Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg

Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries- a systematic review

Dissertation
zur Erlangung des akademischen Grades
Doktor der Medizin (Dr. med.)

vorgelegt
der Medizinischen Fakultät
der Martin-Luther-Universität Halle-Wittenberg

von Angelika Sabine Sandholzer-Yilmaz
geboren am 21.05.1992, in Göttingen

Betreuer*in:
Prof. Dr. med. Thomas Frese
PD. Dr. rer. nat. Susanne Unverzagt

Gutachter*innen:
Frau Prof. I Kopp, Marburg
Frau Prof. J. Bleidorn, Jena

03.11.2020
02.09.2021

Referat (English Version)

Introduction and objective: Diabetes with its complications and consecutive deaths has already become a global health burden and its prevalence will further increase during the coming years. Low- and middle income countries (LMIC) are expected to experience the highest increase over the years causing premature mortality. Therefore, it is necessary to conduct baseline research on interventions to treat patients with diabetes to approach the specific African context and regional circumstances with the aim to implement adequate diabetes management strategies. The objective of this review was, to collect the best locally generated evidence on diabetes interventions, identify knowledge gaps and underexplored research areas.

Methods: The protocol was prospectively registered on PROSPERO (CRD42019122785) and follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the methods described in the Cochrane Handbook for systematic reviews of interventions. Three electronic databases (MEDLINE Ovid, CENTRAL, CINAHL) and register of ongoing and completed studies (International Clinical Trials Registry Platform) were searched. Main characteristics of all eligible randomized controlled trials (RCTs) were extracted and narratively described, presented in form of tables and their main results on HbA1c were visualized as forest plots. The risk of bias was assessed.

Results. A total of 50 RTCs in 56 publications were identified, in which a wide variety of interventions were carried out in different parts of Africa. Interventions addressed non-pharmacological strategies on education, lifestyle modification (Nutrition and activity) and substance related therapies. Most were conducted in urban regions. Only nine studies were conducted in a primary care setting.

Conclusions: This systematic review shows that even though diabetes is a critical health problem in different regions and settings in Africa, the number of RCTs conducted on the African continent is still low. Available RCTs might not be representative for all Africans, as they are focusing only on a few countries and urban settings. The empowerment of the primary care doctors and nurses is crucial to establish a continent wide diabetes care system. The benefits and challenges of the implementation of a digital health system should be proved. Therefore, feasible RCTs adapted to local resources need to be conducted in order to form local guidelines and recommendations continent-wide.

Sandholzer, Angelika Sabine, Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries- a systematic review, Halle (Saale), Univ., Med. Fak.; Diss., 90 Seiten, 2020

Referat (Deutsche Version)

Einleitung und Zielsetzung: Diabetes, seine Komplikationen und die damit verbundenen Todesfälle sind bereits zu einer globalen Gesundheitsbelastung geworden. Die Prävalenz wird auch in den nächsten Jahren zunehmen, besonders in Ländern mit niedrigem und mittlerem Einkommen. Daher ist es notwendig, dass klinische Forschung angepasst an den spezifischen afrikanischen Kontext, durchgeführt wird, um angemessene Strategien für das Diabetesmanagement zu entwickeln. Das Hauptziel dieser systematischen Übersichtsarbeit, ist die Zusammenfassung der lokal durchgeführten, bereits vorhandenen randomisierten klinischen Studien (RCTs) , um Wissenslücken und unerforschte Forschungsbereiche zu identifizieren.

Methoden: Das Protokoll wurde im Voraus in der PROSPERO-Datenbank registriert (CRD42019122785) und folgt den, in den PRISMA Statement und dem Cochrane-Handbuch empfohlenen Methoden. Eine systematische Suche in drei elektronischen Datenbanken (MEDLINE Ovid, CENTRAL, CINAHL) und im Register laufender und abgeschlossener Studien (International Clinical Trials Registry Platform) wurde durchgeführt. Die Hauptmerkmale aller in Frage kommenden RCTs wurden extrahiert und narrativ beschrieben, in Form von Tabellen dargestellt und deren Ergebnisse hinsichtlich des HbA1c als Forest Plots visualisiert. Das Risiko einer Verzerrung der Ergebnisse wurde bewertet.

Ergebnisse. Insgesamt 50 Studien (56 Publikationen) mit unterschiedlichen Interventionen aus verschiedenen Teilen Afrikas wurden identifiziert. Die Interventionen bezogen sich auf nicht-pharmakologische Strategien zur Aufklärung, Lebensstiländerung (Ernährung und Aktivität) und substanzbezogene Therapien. Die meisten wurden in städtischen Regionen durchgeführt. Nur neun Studien untersuchten Interventionen in der Primärversorgung.

Folgerungen: Diese systematische Übersicht zeigt, dass die Zahl der auf dem afrikanischen Kontinent durchgeführten RCTs insgesamt niedrig ist. Die verfügbaren Studien sind möglicherweise nicht repräsentativ für alle Afrikaner, da sie sich nur auf einige wenige Länder und überwiegend städtische Gebiete konzentrieren. Die Primärversorgung sollte durch eine verstärkte Zusammenarbeit von ärztlichem und nicht ärztlichem Personal intensiviert werden. Außerdem sollten in Zeiten der zunehmenden Digitalisierung der vermehrte Ausbau eines digitalen Gesundheitssystems eruiert werden.

Sandholzer, Angelika Sabine, Randomized controlled trials on prevention, diagnosis and treatment of diabetes in African countries- a systematic review, Halle (Saale), Univ., Med. Fak.; Diss., 90 Seiten, 2020

Table of Contents

1 Introduction 1

2 Objective 3

3 Methods 4

3.1 Inclusion criteria and exclusion criteria 4

3.2 Search strategy 5

3.3 Study selection and data extraction. 5

3.4 Quality assessment and risk of bias 6

3.5 Effect sizes 7

4 Results 8

4.1 Description of included studies 8

4.1.1 Setting 8

4.1.2 Participants 12

4.1.3 Interventions 12

4.1.4 Non-pharmacological strategies 13

4.1.5 Substance-related strategies 14

4.1.6 Intervention effects 15

4.2 Risk of bias 18

5 Discussion 20

5.1.1 Strength and limitations 24

6 Conclusion 26

7 References 27

Theses 40

Supplementary Material 40

Search strategies 41

Medline (Ovid) 41

CENTRAL 43

CINAHL 44
International Clinical Trials Registry Platform 44
List of included studies 46
Characteristics of included studies 54
Risk of bias judgement 77

