = 288	SGA, N= 21	ANOVA P-value	LGA vs AGA	LGA vs SGA	SGA vs AGA
Maternal age at booking	30.79 (6.02)	30.44 (6.02)	30.71 (6.61)	0.854			
Maternal BMI at booking	36.50 (7.07)	33.79 (8.63)	32.47 (9.81)	0.009	0.013	0.138	1.000
FBG at HFDP diagnosis	6.58 (1.85)	6.12 (1.61)	5.74 (1.77)	0.020	0.041	0.131	1.000
OGTT 1-hour glucose at HFDP diagnosis	11.43 (2.43)	10.74 (6.38)	9.51 (2.30)	0.322			
OGTT 2-hour glucose at HFDP diagnosis	10.13 (2.43)	9.45 (2.27)	9.25 (3.24)	0.036	0.039	0.466	1.000
Third trimester 2-hour postprandial blood glucose	6.05 (1.03)	5.65 (0.79)	5.32 (0.61)	<0.001	<0.001	0.001	0.264

Overweight and obesity at preschool age

	Overweight and obese, N = 41	Normal BMI, N = 88	Underweight, N= 26	P-value

Maternal age at booking	31.50 (5.02)	30.66 (6.33)	29.73 (5.64)	0.489
Maternal BMI at booking	37.67 (7.02)	34.34 (7.97)	36.16 (10.92)	0.106
FBG at HFDP diagnosis	6.44 (2.05)	5.92 (1.64)	6.14 (1.73)	0.288
OGTT 1-hour glucose at HFDP diagnosis	10.70 (2.15)	10.32 (2.22)	10.00 (2.05)	0.464
OGTT 2-hour glucose at HFDP diagnosis	9.50(2.50)	9.10 (2.45)	8.95 (1.50)	0.616
Third trimester 2-hour postprandial blood glucose	5.87 (0.74)	5.72 (0.85)	5.67 (1.06)	0.583

**All tests carried out using one-way ANOVA*

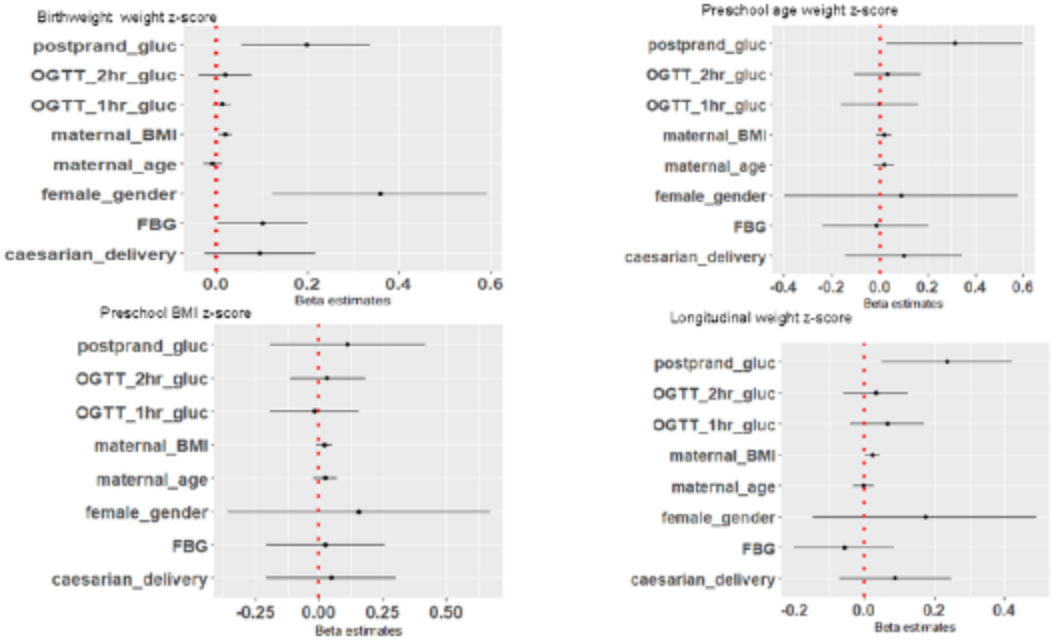
Post hoc tests were done with Bonferroni correction and only out when omnibus ANOVA was significant at p=0.05

Abbreviations: LGA, large for gestational age, AGA, appropriate for gestational age, SGA, small for gestational age, BMI, body mass Index, FBG, fasting blood glucose, HFDP, hyperglycaemia first detected in pregnancy, OGTT, oral glucose tolerance test

7.4.4. Association between maternal blood glucose and offspring weight outcomes at birth and preschool age

In multivariable analysis, maternal 2-hour postprandial glucose in the third trimester was significantly associated with weight z-score at birth (OR 1.23, 95%CI: 1.07 - 1.42, p = 0.005), at preschool age (OR 1.37, 95%CI: 1.03 - 1.81, p = 0.031), as well as weight z-score in longitudinal analysis (OR 1.26 (95%CI: 1.05 - 1.52, p = 0.014). Maternal 2-hour postprandial blood glucose was also significantly associated with both SGA at birth (OR 0.41, 95%CI0.170.95) and LGA (OR 1.58, 95%CI 1.15-2.16) (Table 7.4), after multinomial logistic regression. Maternal fasting blood glucose at HFDP diagnosis was significantly associated with weight z-score at birth only (OR 1.11, 95%CI 1 -1.22, p=0.046). Notably, maternal BMI at booking of pregnancy was consistently associated with weight outcomes at both time points (Fig 7.3). There were no significant associations between maternal blood glucose during the pregnancy and preschool-age BMI z-score or overweight and obesity (Fig 7.3).

Fig 7.3: Association between maternal blood glucose and z-scores for weight at birth and preschool age – multiple variable linear regression



Abbreviations: postprandial_gluc – Maternal 2-hour postprandial glucose during the third trimester
OGTT_1hr_gluc – Maternal OGTT 1-hour glucose at HFDP diagnosis
OGTT_2hr_gluc - Maternal OGTT 2-hour glucose at HFDP diagnosis
Maternal_BMI – Maternal Body Mass Index at pregnancy booking
Maternal_age – Maternal age at pregnancy booking
FBG – Maternal fasting blood glucose at HFDP diagnosis
Caesarian_delivery – Caesarian delivery at birth

Table 7.4: Association between maternal blood glucose during pregnancy and size at birth and BMI category at preschool age – Multinomial logistic regression

Preschool age					Birth			
Underweight BMI at preschool age					SGA at birth			
	RRR	p-value	lower 95%CI	Upper 95%CI	RRR	p-value	lower 95%CI	Upper 95%CI
2-hour postprandial glucose	0.67	0.24	0.35	1.30	0.41	0.04	0.17	0.95
FBG	1.08	0.76	0.68	1.71	0.61	0.17	0.30	1.23

OGTT 1hr glucose	0.85	0.35	0.60	1.20	0.90	0.47	0.67	1.21
OGTT 2hr glucose	1.06	0.71	0.79	1.42	0.91	0.54	0.67	1.23
Maternal age	0.95	0.33	0.87	1.05	1.06	0.18	0.97	1.17
Maternal BMI	1.06	0.08	0.99	1.13	0.96	0.30	0.88	1.04
Female gender	0.45	0.14	0.16	1.31	0.34	0.07	0.11	1.11
Caesarian delivery	1.05	0.85	0.63	1.74	1.20	0.51	0.69	2.09
SGA at birth	0.50	0.61	0.04	7.14				
LGA at birth	0.41	0.21	0.10	1.68				
Overweight and obese BMI at preschool age					LGA at birth			
2-hour postprandial glucose	1.16	0.57	0.69	1.97	1.58	0.01	1.15	2.16
FBG	1.12	0.56	0.76	1.65	1.08	0.47	0.87	1.34
OGTT 1-hr glucose	0.94	0.67	0.69	1.27	1.00	0.97	0.95	1.06
OGTT 2-hr glucose	1.02	0.89	0.79	1.31	1.06	0.36	0.93	1.21
Maternal age	1.00	0.94	0.92	1.09	1.00	0.86	0.96	1.05
Maternal BMI	1.06	0.04	1.00	1.12	1.03	0.12	0.99	1.06
Female gender	0.96	0.94	0.39	2.37	1.46	0.16	0.86	2.48
Caesarian delivery	1.44	0.10	0.93	2.24	1.46	0.01	1.10	1.92
SGA at birth	1.85	0.56	0.23	14.82				
LGA at birth	1.21	0.69	0.46	3.17				

Abbreviations: LGA, large for gestational age, AGA, appropriate for gestational age, SGA, small for gestational age, BMI, body mass Index, FBG, fasting blood glucose at HFDP diagnosis, HFDP, hyperglycaemia first detected in pregnancy, OGTT, oral glucose tolerance test

7.5. Discussion

Birth weight outcomes

At birth, we found that almost one third (29.6%) of children exposed to HFDP during pregnancy were LGA at birth; 12.2% had macrosomia and 7.5% LBW. Significantly higher proportions of neonates exposed to DIP were either LGA or had macrosomia at birth, compared to GDM-exposed neonates, although there were no significant differences in overweight and obesity at preschool age. We also found that maternal fasting blood glucose at HFDP diagnosis and maternal postprandial blood glucose during the third trimester were both associated with weight z-score at birth.

There are limited data on the effect of either HFDP or maternal blood glucose levels during pregnancy and offspring weight outcomes in Africa. In one study from Soweto, South Africa, out of 82 neonates born to women with GDM (defined using the IADPSG criteria), the prevalence of LGA was 6% while only 1% of the neonates had macrosomia (28). Our findings in a larger cohort show a high prevalence of both LGA and macrosomia at birth and suggest a need for interventions to either prevent GDM or treat more aggressively. LGA and macrosomia (birthweight >400 grams) are established risk factors for both childhood and adult overweight and obesity (5). On the other hand, LBW is a risk factor for developmental origins of adult cardiometabolic disease, with findings from several studies showing that infants with LBW have a higher risk for adult high blood pressure, diabetes and dyslipidaemia (6). In this study, 37.1% of the neonates were either LGA (29.6%) or LBW (7.5%). Apart from interventions to reduce risk of HFDP, and to improve treatment of HFDP, interventions may need to be targeted at these neonates, at an early age, to reduce risk of both childhood and adulthood overweight and obesity.

We found that both maternal fasting blood glucose at HFDP diagnosis and 2-hour postprandial glucose during the third trimester were associated with z-score for birthweight. Besides, 2-hour postprandial glucose was associated with both SGA and LGA, after adjusting for other glucose indices and maternal BMI at booking of pregnancy. Our findings on the effect of fasting glucose on offspring birthweight agree with published data (10). However, in contrast to the HAPO study, we found that OGTT 1-hour and 2-hour maternal glucose was not significantly associated with birth size. Instead, we found that postprandial exerted the strongest effect on weight outcomes. While data on the influence of postprandial glucose on offspring weight outcomes are sparse (29), data from trials have shown that tighter control of maternal blood glucose during the pregnancy reduces the risk of adverse perinatal outcomes, including both macrosomia and LGA (30), although data from Africa are scarce. Research is needed to provide evidence of Africa-specific interventions to improve maternal glucose.

We found that neonates exposed to DIP had birthweight z-scores which were 5 times higher than those for neonates exposed to GDM, with corresponding higher

proportions of LGA and macrosomia. Research comparing the effects of DIP and GDM on offspring weight outcomes is scarce. Women with DIP do not only have more severe dysglycaemia during the pregnancy but are more likely to have a higher risk of diabetes complications, during and after the pregnancy (8). In Africa, the high prevalence of undiagnosed diabetes of 69% (31) raises the possibility that some of the women with DIP may have had undiagnosed type 2 diabetes before the pregnancy (32). In South Africa, 83% of the mothers with DIP progressed to type 2 diabetes within 6 years (22), perhaps partly because a significant proportion of these women may have undiagnosed type 2 diabetes. By extension, offspring of women with DIP are more likely to have been exposed to hyperglycaemia for a longer period during the pregnancy, compared to the offspring of women with GDM. Our findings show a clear need to reduce exposure to untreated DIP in the offspring. One possible solution is to screen for diabetes earlier than the 24-28-week window recommended for GDM. An immediate drawback of the early screening using glucose testing, during the first trimester, for example, is the increased burden in costs and human resources required for glucose testing, as women who don't have DIP at the initial screening will still need to be screened for GDM later in the pregnancy. One way of overcoming the costly implications of first-trimester glucose testing is by using non-invasive prediction models which use routine clinical data. However, there are currently no prediction models for Africa populations and most of the existing prediction models lack external validity (33). Recent data from Johannesburg suggest that the use of a dual-threshold fasting plasma glucose, ≥4.5mmol/L to rule out, and 5.1mmol/L to rule in GDM, may result in only 2.4% missed cases of GDM (19). Using fasting blood glucose only for the diagnosis of HFDP will be less costly than the standard OGTT, and maybe a useful solution in the meantime. The lack of universal screening in South Africa, due to resource limitations is also another limitation as the selective screening currently in use in many provinces in South Africa uses non-validated risk factors and may leave almost half of women with HFDP undiagnosed (14). A non-invasive screening tool for GDM could be equally useful as it can be deployed in a universal testing strategy without adding an extra burden to the health system.

Preschool age weight outcomes

At preschool age, we found that more than a quarter (26.5%) children were either overweight or obese. This is almost twice as high as the 14% reported from recent South African national surveys (34, 35), and demonstrates a need for intervention in these children. Again, the lack of data from Africa in this area makes comparisons with published literature difficult. Evidence from a retrospective and prospective analysis of 51 505 adults, showed that those children who were overweight and obese during adolescence experienced the highest increases in BMI during the preschool ages 2-6 years, but not during the school years (4). Thus, the preschool age may be the critical time during childhood during which susceptibility to adulthood overweight and obesity occurs and when interventions may have the greatest impact.

We found that maternal 2-hour postprandial glucose during the third trimester was associated with weight z-score at preschool age but no significant associations between maternal blood glucose levels during pregnancy and preschool age BMI z-scores. In the HAPO follow-up study, there were no significant associations between a GDM diagnosis and child BMI at ages 10-14 years, although the authors found associations between GDM and other measures of adiposity (16). The 2-hour postprandial blood glucose is a measure of maternal blood glucose control during the third trimester and the possibility that poor glucose control during pregnancy could still exert an effect during preschool years has important clinical implications. More aggressive maternal blood glucose targets during the pregnancy may be required to reduce the risk of both LGA at birth and childhood overweight and obesity in the offspring.

An important observation from our study is the consistent association between maternal BMI and child weight outcomes at birth and preschool age. This may be particularly important in the South African setting where the prevalence of overweight in women was 65% in 2015 (34) and therefore women are more likely to be either overweight at preconception. Intervening to reduce pre-conception overweight and obesity may have many benefits as overweight and obesity is also the strongest risk factor for HFDP.

A limitation of our study is the use of routinely collected clinical data for maternal blood glucose values and birthweight. Conversely, the measurement of maternal blood glucose and birthweight by clinicians unrelated to the study is a strength as clinicians were not aware of the study and these measurements would not have been affected by ascertainment bias. As is usual with all routinely collected data, missing data made it difficult to assess the effect of all variables, in particular, maternal fasting and postprandial 1-hour glucose during the pregnancy. The loss to follow up in our study was high at preschool age, typical for longitudinal studies in our setting where in-and-out migration is high. Lastly, we did not include a comparison group of children who were not exposed to HFDP and future studies should include this group.

7.6. Conclusion

In offspring exposed to HFDP, there is a high prevalence of LGA and macrosomia at birth and overweight and obesity at preschool age, with higher prevalence in offspring exposed to DIP. Poor maternal blood glucose control during the pregnancy, represented by maternal postprandial 2-hour glucose increased the risk of both LGA and SGA at birth and was associated with weight z-score at preschool age. There is a need for earlier screening for HFDP in this setting, to allow earlier detection of DIP and intervention. Improved management of maternal blood glucose during pregnancy is needed to reduce the risk of both LGA and SGA at birth and overweight and obesity at preschool age.

Abbreviations

Hyperglycaemia first detected in pregnancy (HFDP), gestational diabetes mellitus (GDM), diabetes in pregnancy (DIP), World Health Organization (WHO), Hyperglycaemia and Adverse Pregnancy Outcomes Study (HAPO Study), International Association of Diabetes and Pregnancy Study Groups (IADPSG), glycated haemoglobin A1C (HbA1c), oral glucose tolerance test (OGTT), low-to-middle-income

(LMIC), large-for-gestational-age (LGA), low birth weight (LBW), standard deviation (SD), National Institute for Health and Care Excellence (NICE).

Acknowledgements

We thank Ms Chantal Stuart (administration) and Ms Siphokazi Khonkwane (data collection) at the Chronic Disease Initiative for Africa for their support during the data collection.

Funding

This research was funded by the Chronic Disease Initiative for Africa (http://www.cdia.uct.ac.za/). We acknowledge funding from the International Development Research Centre (IDRC) (fund number: 411592) for TC (under the IINDIAGO project). The funders played no role in the conception, the conduct or writing up of or the decision to submit this research for publication.

7.7. References

1. World Health Organization. Report of the commission on ending childhood obesity 2016 [cited 2019 25 April]. Available from: https://apps.who.int/iris/bitstream/handle/10665/204176/9789241510066_eng.pdf;jsessionid=7B 771A86BF399EC2867F54EDB97B8D12?sequence=1.
2. UNICEF-WHO-The World Bank Group. Joint child malnutrition estimates - Levels and trends (2018 edition) WHO WHO; 2018 [cited 2019 19 October]. Available from: https://www.who.int/nutgrowthdb/estimates2017/en/.
3. World Health Organisation. Consideration of the evidence on childhood obesity for the Commission on Ending Childhood Obesity: report of the ad hoc working group on science and evidence for ending childhood obesity, Geneva, Switzerland. 2016 [cited 2019 19 October]. Available from: https://apps.who.int/iris/bitstream/handle/10665/206549/9789241565332_eng.pdf?sequence=1 &isAllowed=y.

4. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in Early Childhood and Risk of Sustained Obesity. New England Journal of Medicine. 2018;379(14):1303-12.
5. Tanvig M. Offspring body size and metabolic profile: effects of lifestyle intervention in obese pregnant women: Syddansk Universitet; 2014.
6. Silveira PP, Portella AK, Goldani MZ, Barbieri MA. Developmental origins of health and disease (DOHaD). Jornal de pediatria Vol 83, n 6 (nov-dez 2007), p 494-504. 2007.
7. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. Experimental diabetes research. 2011;2011.
8. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy 2013 [Available from: https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessio nid=48ABC998E153A412E00E1CD62B90C1EC?sequence=1.
9. Ma RCW, Tsoi KY, Tam WH, Wong CKC. Developmental origins of type 2 diabetes: a perspective from China. European journal of clinical nutrition. 2017;71(7):870-80.
10. HAPO Study Cooperative Research Group. Hyperglycaemia and adverse pregnancy outcomes. New England Journal of Medicine. 2008;358(19):1991-2002.
11. Olagbuji BN, Atiba AS, Olofinbiyi BA, Akintayo AA, Awoleke JO, Ade-Ojo IP, et al. Prevalence of and risk factors for gestational diabetes using 1999, 2013 WHO and IADPSG criteria upon implementation of a universal one-step screening and diagnostic strategy in a subSaharan African population. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2015; 189:27-32.
12. Pastakia SD, Njuguna B, Ajwang'Onyango B, Washington S, Christoffersen-Deb A, Kosgei WK, et al. Prevalence of gestational diabetes mellitus based on various screening strategies in western Kenya: a prospective comparison of point of care diagnostic methods. BMC pregnancy and childbirth. 2017;17(1):226.

13. Macaulay S, Ngobeni M, Dunger DB, Norris SA. The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. Diabetes research and clinical practice. 2018; 139:278-87.
14. Adam S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: Prevalence, comparison of diagnostic criteria and the role of risk factors. South African Medical Journal. 2017;107(6):523-7.
15. Pedro TM, Kahn K, Pettifor J, Tollman S, Norris S. Under-and overnutrition and evidence of metabolic disease risk in rural black South African children and adolescents. South African Journal of Clinical Nutrition. 2014;27(4):194-200.
16. Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, et al. Association of Gestational Diabetes with Maternal Disorders of Glucose Metabolism and Childhood Adiposity. JAMA. 2018;320(10):1005-16.
17. Philipps L, Santhakumaran S, Gale C, Prior E, Logan K, Hyde M, et al. The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. Diabetologia. 2011;54(8):1957-66.
18. Kawasaki M, Arata N, Miyazaki C, Mori R, Kikuchi T, Ogawa Y, et al. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: a systematic review and metaanalysis. PLoS One. 2018;13(1): e0190676.
19. Dickson L, Buchmann E, van Rensburg CJ, Norris S. Fasting plasma glucose and risk factor assessment: Comparing sensitivity and specificity in identifying gestational diabetes in urban black African women. South African Medical Journal. 2019;110(1):21-6.
20. Guideline Development Group. Guidelines: management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ: British Medical Journal. 2008;336(7646):714.
21. Chivese T, Norris SA, Levitt NS. High prevalence of cardiovascular risk factors and insulin resistance 6 years after hyperglycaemia first detected in pregnancy in Cape Town, South Africa. BMJ Open Diabetes Research and Care. 2019;7(1).

22. Chivese T, Norris SA, Levitt NS. Progression to type 2 diabetes mellitus and associated risk factors after hyperglycaemia first detected in pregnancy: A cross-sectional study in Cape Town, South Africa. PLOS Medicine. 2019;16(9): e1002865.
23. INTERGROWTH-21st. The International Newborn Size at Birth Standards Application Oxford Oxford University 2017 2017 [cited 2019. Available from: https://intergrowth21.tghn.org/foetal -growth/#c2.
24. World Health Organization. The WHO Child Growth Standards 2007 [Available from: https://www.who.int/childgrowth/standards/en/.
25. Stata C. College Station (TX). Stata Press. 2016.
26. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.
27. World Medical Association (WMA). WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 2013 [Available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medicalresearch-involving-human-subjects/.
28. Macaulay S, Munthali RJ, Dunger DB, Norris SA. The effects of gestational diabetes mellitus on foetal growth and neonatal birth measures in an African cohort. Diabet Med. 2018;35(10):1425-33.
29. Prutsky GJ, Domecq JP, Wang Z, Carranza Leon BG, Elraiyah T, Nabhan M, et al. Glucose targets in pregnant women with diabetes: a systematic review and meta-analysis. The Journal of Clinical Endocrinology & Metabolism. 2013;98(11):4319-24.
30. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005;352(24):2477-86.
31. International Diabetes Federation. IDF Diabetes Atlas: International Diabetes Federation.; 2019 [cited 2020 13 January]. 9: [Available from: http://www.diabetesatlas.org.
32. International Association of Diabetes Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations

on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes care. 2010;33(3):676-82.

33. Lamain – de Ruiter M, Kwee A, Naaktgeboren CA, Franx A, Moons KGM, Koster MPH. Prediction models for the risk of gestational diabetes: a systematic review. Diagnostic and Prognostic Research. 2017;1(1):3.

34. Shisana O, Labadarios D, Rehle T, Simbayi L, Zuma K, Dhansay A, et al. The South African National Health and Nutrition Examination Survey, 2012: SANHANES-1: the health and nutritional status of the nation: HSRC press; 2014.

35. Pienaar AE. Prevalence of overweight and obesity among primary school children in a developing country: NW-CHILD longitudinal data of 6–9-yr-old children in South Africa. BMC obesity. 2015;2(1):2.

PART C. INTEGRATED DISCUSSION AND CONCLUSION

"If we do discover a complete theory, it should be in time understandable in broad principle by everyone. Then we shall all, philosophers, scientists, and just ordinary people be able to take part in the discussion of why we and the universe exist."

Stephen Hawking

CHAPTER 8. INTEGRATED DISCUSSION AND CONCLUSION

This chapter summarises findings of the body of work, followed the emerging methodological and empirical themes, implications for policy, practice and future research.

8.1 Principal findings and emerging themes

8.1.1. Principal findings

The findings of the body of work undertaken are summarized in Table 8.1.1.