Appendix

Declaration under oath V
Declaration of previous attempts at doctoral application VI
Declaration concerning the truth of information given VII
Acknowledgements VIII

List of abbreviations

ADA: American Diabetes Association
aRR: adjusted Relative Risk
BMI: Body mass index
CG: Control group
C/I: crossover from CG to IG
CI: confidence interval
CHC: community health center
CONSORT: Consolidated Standards of Reporting Trials
DBGP: designed breakfast glucose profile
DBP: diastolic blood pressure
DM: diabetes mellitus
DM1: type 1 diabetes
DM2: type 2 diabetes
DMPs: disease management programms
ER: emergency room
FBS: fasting blood sugar
FBG: fasting blood glucose
FPG: fasting plasma glucose
GDM: gestational diabetes
HbA1c: hemoglobin A1c
2HPG: 2-hour post prandial blood glucose
HDL: high density lipopreotein
I/C: cross over from IG to CG
ICTRP: International Clinical Trials Registry Platform (ICTRP)
IDF: International Diabetes Federation
IG: intervention group
LDL: low density lipoprotein
LILT: low-intensity laser therapy
LMIC: low- and middle income countries
MD: mean difference
MDa: adjusted mean difference
N: number of participants
NCD: Non-communicable disease
NPH: neutral protamine Hagedorn

OGTT: Oral glucose tolerance test

Pat: patients

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QALY: Quality Adjusted Life Years

QoL: quality of life

RCT: randomized controlled trial

RRa: adjusted relative risk

SBP: Systolic blood pressure

SAE: Serious adverse events

SBP: Systolic blood pressure

SCI: Diabetes Self-Care Inventory

SMBG: self-monitoring of blood glucose

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

WHO: World Healh Organization

Wks: weeks

Yrs: years

1 Introduction

Within the last years, the prevalence of diabetes has increased worldwide, becoming a serious global health burden [1]. According to the World Health Organization (WHO) the prevalence of diabetes, its complications and consecutive deaths will further increase during the next years, becoming the seventh global leading cause of death by 2030 [2–5].

For a long time, diabetes was considered to be a disease of affluence [1]. Today most people suffering from diabetes live in the low- and middle income countries (LMIC) where the highest increase of diabetes cases is expected over the next years [2]. For these countries predictions are of high relevance, as these countries suffer from a double burden due to the epidemiological transition from the communicable (infectious) to the non-communicable diseases (NCDs) with a relevant shift in causes of disability and death [3, 6, 7]. Focussing on reducing the burden of high premature mortality due to NCDs like diabetes through prevention and treatment has been designated as a target within the United Nations 2030 Agenda (Target 3.4) [8]. According to the International Diabetes Federation (IDF), an estimated 19.4 million adults between the 20 - 79 years of age were suffering from diabetes in the African region in 2019. The regional reported prevalence in Africa is 3.9 % with a high variation between the different countries [9]. This number is estimated to increase to about 47 million by 2045. Africa has the highest amount of undiagnosed diabetes cases among all IDF regions. The IDF estimates that approximately 60 % of the adults living with diabetes are unaware of it. Egypt is belonging to the Middle East and Northern Africa IDF region and is ranked at the ninth place of the top ten worldwide countries with diabetes in adults between 20-79 years [9]. In this region an 96 % increase of diabetes cases is expected by 2045 [9].

The increasing prevalence and premature mortality due to diabetes leads to substantial financial costs to households and governments [5, 10].

Diabetes is a non-communicable chronic disease affecting the glucose metabolism. The pathomechanism differs between the different diabetes entities. However, what they all have in common is leading to a high blood glucose level, which eventually damages organs like the heart, the blood vessels, the kidneys, the nervous system, the eyes and the teeth and are associated with an increased risk of infections [11, 12].

All interventions on diabetes aim for achieving glycemic control since longer lasting elevated blood glucose levels will contribute to diabetes related complications. The interventions include a regular evaluation of risk factors, detection of early stages of diseases, a step therapy with a combination of non-pharmacological and

pharmacological treatment, a long term follow up with regular monitoring and promotion to improve treatment adherence [13]. For both, the prevention and the treatment of type 2 diabetes (DM2) and gestational diabetes mellitus (GDM), the first step will be a modification of the lifestyle including frequent activity and nutritional optimization in order to regulate body weight [14, 15]. If the target HbA1c/blood glucose level cannot be achieved, the next step then will be a substance related therapy with the first line of treatment being metformin for DM2 and Insulin for GDM [16, 17].

Prediabetic conditions, which are strongly associated to a low physical activity and elevated body weight, are characterised by impaired glucose tolerance and impaired fasting glucose and can lead to DM2. Therefore, especially the non-pharmacological strategies such as lifestyle modification can prevent developing overt diabetes [18].

The underlying pathomechanism of diabetes mellitus type 1 (DM1) differs from the other diabetes entities. People suffering from DM1 have an absolute insulin deficiency resulting in the necessity of substituting insulin [11].

Secondary and tertiary prevention of all diabetes entities include at least screening and treatment for retinopathy, elevated blood cholesterol levels, elevated blood pressure, screening for early signs of diabetes related kidney disease and foot care [4].

It is necessary to conduct baseline research on diabetes to approach the specific African context and regional circumstances with the aim to implement adequate diabetes management strategies. Interventions have to be adjusted to the local context including the environmental, cultural and social settings (e.g. relatively young age of the patients, co-infections with for example malaria, tuberculosis etc., distance to health care, traditional beliefs, decision making in the families and socioeconomic status) as well as the huge genetic diversity on the African continent [19].

There is a demand for well-informed solutions to formulate effective health agendas for prevention, availability and affordability of treatment options. This emphasizes the need of research on interventions to prevent, diagnose and treat diabetes in appropriate settings, organized around the needs and expectations of people in African context.

2 Objective

This study aims to collect the best available evidence on benefits and harms of prevention, diagnostic and therapeutic interventions on diabetes in the African context with the purpose of helping to address the existing knowledge gaps and unexplored research areas and to identify resources of application of evidence-based interventions. This may support the formulation of strategies to strengthen clinical and preventive capacities of current healthcare systems in African countries.

3 Methods

This systematic review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] and the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [21]. The protocol has been registered in the PROSPERO International Prospective Register of systematic reviews and published (CRD42019122785).

3.1 Inclusion criteria and exclusion criteria

Studies initiated and conducted in African countries investigating the efficacy of interventions for screening, diagnosis and treatment of patients with diabetes illnesses (DM1, DM2, GDM and prediabetes) on mortality, quality of life, hospital admission, intensification rates of therapy, treatment adherence, adverse effects, complications, costs and glycemic control were identified. Included were full-text publications on individual RCTs, cluster-RCTs and randomized cross-over trials according to the Consolidated Standards of Reporting Trials (CONSORT) [22] or Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [23]. International multicenter studies with less than 50 % of sites in African countries and non-English published studies were excluded (Table 1).

Table 1: Inclusion and exclusion criteria

Design and setting	RCTs initiated and conducted in African countries, at least 50 % African countries
Population	African patients in African countries in secondary or tertiary prevention with a clinical diagnosis of diabetes – DM2 – DM1 – GDM – Prediabetes
Interventions	All interventions to screen, diagnose and treat patients with diabetes Exclusion of trials if diabetes is only a possible side effect of treatment
Comparison	– Placebo – Standard care – Another intervention – Same intervention with a different dose or timing
Outcome	Primary: all-cause mortality, quality of life Secondary: hospital admission, intensification rates of therapy, treatment adherence, adverse effects, complications, costs and glycaemic control (HbA1c, fasting plasma glucose, random plasma/blood glucose, two hour plasma/blood glucose during oral glucose tolerance test, insulin resistance, fasting glucose insulin ratio) at longest follow-up
Publications	Full-text publications according to CONSORT or SPIRIT Exclusions of protocol or design papers, conference proceedings or papers where full-text publications were not available

CONSORT: Consolidated Standards of Reporting Trials; DM: Diabetes mellitus; HbA1c: hemoglobin A1c; RCT: randomized controlled trial; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

3.2 Search strategy

A systematic search in three electronic databases (MEDLINE Ovid, CENTRAL, CINAHL) was performed in 2019. And a search in registers of ongoing and completed studies (International Clinical Trials Registry Platform (ICTRP)) without any time restriction was added in 2020. The search strategy is available in the supplementary material. Search strings included MESH-terms and terms on diabetes, Africa and a list of all 54 African countries and terms related to RCTs.

3.3 Study selection and data extraction.

For the first step, titles and abstracts were screened independently by my supervisor, Susanne Unverzagt, hereinafter referred to as SU and me, on the basis of the inclusion criteria (Table 1). The full texts of those potentially eligible papers were obtained and

further assessed for final inclusion. Disagreements were resolved by discussion including a third investigator, Thomas Frese (TF), until consensus was obtained.

In a second step, the reported pre-defined information on:

- Author, study name and design
- Country, environmental settings (urban vs. rural) and health care settings (primary vs. other settings (secondary or tertiary), period for inclusion
- Study population (including inclusion and exclusion criteria, sample size and baseline characteristics on age, gender, type and length of diabetes, diagnostic criteria, BMI, co-morbidities)
- Intervention vs. control group and number of randomized participants per group
- Outcome parameters (primary, secondary, non-specified) and
- Results on pre-planned outcomes within longest follow up period with intervention effects, 95 % confidence intervals (CI) and p-values

of all included studies was extracted by me. All extracted information was checked by SU.

The study names consist of the surname of the first author and the year of the first full-text publication of the results.

The study selection process was described in a flow chart (Figure 1) according to the PRISMA statement [20].

3.4 Quality assessment and risk of bias

In a third step, the risk of bias on the basis of the Cochrane risk of bias tool along seven specific categories (sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias) was described and judged as 'low', 'high' or 'unclear' due to insufficient information [21]. A summary table and a diagram illustrate these findings. The critical appraisal of the included studies was checked by SU. Discrepancies were resolved by discussion.

Judgements on blinding and incomplete outcome data were based on the primary outcome of included studies. Selective outcome reporting was defined as low, when the study protocol was available and high when any result of pre-planned outcomes was missing. Incomplete outcome data was judged as high when more than 10 % of randomized participants dropped out from analyses. Other sources of bias judged as high risk of bias include missing reporting of sample size calculation, no definition of a primary endpoint and missing reporting or relevant differences of baseline values between intervention and control group [21].

3.5 Effect sizes

The results of all outcomes were narratively described. For all RCTs in which most participants suffered from DM2, intervention effects for HbA1c at the longest follow-up period were calculated and visualized in forest plots using the Cochrane Revman Manager [24]. Negative mean differences (MDs) describe lower HbA1c in the intervention group. Statistical significant results on HbA1c with MDs over 0.25 % for HbA1c were named clinically relevant [25].

4 Results

Having used the mentioned criteria to identify potentially relevant articles, a total of 1928 records were identified of which the majority was found in MEDLINE (Ovid; November 2018, n = 1470). In CENTRAL, another 439 records were identified (January, 2019). Additional 871 studies in Clinical Trials registry Platform were checked and searched for full-text publications (October 2019). In total, 191 potentially eligible publications were evaluated as full-texts to be of relevance. In January 2020, a search in CINAHL (n = 19) was added without identifying new potentially eligible studies. A total of 50 eligible studies in 56 publications were included in this review (Figure 1). A list of the included is documented in the supplementary material.