Table 8.1.1. Key findings

Objective(s)	Chapter	Key findings
Objective 1: To estimate the prevalence of T2DM and impaired glucose metabolism in women of childbearing age (15-54 years) living in Africa during 2000-2016	4	The pooled prevalence of T2DM was 7.2%, impaired fasting glucose (IFG) 6.0%. The prevalence of impaired glucose tolerance ranged from 0.8% to 37.0%
Objective 2: To estimate the proportion of	5	• Almost half (48%) of the women progressed to T2DM; 83% with DIP 31% of those with GDM.

women who progressed to T2DM within 6 years after HFDP, and investigate factors associated with the risk of postpartum T2DM in these women in Cape Town, South Africa		• Risk factors associated with T2DM at follow up were; treatment with insulin and oral hypoglycemics during the pregnancy, fasting and OGTT 2-hour glucose at HFDP diagnosis and BMI, waist and hip circumference at follow-up.
-Objective 3: To investigate the prevalence of CVD risk factors in women 6 years after HFDP, in Cape Town, South Africa	6	• There was a high prevalence of central obesity; (90%), measured using waist circumference ≥88cm) and generalized obesity measured using BMI≥30kg/m^2 (69%). • There was a high prevalence of insulin resistance (75%), dyslipidaemia (75%), and raised blood pressure (41%) • Almost two-thirds of the women (62%) had metabolic syndrome
Objective 4: To investigate the association between maternal blood glucose concentrations	7	• The mean birthweight z-score for children exposed to DIP was 5 times higher than that for neonates exposed to GDM. • Maternal blood glucose at diagnosis of HFDP (fasting and OGTT 2-hour blood glucose) and postprandial 2-hour glucose during the third trimester were associated with both increased

during HFDP and offspring weight at birth and overweight/ obesity at preschool age and		birthweight z-score and increased risk of LGA at birth. • At preschool age, the prevalence of overweight and obesity was 27%, with a slightly higher prevalence in children exposed to DIP compared to those exposed to GDM. • Postprandial glucose was significantly associated with a 37% increase in child weight z-score at preschool age but not with child BMI z-score.

8.1.2. Emerging themes

There were 2 main themes: the first being methodological and the second empirical. Two main quantitative study designs were employed to answer the prespecified specific objectives. The systematic review and meta-analysed method was used to estimate the prevalence of T2DM and impaired glucose metabolism in African women childbearing age. The systematic review and meta-analysis allowed us to understand the background prevalence of T2DM and the estimates from the meta-analysis could be used to monitor trends and the success of intervention to prevent T2DM. However, several challenges were encountered. First, as discussed in Chapter 4, is the lack of good quality gender and age-group specific data. This is particularly why the estimate of T2DM, and prediabetes included women between the ages 49-54 years, outside the definition of childbearing age. Second, the unexplained heterogeneity in the prevalence estimates also poses a challenge, which could be explained by a combination of differences in setting, screening and diagnosis methods. However, limitations exist in the current meta-analysis regarding examining the effects of multiple variables on the prevalence of diabetes. These limitations include the lack of study-level data on some of the variables that could have helped explain the heterogeneity. Individual participant meta-analyses may provide a solution if data from individual studies can be accessed.

The PRO2D was a hybrid of a case series during pregnancy, followed by a cross-sectional study at follow-up. A cohort study, with a comparative group of unexposed women and their offspring, would have been best suited to study the cardiometabolic outcomes of women and their offspring after HFDP. The cohort study will have enabled us to compare the cardiometabolic outcomes between the two groups and make stronger inferences. However, a lack of resources and time constraints made such a design impractical at the time of the study. One possible solution could be to extend existing trials into cohorts, although there is a scarcity of trials in this area in Africa.

Diabetes at this age affects a woman's family, as African women play multiple critical roles in their families and has the potential to affect future generations through the transmission of T2DM risk to her offspring through epigenetic mechanisms. Our findings suggest that maternal blood glucose during pregnancy increased the risk of higher weight z-score at preschool age, which may contribute to increased risk of cardiometabolic disease for the offspring. Notably, our findings are not novel, as data from other parts of the world have shown a similar association between maternal blood glucose levels during pregnancy and child cardiometabolic outcomes, albeit with a great degree of heterogeneity from different settings. However, our findings are novel in the African context, a context where undernutrition and overnutrition are highly prevalent, and where social determinants of health and disease are complex and under-studied. The lack of research in this area is a challenge that needs to be addressed urgently in Africa.

During the index pregnancy, women in our study were screen using risk-factor-based screening, which may leave many women with HFDP undiagnosed. Further, this may mean that the women in our study are not entirely representative of the women with HFDP in the Western Cape. Universal screening may help arrive at a closer estimate of women who develop diabetes after HFDP. But the capacity to screen more women for HFDP or to introduce preventive programs for African women with HFDP is limited. Innovative use of the existing health resources so women can be screened for HFDP earlier and for T2DM and CVD after the pregnancy may provide a solution to the

problem. Both HFDP and T2DM are preventable and additional investment in this area would have high benefits to the individual women, the health system and the larger society. Some of the empirical themes are discussed in detail in the next sections.

8.2. Implications for policy and practice

Our findings have notable implication for policy and practice, as discussed below.

8.2.1. Prevention of hyperglycaemia first detected in pregnancy is critical

Findings from the PRO2D study, in the context of literature, have several ramifications for policy and practice. Although data from Africa continue to be sparse, several studies have already reported a high prevalence of HFDP, between 25-31%, in South Africa and Cameroon (9, 10). This implies that a large proportion of African women are potentially at risk of long-term cardiometabolic disease risk. Indications are that the prevalence will increase as the prevalence of obesity, one of the strongest drivers of HFDP, continues to increase across the African continent (14). Preventing HFDP itself may be the single most important intervention, as this will result in fewer pregnancy complications and reduce the risk of cardiometabolic disease in the women and their offspring.

A yet unanswered question concerns the best interventions to prevent HFDP in Africa. Similar to the prevention of T2DM, prevention of HFDP could be done either through population-wide measures or targeted intervention. One of the population-wide interventions involves policies that mitigate against obesogenic environments. South Africa is one of the first African countries to implement a “sugar tax”. Life table-based models suggest that if the sugar tax is implemented over 20 years in South Africa, the prevalence of T2DM could be reduced by up to 4% (15). This reduction in T2DM prevalence will be mediated mainly by the reduction of body mass index (BMI) through reduced consumption of sugar-sweetened beverages (SSBs) (15).

Although there are no projections on the possible impact of the sugar tax on HFDP prevalence in Africa, the prevalence may also decline as decreased

consumption of SSBs may result in a population-level decrease in BMI. However, whether the sugar tax will have the expected impact on either T2DM or HFDP remains debatable as the tax is in the early stages of implementation in South Africa. A systematic review of 17 studies found that purchases of SSBs decreased by 8% in California and 10% in Mexico (16). In California, the reduction in sugar-sweetened beverages intake was sustained over 3 years after the implementation of the sugar tax (17). However, in Chile, a low-to-medium-income country (LMIC) similar to South Africa, the reductions in SSBs intake after a year of implementation of a sugar tax in 2014 were small and were not likely to change overweight and obesity profile at a population level (18, 19). This was partly explained by the availability of untaxed substitutes which were not affected by the sugar tax and remained available at cheap prices. The availability of untaxed substitutes may pose a similar problem in South Africa.

Even if the population BMI does not decrease, the sugar tax will have benefit if the proceeds are channelled towards programs for the prevention of cardiometabolic disease in the population. Diabetes in women and HFDP have such wide-ranging consequences on the population health in the short and long term and could potentially affect generations after the initially exposed offspring (20). Therefore, a prime candidate for the use of the sugar tax could be the funding of programs to prevent and better screen for HFDP and mitigate against the risk of T2DM and CVD after the pregnancy.

Interventions targeting women who are planning to be pregnant, or women in the early stages of pregnancies are another way that can be used to prevent HFDP. However, many previous meta-analyses of randomized controlled trials have demonstrated contradicting results from either lifestyle interventions (21) or pharmacological interventions (22) in preventing HFDP. One meta-analysis of 13 randomized studies showed that structured physical activity throughout the pregnancy reduced risk of GDM by 36% (23). Another meta-analysis of 29 randomized controlled trials showed an 18% GDM risk reduction (24). On the hand, other meta-analyses have not found clinically significant effects from lifestyle interventions on either reducing excessive weight gain during pregnancy or reducing the risk of HFDP (25)(26).

The heterogeneous findings from the many existing clinical trials and meta-analyses make it difficult to produce either evidence-based interventions or policy to prevent HFDP in Africa. There is evidence that a combination of both diet and exercise significantly reduced risk of HFDP by 23% (27). However, for these interventions to be effective, certain elements had to be present. The interventions were most effective when intensified diet and exercise were used during early pregnancy in women at high risk. Besides, interventions were successful when risk evaluation models were used to identify women at high risk and when the interventions targeted gestational weight gain. Notably, none of the aforesaid reviews included data from Africa, and it is doubtful whether these findings could be applied in the same way in Africa, where food insecurity is still prevalent and, in many cases, structured physical activity is not feasible due to time and resource limitations.

8.2.2. Early screening for HFDP may help detect HFDP early and reduce the length of exposure to hyperglycaemia

The SEMDSA in its 2017 guidelines, in line with the IADPSG, recommended that women with risk factors be screened for GDM at first booking using a 2-hour OGTT, to allow for earlier diagnosis of DIP (28). The 2-hour OGTT should then be repeated at 24-28 weeks gestation for women without DIP at the initial screening (28). For the diagnosis of DIP during early pregnancy, the WHO (13), the IADPSG (29) and other international bodies recommend the use of criteria for diabetes diagnosis outside of pregnancy.

Findings from our meta-analysis show that one in 14 women of childbearing age is affected by T2DM. In a continent where up to 69% of people living with diabetes are not diagnosed (1), early screening for HFDP would help detect women with undiagnosed diabetes. Further, findings from the PRO2D study showed that women with DIP and their offspring had worse outcomes. Some of the women could have had undiagnosed T2DM during the pregnancy and early screening would have helped detect this.

In the PRO2D study we found a high proportion of women with DIP, about 40% during the index proportion and it highly likely that undiagnosed pre-existing diabetes may have contributed to this. If undiagnosed diabetes and DIP in early pregnancy are to be detected efficiently during early pregnancy, an acceptable, accurate and relatively cheap screening method is needed. Currently, the OGTT is the accepted standard for testing for diabetes in pregnancy (13, 30-32), but it is resource intensive. Alternative, cheaper tests that have diagnostic accuracy comparable to the OGTT are therefore required. Random blood glucose can be used to diagnose DIP at a cut-off of 11.1mmol/L (13) (33) but had a reported low sensitivity of 71% from one study (34) and therefore may leave many women with DIP undiagnosed. Using fasting blood alone has also been suggested but it also has poor sensitivity compared to the OGTT (35). The use of the HbA1c is also hampered by similar constrains of poor diagnostic accuracy compared to the OGTT (35). The use of prediction models, based on non-invasive risk factors, which identify women at high risk who then undergo an OGTT, may offer a solution. However, prediction models are usually context-specific (36-39) and research is needed to develop models that are specific to different Africa contexts.

Early screening for HFDP can also be used to detect early onset GDM. Findings from a systematic review suggest that, depending on the setting, the screening strategy and methods used, between 15-70% of GDM can be detected before 24 weeks (40). Although there is consensus on the criteria for the diagnosis of DIP/ overt diabetes in early pregnancy (13, 29), debate on the optimum cut-offs for early GDM is still ongoing (35, 40). For example, the IADPSG (29) initially recommended that the same criteria used at 24-28 weeks' gestation be used at the first antenatal visit. However, after findings from Italy (41) and China (42) showed that the fasting plasma glucose between 5.1-6.9 mmol/L was a poor predictor of GDM during 24-28 weeks gestation, the IADPSG (43) subsequently cautioned against the use of fasting plasma glucose between 5.1-6.9 mmol/L for the diagnosis of early GDM. Other researchers have investigated the use of the glycated haemoglobin A1C (HbA1c) for the diagnosis of GDM during the first trimester (40). However, most of the studies have found low sensitivity, ranging from 13-29%, in predicting OGTT-diagnosed GDM when the HbA1C

cut-offs for prediabetes outside of pregnancy (5.7-5.9%) were used (34, 44-46). In our setting, policy on the diagnosis of early GDM is needed but requires more research to establish appropriate screening methods and criteria for diagnosis.

Lastly, although universal screening for HFDP is recommended by many of the international bodies, it may not be feasible in African health systems as it would overburden healthcare systems. The SEMDSA recommends the use of universal screening, where resources are available. The National Guidelines for Maternity Care in South Africa (47) and the Western Cape province Diabetes in Pregnancy guidelines (48) both recommend a risk-factor-based approach. These risk factors include any of; repeated glycosuria, previous GDM, family history of diabetes, history of stillbirths, a previous baby with macrosomia, BMI≥30kg/m2, polycystic ovarian syndrome and history of perinatal death and South Asian descent. The limited evidence available suggests this risk factor-based screening is applied inconsistently across and within the provinces (49). Further, the risk factors used have not been evaluated fully to improve their diagnostic accuracy for HFDP in South African women. Findings from one study showed that the use of this risk factor-based approach in the Western Cape could result in half of the women with GDM being missed (50). If the risk-factor based approach is to be continued, then the risk factors need to be evaluated and appropriately weighted for the South Africa context.

8.2.3. Screening for T2DM and CVD risk factors after HFDP needs to be improved

We found that almost half of the women with T2DM, 80% with raised blood pressure and 91% of those with dyslipidaemia were undiagnosed. In line with international standards (13, 30, 51), the SEMDSA (12) recommends that women with HFDP should be assessed at delivery and diabetes treatment stopped if their blood glucose returns to normal after delivery. If a woman has persistent hyperglycaemia after the pregnancy, she must continue treatment. For women whose blood glucose returns to normal after delivery, the SEMDSA recommends that they must be assessed

for diabetes using a 2-hour OGTT 6-weeks after the pregnancy and screened for T2DM using HbA1c annually thereafter.

In the Western Cape, women are given a referral letter to be screened for diabetes after 6 weeks at a primary health care facility close to their homes (49). The proportion of women who attend the 6-week OGTT is low, estimated to be below 30% (52). This could be because there are several barriers to women attending this 6-weeks screening. The health system is fragmented as the women have to go to a separate facility for the 6-weeks screening while at the same time taking their babies to a “Well baby clinic” for the mandatory 6-week check-up and immunization (49). This may discourage many women from attending the 6-weeks screening, as women naturally prioritize their babies’ appointments over theirs. Besides, because many of the primary care facilities are overburdened, even when the women go for the 6-week’s visit, they may not be screened as the OGTT is not offered routinely (49). Low perception of T2DM risk in women with GDM whose blood glucose returns to normal at delivery may also contribute to the low attendance for the 6-weeks diabetes screening (49). Other barriers against attendance are a lack of money to travel to the health facility and a lack of time as some women would have returned to work (49).

The OGTT could impede women attending the 6-week visit due to the need for fasting, the time commitment and the discomfort associated with drawing blood (53). The use of HbA1c has been suggested (53) but the test has low sensitivity, 19% in one study 6-12 weeks post GDM (54) and poor concordance with the OGTT (Kappa = 0.058) in another study (55). Using either fasting blood glucose only or with HBA1C, either alone or in a two-step way process, to screen for post-partum T2DM, could offer cost-effective and attractive alternatives to the OGTT. However, the use of the HBA1C as an alternative to the OGTT still requires more research and possibly requires moving the screening timing further than 3 months after the pregnancy, to avoid capturing pregnancy-related hyperglycaemia.

Innovative solutions are needed so that screening for T2DM after HFDP could be improved but the dearth of context-specific evidence is an impediment. A currently ongoing trial (Trial registration: PACTR201805003336174) is investigating whether

integrating the post-partum care of the mother with the scheduled clinic visits for her offspring will improve screening rates. Another possible solution could be extending the screening period from 6 weeks to give women more time to get over early postpartum pressures. There is also a need for innovative solutions for women who go back to work soon after pregnancy.

Poor follow-up for long term post-partum screening for T2DM is also a problem that needs to be addressed. There are sparse data about attendance for medium to long term screening for wither T2DM or the other CVD risk factors. Using the OGTT for medium to long term screening is likely to have the same limitation that the data for 6-week screening has shown – health system constrains compounded by individual constrains. The HbA1C does not require prior fasting, is simple to use, costs less overally, can be done with capillary blood using a pin prick and can easily be done at the point of care. The advantages of the HbA1C in screening for T2DM in women with a previous history of GDM are many especially in resource limited settings, like Africa. Using either the FPG alone or the HbA1C may offer an alternative to the OGTT again but there are still unanswered research questions. These questions include; the proportion of women with T2DM who will be missed if either the FPG or the HbA1C are used, whether combining the two (FPG and HbA1C) is advisable, and whether combining the two tests is cost effective.

Finally, our findings suggest the need to screen for other CVD risk factors during the postpartum period, specifically hypertension and dyslipidaemia. An advantage of this is that the additional screening would not significantly add to the burden on health workers and adds a small extra cost for laboratory testing for lipids. The lipids could be assessed from the same blood drawn for fasting blood glucose during screening for T2DM while blood pressure measurement is a relatively simple and quick process.

8.2.4. Interventions for the prevention of T2DM and CVD after HFDP are needed

Similar to the prevention of HFDP, prevention of T2DM and CVD during the postpartum period could be through either population-wide intervention such as the sugar tax discussed earlier or targeted intervention. Diabetes prevention programs (DPPs) have shown that lifestyle modification interventions can reduce the risk of T2DM in women after HFDP. A meta-analysis of 12 randomized controlled trials, with a median follow-up of 6 months, showed that postpartum interventions can reduce the risk of T2DM progression, reduce risk of insulin resistance and decrease weight (56). Further, a network meta-analysis of 44 DPPs in the USA (57), showed that the DPPs resulted in meaningful change in cardiometabolic health profile, apart from reducing diabetes risk. The pooled changes over a median follow-up of 9 months included a weight loss of 4kg, reductions of systolic and diastolic blood pressure of 4mmHg and 2.6mmHg, respectively, an increase in HDL of 0.05 mmol/L and a decrease of total cholesterol of 0.3 mmol/L. These findings show that prevention of T2DM and CVD can be successfully achieved using the same intervention. Incorporating lifestyle modification counselling in postpartum settings may have benefit, although there is a need to test interventions that can work in Africa.

There is also a need to address the barriers to lifestyle modification in women after HFDP. Considerable evidence from both international research (58) and data from Cape Town, South Africa (49, 59) suggests that women modify their diet and physical activity during the HFDP complicated pregnancy. However, the women revert to their lifestyles after the pregnancy (49, 58). In Cape Town, 6 months after the HFDP-complicated pregnancy, women increased their intake of SSBs, added sugar, carbohydrates and energy-dense snacks, relative to their diet during the pregnancy (60). The failure to maintain the pregnancy lifestyle modification after the pregnancy could be partly due to two factors: for most women, the blood glucose returns to normal levels and the delivery of a healthy baby. These factors combined may make them feel that there is no longer a need to keep on with lifestyle modifications. Many studies have also reported a lower T2DM risk perception in women after delivery, once their blood glucose returns to normal (58). Other barriers to sustained lifestyle modification after the pregnancy include multiple roles in the family, demands of family life and raising the child, a lack of support from family and peers, and lack of information about diabetes

prevention (61-66). Lack of money and resources is also a frequently cited barrier as most women perceive healthy lifestyles as expensive (67). The format of interventions also affects their acceptability with many women preferring face-to-face interviews and flexible timing which allows them to attend to their jobs and families (63, 68, 69). Policies that address barriers to the maintenance of lifestyle modifications in the postpartum period are needed in Africa.

Interventions for the prevention of HFDP itself or targeting an improved diet and physical activity are beneficial for the offspring but data are not conclusive. A meta-analysis of 105 studies showed a 39% reduction in the odds of macrosomia in women who exercised during pregnancy, compared to those who did not (70). However, maternal exercise had no impact on childhood risk of overweight and obesity.

Population-based approaches, such as the sugar tax, school-based nutritional and physical activity interventions may also have a positive effect on the cardiometabolic health of the children. In offspring at risk of overweight and obesity, there is a need for intervention as early as possible to reduce the risk of childhood overweight and obesity. However, an overview of meta-analyses found that interventions to reduce the risk of obesity in children have not shown much effect (71). More research is needed to study the interventions that can be effective in reducing the risk of adulthood overweight and obesity in children at risk.

8.3. Implications for future research

While our research presents some important findings, it also raises several pertinent research questions. These implications relate to the lack of data for monitoring trends and progress in reducing diabetes prevalence in Africa, and data about effective interventions for the prevention of HFDP, T2DM and CVD in women of childbearing age.

8.3.1. The burden of T2DM in African women of childbearing age is not known

There is a dearth of good quality data on T2DM prevalence in women of childbearing age, as we found data from 27 African countries only. Besides, data from nationally representative studies are also lacking. Further, three-quarter of the studies included in our systematic review and meta-analysis used FPG while the remainder used the the 2-hour OGTT. Given that the prevalence of T2DM was higher (10%) in studies which used the OGTT compared to those that used the FPG (6%), the prevalence estimate we found could be an underestimate of the true prevalence of T2DM in women of children bearing age. The issue of lack of good quality data could be addressed by using the WHO STEPWise approach, which would ensure similar rigorous research collection methods are used across different countries to obtain diabetes estimates.

8.3.2. Effective interventions for the prevention of HFDP in Africa are not known

To prevent HFDP, there is a need for interventions that are context-specific and informed by research findings from Africa. Research is also needed to investigate the best timing of these interventions, the core outcomes for the interventions and appropriateness to the African setting. Qualitative research may also help explain how women feel about the proposed interventions. Further, studies on the cost-effectiveness of the interventions and their impact on offspring cardiometabolic outcomes are also needed.

8.3.3. The most cost-effective screening methods for HFDP in early pregnancy in Africa are not known

To our knowledge, there are no studies in Africa on long term cardiovascular risk that have been carried out in women who have HFDP detected using less stringent screening criteria. There is need to investigate outcomes for both offspring and mothers

The case against universal screening for HFDP is strong due to the cost to the health system. However, the risk-factor based screening currently in use is based on factors that are not well tested in Africa. Studies are needed on risk factors for GDM and their relative contribution in the African context. Besides, more research is required to find the most cost-effective method for screening for HFDP that can be used in early pregnancy with good diagnostic accuracy, compared to the standard OGTT. A related research need is to establish criteria for the diagnosis of GDM in early pregnancy, preferably linked to maternal and foetal outcomes.

8.3.4. Research on interventions to promote the uptake of the postpartum screening for T2DM and CVD of women with HFDP is needed

Our findings suggest that many women could have benefitted from the postpartum follow-up, either with encouragement to maintain lifestyle modification or screening to detect diabetes early and reduce the risk of complications. Research on the best ways to encourage uptake of postpartum follow-up for women after HFDP is needed.

8.3.5. Effective interventions to prevent or delay T2DM and CVD risk after HFDP in Africa are not known

Apart from one ongoing trial (Trial registration: PACTR201805003336174), to our knowledge, there are no other data on effective interventions to reduce risk of both T2DM and CVD in women after HFDP. Research is needed to investigate the most cost-effective interventions to reduce T2DM and CVD risk in African women after

HFDP. Trials are also needed to investigate the best timing, type of interventions, length and dose and acceptability of these interventions.

8.4. Strengths and limitations of this research study

This research contributes data on the prevalence of T2DM and prediabetes in women of childbearing age in Africa, to date. Further, this research contributes to the understudied area of the effects of HFDP on the cardiometabolic health of the mother and her offspring in Africa.

This research has several limitations. The lack of age-group specific data from many African countries resulted in the inclusion of only 27 countries in our estimate of the overall pooled prevalence of T2DM in women of childbearing age in Africa in the systematic review and meta-analysis. Further, poor data quality in some of the included studies in the systematic review and meta-analysis may have resulted in a T2DM estimate that may not be very accurate. Lastly, we found high unexplained statistical heterogeneity in our meta-analysis and again this affects the accuracy of the pooled estimates from the systematic review and meta-analysis.