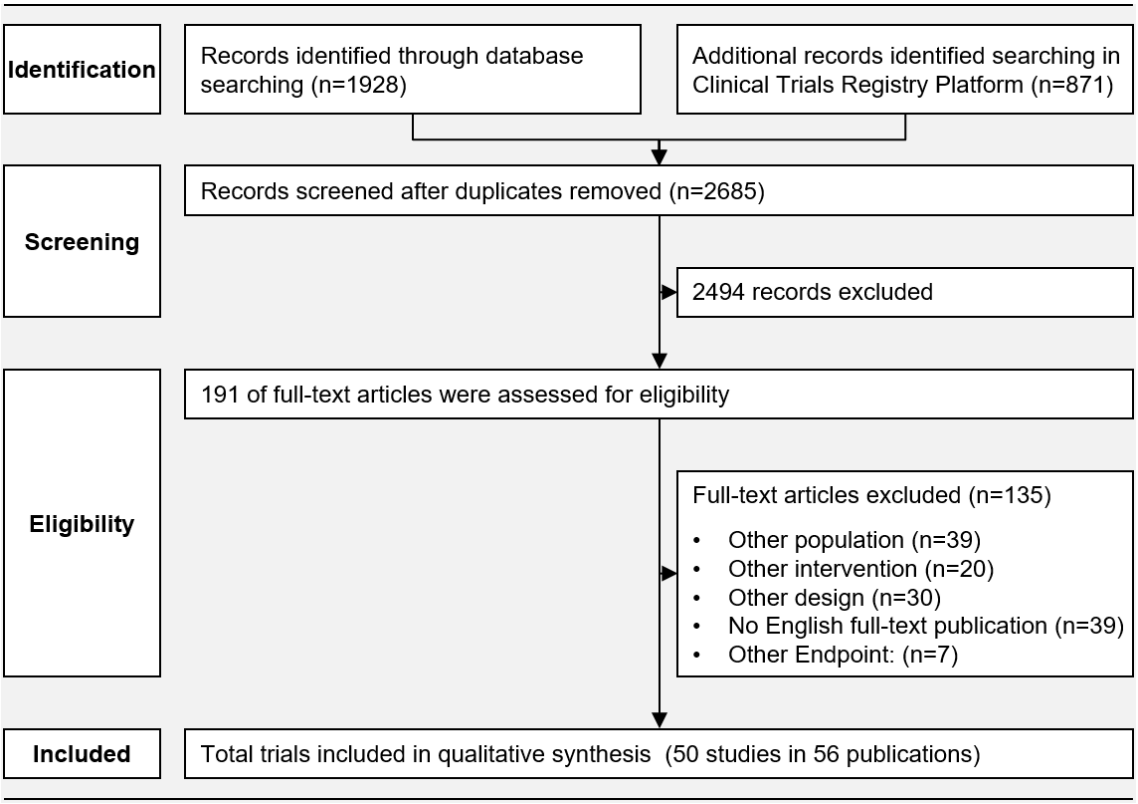


Figure 1: PRISMA flow chart demonstrating the flow of studies in this review

4.1 Description of included studies

4.1.1 Setting

4.1.1.1 Geographical aspects

In total RCTs from 15 countries from all 5 geographical regions were included: Northern Africa (23 RCTs from 4 countries), Western Africa (10 RCTs from 3 countries), Eastern Africa (4 RCTs from 5 countries), Central Africa (3 RCTs from 2 countries) and Southern Africa (13 RCTs only from South Africa). Another two RCTs

(Malek 2015 and Chraibi 2017) were conducted in more than one country and were partially conducted in non-African countries [26, 27]. Egypt was the number one country in terms of overall number of publications (21 RCTs), followed by South Africa (13 RCTs) and Nigeria (6 RCTs) (Table 2 available in the appendix, Figure 2 and 3). Since some studies had been conducted in more than one country and the separate publications of the included RCTs have been counted individually, a deviation from the number of included studies and the number of studies in Figure 2 resulted.

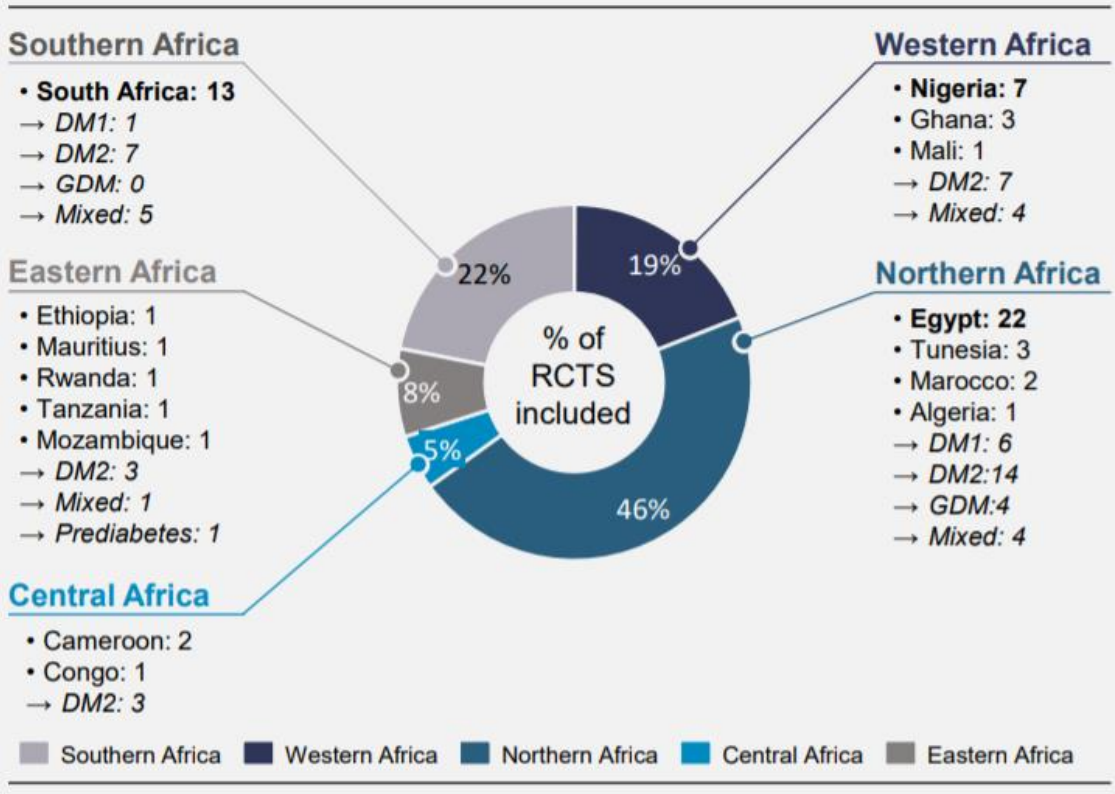
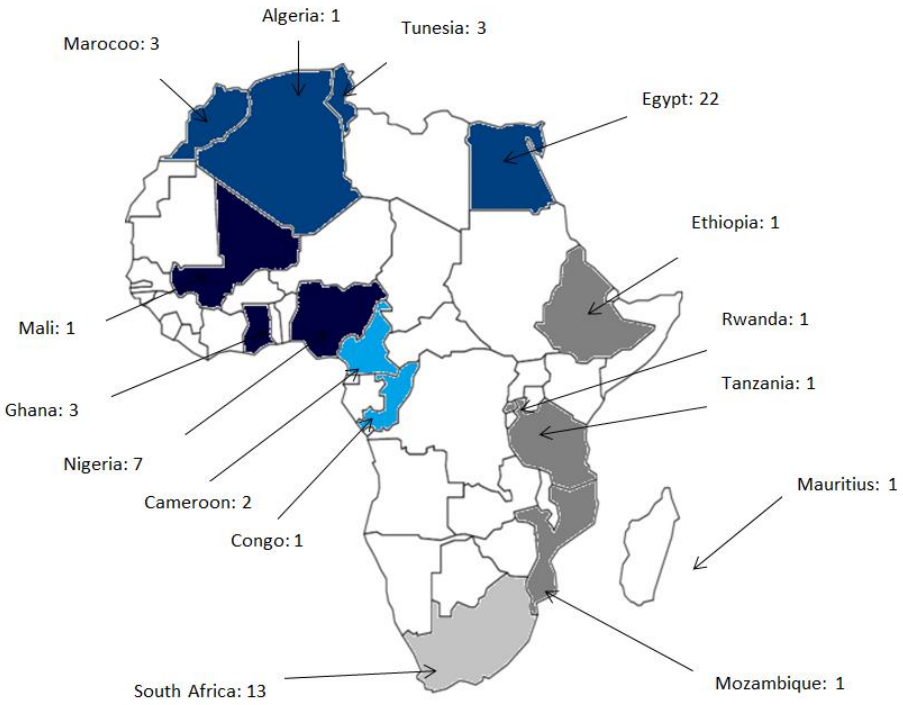