A key limitation of the PRO2D study was the absence of a control group, due to resource limitations. A control group would have enabled us to study the risk attributable to HFDP, for the future development of T2DM and CVD in women and risk for overweight and obesity in the offspring. Most of the women in our study were not assessed for T2DM at the recommended 6-week follow-up, and this could have contributed to the high prevalence of T2DM observed in the DIP group.

We used routinely collected clinical data, for OGTT glucose results at HFDP, intra-pregnancy data and birthweight measurements. Apart from missingness in these data, one other disadvantage of using these data is that there may not be enough data quality control mechanisms in clinical settings. However, the measurement of key variables by clinicians who were not associated with this study was a strength as it reduced the risk of ascertainment bias.

Due to a lack of resources, we were only able to assess overweight and obesity in the offspring using weight and height, instead of comprehensive assessments. A further limitation of this research was the loss to follow-up at the 5-6 years assessment. However, this is typical of many longitudinal studies which have followed up women and their offspring after HFDP, in many parts of the world.

8.5. Conclusion

The high prevalence of T2DM and CVD risk factors in relatively young women and overweight and obesity in their offspring within 6 years of the index pregnancy demonstrates the need for context-specific interventions to prevent HFDP, to optimise screening for HFDP and to reduce cardiometabolic disease risk in the postpartum period.

8.6. References

1. International Diabetes Federation. IDF Diabetes Atlas: International Diabetes Federation.; 2019 [cited 2020 13 January]. 9: [Available from: http://www.diabetesatlas.org.]
2. Abell SK, Boyle JA, de Courten B, Soldatos G, Wallace EM, Zoungas S, et al. Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57(3):308-14.
3. Schaefer-Graf U, Napoli A, Nolan CJ, Diabetic Pregnancy Study G. Diabetes in pregnancy: a new decade of challenges ahead. Diabetologia. 2018;61(5):1012-21.
4. Becker M, Breuing J, Nothacker M, Deckert S, Brombach M, Schmitt J, et al. Guideline based quality indicators—a systematic comparison of German and international clinical practice guidelines. Implementation Science. 2019;14(1):71.
5. Zand A, Ibrahim K, Patham B. Prediabetes: Why Should We Care? Methodist Debakey Cardiovasc J. 2018;14(4):289-97.

6. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis. BMJ. 2016;355: i5953.
7. Macaulay S, Dunger DB, Norris SA. Gestational diabetes mellitus in Africa: a systematic review. PloS one. 2014;9(6): e97871-e.
8. Mwanri AW, Kinabo J, Ramaiya K, Feskens EJ. Gestational diabetes mellitus in subSaharan Africa: systematic review and metaregression on prevalence and risk factors. Tropical Medicine & International Health. 2015;20(8):983-1002.
9. Natamba BK, Namara AA, Nyirenda MJ. Burden, risk factors and maternal and offspring outcomes of gestational diabetes mellitus (GDM) in sub-Saharan Africa (SSA): a systematic review and meta-analysis. BMC pregnancy and childbirth. 2019;19(1):450.
10. Muche AA, Olayemi OO, Gete YK. Prevalence and determinants of gestational diabetes mellitus in Africa based on the updated international diagnostic criteria: a systematic review and meta-analysis. Archives of Public Health. 2019;77(1):36.
11. Guideline Development Group. Guidelines: management of diabetes from preconception to the postnatal period: summary of NICE guidance. BMJ: British Medical Journal. 2008;336(7646):714.
12. SEMDSA Type 2 Diabetes Guidelines Expert Committee. Chapter 3: Screening and diagnosis of type 2 diabetes and intermediate hyperglycaemia 2017 [cited 2020. Available from: https://www.semdsa.org.za/images/647-4385-1-PB.pdf.
13. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy 2013 [Available from: https://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf ;jsessio nid=48ABC998E153A412E00E1CD62B90C1EC?sequence=1.]
14. Group NRFCAW. Trends in obesity and diabetes across Africa from 1980 to 2014: an analysis of pooled population-based studies. International Journal of Epidemiology. 2017;46(5):1421-32.

15. Manyema M, Veerman JL, Chola L, Tugendhaft A, Labadarios D, Hofman K. Decreasing the Burden of Type 2 Diabetes in South Africa: The Impact of Taxing Sugar-Sweetened Beverages. PLoS One. 2015;10(11): e0143050.
16. Redondo M, Hernández-Aguado I, Lumbreras B. The impact of the tax on sweetened beverages: a systematic review. Am J Clin Nutr. 2018;108(3):548-63.
17. Lee MM, Falbe J, Schillinger D, Basu S, McCulloch CE, Madsen KA. Sugar-Sweetened Beverage Consumption 3 Years After the Berkeley, California, Sugar-Sweetened Beverage Tax. American journal of public health. 2019;109(4):637-9.
18. Caro JC, Corvalán C, Reyes M, Silva A, Popkin B, Taillie LS. Chile's 2014 sugar-sweetened beverage tax and changes in prices and purchases of sugar-sweetened beverages: An observational study in an urban environment. PLoS medicine. 2018;15(7): e1002597-e.
19. Nakamura R, Mirelman AJ, Cuadrado C, Silva-Illanes N, Dunstan J, Suhrcke M. Evaluating the 2014 sugar-sweetened beverage tax in Chile: An observational study in urban areas. PLoS Med. 2018;15(7): e1002596.
20. King SE, Skinner MK. Epigenetic Transgenerational Inheritance of Obesity Susceptibility. Trends in Endocrinology & Metabolism. 2020.
21. Egan AM, Simmons D. Lessons learned from lifestyle prevention trials in gestational diabetes mellitus. Diabetic Medicine. 2019;36(2):142-50.
22. Doi SAR, Furuya-Kanamori L, Toft E, Musa OAH, Islam N, Clark J, et al. Metformin in pregnancy to avert gestational diabetes in women at high risk: Meta-analysis of randomized controlled trials. Obesity Reviews. 2020;21(1): e12964.
23. Sanabria-Martínez G, García-Hermoso A, Poyatos-León R, Álvarez-Bueno C, SánchezLópez M, Martínez-Vizcaíno V. Effectiveness of physical activity interventions on preventing gestational diabetes mellitus and excessive maternal weight gain: a meta-analysis. BJOG: An International Journal of Obstetrics & Gynaecology. 2015;122(9):1167-74.
24. Song C, Li J, Leng J, Ma RC, Yang X. Lifestyle intervention can reduce the risk of gestational diabetes: a meta-analysis of randomized controlled trials. Obesity Reviews. 2016;17(10):960-9.

25. Shepherd E, Gomersall JC, Tieu J, Han S, Crowther CA, Middleton P. Combined diet and exercise interventions for preventing gestational diabetes mellitus. Cochrane Database of Systematic Reviews. 2017(11).
26. International Weight Management in Pregnancy Collaborative G. Effect of diet and physical activity-based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. BMJ (Clinical research ed). 2017;358: j3119-j.
27. Guo X-Y, Shu J, Fu X-H, Chen X-P, Zhang L, Ji M-X, et al. Improving the effectiveness of lifestyle interventions for gestational diabetes prevention: a meta-analysis and metaregression. BJOG: An International Journal of Obstetrics & Gynaecology. 2019;126(3):311-20.
28. SEMDSA Type 2 Diabetes Guidelines Expert Committee. SEMDSA 2017 guidelines for the management of type 2 diabetes mellitus. J Endocr Metab Diabetes S Afr. 2017;22(1 Suppl 1): S1-196.
29. International Association of Diabetes Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care. 2010;33(3):676-82.
30. (NICE). NIfHaCE. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. Clinical guideline NG3 (2015). 2015 [Available from: www.nice.org.uk/guidance/ng3/resources/diabetes-in-pregnancy-management-of-diabetes-anditscomplications-from-preconception-to-the-postnatal-period-51038446021
31. Nankervis A, McIntyre H, Moses R, Ross G, Callaway L, Porter C, et al. ADIPS consensus guidelines for the testing and diagnosis of gestational diabetes mellitus in Australia. Modified June. 2014.
32. Kautzky-Willer A, Harreiter J, Winhofer-Stöckl Y, Bancher-Todesca D, Berger A, Repa A, et al. [Gestational diabetes mellitus (Update 2019)]. Wien Klin Wochenschr. 2019;131(Suppl 1):91-102.

33. Meek CL, Murphy HR, Simmons D. Random plasma glucose in early pregnancy is a better predictor of gestational diabetes diagnosis than maternal obesity. Diabetologia. 2016;59(3):445-52.
34. Maegawa Y, Sugiyama T, Kusaka H, Mitao M, Toyoda N. Screening tests for gestational diabetes in Japan in the 1st and 2nd trimester of pregnancy. Diabetes research and clinical practice. 2003;62(1):47-53.
35. Vitacolonna E, Succurro E, Lapolla A, Scavini M, Bonomo M, Di Cianni G, et al. Guidelines for the screening and diagnosis of gestational diabetes in Italy from 2010 to 2019: critical issues and the potential for improvement. Acta Diabetol. 2019;56(11):1159-67.
36. Brown N, Critchley J, Bogowicz P, Mayige M, Unwin N. Risk scores based on selfreported or available clinical data to detect undiagnosed type 2 diabetes: a systematic review. Diabetes research and clinical practice. 2012;98(3):369-85.
37. Dall TM, Narayan KV, Gillespie KB, Gallo PD, Blanchard TD, Solcan M, et al. Detecting type 2 diabetes and prediabetes among asymptomatic adults in the United States: modeling American Diabetes Association versus US Preventive Services Task Force diabetes screening guidelines. Population health metrics. 2014;12(1):12.
38. Dugee O, Janchiv O, Jousilahti P, Sakhiya A, Palam E, Nuorti JP, et al. Adapting existing diabetes risk scores for an Asian population: a risk score for detecting undiagnosed diabetes in the Mongolian population. BMC public health. 2015;15(1):938.
39. Sulaiman N, Mahmoud I, Hussein A, Elbadawi S, Abusnana S, Zimmet P, et al. Diabetes risk score in the United Arab Emirates: a screening tool for the early detection of type 2 diabetes mellitus. BMJ Open Diabetes Research and Care. 2018;6(1): e000489.
40. Immanuel J, Simmons D. Screening and Treatment for Early-Onset Gestational Diabetes Mellitus: A Systematic Review and Meta-analysis. Current diabetes reports. 2017;17(11):115.
41. Corrado F, D'Anna R, Cannata M, Interdonato M, Pintaudi B, Di Benedetto A. Correspondence between first trimester fasting glycaemia, and oral glucose tolerance test in gestational diabetes diagnosis. Diabetes & metabolism. 2012;38(5):458-61.

42. Zhu W-w, Yang H-x, Wei Y-m, Yan J, Wang Z-l, Li X-l, et al. Evaluation of the value of fasting plasma glucose in the first prenatal visit to diagnose gestational diabetes mellitus in China. Diabetes Care. 2013;36(3):586-90.
43. McIntyre HD, Sacks DA, Barbour LA, Feig DS, Catalano PM, Damm P, et al. Issues with the Diagnosis and Classification of Hyperglycaemia in Early Pregnancy. Diabetes Care. 2016;39(1):53-4.
44. Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c≥ 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes Care. 2014;37(11):2953-9.
45. Mañé L, Flores-Le Roux JA, Benaiges D, Rodríguez M, Marcelo I, Chillarón JJ, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multiethnic cohort. The Journal of Clinical Endocrinology & Metabolism. 2017;102(2):390-7.
46. Osmundson SS, Zhao BS, Kunz L, Wang E, Popat R, Nimbal VC, et al. First trimester hemoglobin A1c prediction of gestational diabetes. American journal of perinatology. 2016;33(10):977-82.
47. Department of Health SA. Guidelines for maternity care in South Africa 2015 [Available from: https://health-e.org.za/wp-content/uploads/2015/11/Maternal-Care-Guidelines2015_FINAL-21.7.15.pdf.
48. Western Cape Government. Diabetes in pregnancy: a guideline for the management of diabetes and its complications from pre-conception to the postnatal period. 2010 [Available from: https://www.scribd.com/document/252323279/Diabetes-in-Pregnancy-Western-CapeGuidelines.
49. Muhwava LS, Murphy K, Zarowsky C, Levitt N. Policies and clinical practices relating to the management of gestational diabetes mellitus in the public health sector, South Africa - A qualitative study. BMC Health Services Research. 2018;18(1).
50. Adams S, Rheeder P. Screening for gestational diabetes mellitus in a South African population: prevalence, comparison of diagnostic criteria and the role of risk factors. South African medical journal. 2017;107(6):523-7.

51. American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37: S14.
52. Coetzee A, Mason D, Hall DR, Conradie M. Prevalence and predictive factors of early postpartum diabetes among women with gestational diabetes in a single-center cohort. International Journal of Gynecology & Obstetrics. 2018.
53. Venkataraman H, Sattar N, Saravanan P. Postnatal testing following gestational diabetes: time to replace the oral glucose tolerance test? The Lancet Diabetes & Endocrinology. 2015;3(10):754-6.
54. Kim KS, Kim SK, Cho YW, Park SW. Diagnostic value of haemoglobin A(1c) in postpartum screening of women with gestational diabetes mellitus. Diabet Med. 2016;33(12):1668-72.
55. Duke A, Yap C, Bradbury R, Hng TM, Kim C, Wansbrough A, et al. The discordance between HbA1c and glucose tolerance testing for the postpartum exclusion of diabetes following gestational diabetes. Diabetes Research and Clinical Practice. 2015;108(1):727.
56. Guo J, Chen JL, Whittemore R, Whitaker E. Postpartum Lifestyle Interventions to Prevent Type 2 Diabetes Among Women with History of Gestational Diabetes: A Systematic Review of Randomized Clinical Trials. Journal of women's health (2002). 2016;25(1):38-49.
57. Mudaliar U, Zabetian A, Goodman M, Echouffo-Tcheugui JB, Albright AL, Gregg EW, et al. Cardiometabolic Risk Factor Changes Observed in Diabetes Prevention Programs in US Settings: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(7): e1002095.
58. Dennison RA, Ward RJ, Griffin SJ, Usher-Smith JA. Women's views on lifestyle changes to reduce the risk of developing Type 2 diabetes after gestational diabetes: a systematic review, qualitative synthesis and recommendations for practice. Diabetic Medicine. 2019;36(6):702-17.
59. Krige SM, Booley S, Levitt NS, Chivese T, Murphy K, Harbron J. Dietary Intake and Beliefs of Pregnant Women with Gestational Diabetes in Cape Town, South Africa. Nutrients. 2018;10(9):1183.

60. Krige SM. Lifestyle behaviours and beliefs of pregnant women with gestational diabetes: a longitudinal follow-up study: Faculty of Health Sciences; 2019.
61. Dasgupta K, Da Costa D, Pillay S, De Civita M, Gougeon R, Leong A, et al. Strategies to optimize participation in diabetes prevention programs following gestational diabetes: a focus group study. PloS one. 2013;8(7).
62. Graco M, Garrard J, Jasper AE. Participation in physical activity: perceptions of women with a previous history of gestational diabetes mellitus. Health Promotion Journal of Australia. 2009;20(1):20-5.
63. Nicklas JM, Zera CA, Seely EW, Abdul-Rahim ZS, Rudloff ND, Levkoff SE. Identifying postpartum intervention approaches to prevent type 2 diabetes in women with a history of gestational diabetes. BMC pregnancy and childbirth. 2011;11(1):23.
64. Lie M, Hayes L, Lewis-Barned N, May C, White M, Bell R. Preventing type 2 diabetes after gestational diabetes: women's experiences and implications for diabetes prevention interventions. Diabetic Medicine. 2013;30(8):986-93.
65. Abraham K, Wilk N. Living with gestational diabetes in a rural community. MCN: The American Journal of Maternal/Child Nursing. 2014;39(4):239-45.
66. Bandyopadhyay M, Small R, DAVEY MA, Oats JJ, Forster DA, Aylward A. Lived experience of gestational diabetes mellitus among immigrant South Asian women in Australia. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2011;51(4):360-4.
67. Gaudreau S, Michaud C. Cultural factors related to the maintenance of health behaviours in Algonquin women with a history of gestational diabetes. Chronic diseases and injuries in Canada. 2012;32(3).
68. Jones EJ, Peercy M, Woods JC, Parker SP, Jackson T, Mata SA, et al. Peer Reviewed: Identifying Postpartum Intervention Approaches to Reduce Cardiometabolic Risk Among American Indian Women with Prior Gestational Diabetes, Oklahoma, 2012–2013. Preventing chronic disease. 2015;12.
69. Lim S, Dunbar JA, Versace VL, Janus E, Wildey C, Skinner T, et al. Comparing a telephone-and a group-delivered diabetes prevention program: characteristics of

engaged and non-engaged postpartum mothers with a history of gestational diabetes. Diabetes research and clinical practice. 2017; 126:254-62.

70. Davenport MH, Meah VL, Ruchat SM, Davies GA, Skow RJ, Barrowman N, et al. Impact of prenatal exercise on neonatal and childhood outcomes: a systematic review and metaanalysis. Br J Sports Med. 2018;52(21):1386-96.

71. Bahia L, Schaan CW, Sparrenberger K, Abreu GdA, Barufaldi LA, Coutinho W, et al. Overview of meta-analysis on prevention and treatment of childhood obesity. Jornal de Pediatria. 2019;95(4):385-400.

APPENDICES

Appendix 3.1. Systematic review protocol

Open Access Protocol

BMJ Open

Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: protocol of a systematic review and meta-analysis

Tawanda Chivese,[1,2] Werfalli Mahmoud,[1] Itai Magodoro,[3] Andre P Kengne,[4] Shane A Norris,[2] Naomi S Levitt[5]

To cite: Chivese T, Mahmoud W, Magodoro I, *et al*. Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: protocol of a systematic review and meta-analysis. *BMJ Open* 2016;**6**:e012255. doi:10.1136/bmjopen-2016-012255

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012255).

Received 12 April 2016
Revised 6 September 2016
Accepted 8 November 2016

For numbered affiliations see end of article.

Correspondence to
Tawanda Chivese;
tchivese@gmail.com

ABSTRACT

Introduction: African women of childbearing age are increasingly being exposed to risk factors for type 2 diabetes mellitus (T2DM), most particularly obesity. A differentiating feature of diabetes in women of childbearing age is that the disease may affect the mother and the developing fetus. Apart from mapping the extent of the problem, understanding the prevalence of T2DM in African women of childbearing age can help to galvanise targeted interventions for reducing the burden of T2DM. This is a protocol for a systematic review aiming to assess the prevalence of and risk factors for T2DM in women of childbearing age (15–49 years) in Africa.

Methods and analyses: We will carry out a comprehensive literature search among a number of databases, using appropriate adaptations of the African search filter to identify diabetes prevalence studies, published from 2000 to 2016, among African women of childbearing age (15–49 years) according to the WHO definition. Full copies of articles identified through searches and considered to meet the inclusion criteria will be obtained for data extraction and synthesis. The analysis of the primary outcome (prevalent diabetes) will include two steps: (1) identification of data sources and documenting estimates and (2) application of the random-effects meta-analysis model to aggregate prevalence estimates and account for between-study variability in calculating the overall pooled estimates and 95% CI for diabetes prevalence. We will assess heterogeneity and publication bias using established methods. This systematic review will be reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol (PRISMA-P) 2015.

Ethics and dissemination: Ethical approval is not required for this study, given that this is a protocol for a systematic review, which utilises published data. The findings of this study will be widely disseminated through peer reviewed publications and conference presentations.

Trial registration number: CRD42015027635.

Strengths and limitations of this study

- This research will provide a comprehensive overview of all the data on the prevalence of type 2 diabetes in women of childbearing age in Africa, using repeatable transparent robust systematic review methods.
- Age-specific prevalence data may not be available for some studies.

INTRODUCTION

The number of people with diabetes has increased considerably from 108 million people in 1980 to 422 million in 2014 and is expected to reach 700 million by 2025.[1] Globally, the diabetes prevalence among women increased from 5.0% in 1980 to 7.9%.[1] Notably, the growing global burden of diabetes is occurring predominantly in low-income or middle-income countries where health systems, ravaged by infectious disease, are ill-equipped to deal with the new costly burden (estimated worldwide annual cost of US$825[1]). In Africa, there has been a rapid increase in the prevalence of diabetes, and consistent with other regions, 90% of cases are type 2 diabetes mellitus (T2DM).[2–4] For example, in Tanzania and Cameroon, repeated local surveys using similar methods revealed that T2DM increased by 6-fold and 10-fold in a decade, respectively.[3 5] This increase in prevalence has led to estimates by the International Diabetes Federation (IDF) that the number of people in the region with T2DM is expected to more than double by 2035 relative to 2013.[6] Considerations for the huge human and economic burden that results from treating T2DM and its complications have led to calls by the IDF for the

establishment of national diabetes programmes to better deliver prevention and control solutions.[6] At the heart of these efforts is a drive to identify high-risk populations, context specific-risk factors and implementing effective interventions to prevent or delay the onset of T2DM.

Women of childbearing age, defined by the WHO as women aged between 15 and 49 years,[7] are affected by T2DM in a unique way. If a woman has T2DM and becomes pregnant, her unborn child is at high risk of developing T2DM in adulthood,[8] thereby accelerating the intergenerational risk of T2DM. Interventions to prevent and control T2DM in this group is further warranted given the important contribution women make to the social and economic development of nations, the health and well-being of their children and families. Furthermore, women are valuable conduits for introducing healthy lifestyles in their families and communities.

The modifiable risk factors for T2DM are on the rise in all populations. In particular, overweight and obesity, the main drivers of the T2DM epidemic, are increasing worldwide and especially so in women.[9] In Africa, the increase in overweight and obesity is attributed to the nutrition transition and modernisation characterised by adoption of energy dense 'Western' diets and decreased physical activity,[10] although the evidence linking these factors to obesity in Africa is sparse. Other context specific factors such as cultural practices where being overweight is associated with higher economic status[11 12] may also be contributing to overweight and obesity in this group. Obesity is thought to result in T2DM through excess visceral fat deposition that often results in ectopic fat deposition in the liver and other abdominal organs, leading to insulin resistance.[13] Epidemiological studies have demonstrated a strong association with up to 90% of T2DM being attributable to overweight and obesity.[14] Worldwide, the proportion of women who are obese is marginally higher than that of men (40% vs 38%).[14] However, in low-income to middle-income countries, Africa included, more women are obese compared to men.[9]

Multiparity may increase a woman's risk of obesity[15] and resultant T2DM, although the evidence is inconsistent.[16] A higher gestational weight has also been, in turn, associated with increased risk of weight gain, and a consequent risk of overweight and obesity after pregnancy.[17] In Africa, the data on weight gain after pregnancy appear to be even scarcer, although women tend to have more children, compared to those in the developed world and therefore go through multiple pregnancy cycles,[18 19] with the associated incremental weight gain after each cycle.

Africa has the greatest global burden of HIV, with women of childbearing age the group most affected.[20] As a consequence of the successful rollout of antiretroviral therapy (ART) in many African countries, a large number of women have access to ART and life expectancy has increased. ART, including the drugs in widespread use in the region, however, has been linked with T2DM risk,[21] which may impact the prevalence of T2DM in women of childbearing age.

The existing studies in Africa have not been previously collated, although there are perceptions that the prevalence of T2DM in women of childbearing age may be on the increase in the continent. This research will provide information on patterns and the distribution of T2DM to policymakers and possibly identify priority areas for intervention. We hope that the identification of risk factors specific to the African women of childbearing age will improve the development of effective interventions to delay or prevent T2DM in the continent.

Aim

The aim of this systematic review is to assess the prevalence of and the risk factors for the development of T2DM in African women aged between 15 and 49 years as reported in studies during the period 2000 to 2016. The lower cut-off of the year 2000 will be used as studies conducted earlier may have used different criteria for the diagnosis of T2DM.

Objectives

To achieve the above aim, the research objectives will be:

1. To estimate the prevalence of T2DM in women of childbearing age in Africa, as reported in studies during the years 2000 to 2016.
2. To determine risk factors for T2DM in women of childbearing age in Africa, as reported in research studies conducted during the years 2000 to 2016.

Research question

This systematic review will answer the following question: what is the prevalence of and risk factors for T2DM in women of childbearing age in Africa as reported in studies published during the period 2000 to 2016?

Study design

This protocol is registered online on PROSPERO, the International prospective register of systematic reviews (http:www.crd.york.ac.uk/PROSPERO, registration no. CRD42015027635). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[22] guidelines for reporting systematic reviews will be followed.

Criteria for considering studies for review

Types of studies

The systematic review will include cross-sectional studies and any other observational studies that assessed the prevalence of and risk factors for T2DM.

Studies inclusion criteria

1. All published and unpublished cross-sectional and community-based studies during the period 2000 to 2016 are reporting the prevalence of, risk factors for, T2DM in women aged 15–49 years, where the sample of women in this age range was at least 100.

2. Diagnosis of T2DM should have been according to the WHO 1999 guidelines[23] or an equivalent.
3. No language restriction will be applied.

Studies exclusion criteria

Studies will be excluded if:

1. Used criteria not comparable to the WHO 1999 guidelines in diagnosing T2DM.
2. They are duplicate publications. In the case of duplicate publications, only one article that contains the most information will be included in the review.
3. They are narrative review, letters to the editor, opinions or other publications that do not have primary data.
4. Studies in migrant Africans.

Types of outcomes

The prevalence of the following will be assessed from studies included in the systematic review.

Primary outcomes

T2DM as diagnosed according to the WHO 1999 guidelines: fasting blood glucose of at least 7.0 mmol/L or 2-hour oral glucose tolerance test (OGTT) blood glucose of 11.1 mmol/L.[23]

Secondary outcomes

Impaired glucose regulation (IGR), which will be defined as either impaired glucose tolerance (fasting blood glucose <7.0 mmol/L and 2-hour OGTT blood glucose of at least 7.8 mmol/L but <11.1 mmol/L) or impaired fasting glucose (fasting blood glucose >6.1 mmol/L but <7.0 mmol/L).[23]

Search strategy for identification of relevant studies

Data sources

The following sources will be searched for studies conducted during the period January 2000 to March 2016:

Electronic databases

1. Electronic databases including PubMed–MEDLINE, the Cochrane Central, Global Health, Scopus, CINAHAL, ISI web of science and POPLINE and AfricaWide
2. Grey literature databases such as OpenSigle

Hand searching

1. All references of retrieved articles will be scanned for further studies.
2. Prominent authors of articles will be contacted for information on other studies they may know.

Search methods for identification of studies

A comprehensive and sensitive search strategy using an African search filter will be utilised to identify research articles from the year 2000 to 2016 (see online supplementary appendix 1). An expert librarian will be consulted during the design of the search strategy. Individual African country names and regional grouping names, such as sub-Saharan Africa and North Africa, will also be used to identify studies that may have been indexed under regional names. For countries with non-English as well as English names, both names will be used during searching while countries that have changed names during the period 2000–2016 will have all the names included in the search. Medical Subject Headings (MeSH) terms will be used when searching for studies in MEDLINE and PubMed. Endnote 7 will be used to manage retrieval of articles and screening for duplicates.

Procedure for selection of studies

Articles retrieved from the search will be exported to Endnote X7 where duplicates will be identified. Two investigators will screen titles, abstracts and if necessary full articles for inclusion. The full articles will then be screened for eligibility independently by the two investigators. If the investigators do not agree, a third investigator will be consulted. Trained interpreters will translate articles in languages other than English and French into English.

Assessment of the quality of and risk of bias in included studies

Two investigators will independently assess the included articles for the risk of bias and quality. They will resolve any differences by discussion and a third investigator will be consulted if they fail to reach consensus. Included studies will be assessed for quality (internal and external validity as well as risk of bias) using the validated quality appraisal tool developed by Hoy *et al*.[24]

Data extraction and management

After the studies have been assessed for risk of bias, two authors will independently extract data from the selected articles into a predefined data extraction form in Microsoft Office Excel 2016, which will first be piloted using five studies. The two investigators will compare their findings and discuss to resolve any differences.

Data to be extracted from the articles will include author names, date of publication, country where study was conducted, number of participants included and proportion of participants who were women of childbearing age, main findings, study design, language, sampling method, response rate, risk factors for T2DM and unadjusted T2DM prevalence estimates which will be extracted as the number of cases (denominator) out of the number in each age group (numerator).

We will use a predefined data extraction form in Microsoft Office Excel 2016, which will first be piloted using five studies.

We will contact authors to get information on age-specific prevalence should it not be reported.

Data synthesis and analysis

For data that we are unable to conduct a meta-analysis, we will provide a narrative description. These data will include study characteristics such as year of publication, sample size and country where study and attributes associated with T2DM in women of childbearing age.

We will recalculate unadjusted estimates of the prevalence of T2DM and IGR among women within the age groups of (15–49) years (number of cases/sample size) together with SEs based on the information on crude numerators and denominators provided in the individual studies. We will pool the T2DM prevalence using the statistical software R V.3.2.3, (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2015; http://www.R-project.org/ (accessed 30 Mar 2016)) and applying the appropriate variance stabilising transformations.

Should included studies not have age-specific prevalence of T2DM we will write to the authors and request the data.

We will assess heterogeneity between studies using Cochran's Q statistic.[25] The Q-statistic tests for heterogeneity based on the null hypothesis that all studies share a common effect size. We will do the hypothesis testing based on a 0.10 level of significance, that is a p value of <0.10, implying that studies do not share a common effect size. To estimate the percentage of total variation across studies due to true between-study differences rather than chance, we will use the I^2 statistic (<25% as low, between 25% and 50% as moderate and >75% high heterogeneity).[25 26] Sources of heterogeneity will be explored through subgroup analysis using study-level characteristics such as geographical regions, rural/urban settings, age groups, study period, year of publication and sample sizes. This will be complemented where relevant, by meta-regression to further explain the heterogeneity, if any.

Assessment of publication bias

We will assess the presence of publication bias examining the funnel plots, supplemented with a formal statistical testing using the Egger test,[27] and the Begg's test[28] for publication bias. To test the robustness of our findings to publication bias, we will apply the Duval and Tweedie's trim and fill methods.[29]

Author affiliations
[1]Chronic Disease Initiative for Africa, Department of Medicine, University of Cape Town, South Africa
[2]Faculty of Health Sciences, South Africa Medical Research Council Developmental Pathways for Health Research Unit, Department of Paediatrics, University of the Witwatersrand, Johannesburg, South Africa
[3]Harvard Medical School, Boston, USA
[4]Non-communicable Disease Research Unit, South African Medical Research Council, Cape Town, South Africa
[5]Division of Endocrinology, Department of Medicine, University of Cape Town, Cape Town, South Africa

Twitter Follow Tawanda Chivese @TChivese

Contributors TC contributed to conception of the study, and drafted and revised the manuscript. He is the guarantor of the review. IM and WM revised the manuscript. APK revised the manuscript and approved the final submission. SAN and NSL contributed to conception of the study, and revised and approved the final submission.

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

Competing interests None declared.

Ethics approval This review will use secondary data from published and unpublished studies and will not require ethical clearance.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 2016;387:1513–30.
2. Peer N, Steyn K, Lombard C, *et al*. Rising diabetes prevalence among urban-dwelling black South Africans. *PLoS ONE* 2011;7:e43336.
3. Mbanya JCN, Motala AA, Sobngwi E, *et al*. Diabetes in sub-saharan Africa. *Lancet* 2010;375:2254–66.
4. Peer N, Kengne AP, Motala AA, *et al*. Diabetes in the Africa Region: an update. *Diabetes Res Clin Pract* 2014;103:197–205.
5. Aspray TJ, Mugusi F, Rashid S, *et al*. Rural and urban differences in diabetes prevalence in Tanzania: the role of obesity, physical inactivity and urban living. *Trans R Soc Trop Med Hyg* 2000;94:637–44.
6. International Diabetes Federation. *IDF Diabetes Atlas*. 6th edn. 2015. https://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf (accessed 07 Dec 2015).
7. World Health Organisation. Sexual and reproductive health. 2015. http://www.who.int/reproductivehealth/topics/infertility/definitions/en/ (accessed 13 Nov 2015).
8. Clausen TD, Mathiesen ER, Hansen T, *et al*. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 2008;31:340–6.
9. Ng M, Fleming T, Robinson M, *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:766–81.
10. Steyn NP, Mchiza ZJ. Obesity and the nutrition transition in sub-Saharan Africa. *Ann N Y Acad Sci* 2014;1311:88–101.
11. Treloar C, Porteous J, Hassan F, *et al*. The cross cultural context of obesity: an INCLEN multicentre collaborative study. *Health Place* 1999;5:279–86.
12. Walker AR, Adam F, Walker BF. World pandemic of obesity: the situation in Southern African populations. *Public Health* 2001;115:368–72.
13. Neeland IJ, Turer AT, Ayers CR, *et al*. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. *JAMA* 2012;308:1150–9.
14. Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world—a growing challenge. *N Engl J Med* 2007;356:213–15.
15. Heliovaara M, Aromaa A. Parity and obesity. *J Epidemiol Commun Health* 1981;35:197–9.
16. Kritz-Silverstein D, Barrett-Connor E, Wingard DL. The effect of parity on the later development of non-insulin-dependent diabetes mellitus or impaired glucose tolerance. *N Engl J Med* 1989;321:1214–9.
17. Gunderson EP, Abrams B. Epidemiology of gestational weight gain and body weight changes after pregnancy. *Epidemiol Rev* 1999;21:261–75.
18. Hoque M, Hoque E, Anwar M, *et al*. Assessment and comparison of obstetric characteristics and perinatal outcomes of rural population of South Africa. *Trop J Obstet Gynaecol* 2013;26:60–7.
19. Nergard CS, Ho TPT, Diallo D, *et al*. Attitudes and use of medicinal plants during pregnancy among women at healthcare centers in three regions of Mali, West-Africa. *J Ethnobiol Ethnomed* 2015;11:1.

20. Harrison A, Colvin CJ, Kuo C, *et al*. Sustained high HIV incidence in young women in Southern Africa: social, behavioral, and structural factors and emerging intervention approaches. *Curr HIV/AIDS Rep* 2015;12:207–15.
21. Karamchand S, Leisegang R, Schomaker M, *et al*. Risk factors for incident diabetes in a cohort taking first-line nonnucleoside reverse transcriptase inhibitor-based antiretroviral therapy. *Medicine (Baltimore)* 2016;95:e2844.
22. Shamseer L, Moher D, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.
23. World Health Organization. Dept. of Noncommunicable Disease Surveillance. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: World Health Organization, 1999.
24. Hoy D, Brooks P, Woolf A, *et al*. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. *J Clin Epidemiol* 2012;65:934–9.
25. Borenstein MH, Higgins LV, Rothstein JPTHR. *Introduction to meta-analysis*. Vol. 10. Chichester, UK: Wiley, 2009: 187–204.
26. Higgins JP, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
27. Egger M, Smith GD. Meta-analysis. Potentials and promise. *BMJ* 1997;315:1371–4.
28. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
29. Taylor S, Tweedie R. *Trim and fill: a simple funnel plot based method of testing and adjusting for publication bias in meta-analyses*. Fort Collins, CO: Colorado State University, 1998.

BMJ Open

Prevalence of type 2 diabetes mellitus in women of childbearing age in Africa during 2000–2016: protocol of a systematic review and meta-analysis

Tawanda Chivese, Werfalli Mahmoud, Itai Magodoro, Andre P Kengne, Shane A Norris and Naomi S Levitt

BMJ Open 2016 6:
doi: 10.1136/bmjopen-2016-012255

Appendix 4.1. Search Strategy

PubMed Draft Search Strategy

(((((("Diabetes Mellitus, Type 2"[Mesh]) OR Diabetes Mellitus, Type 2) OR diabetes type 2) OR T2DM) OR diabetes Type II) OR diabetes)) AND ((((((((("Adolescent"[Mesh]) OR "Young Adult"[Mesh]) OR "Adult"[Mesh]) OR "Middle Aged"[Mesh])) OR teenage*) OR adolescen*) OR young adult) OR adult) OR Middle Age*)) AND (((((((("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "Cross-Sectional Studies"[Mesh])) OR Prevalence) OR Epidemiology) OR Cross-Sectional Studies) OR "Longitudinal Studies"[Mesh]) OR "Cohort Studies"[Mesh]) OR Cohort Studies) OR Longitudinal Studies)) AND ((((((((((Africa, Northern OR Algeria OR Libya OR Egypt OR Morocco OR Tunisia OR Northern Africa))) OR ((Benin OR Burkina Faso OR Cape Verde OR Cote d'Ivoire OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Liberia OR Mali OR Mauritania OR Niger OR Nigeria OR Senegal OR Sierra Leone OR Togo))) OR ((Ethiopia OR Kenya OR Rwanda OR Somalia OR Sudan OR Tanzania OR Uganda OR Africa, Southern OR Angola OR Lesotho OR Mozambique OR Namibia OR South Africa OR Swaziland OR Zambia OR Zimbabwe OR Africa, Western))) OR Sub-Saharan Africa) OR ((Africa OR Africa South of the Sahara OR Africa, Central OR Cameroon OR Central African Republic OR Chad OR Congo OR Democratic Republic of the Congo OR Equatorial Guinea OR Gabon OR Burundi OR Djibouti OR Eritrea))) OR (((((("Africa, Northern"[Mesh]) OR "Algeria"[Mesh]) OR "Libya"[Mesh]) OR "Egypt"[Mesh]) OR "Morocco"[Mesh]) OR "Tunisia"[Mesh])) OR africa) OR ((((((((((((((("Benin"[Mesh]) OR "Burkina Faso"[Mesh]) OR "Cape Verde"[Mesh]) OR "Cote d'Ivoire"[Mesh]) OR "Gambia"[Mesh]) OR "Ghana"[Mesh]) OR "Guinea"[Mesh]) OR "Guinea-Bissau"[Mesh]) OR "Liberia"[Mesh]) OR "Mali"[Mesh]) OR "Mauritania"[Mesh]) OR "Niger"[Mesh]) OR "Nigeria"[Mesh]) OR "Senegal"[Mesh]) OR "Sierra Leone"[Mesh]) OR "Togo"[Mesh])) OR ((((((((((("Africa"[Mesh]) OR "Africa South of the Sahara"[Mesh]) OR "Africa, Central"[Mesh]) OR "Cameroon"[Mesh]) OR "Central African Republic"[Mesh]) OR "Chad"[Mesh]) OR "Congo"[Mesh]) OR "Democratic Republic of the Congo"[Mesh]) OR "Equatorial Guinea"[Mesh]) OR "Gabon"[Mesh]) OR "Burundi"[Mesh]) OR "Djibouti"[Mesh]) OR "Eritrea"[Mesh])) OR ((((((((((((((("Ethiopia"[Mesh]) OR "Kenya"[Mesh]) OR "Rwanda"[Mesh]) OR "Somalia"[Mesh]) OR "Sudan"[Mesh]) OR "Tanzania"[Mesh]) OR "Uganda"[Mesh]) OR "Africa, Southern"[Mesh]) OR "Angola"[Mesh]) OR "Lesotho"[Mesh]) OR "Mozambique"[Mesh]) OR "Namibia"[Mesh]) OR "South Africa"[Mesh]) OR "Swaziland"[Mesh]) OR "Zambia"[Mesh]) OR "Zimbabwe"[Mesh]) OR "Africa, Western"[Mesh])))

((((((((((("Adolescent"[Mesh]) OR "Young Adult"[Mesh]) OR "Adult"[Mesh]) OR "Middle Aged"[Mesh])) OR teenage*) OR adolescen*) OR young adult) OR adult) OR Middle Age*)) AND (((((((("Prevalence"[Mesh] OR "Epidemiology"[Mesh] OR "Cross-Sectional

Studies"[Mesh])) OR Prevalence) OR Epidemiology) OR Cross-Sectional Studies) OR "Longitudinal Studies"[Mesh]) OR "Cohort Studies"[Mesh]) OR Cohort Studies) OR Longitudinal Studies)) AND ((((((((((Africa, Northern OR Algeria OR Libya OR Egypt OR Morocco OR Tunisia OR Northern Africa))) OR ((Benin OR Burkina Faso OR Cape Verde OR Cote d'Ivoire OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Liberia OR Mali OR Mauritania OR Niger OR Nigeria OR Senegal OR Sierra Leone OR Togo))) OR ((Ethiopia OR Kenya OR Rwanda OR Somalia OR Sudan OR Tanzania OR Uganda OR Africa, Southern OR Angola OR Lesotho OR Mozambique OR Namibia OR South Africa OR Swaziland OR Zambia OR Zimbabwe OR Africa, Western))) OR Sub-Saharan Africa) OR ((Africa OR Africa South of the Sahara OR Africa, Central OR Cameroon OR Central African Republic OR Chad OR Congo OR Democratic Republic of the Congo OR Equatorial Guinea OR Gabon OR Burundi OR Djibouti OR Eritrea))) OR ((((("Africa, Northern"[Mesh]) OR "Algeria"[Mesh]) OR "Libya"[Mesh]) OR "Egypt"[Mesh]) OR "Morocco"[Mesh]) OR "Tunisia"[Mesh])) OR africa) OR ((((((((((((("Benin"[Mesh]) OR "Burkina Faso"[Mesh]) OR "Cape Verde"[Mesh]) OR "Cote d'Ivoire"[Mesh]) OR "Gambia"[Mesh]) OR "Ghana"[Mesh]) OR "Guinea"[Mesh]) OR "Guinea-Bissau"[Mesh]) OR "Liberia"[Mesh]) OR "Mali"[Mesh]) OR "Mauritania"[Mesh]) OR "Niger"[Mesh]) OR "Nigeria"[Mesh]) OR "Senegal"[Mesh]) OR "Sierra Leone"[Mesh]) OR "Togo"[Mesh])) OR ((((((((((("Africa"[Mesh]) OR "Africa South of the Sahara"[Mesh]) OR "Africa, Central"[Mesh]) OR "Cameroon"[Mesh]) OR "Central African Republic"[Mesh]) OR "Chad"[Mesh]) OR "Congo"[Mesh]) OR "Democratic Republic of the Congo"[Mesh]) OR "Equatorial Guinea"[Mesh]) OR "Gabon"[Mesh]) OR "Burundi"[Mesh]) OR "Djibouti"[Mesh]) OR "Eritrea"[Mesh])) OR ((((((((((((((("Ethiopia"[Mesh]) OR "Kenya"[Mesh]) OR "Rwanda"[Mesh]) OR "Somalia"[Mesh]) OR "Sudan"[Mesh]) OR "Tanzania"[Mesh]) OR "Uganda"[Mesh]) OR "Africa, Southern"[Mesh]) OR "Angola"[Mesh]) OR "Lesotho"[Mesh]) OR "Mozambique"[Mesh]) OR "Namibia"[Mesh]) OR "South Africa"[Mesh]) OR "Swaziland"[Mesh]) OR "Zambia"[Mesh]) OR "Zimbabwe"[Mesh]) OR "Africa, Western"[Mesh])))) AND ((((((("Diabetes Mellitus, Type 2"[Mesh]) OR Diabetes Mellitus, Type 2) OR diabetes type 2) OR T2DM) OR diabetes Type II) OR diabetes)

Search filters

a. human studies

b. year – from 2000

Appendix 4.2. Characteristics of included studies

Country	Citation	Setting [rural/urban]	Diagnostic Method [OGTT, FPG, Other]	Total participated	Total women, n[%)	T2DM prevalence in all women [%)	T2DM proportion [15-24]	T2DM proportion [25-34]	T2DM proportion [35-44]	T2DM proporti [45-54]y
Algeria	Algeria STEPS 2003 [54]	both	FPG	4136	2483 [60.6%)	10.2	-	0.4	1.3	
Angola	Evaristo-Neto 2010 [55]	rural	OGTT	421	295 [70%)	2.7	-	-	-	-
Angola	Capingana 2013 [56]	urban	FPG	615	320 [52%)	5.9	-	-	-	-
Benin	Benin STEPS 2008 [57]	both	FPG	3688	1891 [51.3%)	2	-	-	-	-
Benin	Benin STEPS 2015 [58]	both	FPG	5035	2750 [54.6%)	12.2	97/955 [10.1%) 18-29yrs		111/1100 [10.1%) 30-44 yrs	89/503 [17.7%)
Burkina Faso	Burkina Faso STEPS 2013 [59]	both	FPG	4695	2438 [51.9%)	4.7	-	39/1044 [3.7%)	20/524 [3.8%)	21/375 [5.5%)
Cameroon	Sobngwi 2002 [60]	both	FPG	2325	-	-	-	-	-	-
Cameroon	Cameroon STEPS 2004 [61]	urban	OGTT	10011	-	5.5	-	-	-	-
Cameroon	Katte 2014 [62]	urban	FPG	1702	967 [56.8%)	5.6	1/56 [1.8%)	18/174 [10.3%)	23/245 [9.4%)	36/257 [14.0]
Cameroon	Kufe 2015 [63]	urban	FPG	2499	850 [34%)	2.7	-	4/451 [0.9%)	4/178 [2.3%)	10/26 [38.5]
DRC	DRC STEPS 2005 [64]	both	FPG	1943	1185 [60.7%)	16.5	24.10%	12.50%	22.20%	11.
DRC	Katshunga 2016 [65]	rural	FPG	3962	2213 [56.2%)	-	-	-	-	-
Egypt	Egypt STEPS 2006 [66]	both	FPG	9780	4369 [44.6%)	18	2.9	3.6	15.3	
Ethiopia	Ethiopia STEPS 2016 [67]	both	FPG	8770	5225 [59.6%)	5.6	109/2229 [4.9%) 15-29 yrs		223/1863 [6.1%) 30-44yrs	54/822 [6.6%) 4 59 yrs
Ethiopia	Tesfaye 2016 [68]	urban	FPG	936	196 [20.9%)	-	-	-	-	-
Gabon	Gabon STEPS 2009 [69]	both	FPG	2800	1647 [58.8%)		-	-	-	-
Ghana	Amoah 2002 [70]	both	FPG, OGTT	4733	2225 [47%)	5.4	-	19/901 [2.1%)	30/769 [3.9]	39/557 [7.0]
Ghana	Obirikorang 2015 [71]	both	FPG	672	-	11.5	-	-	-	-
Guinea Conarkry	Balde 2007 [72]	both	FPG	1537	807 [52.5%)	-	-	-	-	-
Guinea Conarkry	STEPS 2009 [73]	both	FPG	-	1351	4.4	7/433 [1.6%)	12/387 [3.0%)	11/227 [4.6%)	17/152 [10.1%)
Kenya	STEPS 2015 [74]	both	FPG	4087	2470 [60%)	2.3	3/859 [0.4%) 18-29yrs	27/908 [3%) 30-44 yrs	20/325 [6%) 45-59 yrs	
Kenya	Ayah 2013 [75]	urban	FPG	2061	995[48%)	3.7	0/287 [18 - 24 yrs]	6/335 [1.8%)	9/219 [4.1%)	15/112 [13.4%)
Kenya	Christensen 2009 [76]	both	OGTT	1459	819[56%)	-	-	-	-	-
Kenya	Wanjihia 2009 [77]	rural	OGTT	299	165 [55%)	-	-	-	-	-