Figure 2: Geographical regions, countries and type of diabetes based on the results of this RCT.



:

Figure 3: Overview of the geographical distribution of the included studies

Figure adopted from http://www.supercoloring.com/de/ausmalbilder/karte-von-afrika and edited in Microsoft Paint.

4.1.1.2 Temporal aspects

Considering that the systematic search was carried out without any time restriction, it is interesting, that our oldest eligible RCT (Anderson 2001) was published in 2001 [28]. More than 75 % were published within the last 5 years and 3 of them had been published in 2019 (Table 2).

4.1.1.3 Environmental aspects

Over 75 % (38/50) of the RCTs were carried out in an urban area, only 6 % (3/50) of the RCTs were conducted in a rural area and for 18 % (9/50) of the RCTs, it was mixed or remained unclear (Table 2). The majority of the RCTs took place in secondary and tertiary health care centres. Only 18 % (9/50) of the RCTs were conducted in a primary care setting.

4.1.1.4 Design

In total 41 parallel-group RCTs with random assignment of participants, six cluster-RCTs where each participant receives interventions in a random sequence and six cross-over RCTs where pre-existing groups of participants where randomly assigned to different interventions, were included.

The six cluster RCTs [29–37] can be described as follows. Fairall 2016 randomised public sector primary care clinics [33]. Labhard 2011 evaluated treatment adherence of patients which received free treatment for one month, if they regularly attended follow up visits or received reminder letters, when they missed on appointment vs. no additional intervention in the control group in 33 nurse-led facilities in rural health districts in Cameroon [29]. Mash 2014 evaluated group education programs in 34 public sector community health centres [30, 31]. Steyn 2013 randomized implementing structured clinical guidelines vs. usual care in 18 community health centres [32]. The last two cluster RCTs evaluated different screening strategies: Utz 2018 for GDM in 20 health care centers [34] and Webb 2015 for diabetes related complications in 12 primary health care clinics [35–37].

All of the three cross-over RCTs evaluated nutritional strategies [38–40]. Abdulrhman 2013 evaluated metabolic effects of honey consumption on patients with DM1 over 12 weeks [38]. Krawinkel 2018 included individuals with prediabetes who received bitter gourd supplementation for 8 weeks followed by placebo for another 8 weeks or starting with placebo first and then changed after 8 weeks to bitter gourd supplementation with a wash out time of 4 weeks in between [39]. Van der Hoogt 2017 evaluated different composition of meals (low vs. high protein and fat content meals) in patients with DM1

in both cases blood glucose was measured after 10 h post-meal. There had to be at least one day and maximum one month between meals [40].

4.1.2 Participants

In total 9331 patients were included with less than 100 patients in 55 % of the RCTs (Table 2). Overall 65 % of the study participants were women; 6 RCTs included only female [34, 41–45] and one RCT, Yan 2014, included only male participants [46]. Mean age differs between 10.4 years in van de Hoogt 2017 [40] to 19.9 years in Mohamad 2019 [47] for patients with DM1, 24.2 years in El-Shamy 2018 [41] to 27.6 years in Utz 2018 [34] for pregnant women with GDM and 39.4 years in Maharaj 2016 [48] to 59.8 years in Labhard 2011 [29] for patients with DM2. The mean age of the prediabetic participants in Krawinkel 2018 was 47.5 ± 8.7 years [39].

The majority of RCTs included patients suffering from DM2 only (26 RCTs) [26–31, 46, 48–70] followed by RCTs with DM1 patients (seven RCTs [38, 40, 47, 71–74]). Only 4 RCTs were on GDM only [34, 41–43] and one on prediabetes [39]. Two RCTs, Beyuo 2015 and Ibrahim 2014, included pregnant patients with either pre-existing diabetes or GDM [44, 45]. Another 10 RCTs [32, 33, 35–37, 75–81] included patients with more than one diabetes category or did not provide sufficient information for further categorization (Figure 2). The included RCTs present a wide variety of patients in different stadiums of DM and general conditions. Including rather healthy pregnant young women suffering from GDM and children with DM1 without any other comorbidities, to patients with severe diabetes related complications. Mean duration of diabetes (reported in 26 RCTs) ranged from 2.5 years in Maharaj 2016, a RCT including patients with DM2 for rebound exercise as intervention [48] until 16.7 years in Netleki 2015, including patients with diabetic ulcers as a typical diabetes related complication [63].

Mean baseline HbA1c (reported in 46 RCTs) ranged from 6.75 % in Rashad 2017 [64] to 11.1 % in Muchiri 2015 [62] for patients with DM2. Body mass Index (BMI) as a relevant risk factor for GDM and DM2 [14] (reported in 31 RCTs) varied for patients with DM2 between mean values of 22.4 kg/m² in Fayehun 2018 [60] and 40.8 kg/m² in Distiller 2014 [55]. A total of 84 % of RCTs reported mean BMI values over 25 kg/m² and 48 % even over 30 kg/m².