Liberia	Liberia STEPS 2011 [78]	both	FPG	2503	1438 [57.5%)	19.3	-	163/970 [16.8%) 25-44 yrs		80/328 [24.4%) 64 yrs
Libya	Libya STEPS 2009 [79]	both	FPG	3625	-	15.1	-	34/324 [10.4%)	37/353 [10.6%)	50/205 [24.2%)
Malawi	Malawi STEPS 2010 [80]	both	FPG	5206	3082 [70.8%)	4.7	-	33/898 [3.6%)	26/544 [4.7%)	26/400 [6.4%)
Mauritania	Mauritania STEPS 2006 [81]	both	FPG	2600	1415 [54.5%)	6.2	10/309 [3.2%)	11/316 [3.5%)	23/264 [8.7%)	20/218 [9.2%)
Mauritania	Meilouda 2013 [25]	NR	FPG	1278	-	6.4	-	-	-	-
Mauritius	Mauritius STEPS 2004 [82]	both	OGTT	4500	-	19.7	2.2% 20-29 yrs	8.9% 30-39 yrs	15.4% 40-49 yrs	-
Mayotte	Solet 2010 [83]	both	OGTT	544	332 [61%)	19.9	-	-	-	-
Mozambique	Silva-Matos 2010 [84]	both	FPG	2343	1757 [75%)	-	-	-	-	-
Morocco	Tazi 2003 [85]	both	FPG	1802	1047 [58.1%)	8.2	-	-	-	-
Namibia	Namibia DHS 2013 [28]	both	FPG	1873	1873	5.6	-	-	42/835 [5.0%)	40/658 [6.1%)
Niger	Niger STEPS 2007 [86]	both	FPG	2780	1316 [47.3%)	3.6	13/337 [3.9%)	12/325 [3.7%)	10/273 [3.7%)	11/234 [4.7%)
Nigeria	Nyewe 2003 [87]	urban	OGTT	502	229 [40-90][45.6%)	5.7	-	-	-	-
Nigeria	Oladapo Salako 2010 [88]	rural	FPG	2000	1127 [56.3%)	2.8	-	-	-	-
Nigeria	Ejim 2011 [89]	rural	FPG	858	611 [71.2%)	-	-	-	-	-
Nigeria	Ojewale 2012 [90]	urban	FPG	301	189 [62.8%)	2.7	-	-	-	-
Nigeria	Ekpenyong 2012 [91]	urban	FPG	3500	1968 [56.2%)	11.2	28/709 [4%) 18-25 yrs	40/412 [9.7%) 26-35 yrs	76/584 [13%) 36-45 yrs	77/262 [29.4%) 60 yrs
Nigeria	Osuji 2012 [27]	urban	FPG	253	253 [100%)	6.7	-	-	4/99 [4%) <50 yrs	-
Nigeria	Sabir 2013 [30]	rural	OGTT	393	183 [46.6%)	0.5	-	-	-	-
Nigeria	Okpechi 2013 [92]	both	FPG	2983	1554 [52.1%)	3.6	-	-	-	-
Nigeria	Enang 2014 [93]	urban	OGTT	1134	489 [43.1%)	4.7	-	-	-	-
Nigeria	Nwatu 2014 [94]	rural	OGTT	824	538 [65.3 %)	-	-	-	-	-
Nigeria	Oluyombo 2014 [95]	semi-urban	FPG	750	529 [70.6%)	6	-	-	-	-
Nigeria	Tagurum 2015 [96]	rural	FPG	195	152 [77.9%)	8.6	-	-	-	-
Nigeria	Oguoma 2015 [97]	both	FPG	422	273 [64.7%)	2.6	-	-	-	-
Nigeria	Chukwunonso 2015 [98]	semi-urban	FPG	365	193 [52.9%)	3.6	-	-	-	-
Rwanda	Rwanda STEPS 2015 [99]	both	FPG	7233	4542 [62.8%)	2.8	19/841 [2.3%)	31/1341 [2.3%)	32/933 [3.4%)	22/619 [3.6%)
La Re'union	Favier 2004 [100]	both	OGTT	3600	2024 [56.2%)		-	44/745 [5.9%) 30-39 yrs	99/609 [16.3%) 40-49 yrs	-

Senegal	Pessinaba 2013 [101]	urban	FPG	1424	983 [69%)	10.5	-	-	-	-
Senegal	Duboz 2016 [102]	rural	FPG	600	293 [48.8%)	5.4	-	-	-	-
Seychelles	Seychelles STEPS 2004 [103]	both	OGTT	1255	509[40.6%)	12.1	-	6/157 [3.4%)	11/171 [6.3%)	27/181 [14.9%)
Seychelles	Seychelles STEPS 2014 [104]	both	FPG	1240	514[41.5%)	13.6	-	4/161 [2.5%)	12/170 [7.1%)	26/183 [14.2%)
South Africa	Peer 2015 [105]	urban	OGTT	1099	707[64.3%)	13.8	-	14/235 [5.9%)	17/163 [10.6%)	39/168 [23.3%)
South Africa	Erasmus 2012 [106]	urban	OGTT	642	454 [70.7%)	-	-	0/1	20/146 [13.7%)	35/165 [21.2%)
South Africa	Motala 2008 [107]	rural	OGTT	1025	815[79.5%)	3.9	0/108	4/126[3.2%)	6/151[4%)	8/113[7
South Africa	Prakashandra 2016 [31]	urban	OGTT	1428	1026 [71.8%)	35.5	8/69 [11.6%)	13/99 [13.1%)	64/221 [29%)	126/336 [37.5%)
South Africa	Alberts 2005 [108]	rural	FPG	2062	1563 [75.8%)	10	-	5/162 [3.3%) 30-34 yrs	13/334 [4%)	37/318 [11.7%)
South Africa	Erasmus 2001 [109]	both	OGTT	374	137 [36.6%)	2.1	-	-	2/59 [3.4%) - 40-49 yrs	-
South Africa	SANHANES 2014 [110]	both	HbA1C	4740	3010 [63.5%)	11	-	-	-	-
South Africa	Hird 2016 [111]	urban	OGTT & HbA1C	1190	851 [71.5%)	14.8 [OGTT]	0% [18-24 yrs], FPG, OGTT, HbA1C	4.4% [HbA1C & OGTT], 4.3% FPG	5.7% [HbA1C & OGTT], 4.8% FPG	24.5% [OGTT], 27.2% [HbA1C] 23.2% [F
Sudan	Sudan STEPS 2006 [112]	both	FPG	1573	921[58.6%)	17.8	-	12/98 [12.2%)	14/98 [14.3%)	20/84 [23.8%)
Sudan	Elmadhoun 2016 [113]	urban	FPG	954	-	19.9	-	-	-	-
Swaziland	Swaziland STEPS 2014 [114]	both	OGTT	2892	1876 [64.9%)	16.7	88/686 [12.9%) 15-29 yrs	92/567 [16.3%) 30-44 yrs		177/623 [28.2%) 69yrs
Tanzania	Aspray 2000 [115]	rural	FPG	928	527 [56.8%)	1.1	1/203 [0.5%) 15-34 yrs		3/201 [1.5%) 35-54 yrs	
Tanzania	Aspray 2000 [115]	urban	FPG	770	438 [56.9%)	4	7/320 [2.3%) 15-34 yrs		7/89 [8.1%) 35-54 yrs	
Tanzania	Tanzania STEPS 2012 [116]	both	FPG	5680	3057 [53.8%)	10	-	79/885 [8.9%)	87/789 [11.0%)	59/539 [10.9%)
Tanzania	Miller 2013 Thesis [117]	rural	FPG	644	-	-	-	-	-	-
Tanzania	Ruhembe 2014 [118]	urban	FPG	640	352[55%)	13.1	-	7/154 [4.5%)[20-40yrs]	16/100 [16%) [41-50 yrs]	
Togo	Togo STEPS 2010 [119]	both	FPG	4370	2282 [52.2%)	9.4	37/615 [6%)	57/681 [8.4%)	52/458 [11.3]	47/293 [16%)

Tunisia	Romdhane 2014 [120]	both	FPG	7700	4475 [58.1%)	5.6	-	-	-	-
Tunisia	Bouguerra 2007 [121]	both	FPG	3729	2482 [66.6%)	10.1	5/590 [0.8%) 20-29 yrs	28/641 [4.3%) 30-39 yrs	57/462 [12.4%) 40-49 yrs	-
Tunisia	Belfki 2013 [122]	both	FPG	4654	2814 [60%)	-	-	-	-	-
Uganda	Mayega 2013 [123]	rural	FPG	1656	786 [52.5%)	-	-	-	-	-
Uganda	Uganda STEPS 2014 [124]	both	FPG	3987	2392 [60%)	1	0.3 [18-29 yrs]		1.6%[30-49 yrs]	
Uganda and Tanzania	Chiwanga 2016 [125]	both	FPG	586	360 [61%)	8.1	-	-	-	-
Zambia	Zambia STEPS 2008 [126]	both	FPG	1928	1275 [66.1%)	2.9	-	-	-	-
Zanzibar	Zanzibar STEPS 2011 [127]	both	FPG	2464	1438 [58.4%)	3.8	-	22/910 [2.4%) [Age group - 25-44]		46/530 [8.6%) 4 64yrs
Zimbabwe	Zimbabwe STEPS 2005 [128]	both	OGTT	3081	2311 [75%)	10.2	-	34/371 [9.1%)	37/331 [11.2%)	30/298 [10.1%)

Appendix 4.3. Risk of bias of included studies

Country	Year	citation	1	2	3	4	5	6	7	8	9	10	11	ROB Score out of 10
Algeria	2003	Algeria STEPS 2003	NCS	NCS	Low	Low	Low	Low	Low	Low	Low	NCS	Low	7
Angola	2013	Capingana 2013	Low	High	High	High	Low	Low	Low	Low	Low	Low	Low	7
Angola	2010	Evaristo-Neto 2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Benin	2008	Benin STEPS 2008	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Benin	2015	Benin STEPS 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Burkina Faso	2016	Burkina Faso STEPS 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Cameroon	2003	Cameroon STEPS 2003	Low	Low	Low	Low	Low	Low	Low	Low	Low	NCS	Low	9
Cameroon	2014	Katte 2014	Low	High	High	High	Low	Low	Low	Low	Low	High	Moderate	6
Cameroon	2015	Kufe 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Cameroon	2002	Songwi 2002	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
DRC	2016	Katshunga 2016	Low	Low	Low	Low	Low	High	Low	Low	Low	High	Low	8
DRC	2005	DRC STEPS 2005	High	Low	Low	High	Low	Low	Low	Low	Low	High	Low	7
Egypt	2006	Egypt STEPS 2006	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Ethiopia	2016	Ethiopia STEPS 2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Ethiopia	2016	Tesfare 2016	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	9

Gabon	2009	Gabon STEPS 2009	NCS	NCS	Low	Low	Low	Low	Low	Low	NCS	Low	Low	7
Ghana	2002	Amoah 2002	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Ghana	2015	Obirikorang 2015	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Guinea Conarkry	2007	Balde 2007	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Guinea Conarkry	2009	Guinea STEPS 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Kenya	2015	Kenya STEPS 2015	Low	Low	Low	NCS	Low	Low	Low	Low	Low	Low	Low	10
Kenya	2013	Ayah 2013	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Kenya	2009	Christensen 2009	Low	Low	High	High	Low	Low	Low	Low	Low	Low	Low	8
Kenya	2009	Wanjihia 2009	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Libya	2009	Libya STEPS 2009	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Liberia	2011	Liberia STEPS 2011	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Malawi	2009	Malawi STEPS 2009	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Mauritania	2006	Mauritania STEPS 2006	Low	Low	Low	High	Low	Low	Low	Low	High	High	Low	7
Mauritania	2013	Meiloud 2013	Low	High	Low	High	Low	Low	Low	Low	Low	Low	Low	8
Mauritius	2004	Mauritius STEPS 2004	Low	Low	Low	Low	Low	Low	Low	Low	Low	NCS	Low	9
Mayotte	2010	Solet 2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Morocco	2003	Tazi 2003	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Mozambique	2012	Silva-Matos 2012	Low	Low	Low	High	Low	Low	Low	Low	NCS	NCS	Moderate	8

Namibia	2013	Namibia DHS 2013	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Niger	2008	Niger STEPS 2008	Low	High	Low	NCS	Low	Low	Low	Low	Low	NCS	Low	7
Nigeria	2015	Chukwunonso 2015	High	High	High	High	Low	Low	Low	Low	Low	Low	High	6
Nigeria	2011	Ejim 2011	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	low	9
Nigeria	2012	Ekpenyong 2012	High	High	High	High	Low	Low	Low	Low	Low	Low	High	6
Nigeria	2014	Enang 2014	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	low	10
Nigeria	2015	Nwatu 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Nigeria	2015	Oguoma 2015	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Nigeria	2013	Okpechi 2013	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	Low	9
Nigeria	2010	Oladapo 2010	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Nigeria	2015	Oluyombo 2014	High	High	High	Low	Low	Low	Low	Low	Low	Low	Low	7
Nigeria	2012	Osuji 2012	Low	Low	High	High	Low	Low	Low	Low	Low	Low	Low	8
Nigeria	2013	Sabir 2013	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	8
Nigeria	2015	Tagurum 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Nigeria	2003	Nyewe,2003	Low	Low	Low	low	Low	Low	Low	Low	Low	Low	Low	10
Nigeria	2012	Ojewele,2012	High	High	Low	High	Low	Low	Low	Low	Low	Low	Low	8
Reunion	2004	Favier 2004	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	8
Rwanda	2015	Rwanda STEPS 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Senegal	2016	Duboz 2016	Low	Low	High	High	Low	Low	Low	Low	Low	Low	Low	8
Senegal	2013	Pessinaba 2013	Low	Low	Low	Low	Low	Low	Low	High	Low	High	Low	8
Seychelles	2004	Seychelles STEPS 2004	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10

Seychelles	2015	Seychelles STEPS 2015	Low	Low	Low	Low	NCS	NCS	Low	Low	Low	Low	Low	7
South Africa	2012	Erasmus 2012	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
South Africa	2016	Prakaschandra 2016	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
South Africa	2012	SANHANES 2012	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
South Africa	2005	Alberts, 2005	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
South Africa	2001	Erasmus, 2001	Low	Low	High	High	Low	Low	Low	Low	Low	Low	Low	8
South Africa	2016	Hird 2016	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
South Africa	2015	Peer 2015	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
South Africa	2008	Motala, 2008	Low	High	Low	low	Low	Low	Low	Low	Low	Low	Low	9
Sudan	2006	Sudan STEPS 2006	Low	Low	Low	Low	Low	low	Low	Low	Low	Low	Low	10
Sudan	2016	Elmadhoun 2016	Low	Low	Low	Low	Low	low	Low	Low	Low	Low	Low	10
Swaziland	2014	Swaziland STEPS 2014	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Tanzania	2012	Tanzania STEPS 2012	Low	Low	Low	NCS	Low	Low	Low	Low	Low	Low	Low	10
Tanzania	2000	Aspray 2000	High	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	8
Tanzania	2013	Miller 2013	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Tanzania	2014	Ruhembe 2014	Low	High	Low	High	Low	Low	Low	Low	Low	Low	Low	8
Togo	2010	Togo STEPS 2010	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Tunisia	2013	Belfki 2013	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Tunisia	2014	Romdhane 2014	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10
Tunisia	2007	Bouguerra 2007	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10

Uganda	2014	Uganda STEPS 2014	Low	Low	Low	NCS	Low	Low	Low	Low	Low	Low	Low	9
Uganda and Tanzania	2016	Chiwanga 2016	High	High	High	High	Low	Low	Low	Low	Low	Low	High	6
Uganda	2013	Mayega 2013	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Zambia	2006	Zambia STEPS 2006	Low	Low	Low	NCS	Low	NCS	Low	NCS	Low	NCS	Moderate	6
Zanzibar	2011	Zanzibar STEPS 2011	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low	9
Zimbabwe	2005	Zimbabwe STEPS 2005	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	10

Appendix 5.1. PRO2D Questionnaire

PRO2D - The prevalence of Type 2 diabetes mellitus and associated risk factors 5 years after gestational diabetes mellitus in South Africa

QUESTIONNAIRE

Tawanda Chivese, Professor Shane Norris, Professor Naomi Levitt

SECTION 1: GENERAL INFORMATION

Participant study number: ……

Interviewer's name……

Participant suburb of residence……

Consent has been read and obtained? Yes, if yes continue

No, if no, STOP

Telephone……..

2nd contact person's details:

Relationship…..……..……..……..……

Telephone ……..

Date of interview:

D D M M Y Y Y Y

Age of participant at last birthday ……..……

Participant date of birth:

D D M M Y Y Y Y

SECTION 2: SOCIO-DEMOGRAPHIC INFORMATION

	QUESTIONS AND FILTERS	CODING CATEGORIES	
2A	What is the highest level of education that you have achieved?		
		Never went to school	1
		Grade 1 to 7 (Primary school)	2
		Grade 8 to 10	3
		Matric	4
		Tertiary / Diploma	5
2B	Are you …	Employed, salaried	1
		Self-employed	2
		Unemployed	3
		A full-time homemaker	4
		A pensioner	5
		On a disability grant	6
		A student	7
2C	Do you own a house?	Yes …….. 1	No … 0
2D	What type of housing do you live in?	Built formal unit	1
		Informal shack / shelter/hostel/other	2
2E	How many rooms does your house have? (don't include bathroom & kitchen if separate)	…….	
2F	How many people, older than 18 years old, are living with you in your house?	……..	
2G	Does your household have:	YES	NO
	Electricity?	1	0
	A radio?	1	0
	A television	1	0
	A telephone	1	0
	A refrigerator?	1	0
	A personal computer (PC)?	1	0
	A washing machine?	1	0
	Access to tap water:	1	0
	Tap in house	1	0

	QUESTIONS AND FILTERS	CODING CATEGORIES	
	Tap outside house	1	0
	Shared tap (4 houses)	1	0
	Communal tap (5 or more houses)	1	0
	A toilet	1	0
	A motor car	1	0
	A bicycle (adults)	1	0
2H	What ethnicity do you identify yourself as?		
		Black African	1
		Coloured	2
		White	3
		Indian/Asian	4
		Other	5
2I	Are you…….	Single	1
		Married (civil)	2
		Widowed/divorced	3
		Other	4
	If you answered other, please specify	……	
2M	When were you last tested for diabetes?	Months (……..)	
2N	What was the result of the test, if you tested for diabetes?	Diabetes …….1 No diabetes …….2 Can't remember ……3 Not applicable ……..4	

SECTION 3: SELF-REPORTED REPRODUCTIVE HISTORY

In this section I am going to ask you about your health as a mother		
3A	Would you say your health is poor, average, good, or very good/excellent?	Poor ..... 1 Average ..... 2 Good..... 3 Very good/excellent. 4

3B	Do you personally think that you are underweight, normal weight or overweight?	Underweight.....1 Normal weight.....2 Overweight.....3 Don't know 9
3C	How many times have you been pregnant?	……
3D	Have you ever had any miscarriages?	Yes ……. 1 No …… 0
3E	How many children do you have? Please list the children and their details below, in 3F	……

3F	Name of child	Which year was the child born?	Did you breastfeed this child? (yes/no)	If you breastfed, how long did you breastfeed this child	Did you have diabetes during the pregnancy? (yes/no)	If you had diabetes, how were you treated?

3G	**Before your pregnancy in 2010/2011,** were you ever told by a doctor or a nurse that you had diabetes?	Yes……1 No…….0
3H	If you answered yes to question 3G, were you being treated for diabetes (**before your pregnancy in 2010/2011**)	Yes……1 No……..0 Not applicable….5
3I	If you were being treated for diabetes **before your pregnancy in 2010/2011**, what treatment were you on?	Insulin only……1 Orals pills only…2 Insulin & oral pills…3 Diet……..4 Not applicable…….5
3J	**After your pregnancy in 2010/2011, w**ere you given a referral letter to have your blood sugar checked**?**	Yes……1 No…….0
3K	Did you go to have your blood sugar checked (for diabetes), **after you baby was born in 2010/2011**?	Yes……1 No……0

3L	If you went to be checked for diabetes, how many months **after your pregnancy in 2010/2011** did you go?	……..
3M	If you went to be checked for diabetes **after your pregnancy in 2010/2011**, what test did you have?	Oral Glucose Tolerance Test ….1 Fingerprick …….2 Other……...3 Don't remember ….4 Not applicable ….5
3N	If you went be checked for diabetes **after your pregnancy in 2010/2011**, what were the results?	Diabetes …….1 No diabetes …….2 Can't remember ……3 Not applicable……4
3O	If you did not go to be checked for diabetes **after your pregnancy in 2010/2011**, why did you not go? ……	

SECTION 4: CHRONIC DISEASES AND MEDICATIONS

	Since your pregnancy in 2011 has a **doctor** or **nurse** or **health worker** at a **clinic** or **hospital told you** that you have or have had any of the following conditions:	
4A	High Blood Pressure?	Yes.....1 No.....0 Don't know.....9
4B	If you have high blood pressure, are you being treated?	Yes……1 No……..0 Not applicable ……99
4C	Heart attack or angina (chest pains)?	Yes.....1 No.....0 Don't know.....9
4D	If you have had a heart attack, are you being treated?	Yes……1 No…….0 Not applicable ……99

4E	Stroke?	Yes.....1 No.....0 Don't know.....9
4F	If you have had a stroke, are you being treated?	Yes……1 No…….0 Not applicable …….99
4G	High blood cholesterol or fats in the blood?	Yes.....1 No.....0 Don't know.....9
4H	If you have had high blood cholesterol, are you being treated?	Yes……1 No…….0 Not applicable …….99
4I	Diabetes	Yes.....1 No.....0 Don't know.....9
4J	If you were told that you have diabetes, what treatment are you on?	Diet only……0 Orals only…… 1 Insulin only …….. 2 Orals and insulin…..3 No treatment ……. 4 Not applicable …….5
4K	Kidney Disease	Yes.....1 No.....0 Don't know.....9
4L	If you have had kidney disease, are you being treated?	Yes……1 No…….0 Not applicable …….99
4M	Cancer	Yes.....1 No……0 Don't know……..9
4N	If you have had cancer, are you being treated?	
4O	Chronic respiratory diseases, including asthma	Yes.....1 No……0 Don't know……9
4P	If you have had a chronic respiratory disease, are you being treated?	Yes……1 No…….0 Not applicable …….99

	QUESTIONS AND FILTERS	CODING CATEGORIES
	Now I want to ask you about any medication you take:	
4Q	Do you use any medicine regularly or daily that a doctor or nurse has prescribed?	Yes .....1 No.....0

	QUESTIONS AND FILTERS	CODING CATEGORIES
		Don't know.....9

Record all the drugs mentioned

Drug	Date started	Date stopped	Still taking y/n	Reason for taking drug
Diabetic medications (Insulin),				
Diabetic medications (Oral hypoglycaemics), e.g.				
Blood pressure medication				
Raised blood cholesterol medications e.g. Statins				
Others (Specify)				

SECTION 5: FAMILY MEDICAL HISTORY

Now I would like to ask you about your family. Do you have a close blood relative (father, mother, brother, sister or child) who has ever been diagnosed by a doctor or nurse with any of the following conditions:

			Who has it?
5A	High Blood Pressure?	Yes .....1 No.....0 Don't know 9	
5B	Heart attack or angina or chest pain when exerting himself/herself?	Yes .....1 No.....0 Don't know 9	
5C	Stroke?	Yes .....1 No.....0 Don't know 9	
5D	Diabetes?	Yes .....1 No.....0 Don't know 9	

SECTION 6: ALCOHOL USE

In this section I would like to ask whether you drink alcohol or not and how you drink it

6A	Have you **ever** consumed any alcohol such as beer, wine, spirits or sorghum beer? **IF NO, GO TO SECTION 7**	Yes ……..1 No…….0
6B	Have you consumed any alcohol within the **past 30 days**?	Yes ……..1 No…….0
6C	If yes, during the past 30 days, **how frequently** have you had at least one standard alcoholic drink?	Daily 1 5-6 days per week 2 3-4 days per week 3 1-2 days per week 4 1-3 days per month 5 Less than once a month 6
6D	IF NO, have you stopped drinking due to health reasons, such as a negative impact on your health or on the advice of your doctor or other health worker?	Yes ……..1 No……....0
6E	If you stopped drinking, when did you stop?	Year……
6F	Have you ever felt that you should cut down on your drinking?	Yes……1 No……...0
6G	Have people annoyed you by criticizing your drinking?	Yes……..1 No……0
6H	Have you ever felt bad or guilty about your drinking?	Yes……1 No……..0
6I	Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?	Yes……1 No……..0

SECTION 7: SMOKING HISTORY

Now, I would like to ask you whether you smoke tobacco products or not and if you do, how you do so.				
7	Have you ever smoked cigarette products? **IF NO, PLEASE GO TO QUESTION 7I**		Yes 1	No 0
7A	Do you currently smoke any tobacco products, such as cigarettes, cigars, or pipes?		Yes 1	No 0
7B	Do you currently smoke tobacco products **daily**?		Yes 1	No 0
7C	**How old** were you when you first **started** smoking daily? Years old			
7D	If you do not remember how old you were, do you remember how long ago you started smoking daily?			
	1	WEEKS AGO		
	2	MONTHS AGO		

	3	YEARS AGO		
7E	On average, how many of the following items do you smoke each day? [NONE = 00]			
	1	Manufactured cigarettes?		
	2	Hand-rolled cigarettes?		
	3	Pipes full of tobacco?		
	4	Cigars/Cheroots/Cigarillos?		
7F	**In the past,** did you ever smoke daily?		Yes 1	No 0
7G	**How old** were you when you first **stopped** smoking daily? Years old			
	Don't remember/not sure = 77			
7H	If you do not remember how old you were, do you remember how long ago you stopped smoking daily?			
	1	Weeks Ago		
	2	Months Ago		
	3	Years Ago		
7I	Before you stopped smoking, how many of the following items did you smoke each day? [NONE = 00]			
	1	Manufactured cigarettes?		
	2	Hand-rolled cigarettes?		
	3	Pipes full of tobacco?		
	4	Cigars/Cheroots/Cigarillos?		
	ASSESSING USE OF SMOKELESS TOBACCO			
7J	Do you **currently use any** smokeless tobacco, such as snuff or chewing tobacco?		Yes 1	No 0
	If No, go to question 7L			
7K	Do you currently use smokeless tobacco **daily**?		Yes 1	No 0
	If No, go to question 7L			
7L	On average, how many times do you use each of the following items per day? [None = 00]			
	1	Snuff (by mouth)?		
	2	Snuff (by nose)?		