4.1.3 Interventions

Most RCTs investigated the efficacy of non-pharmacological interventions (31 RCTs) including educational strategies (17 RCTs), life-style modifications (11 RCTs) and

further non-drug based strategies (three RCTs). The other ones investigated substance-related therapies (19 RCTs) as an intervention.

4.1.4 Non-pharmacological strategies

4.1.4.1 Educational strategies

A total of 15 RCTs [29–31, 33, 37, 49–52, 54, 59, 61, 62, 66–68, 75, 77] with in total 5962 participants and follow-up periods between 2 months in Takenga 2014 [67] and 24 months in Webb 2015 [37] examined training or educational measures for patients (Table 2). Topics included diabetes, treatment of diabetes including life style modification measures, dietary recommendation, drug based therapy and diabetes-related complications. The training sessions were provided on the basis of group based educational sessions or individual treatment plans by nursing staff or pharmacists. They were complemented by lectures, discussion services, brochures, newsletters, computer programs, information and communication technologies and telemonitoring systems and strategies to support self-management. Three of these RCTS were nurse-led interventions in which nurses played the central role in patient education and care [29, 33, 61].

Another two cluster-RCTs and two publications resulting from Webb 2015 [32, 34–37] with in total 1270 participants and follow-up periods between some months until delivery in Utz 2018 [34] and 24 months in Webb 2015 [35, 36] focused on educational strategies to improve adherence. Of those, two focused on diagnostic strategies. Webb 2015 aimed to determine the efficacy of a mobile based intervention on glycaemic control and diabetes related complication screening in a primary care setting in South Africa, however after one year no difference in HbA1c and no change in taken or not taken actions between both groups could be shown [35, 37]. The screening for diabetic complication was significant increasing in both arms. From this cluster randomized trial another publication resulted especially on retinopathy, maculopathy and visual loss being a typical complication of diabetes [36]. Utz 2018 was on diagnostic and initial management of GDM conducted in a primary health care setting without stating a difference of glycaemic control [34]. Steyn 2013 was also carried out in a primary care setting evaluating the effects of structured diabetes and hypertension records with no benefit for the interventional group after one year [32].

4.1.4.2 Life-style modification

A total of seven RCTs [42, 46, 48, 60, 70, 74, 76] with 583 participants and follow-up periods between two months in Asuako 2017 [76] and six months in Salem 2010 [74]

included interventions evaluating the efficacy of strategies to enhance physical activity. The training lessons included both, aerobic and anaerobic exercises but the majority of the interventions were on aerobic exercise. The type of exercise differed between walking in Fayehun 2018 and van Rooijen 2004 [60, 70], training sessions on treadmill in Asuako 2017, Embaby 2016 and Yan 2014 [42, 46, 76], a combination of treadmill, weightlifting, flexibility and neuromuscular exercises in Salem 2010 [74] and rebound exercise in Malek 2015 [26]. The lesson frequency offered per week was between one time, three times and daily. Typically, one lesson consisted of 45 minutes. Walking, on treadmill or without was the main form of exercise.

Another four RCTs [38–40, 47] with 168 participants and follow-up periods between two months in Krawinkel 2018 [39] and four months in Mohamad 2009 [47] evaluated the efficacy of nutritional strategies including special nutritional effects of diverse foods (e.g. camel milk in Mohamad 2009 [47], honey in Abdulrhman 2013 [38], bitter gourd in Krawinkel 2018 [39]) and different composition of meals (low vs. high protein and fat content meals) in van der Hoogt 2017 [40].

4.1.4.3 Further strategies

This category includes three RCTs on non-drug related measures: [41, 63, 69] with 71 participants and follow-up periods of three months, mostly on treating diabetic complications such as diabetic foot disease (phototherapy in Netleki 2015 [63] and periodontitis (ultrasonic scaling in Tsobgny-Tsague 2018 [69]), which are not substance related. El-Shamy 2018 evaluated the effects of acupressure on patients with gestational diabetes [41].

4.1.5 Substance-related strategies

In total 19 RCTs [26–28, 43–45, 53, 55–58, 64, 65, 71–73, 79–81] belong to this group with 1774 participants and follow-up periods between one month in Elbarbary 2016 [72] and 12.5 months in Malek 2015 [26]. These substances included the most common used in diabetes therapy such as Metformin only in Ibrahim 2014 [45], Metformin combined with Insulin in Ashoush 2016, Beyuo 2015 and Distiller 2014 [43, 44, 55]) and Insulin only in Chraibi 2017, Elbarbary 2016 and Malek 2015 [26, 27, 72]. 12 RCTs evaluated other substances [28, 53, 56–58, 64, 65, 78, 79, 81], namely various systematic effecting substances (Ketotifen in El-Haggar 2015 [56], L-Carnitine+glimepiride in El-Sheikh 2019 [58], Propolis in El-Sharkawy 2016 [57], Balanites aegyptiaca in Rashad 2017 [64] or locally applied therapy (intravitreal injections in Ghoneim 2013 and Saeed 2013 [78, 79] or local treatment of diabetic wounds in Yakoot 2019 [81]).

Moreover in this category substances were included, which can be summarized as dietary supplements including various vitamins (Vitamin D in Anyanwu 2016 [53] and Vitamin B in Elbarbary 2019 [71], fermented papaya in Somanah 2012 [80]), trace elements (e.g. Zinc in Anderson 2001 [28, 65]) and other substances (Carnosine in Elbarbary 2018 [73]) and its effects on glycemic control.

4.1.6 Intervention effects

None of the studies reported results on **mortality**.

Two RCTs (Adibe 2013 and Mash 2015) reported results on **quality of life** [30, 31, 51, 52]. Both RCTS investigated the efficacy of different educational strategies to improve understanding and self-care for patients with DM2, but only one study reported an improved quality of life as a result of a structured self-care education program by pharmacists and nurses over 12 months [51, 52]. Adibe 2013 showed an improvement of quality of life (QoL) of 0.86 ± 0.12 vs. 0.64 ± 0.10 ($p = 0.0001$) [51, 52].

Hospital admission was reported in two RCTs [27, 49, 50]. Abaza 2017 stated no difference between the groups [49, 50]. Chraibi 2017 stated less visits to healthcare professionals over 20 weeks for patients with DM2 with patient-driven compared to physician-driven titration of insulin (4.8 ± 0.65 vs. 7.5 ± 1.42 visits / patient) [27].

Intensification rates of therapy was reported in Fairall 2016, a nurse-led intervention RCT, showing no intensified treatment for patients with diabetes in the intervention group over 14 months [33].

Treatment adherence was reported in 4 RCTs [29, 49, 50, 53, 75]. Adjei 2015 was able to improve compliance with appointment dates in the intervention group with electronic reminders (97.8 % vs. 89.4 % p=0.01) [75]. Another cluster-RCT Labhardt 2011 stated better retention rates and adherence of patients with incentives or reminder letters (IG1 + IG2 vs. CG: 38 % vs. 35 % vs. 10 %; MD 26 (14 to 42)) [29]. Abaza 2017 found a significant higher treatment adherence of the intervention group, which received reminder messages [49, 50]. Anyanwu 2016 measured treatment adherence by tablet counting [53].

Adverse effects and complications were reported in 14 RCTs [26, 27, 40, 41, 43, 45, 55, 63, 69, 72, 73, 78, 79, 81]. Ibrahim 2014 could especially show a benefit concerning neonatal hypoglycaemia comparing metformin vs. insulin in treatment of GDM or pre-existing DM in pregnant patients [45]. Similar results concerning neonatal hypoglycaemia and neonatal ICU admission were shown in Ashoush 2016, which included women with GDM and randomized metformin vs insulin [43]. However, the control group had a lower rate of headache reported [43]. Furthermore Ashoush 2016 stated no significant non-inferiority of Metformin during pregnancy concerning the mode

and gestational age at delivery, fetal macrosomia, neonatal hypoglycaemia and admission to the Neonatal Intensive Care Unit. Regarding the maternal weight gain Ashoush 2016 stated a lower rate in the Metformin group 4.4 kg ± 0.6 kg vs. 5.1 kg ± 0.8 kg (p = 0.001) [43].

Elbarbary 2016 was successful in showing a benefit for the intervention group using an insulin pump based therapy during Ramadan fasting with suspension activation vs. without activating the low glucose suspension activation regarding the number of hypo- and hyperglycemic excursions [72]. Elbarbary 2018 did not report any adverse effects, but a benefit for intervention group concerning the HbA1c after 12 weeks [73]. Malek 2015 stated similar rate of hypoglycaemia comparing basal-bolus insulin trice daily biphasic insulin over 50 weeks [26].

Some RCTs focused on diabetes related complications, for example Yakoot 2019, were patients with limb threatening ulceration were included and significant improvement on the healing rate was showed [81]. Netleki 2015 also examined the healing rate of ulcers by applying phototherapy on either the ulcers themselves or regional lymphatic nodes combined with standard podiatric management vs. placebo phototherapy plus standard podiatric management. In this RCT no adverse effects were reported. However, only 7 patients were included [63]. Saeed 2013 was successful showing a significant difference regarding the best-corrected visual acuity and central foveal thickness in patients with diabetic macular edema [79].

Cost effectiveness only has been investigated in four RCTs [27, 30, 31, 43, 51, 52].

Adibe 2013 showed a benefit for the intervention group which received structured self-care education [51, 52]. Mash 2015 showed an incremental cost effectiveness ratio of 1862 Dollar/ Quality Adjusted Life Years (QALY) gained [30, 31]. Chraibi 2017 and Ashoush (2016) also showed a benefit for the intervention group [27, 43].

Glycemic control was reported in 7 RCTs for patients with DM1, in 4 RCTs for GDM, 26 RCTs for DM2 and in 1 RCT for patients with prediabetes.

Of the 7 RCTs with interventions on DM1, 5 were successful in improving the glycemic control (Abdulrhman 2013, Elbarbary 2018, Elbarbary 2019, Salem 2010, Van der Hoogt 2017)- [38, 40, 71, 73, 74]. Ashoush 2016 and Embaby 2016 included patients with GDM and showed an improvement in glycemic control [42, 43]. Ibrahim 2014 included patients with GDM and pre-existing DM and stated an improvement of the glycemic control [45]. Beyuo 2015 showed a significant difference in the 2-hour post prandial blood glucose (2 HPG), but no difference in fasting blood glucose (FBG) between the groups [44]. Krawinkel 2018, the only RCT on prediabetes did not show any difference regarding the HbA1c after 8 weeks [39].

A total of 33 RCTs reported results on HbA1c. 26 of them included mainly patients with DM2 and are graphically presented (see Figures 4-6).

A total of six out of 11 RCTs on educational strategies for patients with DM2 showed clinically relevant changes of HbA1c with significant differences between intervention groups and a higher decrease of HbA1c in the intervention group of at least 0.25 % (Amendezo 2017, Essien 2017, Mash 2015, Takenga 2014, Tawfik 2016, Debussche 2018) [30, 31, 54, 59, 67, 68, 77] (Figure 4). Successful interventions included various lifestyle education approaches (e.g. Amendezo 2017, Debussche 2018, Essien 2017, Tawfik 2016 [54, 59, 68, 77]), and telemedical approaches (Takenga 2014 [67]). For instance, Amendezo 2017 evaluated the efficacy of structured monthly lifestyle education sessions to improve glycaemic control for patients with DM2 in Rwanda with resulting lower HbA1c of -0.72% (95 %-CI -1.14 to -0.30) after 12 months compared to standard care [59].

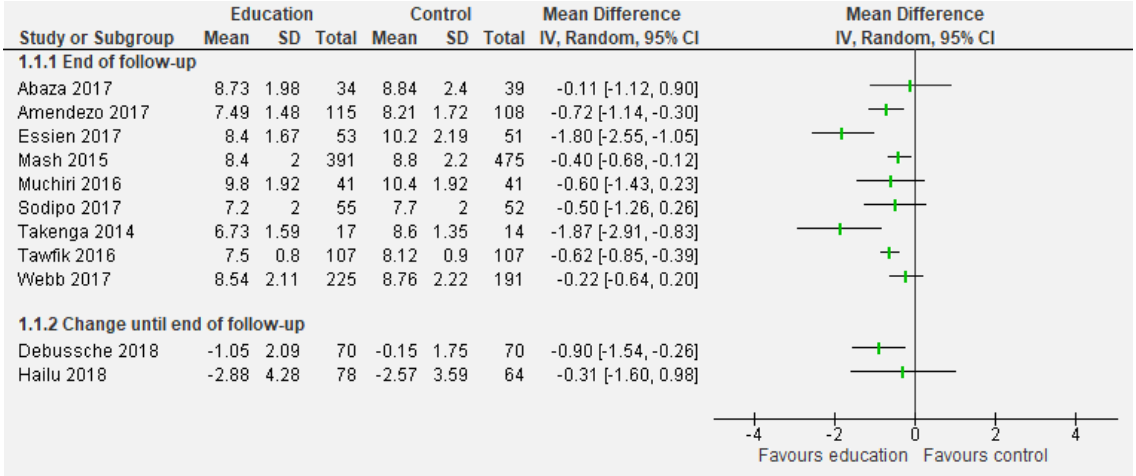


Figure 4: Efficacy of educational and nutritional as well as nurse led interventions strategies on HbA1c in patients with DM2