	3	Chewing tobacco?		
7M	**In the past,** did you ever use smokeless tobacco, such as snuff or chewing tobacco daily?		Yes 1	No 0
7N	During the past **30 days,** did someone smoke in your home?		Yes 1	No 0
7O	During the past **30 days,** did someone smoke in closed areas in your workplace (in the building, in a work area or a specific office)?		Yes 1	No 0

SECTION 8: PSYCHOSOCIAL HEALTH

We are now going to ask you questions relating to certain aspects of our lives. Some of the questions may seem the same but please bear with us because they are not exactly the same.

A) ORIENTATION TO LIFE QUESTIONNAIRE (SOC-13)

Below is a series of questions relating to various aspects of our lives. For each question, you SHOULD first select the response which most closely resembles how you feel. Then, on a scale from 1 to 7, you SHOULD select the number closest to that response which best describes how you feel. You can choose any number between 1 and 7. Please give only one answer to each question.

1. Do you have the feeling that you don't really care about what goes on around you?

very seldom or never						very often
1	2	3	4	5	6	7

2. Has it happened in the past that you were surprised by the behaviour of people whom you thought you knew well?

never happened						always happened
1	2	3	4	5	6	7

3. Has it happened that people whom you relied/depended on disappointed you?

never happened — always happened

1 2 3 4 5 6 7

4. Until now your life has had:

no clear direction or purpose at all — very clear direction and purpose

1 2 3 4 5 6 7

5. Do you have the feeling that you're being treated unfairly?

very often — very seldom

1 2 3 4 5 6 7

6. Do you have the feeling that you are in an unfamiliar situation and don't know what to do?

very often — very seldom or never

1 2 3 4 5 6 7

7. Doing the things you do every day is:

a source of deep pleasure and satisfaction — a source of frustration and boredom

1 2 3 4 5 6 7

8. Do you feel confused or have very mixed-up feelings and ideas?

very often — very seldom or never

1 2 3 4 5 6 7

9. Does it happen that you have feelings inside that you don't like or would rather not feel?

very often — very seldom or never

1 2 3 4 5 6 7

10. Many people--even those who are confident and successful--sometimes feel like losers in certain situations. How often have you felt this way in the past?

never — very often

1 2 3 4 5 6 7

11. When something happened, have you generally found that:

you over-estimated or underestimated its importance? — you saw things in the right perspective?

1 2 3 4 5 6 7

12. How often do you have the feeling that there's little meaning in the things you do in your daily life?

very often very seldom or never

1 2 3 4 5 6 7

13. Sometimes people have strong feelings that they cannot keep under control. How often do you have feelings that you're not sure you can keep under control?

very often very seldom or never

1 2 3 4 5 6 7

B) LOCUS OF CONTROL

To which extent do you agree or disagree with the following statements about your own life:

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
a) At work, I feel I have control over what happens in most situations.					
b) I feel what happens in my life is often determined by factors beyond my control.					
c) Over the next 5-10 years, I expect to have more positive than negative experiences.					

d) I often have the feeling I am being treated unfairly.					
e) In the past 10 years my life has been full of changes without my knowing what will happen next.					
f) I gave up trying to better my life a long time ago.					

C) LIFE EVENTS QUESTIONNAIRE

Have any of the following life events or problems happened to you during the last 6 months? How about more than 6 months ago? If so, please also rate the impact on you.	
1. You yourself suffered a serious illness, injury or an assault. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
2. A serious illness, injury or assault happened to a close relative. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant

Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
3. Your parent, child or spouse died. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
4. A close family friend or another relative (aunt, cousin, Grandparent) died. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
5. You had a separation due to marital difficulties. Yes/No. If no, go to next question.	

Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
6. You broke off a steady relationship. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
7. You had a serious problem with a close friend, neighbor or relative. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant

8. You became unemployed or you were seeking work unsuccessfully for more than one month. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
9. You were fired from your job. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
10. You had a major financial crisis. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant

Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
11. You had problems with the police and a court appearance. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant
12. Something you valued was lost or stolen. Yes/No. If no, go to next question.	
Did this occur in past 6 months?	Yes / No
If yes, Impact:	None / Some / Significant
Did this occur more than 6 months ago?	Yes / No
If yes, Impact:	None / Some / Significant

SECTION 9: PHYSICAL ACTIVITY – MODIFIED STEPS/GPAQ

	The next questions are about the time you spend doing different types of physical activities. This includes activities you do **at home, at work, travelling from place to place and during your spare time**. You are requested to answer the questions even if you don't consider yourself to be an active person.				
	Occupation-Related Physical Activity (paid or unpaid work): When answering the following questions, think back over the **past 12 months** and consider (think of) **a usual week**.				
9A	Does your work involve <u>vigorous</u> activities, (<u>like</u> heavy lifting, digging, or heavy construction)				
	for **at least 9 minutes** at a time?			Yes 1	No 0
	If No, go to question 9D				
9B	In **a usual week**, how many days do you do <u>vigorous</u> activities as part of your work?				
	DAYS:				
9C	On **a usual day** on which you do <u>vigorous</u> activities, how much time do you spend doing such work?				
	1	HOURS:			
	2	MINUTES:			
9D	Does your work involve <u>moderate-intensity</u> activities, (<u>like</u> brisk walking or carrying light loads)				
	for **at least 9 minutes** at a time?			Yes 1	No 0
	If No, go to question 9G				
9E	In **a usual week**, how many days do you do <u>moderate-intensity</u> activities as part of your work?				
	Days:				
9F	On **a usual day** on which you do <u>moderate-intensity</u> activities, how much time do you spend doing such work?				

	1	Hours:			
	2	Minutes:			
	Travel-related physical activity: other than activities that you've already mentioned, i would like to ask you about the way you travel to and from places (to work, to shopping, to market, to church, etc.).				
9G	Do you walk or use a bicycle (pedal cycle) for **at least 9 minutes** at a time to get to and from places?				
				Yes 1	No 0
	If no, go to question 9J				
9H	In **a usual week**, how many days do you walk or cycle for at least 9 minutes to get to and from places?				
	Days:				
9I	On **a usual day,** how much time do you spend walking or cycling for travel?				
	1	Hours:			
	2	Minutes:			
	Non-work related and leisure time physical activity: the next questions ask about activities you do in your leisure or spare time, for recreation or fitness**.** Do not include the physical activities you do at work or for travel already mentioned.				
9J	In your leisure or spare time, do you do any <u>vigorous</u> activities (<u>like</u> running or strenuous				
	Sports, weightlifting) for **at least 9 minutes** at a time?			Yes 1	No 0
	If no, go to question 9M				
9K	In **a usual week**, how many days do you do <u>vigorous</u> activities as part of your leisure or spare time?				
	Days:				
9L	How much time do you spend doing this on **a usual day?**				
	1	Hours:			
	2	Minutes:			
9M	In your leisure or spare time, do you do any <u>moderate-intensity</u> activities (<u>like</u> brisk walking, cycling or				
	Swimming) for **at least 9 minutes** at a time?			Yes 1	No 0

	If no, go to question 9P				
9N	In **a usual week**, how many days do you do <u>moderate-intensity</u> activities as part of your leisure				
	Or spare time? Days:				
9O	How much time do you spend doing this on **a usual day?**				
		Hours:			
		Minutes:			
	Sitting / resting activity: now I would like to ask you about the time spent sitting or resting, not including sleeping, **in the <u>past 7 days</u>**. This may include time sitting at a desk, visiting friends, reading, or sitting down to watch television **during working hours and leisure or spare time**.				
9P	Over the **past 7 days,** how much time did you spend sitting or reclining (lying) on **a usual day (excluding sleeping)?**				
		Hours:			
		Minutes:			
9Q	On average, how much time, each day, do you spend watching television?				
		Hours:			
		Minutes:			

SECTION 10: DIETARY MEASUREMENTS

Food habits

1. Are you on a special diet that has been prescribed for you e.g. by a doctor or one that you have adopted from someone e.g. a TV star/magazine?

YES	1
NO	0

2. If NO, go to question 4.
   If YES, describe what kind of diet you are on and where you got the diet from?

_____

3. How long have you been on that diet?_____months/years.

4. Do you currently take any vitamin and mineral supplements?

YES	1
NO	0

IF YES, what do you take?

	Name of product	Amount/day (or how many tablets)
Vitamins/vitamins and minerals		
Tonics		
Vitamin D		
Calcium		
Body building preparations		
Dietary fibre supplement		
Other: specify		

5. Which meals do you skip almost on a daily basis?

Breakfast	1
Lunch	2
Evening meal	3
None	4

6. Is salt added to your food while it is being cooked?

Always	1
Sometimes	2
Never	3
Don't know	4

7. Do you add salt to your food before you eat it?

YES	1
NO	0

8. If yes, how much salt do you add to your food each day?

¼ teaspoon	1
½ teaspoon	2
¾ teaspoon	3
1 teaspoon	4
Other specify:	5

9. Do you add Aromat to your food before you eat it?

YES	1
NO	0

10. If yes, how much Aromat do you add to your food each day?

¼ teaspoon	1
½ teaspoon	2
¾ teaspoon	3
1 teaspoon	4
Other specify:	5

11. There are some factors which influence the choice of foods we eat. Which of the following statements are true for you?

	Strongly agree	Agree	Disagree	Strongly Disagree
I choose to eat certain foods because they taste good	1	2	3	4
The food I eat depends on whether it is expensive	1	2	3	4
I choose to eat certain foods because it looks good	1	2	3	4
The food I choose to eat differs according to my mood (i.e. happy/sad)	1	2	3	4
My hunger level determines what type of food I eat.	1	2	3	4
I choose foods which are not time consuming to prepare	1	2	3	4
I consider whether a food is good for my health before eating the food.	1	2	3	4

12. Do you ever eat outside the home e.g. at fast food shops such as Nandos, KFC and Steers?

YES	1
NO	0

13. If YES, in an average month how often do you eat from these fast food shops? ……

Dietary intake assessment
NB! Think back to the last two weeks and divide the food cards into two piles i.e. foods you did eat and foods you did not eat.
Now go through the pile of cards that you did eat.
Tell me how many times per day or per week did you eat …(complete column E or F)
Describe the food item in column B (if applicable)
Select the usual portion size in column D (encircle) and Indicate the amount consumed in column C

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
DAIRY – BLUE					
1. Sugar in tea/coffee			Tbs/tsp heaped/level		
1. Sugar in cooking (veg/ porridge)			Tbs/tsp heaped/level		

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
2. Milk in tea/coffee	Full cream / low fat (2%)/ fat-free		Little / milky		
2.Milk with porridge	Full cream/ low fat (2%)/ fat-free		How much? Bowl		
3. Buttermilk/maas			Small or large glass		
4. Milk drinks	Type: Steri-stumpie, etc.		Small or large glass or ml		
5. Yoghurt	Plain / fruit & sweetened Full cream/low fat/fat free		100ml tub/ 180ml tub/ heaped Tbs		
6. Cottage cheese	Full fat/ low fat/ fat free		Heaped Tbs		
7. Hard Cheese			Slice / matchbox		
8. Processed cheese	Type		Wedges/Tbs		
9. Ice cream & Ice lollies	Type		Scoops or heaped Tbs or nr of lollies		
STARCH - BROWN					
1. Brown bread/rolls			Slice		
1. White bread/rolls			Slice		
1. Whole wheat /Low GI bread			Slice		
2. Fat cakes			Small = 1 matchbox; Med = 2 matchboxes Lrg = 3 matchboxes		
3. Breakfast cereals	Specify type		½ or ¾ or full Bowl		
4. Maize porridge soft			½ or ¾ or full Bowl		
4. Maize porridge stiff			½ or ¾ or full Bowl		
4. Mabele/martabella soft			½ or ¾ or full Bowl		
4. Mabele/ stiff			½ or ¾ or full Bowl		

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
4. Oats			½ or ¾ or full Bowl		
5. Pasta without sauce	White/ whole-wheat pasta		Heaped serving spoon		
6. Pasta dishes	White/ whole-wheat pasta		Heaped serving spoon		
7. Rice	White/brown		Heaped serving spoon ½ cup dough model		
7. Samp/mealie meal			Heaped serving spoon ½ cup dough model		
7. Wheat rice			Heaped serving spoon ½ cup dough model		
8. Pizza and savoury tart	Type		pic in booklet		
FATS - TAN					
1. Brick margarine	Type		Tbs/tsp heaped/level		
1. Tub margarine	Type		Tbs/tsp heaped/level		
1. White margarine	Type		Tbs/tsp heaped/level		
1. Butter	Type		Tbs/tsp heaped/level		
2. Animal fat i.e lard			Tbs/tsp heaped/level		
3. Cream and substitutes			Tbs/tsp heaped/level		
4. Oils	Sunflower / fish oil / canola oil / olive oil		Tbs/tsp heaped/level		
5. Salad dressing			Tbs/tsp heaped/level		
5. Mayonnaise			Tbs/tsp heaped/level		

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
SPREADS - PINK					
Cheese spread	Type		Thin / med /thick		
Honey/syrup			Heaped Tbs/tsp		
Jam	Regular/low sugar		Heaped Tbs/tsp		
Peanut butter	Regular/no sugar		Heaped Tbs/tsp		
Sandwich spread	Type		Heaped Tbs/tsp		
EGGS - YELLOW					
Boiled			1 egg		
Fried			1 egg		
Omelet			1egg		
Scrambled			1 egg		
FRUIT - ORANGE					
1. Apples, pears			Small / med /large		
2. Bananas			Small / med /large		
6. Grapes			Nr of grapes		
8. Mango/paw paw			½ cup Slices / cubes		
9. Melons - sweet			½ cup, pic per booklet		
11. Oranges, Naartjies			Small / med /large		
12. Peaches			Small / med /large		
16. Dried fruit			nr		
17. Fruit juice	Type		ml or small glass or tall glass		
SOUP, LEGUMES, NUTS – pale green					
1. Soups			Ladle/bowl		
2. Legumes & lentils			½ cup dough model		
3. Seeds & nuts, peanuts			Handful		
FISH AND SEAFOOD - BEIGE					

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
1. Fried fish			Picture in booklet		
2. Grilled/smoked/dried fish	Type		Picture in booklet		
3. Plichards & sardines	In oil/brine		Tin		
3. Tuna - tinned	In oil/brine		Tin		
MEAT - RED					
1. Beef & Ostrich	Cut		Matchbox		
2. Patties & mince	Type: beef/ostrich Regular/lean/extra-lean		Small/medium		
3. Burgers & take-aways	Type				
4. Chicken – with skin	Grilled/fried		Thigh / wing / drumstick / breast		
4. Chicken – without skin	Grilled/fried		Thigh / wing / drumstick / breast		
5. Cold meat	Type		slice		
7. Meat pies	Type		Size - ruler		
8. Mutton	Type		Line drawings		
9. Pork	Type		Line drawings		
10. Sausage & vienna	Type		Ruler and thick or thin		
11. Traditional & organ meats	Type		Serving spoon		
13. Dry sausage & biltong	Type		½ cup/ length		
VEGETABLES - GREEN					
2. Avocado			½ or ¼ etc.		
5. Orange/yellow veg (butternut, pumpkin, carrots, sweet potato, gem squash, mealies)			½ cup dough model		
6. Green veg (spinach, peas, green beans, broccoli)			½ cup dough model		
7. Cabbage, cauliflower, lettuce			½ cup dough model		

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
12. Mixed vegetables			½ cup dough model		
15. Potatoes			Nr med		
16. Potato chips			½ cup		
20. Tomatoes			Nr or ½ cup		
BISCUITS, CAKES, PUDDINGS					
1. Biscuits/cookies	Type		nr		
2. Biscuits/savoury	Type		nr		
3. Muffins/scones	Type		Picture in file		
4. Cakes and tarts	Type		Line drawings		
5. Doughnuts/éclairs	Type		nr		
6. Pancakes/waffles	Type		nr		
7. Pudding/custard	Type		bowl		
8. Rusks	Type		nr		
SNACKS, SWEETS & COLD DRINKS - PINK					
1. Carbonated cold drinks	Specify		ml or tin or small glass or tall glass		
1. Diet cold drinks	Specify		ml or tin or small glass or tall glass		
2. Energy drinks	Specify		ml or tin or small glass or tall glass		
2. Squashes	Specify		ml or tin or small glass or tall glass		
3. Crisps	Specify		small packet – 40g		
4. Sweets	Specify		nr		
4. Chocolates	Specify		50g bar or slab or nr of blocks from slab		
SAUCES AND CONDIMENTS - GRAY					

A. Food Item (with FMP numbers)	*B. Description of food item*	*C. Amount consume*	*D. Portion size*	*E. Times/ day*	*F. Times/ week*
1. Cheese and white sauces	Specify		Tbs		
2. Tomato sauce & other	Specify		Tbs		
ALCOHOLIC DRINKS - GRAY					
1. Beer & cider & coolers	Type Normal/lite		Cans/bottles Small glass/tall glass		
2. Wine	White/red/rose		Wine glass per booklet		
3. Spirits	Type Mixed with?		Nr of tots Small glass/tall glass		
4. Liquers and fortified wine	Type		Small glass		
Other					

SECTION 11A: MEASUREMENTS (MOTHER ANTHROPOMETRY AND BIOCHEMISTRY)

Weight:					kg
Height:					cm
Waist circumference:					cm
Hip circumference:					cm
During the past two weeks, have you been treated for raised blood pressure with drugs (medication) prescribed by a doctor or other health worker? **Yes** **No**					
Discard 1st blood pressure reading					
1st Systolic blood pressure				mmHg	
1st Diastolic blood pressure :				mmHg	
1st Heart rate :					
2nd Systolic blood pressure :				mmHg	
2nd Diastolic blood pressure :				mmHg	
2nd Heart rate :					
3rd Systolic blood pressure :				mmHg	
3rd Diastolic blood pressure :				mmHg	
3rd Heart rate :					

SECTION 11B: MEASUREMENTS (CHILD ANTHROPOMETRY)

CHILD					
Weight at 5 years:					kg
Height at 5 years:					cm
At birth, head circumference:					cm
At birth, length:					cm
Birthweight:					gm
Gestational age				weeks	
CHILD 2, IF TWINS					
Weight at 5 years:					kg
Height at 5 years:					cm
At birth, head circumference:					cm
At birth, length:					cm
Birthweight:					gm
Gestational age					weeks

BLOOD TEST RESULTS			**Rapid test**
Today, have you taken insulin or other drugs (medication) that have been prescribed by a doctor or other health worker for raised blood glucose?		Yes No	
During the past two weeks, have you been treated for raised cholesterol with drugs (medication) prescribed by a doctor or other health worker?		Yes No	
During the past 12 hours have you had anything to eat or drink, other than water?		Yes No	
Oral glucose tolerance test (OGGT) (mmol/ℓ)	Fasting glucose 0 minutes		
	Blood glucose 120 minutes		
Insulin (MIU/mℓ)	0 minutes		
Insulin (MIU/mℓ)	120 minutes		
	Total cholesterol (mmol/ℓ)		
	HDL cholesterol (mmol/ℓ)		
	Triglycerides (mmol/ℓ)		
	LDL cholesterol (mmol/ℓ)		

SECTION 12 – SLEEP ASSESSMENT

The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

During the past month,

1. What time have you usually gone to bed? …….
2. How long (in minutes) has it taken you to fall asleep each night? ……
3. What time have you usually gotten up in the morning? ……
4. a. How many hours of actual sleep did you get at night? ……..

   b. How many hours were you in bed? ……

5. During the past month, how often have you had trouble sleeping because you	**Not during the past month (0)**	**Less than once a week (1)**	**Once or twice a week (2**	**Three or more times a week (3)**
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
h. Have bad dreams				
i. Have pain				
j. Other reason (s), please describe, including how often you have had trouble sleeping because of this reason (s):				
6. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
9. During the past month, how would you rate your sleep quality overall?	**Very good (0)**	**Fairly good (1)**	**Fairly bad (2)**	**Very bad (3)**

SECTION 13: CHILD DATA

Child's name: ……..

Child's date of birth …… D D M M Y Y Y Y

Child age (years) …… Child gender (male or female?) ……. Race .....

How was the child delivered at birth?
Normal delivery……1
Caesarian section ……...2
Breech ……...3
Other, specify…….4

Is the child taking any medications?
Yes……1
No……0

Has the child ever been hospitalized for at least 1 week with a serious illness? Yes……1
No…….2

If yes, list the medications below

Medication	Reason	Date started	Date stopped	Prescribed by

Further Study Participation

Would you like to be contacted to participate in other research studies related to diabetes in future?

Yes

No

THANK YOU FOR PARTICIPATING IN THE PRO2D STUDY. HAVE A GOOD DAY

Appendix 5.2 PRO2D ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 November 2015

HREC REF: 656/2015

Prof N Levitt
Division of Endocrinology
J-47
OMB

Dear Prof Levitt

PROJECT TITLE: THE PREVALENCE OF TYPE 2 DIABETES MELLITUS AND ASSOCIATED RISK FACTORS 5 YEARS AFTER GESTATIONAL DIABTES MELLITUS IN SOUTH AFRICA (PhD candidate-T Chivese)

Thank you for your response letter dated 23 November 2015, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student:-Tawanda Chivese is also involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

Hrec/ref:656/2015

Appendix 5.3. PRO2D participant consent

Participant information leaflet and Consent Form

Research Title: The prevalence of Type 2 diabetes mellitus and associated risk factors 5 years after gestational diabetes mellitus in South Africa

Principal Investigators: Professor Naomi Levitt, Professor Shane Norris, Professor Christina Zarowsky, Tawanda Chivese

Contact Address: Chronic Disease Initiative for Africa, J47 Room 86, Old Groote Schuur Hospital Building Observatory, 7935, Cape Town

Telephone: +27 21 4066572

Fax: +27 21 4486815

More information: http://www.health.uct.ac.za/fhs/research/groupings/cdia/about

Participant Number:

You are being invited to take part in a research project which asks the question: How many women who had diabetes in their pregnancy have diabetes 5 years later?

This research project is being conducted at the University of Cape Town and the University of the Witwatersrand in Johannesburg. A researcher from the University of Montreal (Christina Zarowsky) will also help with knowledge on how to carry out research properly.

Most women who had diabetes during pregnancy recover from the diabetes after the birth of their babies, but they have a high chance of developing Type 2 diabetes sometime later. Type 2 diabetes is a chronic condition that affects the way your body uses sugar (glucose), your body's source of fuel. If we can find that someone has type 2

diabetes earlier we can start treatment sooner and this may cause fewer long term problems.

We do not know how many women with diabetes during pregnancy end up with type 2 diabetes in South Africa. We also do not know what other factors lead to increased chance of diabetes in this situation. Knowing these factors will enable us to develop better programs to reduce the risk of diabetes in women. Additionally, knowing factors that increase the chance of their children being overweight can help lower the risk of them developing diabetes and heart disease later in their life.

Ethical considerations

This research has been approved by the University of Cape Town Human Research Ethics Committee (Ethics approval number 656/2015). The research will be carried out according to the Declaration of Helsinki, which protects people who take part in research (Fortaleza, Brazil 2013).

You are free to say yes or to say no. If you say no, your medical care will continue just as before, and it will not be held against you. You are also free to withdraw from the study at any point, even if you do agree to take part. If you volunteer to take part in the study, you will only be included if you give written informed consent.

Please ask the study staff any questions about any part of this project that you do not fully understand.

Why have you been invited to participate?

We are inviting all women who live in Cape Town and Soweto who received treatment for diabetes during pregnancy at Groote Schuur Hospital and Chris Hani Baragwanath Hospital to take part in the research.

What will your participation entail?

You have been asked to come to the Groote Schuur Hospital (or Chris Hani Baragwanath Hospital, delete inapplicable) in order to take part in the research. Your participation will be for two and a half hours. You will be asked to complete a questionnaire and have blood taken from a vein in your arm before and after drinking sugar water. In your blood, we will measure glucose, fats and other factors associated with diabetes. We will also store 5ml of your blood, in case we need to retest your blood or carry out additional tests related to the study. We will seek permission from the University of Cape Town Human Research Ethics Committee before we do any additional tests. This stored blood will be destroyed 2 years after the study is finished, if it has not been used.

For the diabetes test, you are requested to fast overnight before the test can be done. We will also measure your blood pressure (BP), height, weight and how wide your waist and hips are. We will also look for information about your pregnancy in your hospital folder. This information will include the sugar level that was in your blood when you were pregnant, any illnesses you had during the pregnancy, and how much your baby weighed when he/she was born.

An interviewer will ask you some questions using a questionnaire. These question may help us identify a pattern of who is more likely to have diabetes. An example of the questions we are asking is whether you or any of your family members has ever been diagnosed with diabetes.

Will you benefit from taking part in this research?

If any illnesses (such as undiagnosed diabetes or high blood pressure) are identified during the research then you will be referred to a clinic for follow-up and management. You will also be told the results of all the tests that will be done.

Are there any risks involved in your taking part in this research?

We will take blood samples from the forearms. The risk are very small. Some of the potential risks in the blood collection include infection, delayed healing, bruising and some physical pain. The blood samples will be drawn using experienced nurses to minimize the risks.

Your name and personal details will be kept strictly confidential and will not be given to anyone to minimise the risk of improper disclosure of information.

What if Something Goes Wrong?

The University of Cape Town (UCT) has insurance which will compensate you if you suffer injuries or harm during your participation in this research. This compensation will pay for reasonable medical charges and this will be according to the South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI) in the event of an injury or side effect resulting directly from your participation in the trial. You will not be required to prove fault on the part of the University.

The University will not be liable for any loss, injuries and/or harm that you may sustain where the loss is caused by

- The use of unauthorised medicine or substances during the study

- Any injury that results from you not following the protocol requirements or the instructions that the study doctor may give you
- Any injury that arises from inadequate action or lack of action to deal adequately with a side effect or reaction to the study medication
- An injury that results from negligence on your part

By agreeing to participate in this study, you do not give up your right to claim compensation for injury where you can prove negligence, in separate litigation. In particular, your right to pursue such a claim in a South African court in terms of South African law must be ensured. Note, however, that you will usually be requested to accept that payment made by the University under the SA GCP guideline 4.11 is in full settlement of the claim relating to the medical expenses.

An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request.

If you do not agree to take part, what alternatives do you have?

Not taking part in the study will not change your future care or treatment when you go to hospitals or clinics. You will be treated the same as other women who decide to participate in the study. The researchers are not the same people as your usual doctors.

Who will have access to your medical records and what information will they collect?

All personal information collected will be treated as confidential and access to it will be strictly controlled and limited to the researchers. The information collected from your medical records will include information about your pregnancy, whether you had any illnesses during that pregnancy, the level of sugar in your blood and blood pressure during that pregnancy and whether your child had any problems when they were born. Your name will be removed from all samples and information provided as soon as possible. Only a study number will be used. Your name will never be published anywhere.

Will you be paid to take part in this study and are there any costs involved?

We will give you a R150 food voucher redeemable at Shoprite to thank you for the time you spend during the study. You will not be able to buy alcohol and smoking products using this voucher. We will compensate you for your travelling expenses.

Please ensure that you have carefully read and understood this information sheet and been given a copy to keep for yourself.

Contact details of researchers: For any questions or concerns, please feel free to contact the researchers whose details are listed below:

Tawanda Chivese	Email: tchivese@gmail.com
	Tel: 0216505131
Professor Naomi Levitt	Email: Naomi.Levitt@uct.ac.za
	Tel: 0216505110
Professor Shane Norris	Email: san@global.co.za
Professor Christina Zarowski	Email: czarowsky@gmail.com

You may contact the University of Cape Town Human Research Ethics Committee if you have any questions or concerns your rights and welfare. The contact details are listed below

Email: sumayahariefdien@uct.ac.za

Tel: 021 406 6338

Fax: 021 406 6411

PARTICIPANT CONSENT

Study Title: The prevalence of Type 2 diabetes mellitus and associated risk factors 5 years after gestational diabetes mellitus in South Africa

By signing this document:

I confirm that I have read the above information and understand it. I confirm that I have had an opportunity to ask questions and I am satisfied with the answers and explanations that have been given to me.

I give my permission for the researchers to use the information in my medical chart for the purposes of this research.

I agree to have left over serum from my blood sample kept and then frozen.

I understand that my participation in this research is voluntary and I am free to withdraw at any time without having to give a reason.

Please tick one of the boxes below:

☐ YES, I would like to take part in this study

☐ NO, I do not wish to take part in this study

Name of research participant: ……. Signature…….
Date: ……

Name of researcher: ……. Signature…….
Date: ……

Name of witness…….. Signature……

Date ……..

If participant is not able to write:

Thumbprint of participant…….

Date ……

Participant Contact Details

Forename	
Surname	
Address	
Suburb	
City	
Postcode	
Telephone	
Cell	
Secondary cell	
Next of kin telephone	
Next of kin cell	
Next of kin address	
Date of birth	
Hospital number	

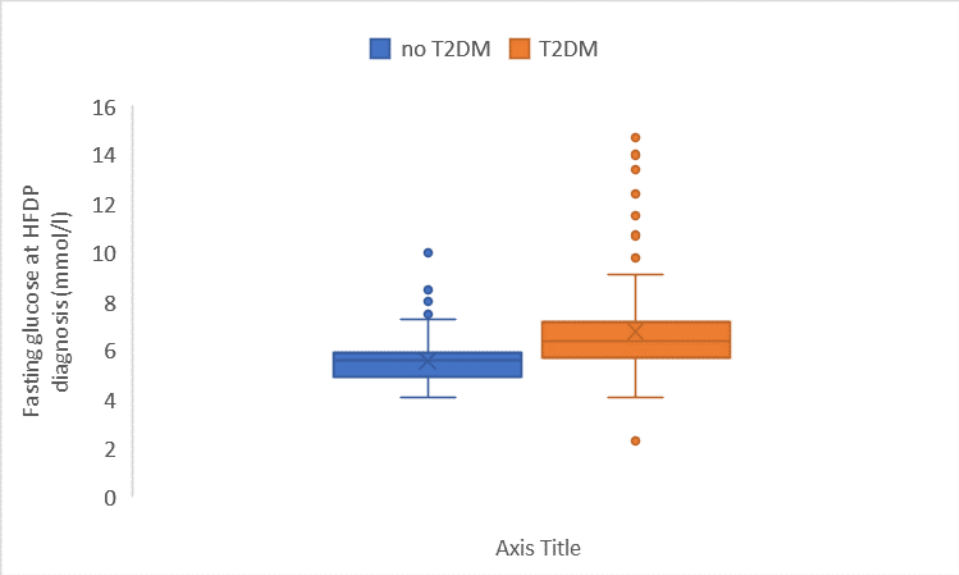
Appendix 5.4. PRO2D Chapter 5 Supplementary materials

S4 Table 1. Comparison of participants followed up 5-6 years later and the participants lost to follow-up

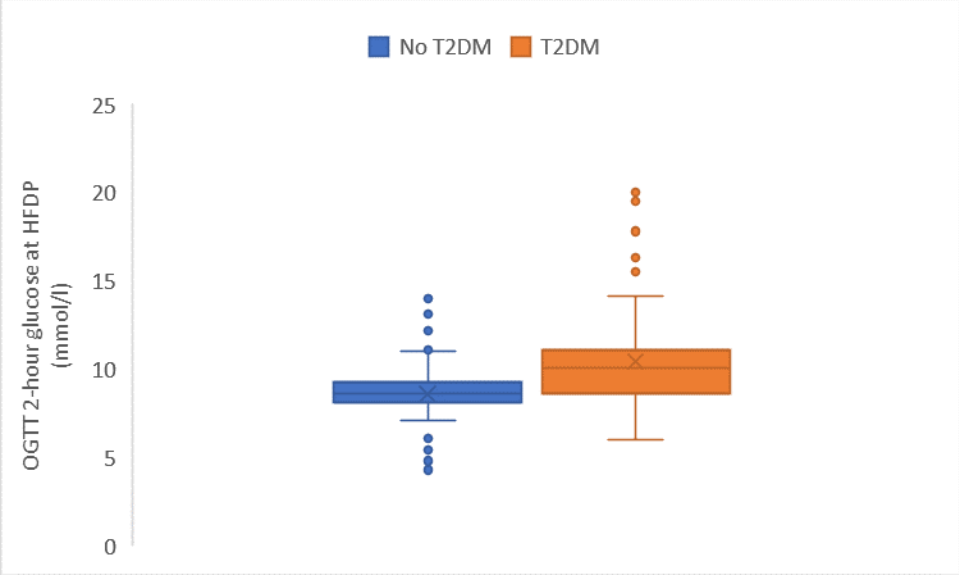
		Not followed-up, N = 278	Followed-up, N = 220
Age at booking	Median (IQR) years	31 (26-35)	31 (27-35)
Number of pregnancies	Median (IQR)	3 (2-4)	3 (2-4)
Number of live births	Median (IQR)	1 (1-2)	1 (0-2)
Gestational age at booking	Median (IQR) weeks	17 (13-22)	15 (11-21)
Syphilis (VDRL positive)	n (%)	5 (1.8)	4(1.8)
HIV positive	n (%)	19 (6.9)	12 (5.5)
CD4 count	Median (IQR) cells/l	454 (406-545)	492.5 (364-774)
BMI at booking	Median (IQR) kg/m^2	32.7 (27.6-38.4)	34.6 (28.8-41.4)
Random blood glucose	Median (IQR) mmol/l	12.7 (11.4-14.4)	12.7 (11.2-14.1)
Fasting plasma glucose at HFDP diagnosis	Median (IQR) mmol/l	5.9 (5.3-6.9)	5.8 (5.1-6.5)
1-hour OGTT plasma glucose at GDM diagnosis	Median (IQR) mmol/l	10.6 (9.4-12.2)	10.5 (9.2-11.5)
2-hour OGTT plasma glucose at HFDP	Median (IQR) mmol/l	12 (11.2-12.8)	9 (8.2-10)
Treated with metformin during HFDP	n (%)	99 (35.6)	61 (28.4)
Treated with glibenclamide during HFDP	n (%)	9 (3.3)	7 (3.3)
Treated with insulin during HFDP	n (%)	80 (28.8)	52 (24.1)
Treated with both orals and insulin during HFDP	n (%)	4 (1.4)	3 (1.4)
Number of hospital admissions during HFDP	Median (IQR)	2 (1-3)	2 (1-3)
HbA_{1c} at booking	Median (IQR) %	6.4 (5.9-7.2)	6.5 (6-7.4)
Type of birth delivery	Caesarian section, n (%)	144 (52.8)	120 (56.3)
	Normal virginal, n (%)	129 (47.3)	93 (43.7)
Fetal outcome	Stillborn or miscarriage, n (%)	10 (3.6)	6 (2.8)
Admitted to NICU	n (%)	2 (0.7)	3 (1.4)
Fetal birthweight	Median (IQR) grams	3230 (2805-3620)	3292 (2925-3610)

**NICE 2008 guidelines were used. GDM referred to women with the following glucose concentrations at diagnosis: fasting>7.0mmol/l and OGTT 2-hours ≥11.1mmol/l. IGT referred to women with the following glucose at diagnosis: fasting between 5.6-6.9mmol/l and OGTT between 7.8-11.0mmol/l. in the WHO 2013 GDM diagnosis guidelines, the "GDM" group in the NICE guidelines is now the diabetes in pregnancy (DIP) group while the IGT group is now the GDM*

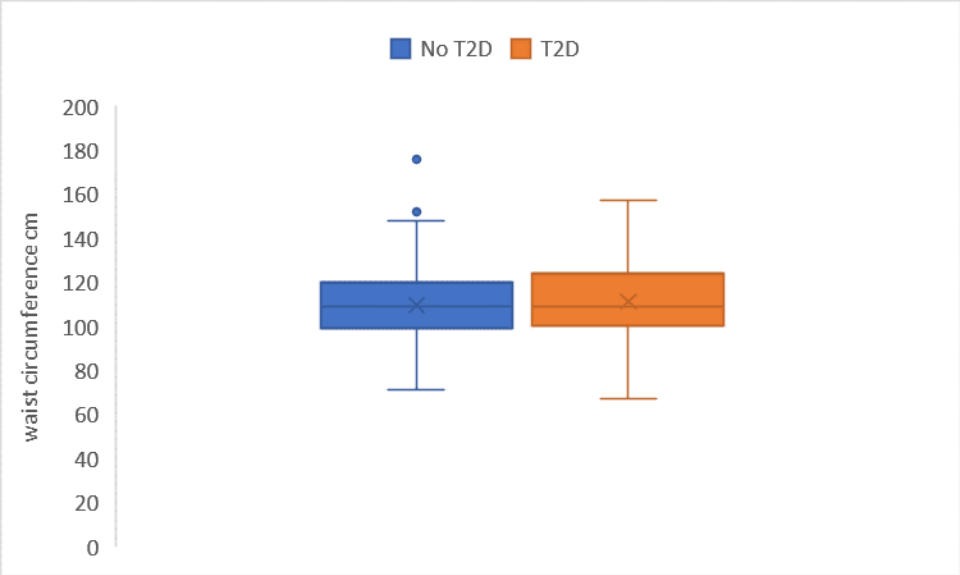
S5_Fig. 1



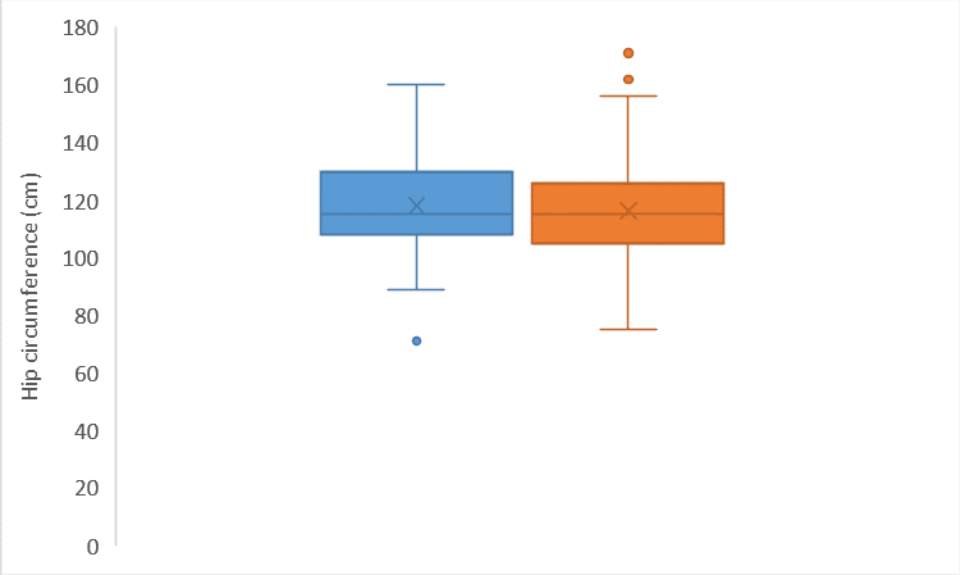
S6_Fig2



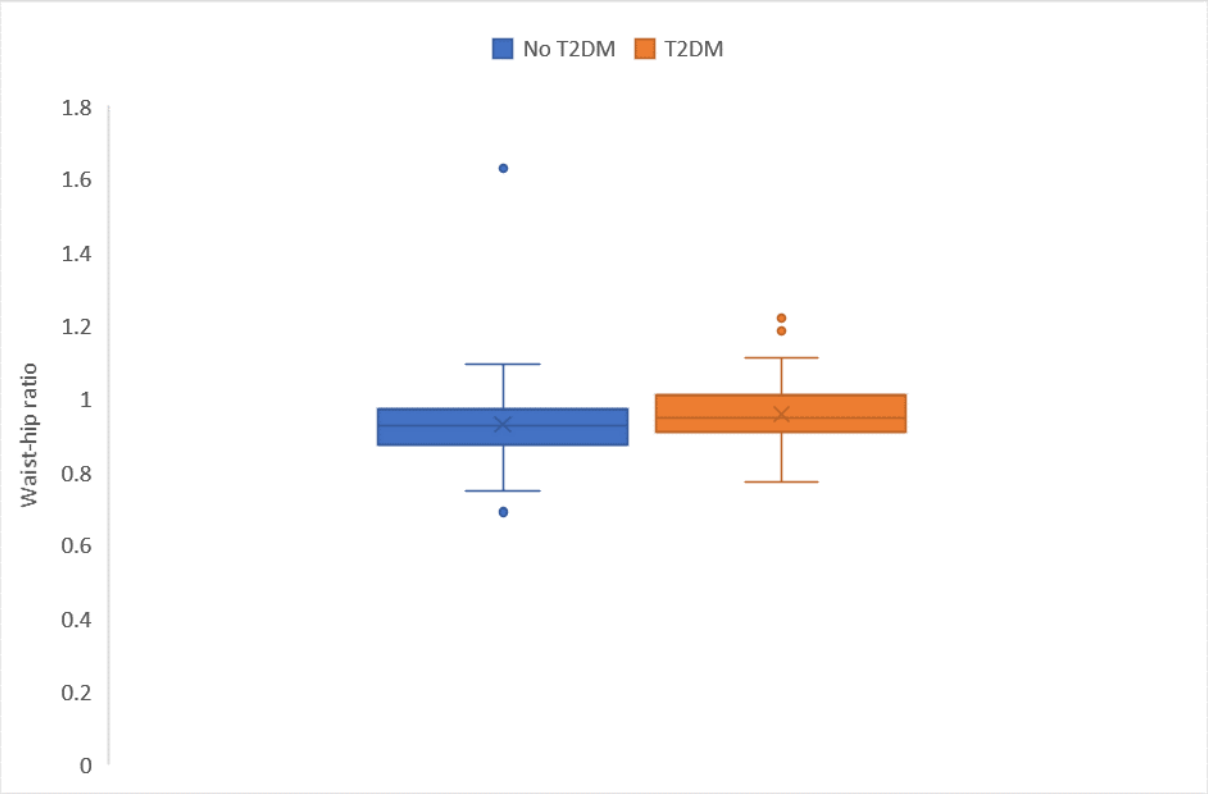
S7_Fig.3



S8_Fig. 4



S9_Fig. 5



S10 Table 2. Progression to T2DM after HFDP – studies published from 2000-2019

Study	Sample Size	Response Rate	Country	Design	GDM Diagnosis	Follow Up Period	Progression to T2D	Progression to impaired glucose regulation*	Risk factors for progression
(Lowe et al., 2018)	4697 (GDM 663)	69.1%	Multicenter (10 countries)	Cohort	IADPSG	11.4 years	10.7%,	41.5%	GDM
(Huvinen et al., 2018)	333	95.7%	Finland	prospective cohort	WHO 1998 (5.3, 10,8.6)	5 years	3.6%	15%	GDM
(Inoue et al., 2018)	77	22.3%	Japan	retrospective cohort	IADPSG	2 years	22%	44.1%	2-hour glucose (OR 1.04), HbA1C% (OR 5.4), perinatal complication (OR 7.4), family history DM (OR 3.7)

(Simmons et al., 2017)	2786 (50 previous GDM)	NR*	Maori New Zealand	cross sectional	self-reported past GDM	lifetime GDM history	20%	NR	GDM
(Chamberlain et al., 2016)	578	NR	Australia indigenous	retrospective cohort	Australian DA, FPG ≥5.5, 2-hour ≥8	3, 5, 7 years	21.9% 3 yrs, 25.5% 5 yrs, 42.4% 7 yrs	NR	early pregnancy BMI≥25(HR 3.16), partial breastfeeding at discharge (HR 2.34), 3. aboriginal status (HR4.6)
	332		Australia non-indigenous				4.2% 3 yrs, 5.7% 5 yrs, 13.5% 7 yrs		
(Gupta et al., 2017)	366	37%	India	Cohort	Carpenter and Coustan, IASDPSG	14 months	40%	32%	high pre-pregnancy-BMI (OR1.16), acanthosis nigrins (OR3.1), post-partum screening interval (by 1 month) (OR1.02), age (OR1.1)
(Tam et al., 2012)	139 (45 GDM)	68.4	China	prospective cohort	WHO 1998	15 years	24.4%	9.8%	Only GDM
(Wang et al., 2012)	19998 (GDM =1142)	NR	USA	cohort	WHO 1998 ADA 2003	8.6 years	28.7%	NR	Black American race, age, BMI
(Madarász et al., 2009)	68 GDM 39NGT	52.50 %	Hungary	Follow up cohort	WHO 1985	4 years	21%	15%	FPG (OR3.4)
(Lee et al., 2008)	868 GDM 868 controls	NR	Korea	case-control	National Diabetes Data Group	2 years	11.5%	NR	GDM (OR 3.7), family history (OR2.2), wc>85cm (OR2.3)
(Rivero et al., 2008)	109	85.8%	Brazil	prospective cohort	ADA 1997 Working Force on DM and Pregnancy 1985	32 months	17.4%	39.4%	pre-pregnancy BMI and follow-up BMI - univariate analysis
(Tam et al., 2007)	203 (63 GDM)	92.6%	China	prospective cohort	WHO 1998	8 years	9%	30.2%	Pre-pregnancy BMI≥23 (OR 3.4)
(Krishnaveni et al., 2007)	555, gdm = 35	88%	India	cohort	Carpenter and Coustan	5 years	37%	31%	GDM, WC (OR 1.1), family history (OR 10.6)
(Kale et al., 2004)	126	69.20 %	India	Follow up cohort	WHO 1985	4.5 years	52%	19%	age≥30yrsGDM (OR3.7), family history (OR2.4), 2-hour glucose>10mmol/l (OR3.6),

	WHR>0.85(OR2.48)

NR* - not reported

References in s10 Table 2

CHAMBERLAIN, C. R., OLDENBURG, B., WILSON, A. N., EADES, S. J., O'DEA, K., OATS, J. J. & WOLFE, R. 2016. Type 2 diabetes after gestational diabetes: greater than fourfold risk among Indigenous compared with non-Indigenous Australian women. *Diabetes Metab Res Rev,* 32**,** 217-27.

GUPTA, Y., KAPOOR, D., DESAI, A., PRAVEEN, D., JOSHI, R., ROZATI, R., BHATLA, N., PRABHAKARAN, D., REDDY, P., PATEL, A. & TANDON, N. 2017. Conversion of gestational diabetes mellitus to future Type 2 diabetes mellitus and the predictive value of HbA1c in an Indian cohort. *Diabet Med,* 34**,** 37-43.

HUVINEN, E., ERIKSSON, J. G., KOIVUSALO, S. B., GROTENFELT, N., TIITINEN, A., STACH-LEMPINEN, B. & RONO, K. 2018. Heterogeneity of gestational diabetes (GDM) and long-term risk of diabetes and metabolic syndrome: findings from the RADIEL study follow-up. *Acta Diabetol,* 55**,** 493-501.

INOUE, H., ISHIKAWA, K., TAKEDA, K., KOBAYASHI, A., KURITA, K., KUMAGAI, J., YOKOH, H. & YOKOTE, K. 2018. Postpartum risk of diabetes and predictive factors for glucose intolerance in East Asian women with gestational diabetes. *Diabetes research and clinical practice,* 140**,** 1-8.

KALE, S., YAJNIK, C., KULKARNI, S., MEENAKUMARI, K., JOGLEKAR, A., KHORSAND, N., LADKAT, R., RAMDAS, L. & LUBREE, H. 2004. High risk of diabetes and metabolic syndrome in Indian women with gestational diabetes mellitus. *Diabetic medicine,* 21**,** 1257-1258.

KRISHNAVENI, G. V., HILL, J. C., VEENA, S. R., GEETHA, S., JAYAKUMAR, M. N., KARAT, C. L. S. & FALL, C. H. D. 2007. Gestational diabetes and the incidence of diabetes in the 5 years following the index pregnancy in South Indian women. *Diabetes research and clinical practice,* 78**,** 398-404.

LEE, H., JANG, H. C., PARK, H. K., METZGER, B. E. & CHO, N. H. 2008. Prevalence of type 2 diabetes among women with a previous history of gestational diabetes mellitus. *Diabetes research and clinical practice,* 81**,** 124-129.

LOWE, W. L., SCHOLTENS, D. M., LOWE, L. P., KUANG, A., NODZENSKI, M., TALBOT, O., CATALANO, P. M., LINDER, B., BRICKMAN, W. J. & CLAYTON, P. 2018. Association of Gestational Diabetes With Maternal Disorders of Glucose Metabolism and Childhood Adiposity. *JAMA,* 320**,** 1005-1016.

MADARÁSZ, E., TAMÁS, G., TABÁK, Á. G. & KERÉNYI, Z. 2009. Carbohydrate metabolism and cardiovascular risk factors 4 years after a pregnancy complicated by gestational diabetes. *Diabetes research and clinical practice,* 85**,** 197-202.

RIVERO, K., PORTAL, V. L., VIEIRA, M. & BEHLE, I. 2008. Prevalence of the impaired glucose metabolism and its association with risk factors for coronary artery disease in women with gestational diabetes. *Diabetes Res Clin Pract,* 79**,** 433-7.

SIMMONS, D., KUMAR, S., CROOK, N. & RUSH, E. 2017. Diabetes among Maori women with self-reported past gestational diabetes mellitus in a New Zealand Maori community. *Aust N Z J Obstet Gynaecol,* 57**,** 599-603.

TAM, W. H., MA, R. C., YANG, X., KO, G. T., LAO, T. T., CHAN, M. H., LAM, C. W., COCKRAM, C. S. & CHAN, J. C. 2012. Cardiometabolic risk in Chinese women with prior gestational diabetes: a 15-year follow-up study. *Gynecol Obstet Invest,* 73**,** 168-76.

TAM, W. H., YANG, X. L., CHAN, J. C. N., KO, G. T. C., TONG, P. C. Y., MA, R. C. W., COCKRAM, C. S., SAHOTA, D. & ROGERS, M. S. 2007. Progression to impaired glucose regulation, diabetes and

metabolic syndrome in Chinese women with a past history of gestational diabetes. *Diabetes/metabolism research and reviews,* 23**,** 485-489.

WANG, Y., CHEN, L., HORSWELL, R., XIAO, K., BESSE, J., JOHNSON, J., RYAN, D. H. & HU, G. 2012. Racial differences in the association between gestational diabetes mellitus and risk of type 2 diabetes. *J Womens Health (Larchmt),* 21**,** 628-33.

Appendix 6. PRO2D Chapter 6 Supplementary materials

Online only supplemental material

Supplemental Table 1. Comparison of participants followed up 5-6 years later and the participants lost to follow-up

		Lost to follow-up, N = 278	Followed-up, N = 220	P-value
Age at booking, years	Median (IQR)	31 (26-35)	31 (27-35)	0.879
Number of pregnancies	Median (IQR)	3 (2-4)	3 (2-4)	0.375
Number of live births	Median (IQR)	1 (1-2)	1 (0-2)	0.339
Gestational age at booking, weeks	Median (IQR)	17 (13-22)	15 (11-21)	0.004*
HIV positive	n (%)	19 (6.9)	12 (5.5)	0.545
CD4 count, cells/dl	Median (IQR)	454 (406-545)	492.5 (364-774)	0.725
BMI at booking, kg/m^2	Median (IQR)	32.7 (27.6-38.4)	34.6 (28.841.4)	0.041*
Random blood glucose at HFDP diagnosis, mmol/l	Median (IQR)	12.7 (11.4-14.4)	12.7 (11.2-14.1)	0.963
Fasting plasma glucose at GDM diagnosis, mmol/l	Median (IQR)	5.9 (5.3-6.9)	5.8 (5.1-6.5)	0.054
1-hour OGTT plasma glucose at HFDP diagnosis, mmol/l	Median (IQR)	10.6 (9.4-12.2)	10.5 (9.2-11.5)	0.064
2-hour OGTT plasma glucose at HFDP diagnosis, mmol/l	Median (IQR)	12 (11.2-12.8)	9 (8.2-10)	0.011*
Type of HFDP*	DIP, n (%)	122 (43.9)	70 (31.8)	0.008
	GDM, n (%)	156 (56.1)	150 (67.7)	
Treated with metformin or other orals during HFDP	n (%)	99 (35.6)	61 (28.4)	0.089
Treated with insulin during HFDP	n (%)	80 (28.8)	52 (24.1)	0.241
Treated with both orals and insulin during HFDP	n (%)	4 (1.4)	3 (1.4)	0.93
Number of hospital admissions during HFDP	Median (IQR)	2 (1-3)	2 (1-3)	0.104

HbA_{1c} at booking, %	Median (IQR)	6.4 (5.9-7.2)	6.5 (6-7.4)	0.327
Type of birth delivery	Caesarian section, n (%)	144 (52.8)	120 (56.3)	
	Virginal, n (%)	129 (47.3)	93 (43.7)	0.439
Gestational age at delivery	Median (IQR) weeks	38 (37-38)	38 (37-39)	0.038
Fetal outcome	Stillborn or miscarriage, n (%)	10 (3.6)	6 (2.8)	0.598
Fetal birthweight, grams	Median (IQR)	3230 (2805-3620)	3292 (2925-3610)	0.207

*HFDP classified post-hoc, using WHO 2013 criteria

Supplemental Table 2. Anthropometry and biochemical characteristics at follow-up

		Overall, n = 220
Waist circumference (cm)	Mean (SD)	110.5 (17.6)
Hip circumference (cm)	Mean (SD)	117.3 (16.1)
Waist-hip ratio	median (IQR)	0.94 (0.89-0.99)
Waist-height ratio	median (IQR)	0.68 (0.61-0.75)
BMI (kg/m^2)	Mean (SD)	34.9 (8.7)
Systolic blood pressure (mmHg)	Mean (SD)	114 (14.6)
Diastolic blood pressure (mmHg)	Mean (SD))	79.7 (10.6)
Fasting blood glucose (mmol/l)	Median (IQR)	5.8 (5.0-8.1)
OGTT 2-hour glucose (mmol/l)	Median (IQR)	8.0 (6.2-11.7)
HbA1c (%, DCCT units)	Median (IQR)	6.0 (5.3-7.8)
Total cholesterol (mmol/l)	Median (IQR)	3.8 (3.2-4.5)
HDL-cholesterol (mmol/l)	Median (IQR)	1.2 (1.0-1.4)
LDL-cholesterol (mmol/l)	Median (IQR)	2.9 (2.3-3.6)
Triglycerides (mmol/l)	Median (IQR)	0.76 (0.55-1.06)
Fasting insulin (uIU/mL), N = 108	Median (IQR)	13.4 (9.3-20)
HOMA-IR, N = 108	Median (IQR)	3.0 (1.9 – 5.1)

Supplemental Table 3. CVD risk factors, insulin resistance and metabolic syndrome prevalence 5-6 years post HFDP and comparison between DIP and GDM groups

Cardiometabolic risk factor	Overall, N = 220		DIP**, N = 70	GDM***, N = 150	p-value
	n (%)	95%CI of prevalence	n (%)	n (%)	
Metabolic syndrome	134 (60.9)	54.3-67.2	52 (74.3)	82 (54.7)	0.010
Obese (30≤BMI<40kg/m2)	104 (47.3)	40.7-53.9	33 (46.5)	71 (47.7)	0.879
Morbidly obese (BMI≥40kg/m2)	48 (21.8)	16.8-27.8	12 (17.1)	36 (24.2)	0.458

Central obesity Waist circumference≥88cm	197 (90.4)	85.6-93.7	62 (89.9)	135 (90.6)	0.862
Dysglycaemia Fasting glucose≥5.6mmol/l or/and 2-hour glucose≥8.5mmol/l	137 (62.3)	55.6-68.5	62 (88.6)	75 (50.0)	<0.001*
Any dyslipidaemia	164 (74.6)	68.3-79.9	52 (74.3)	112 (75.2)	0.759
Triglycerides ≥1.7mmol/l	17 (7.7)	4.8-12.1	9 (12.7)	8 (5.4)	0.058
Total cholesterol ≥5.2mmol/l	21 (10.9)	20.9-32.6	10 (17.5)	11 (8.1)	0.054
HDL<1.3mmol/l	139 (63.2)	56.6-69.3	41 (58.5)	98 (65.3)	0.249
BP≥130/85mmHg	91 (41.4)	35.0-48.0	30 (42.9)	61 (40.7)	0.565
Insulin resistance HOMA-IR >1.95, N = 108	81 (75.0)	65.9-82.3	9(90.0)	72 (73.5)	0.250

Supplemental Table 4a. Multivariate analysis of factors associated with dysglycaemia, raised blood pressure and dyslipidaemia

	Raised Blood pressure					Dyslipidaemia				
	OR	p-value	Bonferroni adjusted p-value	95% CI		OR	p-value	Bonferroni adjusted p-value	95% CI	
				lower	upper				lower	upper
Age at follow-up (years)	1.1	0.079	0.316	1.0	1.2	1.0	0.635	1	0.9	1.1
Follow-up period (years)	0.9	0.002	0.008	0.9	1.0	1.0	0.688	1	1.0	1.1
Ethnicity - mixed ancestry (vs black)	0.6	0.127	0.508	0.3	1.2	1.2	0.74	1	0.5	2.7
Others (vs black)	0.5	0.358	1	0.1	2.3	0.6	0.525	1	0.1	3.2
Education - primary (vs tertiary)	0.8	0.716	1	0.2	3.3	4.2	0.07	0.28	0.9	19.4
Secondary &matric (vs tertiary)	1.7	0.336	1	0.6	4.9	2.2	0.111	0.444	0.8	5.7
Employed (vs unemployed)	0.3	0.002	0.008	0.2	0.7	0.8	0.568	1	0.4	1.7
Family history of hypertension	2.2	0.043	0.172	1.0	4.8	2.0	0.084	0.336	0.9	4.3

Subsequent pregnancy (vs none)	0.8	0.516	1	0.4	1.7	0.7	0.367	1	0.3	1.6
Average length of breastfeeding (months)	1.0	0.539	1	1.0	1.0	1.0	0.322	1	1.0	1.1
Current smoker (vs current non-smoker)	1.0	0.972	1	0.5	2.3	1.7	0.305	1	0.6	4.3
Waist circumference (cm)	1.1	0.009	0.036	1.0	1.1	1.1	0.008	0.032	1.0	1.1
Hip circumference (cm)	1.0	0.449	1	1.0	1.0	0.9	0.008	0.032	0.9	1.0
Weight gain (kg)	1.0	0.701	1	1.0	1.0	1.0	0.497	1	1.0	1.1
Overweight at booking	0.7	0.532	1	0.2	2.4	2.1	0.241	0.964	0.6	7.1
Obese at booking	0.8	0.69	1	0.2	2.9	6.4	0.013	0.052	1.5	27.9
Morbid obese at booking	1.0	0.965	1	0.2	6.1	8.3	0.045	0.18	1.0	65.5
Fasting glucose at HFDP diagnosis	0.9	0.617	1	0.7	1.2	1.0	0.811	1	0.8	1.3
OGTT 2-hour glucose at HFDP diagnosis	1.1	0.451	1	0.9	1.3	0.9	0.187	0.748	0.7	1.1
Insulin treatment during HFDP	1.0	0.984	1	0.4	2.7	0.5	0.14	0.56	0.2	1.3
GPAQ total physical activity	1.0	0.774	1	1.0	1.0	1.0	0.804	1	1.0	1.0
_cons	0	0.038	0.152	0.0	0.7	1.1	0.986	1	0.0	286.8
Model statistics	Number of obs		211.0		Number of obs		211.0			
	LR chi2(21)		55.6		LR chi2(21)		45.3			
	Prob > chi2		0.000		Prob > chi2		0.002			
	Pseudo R2		0.2		Pseudo R2		0.2			
	Log likelihood		-115.6		Log likelihood		-97.4			

NB: For the Bonferroni adjustment – for each outcome, the p-value was multiplied by the number of tests (4 outcomes – 4 tests). Significance was set at p = 0.05

Supplemental Table 4b. Multivariate analysis of factors associated with dysglycaemia and insulin resistance

	Dysglycaemia					Insulin Resistance				
	OR	p-value	Bonferroni adjusted p-value	95% CI		OR	p-value	Bonferroni adjusted p-value	95% CI	
				lower	upper				lower	upper
Age at follow-up (years)	1.0	0.443	1	1.0	1.1	1.1	0.533	1	0.9	1.2
Follow-up period (years)	1.0	0.244	0.976	0.9	1.0	1.0	0.516	1	0.9	1.1
Ethnicity - mixed ancestry (vs black)	1.9	0.159	0.636	0.8	4.4	4.5	0.051	0.204	1.0	20.3
Others (vs black)	0.3	0.182	0.728	0.1	1.8	1.3	0.817	1	0.1	12.6
Education - primary (vs tertiary)	1.2	0.825	1	0.2	6.1	0.2	0.409	1	0.0	8.6
Secondary &matric (vs tertiary)	1.1	0.892	1	0.4	3.0	0.5	0.394	1	0.1	2.3
Employed (vs unemployed)	0.9	0.781	1	0.4	1.9	1.4	0.61	1	0.4	5.1
Family history of hypertension	1.0	0.974	1	0.4	2.2	1.0	0.964	1	0.3	3.6
Subsequent pregnancy (vs none)	0.5	0.125	0.5	0.2	1.2	0.2	0.021	0.084	0.0	0.8
Average length of breastfeeding (months)	1.0	0.704	1	1.0	1.0	1.0	0.375	1	1.0	1.1
Current smoker (vs current non-smoker)	0.8	0.518	1	0.3	1.8	2.1	0.363	1	0.4	9.8
Waist circumference (cm)	1.1	0	0	1.0	1.1	1.1	0.078	0.312	1.0	1.1
Hip circumference (cm)	0.9	0.011	0.044	0.9	1.0	0.9	0.158	0.632	0.9	1.0
Weight gain (kg)	1.0	0.191	0.764	1.0	1.1	1.1	0.138	0.552	1.0	1.1
Overweight at booking	0.5	0.286	1	0.1	1.9	3.5	0.167	0.668	0.6	21.2

Obese at booking	1.0	0.973	1	0.3	4.3	6.7	0.08	0.32	0.8	55.4
Morbid obese at booking	1.1	0.924	1	0.1	8.6	10.4	0.127	0.508	0.5	211.8
Fasting glucose at HFDP diagnosis	1.6	0.018	0.072	1.1	2.4	2.3	0.051	0.204	1.0	5.2
OGTT 2-hour glucose at HFDP diagnosis	1.4	0.013	0.052	1.1	1.7	1.0	0.889	1	0.6	1.7
Insulin treatment during HFDP	5.9	0.013	0.052	1.4	23.9	1.0	omitted			
GPAQ total physical activity	1.0	0.594	1	1.0	1.0	1.0	0.456	1	1.0	1.0
_cons	0.0	0.012	0.048	0.0	0.2	0.0	0.233	0.932	0.0	77.9
Model statistics	Number of obs		211.0			Number of obs		98.0		
	LR chi2(21)		85.3			LR chi2(20)		29.5		
	Prob > chi2		0.000			Prob > chi2		0.078		
	Pseudo R2		0.3			Pseudo R2		0.3		
	Log likelihood		-97.4			Log likelihood		-42.9		

NB: For the Bonferroni adjustment – for each outcome, the p-value was multiplied by the number of tests (4 outcomes – 4 tests). Significance was set at p = 0.05

Appendix 7.1. PRO2D child participation consent

Consent for Child Participation in research

Research Title: The prevalence of Type 2 diabetes mellitus and associated risk factors 5 years after gestational diabetes mellitus in South Africa

Principal Investigators: Professor Naomi Levitt, Professor Shane Norris, Professor Christina Zarowsky, Tawanda Chivese

Contact Address: Chronic Disease Initiative for Africa, J47 Room 86, Old Groote Schuur Hospital Building Observatory, 7935, Cape Town

Telephone: +27 21 4066572

Fax: +27 21 4486815

More information: http://www.health.uct.ac.za/fhs/research/groupings/cdia/about

Participant Number:

Your child is invited to take part in a research project which asks the question: How many 5-6-year-old children born to women who had diabetes in their pregnancy are overweight?

This research project is being conducted at the University of Cape Town and the University of the Witwatersrand in Johannesburg. A researcher from the University of Montreal will also help with knowledge on how to carry out research properly.

This research will be carried out according to the Declaration of Helsinki, which protects people who take part in research.

Most women who had diabetes during pregnancy recover from the diabetes after the birth of their babies, but their children may be overweight when growing up. This makes it easy for them to become sick with type 2 diabetes and other illnesses like heart disease. Type 2 diabetes is a chronic condition that affects the way your body uses sugar (glucose), your body's source of fuel. If we can find that someone has type 2 diabetes earlier, we can start treatment sooner and this may cause fewer long term problems.

We do not know how many 5-6-year-old children born to women with diabetes during pregnancy are overweight in South Africa. Knowing this will enable us to develop better programs to look after children born to mothers who had diabetes during pregancy. Additionally, knowing factors that increase the chance of their children being overweight can help lower the risk of them developing diabetes and heart disease later in their life.

Please ask the study staff any questions about any part of this project that you do not fully understand. You are free to say yes or to say no. If you say no, your child's medical care will continue just as before, and it will not be held against you. You are also free to withdraw your child from the study at any point, even if you do agree to take part.

Why has your child been invited to participate?

We are inviting all 5-6 year-old children who live in Cape Town and Soweto whose mothers received treatment for diabetes during pregnancy at Groote Schuur Hospital and Chris Hani Baragwanath Hospital to take part in the research.

What will your child's participation entail?

Your child has been asked to come to the Groote Schuur Hospital (or Chris Hani Baragwanath Hospital) in order to take part in the research. The participation will be no more than 30 minutes. You will be asked some questions about your child in a questionnaire. Some of the questions will be to see if your child has been sick, if he/she is taking any medicines for any illness and whether you breast fed your child.

Your child will also be weighed on a scale and have his/her height measured.

Will your benefit from taking part in this research?

If any illnesses are identified during the research then your child will be referred to a clinic for follow-up and management. You will also be told the results of the weight and height measurements of your child.

Are there any risks involved in your child taking part in this research?

Your child will only have his/her height and weight measured. He/she will not have any bloods taken and will not be given any medicines during this study. If your child does not want to have their weight and height measured, we will not force him/her.

Your child's name and personal details will be kept strictly confidential and will not be given to anyone to minimise the risk of improper disclosure of information.

If you do not want your child to take part, what alternatives do you have?

Not taking part in the study will not change your child's future care or treatment if and when you take him/her to hospitals or clinics. Your child will be treated the same as other children who participate in the study. The researchers are not the same people as your child's usual doctors.

Please ensure that you have carefully read and understood this information sheet and been given a copy to keep for yourself.

Contact details of researchers: For any questions or concerns, please feel free to contact the researchers whose details are listed below:

Tawanda Chivese	Email: tchivese@gmail.com
	Tel: 0216505131
Professor Naomi Levitt	Email: Naomi.Levitt@uct.ac.za
	Tel: 0216505110
Professor Shane Norris	Email: san@global.co.za
Professor Christina Zarowski	Email: czarowsky@gmail.com

You may contact the University of Cape Town Human Research Ethics Committee if you have any questions or concerns about your child's rights and welfare. The contact details are listed below

Email: sumayahariefdien@uct.ac.za

Tel: 021 406 6338

Fax: 021 406 6411

PARENTAL CONSENT

Study Title: The prevalence of Type 2 diabetes mellitus and associated risk factors 5 years after gestational diabetes mellitus in South Africa

By signing this document:

I confirm that I have read the above information and understand it. I confirm that I have had an opportunity to ask questions and I am satisfied with the answers and explanations that have been given to me.

I give my permission for my child (Insert child's name……) to have their height and weight measured.

I agree to answer question about my child's (Insert child's name……) health

I understand that my participation in this research is voluntary and I am free to withdraw my child (Insert child's name……) at any time without having to give a reason.

Please tick one of the boxes below:

☐ YES, I would like my child (Insert child's name……) to take part in this study

☐ NO, I do not wish my child (Insert child's name……) to take part in this study

Name of mother: ……. Signature…….

Date: ……

Name of researcher: ……. Signature…….
Date: ……

Name of witness…….. Signature……

Date ……..

If participant is not able to write:

Thumbprint of participant……

Date ……

Participant Contact Details

Forename	
Surname	
Address	
Suburb	
City	
Postcode	
Telephone	
Cell	
Secondary cell	

Next of kin telephone	
Next of kin cell	
Next of kin address	
Date of birth	
Hospital number	

Appendix 7.2. PRO2D Chapter 7 Supplementary materials

Online only material

The influence of maternal blood glucose during pregnancy on weight outcomes at birth and preschool age in offspring exposed to hyperglycemia first detected during pregnancy, in a South African cohort

Supplementary Table 1 – comparison of maternal and child characteristics of children followed up and those lost to follow up at 5-6 years age

variable	level	Lost to follow up, N = 276	Followed up, N = 167	p-value
Birthweight (mean (SD))		3320.85 (583.35)	3303.47 (554.96)	0.757
Birthweight z-score (mean (SD))		0.30 (1.08)	0.19 (1.07)	0.294
Maternal age at booking (mean (SD))		30.55 (6.11)	30.41 (6.29)	0.813
Maternal BMI at booking (mean (SD))		33.99 (8.40)	35.20 (8.78)	0.193
Child gender (n (%))	Female	145 (52.5)	80 (47.9)	0.397
	Male	131 (47.5)	87 (52.1)	
Birth delivery method (n (%))	Caesarian Section	147 (53.5)	84 (50.6)	0.629

	Vaginal	128 (46.5)	82 (49.4)	
Maternal HIV infection (n (%))	POS	21 (7.6)	6 (3.6)	0.129
CD4 (median [IQR])		453.00 [360.00, 543.50]	492.50 [382.50, 729.25]	0.75
HFDP type (n (%))	DIP	115 (41.7)	50 (29.9)	0.018
	GDM	161 (58.3)	117 (70.1)	
Insulin during HFDP (n (%))	YES	74 (26.8)	37 (22.3)	0.343
Oral hypoglycemic during pregnancy (n (%))	YES	91 (33.0)	50 (30.1)	0.605
Gestational age at delivery (median [IQR])		38.00 [38.00, 38.00]	38.00 [38.00, 39.00]	0.221
Gravida (median [IQR])		3.00 [2.00, 4.00]	3.00 [1.00, 4.00]	0.65
Parity (median [IQR])		1.00 [1.00, 2.00]	1.00 [0.00, 2.00]	0.472
Gestational age at booking (median [IQR])		17.00 [13.00, 23.00]	15.00 [12.00, 21.00]	0.006
Fasting blood glucose at HFDP diagnosis (median [IQR])		5.80 [5.35, 6.75]	5.80 [5.00, 6.40]	0.136
OGTT 2-hour glucose at HFDP diagnosis (median [IQR])		9.20 [8.30, 10.90]	8.90 [8.20, 10.00]	0.046
Hemoglobin (median [IQR])		12.00 [11.20, 12.80]	12.10 [11.40, 13.10]	0.163
HbA1C (median [IQR])		6.40 [5.80, 7.15]	6.40 [6.00, 7.40]	0.379
Average maternal random blood glucose during pregnancy (median [IQR])		5.60 [5.00, 6.20]	5.60 [5.10, 6.10]	0.824