Strategies to enhance physical activity were successful to lower HbA1c in two RCTs where patients with DM2 were given goals to accumulate 10.000 steps per day (Fayehun 2018 [60] MD -0.56 %; 95 %-CI -0.71 to -0.41) or they allocated to rebound exercise (Maharaj 2016 [48]; MD -1.24 %; 95 %-CI -1.74 to -0.74) compared to normal or sedentary activity habits. No difference was stated in two other RCTs between incremental exercises and education (Van Rooijen 2004 [70]) and exercises with different intensities (Yan 2014 [46]). (Figure 5).

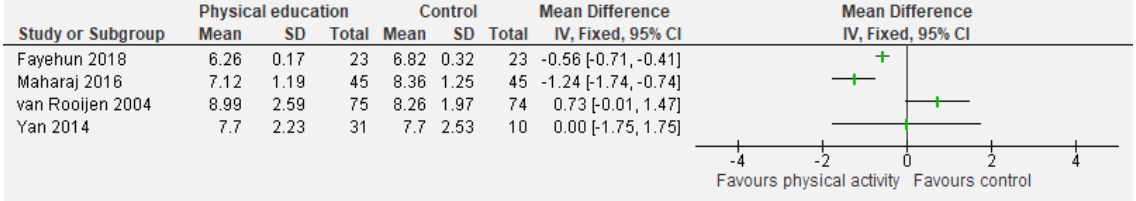


Figure 5: Efficacy of strategies to enhance physical activity

Figure 6 presents effects of drug or nutritional strategies on HbA1c in patients with DM2. Three out of five showed clinically relevant changes of HbA1c [56–58]. El-Sharkawy 2016 analysed scaling and root planning of patients with severe periodontitis combined with propolis vs. same procedure but placebo controlled (MD -1.60%; 95% CI -2.22 to 0.98) [57]. EL-Sheikh 2019 compared glimepiride and L-Carnitine vs. glimepiride alone and showed a benefit for the intervention group (MD -2.09 %; 95 & CI -3.90 to 0.28) [58]. El-Haggar 2015 compared glimepiride and ketotifen vs. glimepiride alone (MD -0.75 %; 95 % CI -1.09 to 0.41) [56]. Anyanwu 2016 compared Vitamin D3 supplements over 12 weeks with placebo [53] and Chraibi 2017 analysed the effectiveness of patient driven vs. physician driven titration of Insulin as part [27].

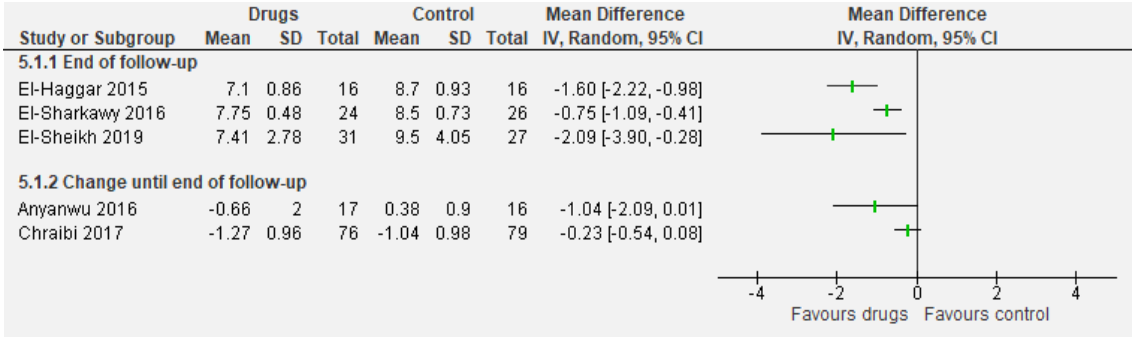


Figure 6: Effects of drug or nutritional strategies on HbA1c in patients with DM2

Some RCTs on DM2 with HbA1c as an outcome were not graphically demonstrated [26, 28, 32, 33, 55, 65, 69, 80]. Of those, only Tsobgny-Tsague 2018 was successful in demonstrating a better glucose control of the intervention group which received a periodontal treatment [69]. Fairall 2016, a nurse led intervention stated a benefit of HbA1c values in the range between 7-10 % [33]. Steyn 2013, Distiller 2014, Malek 2015 and Anderson 2001 reported no difference between the groups [26, 28, 32, 55, 65] and Somanah 2012 had incomplete data [80].

4.2 Risk of bias

None of the included studies were categorized as low risk of bias in all seven domains. 22 RCTs (44 %) of the studies fulfilled the criteria for low risk of bias concerning

random sequence generation, two RCTS (4 %) were assessed as high risk. EL-Shamy 2018 used a non-probability sampling method on the basis of the hospital admission code [41] and Nteleki 2015 randomized different ulcers in the same patient but not the patients from each other [63]. 26 RCTs (52 %) remained unclear. Bias due to allocation concealment was classified as low in 20 RCTs (46 %), high in one RCT (2 %), El-Shamy 2018 [41], and remained unclear in 52 %. Performance bias due to a lack of blinding of participants and personnel was judged as low in six RCTs (12 %), high in 40 RCTs (80 %), and remained unclear in four RCTs (8 %). Detection bias due to blinding of the outcome assessors was classified as low in 15 RCTs (30 %), high in eight (16 %) and unclear in 28 RTCs (56 %). Incomplete outcome data was assessed as low in 20 RCTs (40 %), as high in 24 RCTs (48 %), and stayed unclear in six RCTs (12 %). Reporting bias due to selective outcome reporting was assessed as unclear in the majority of the cases due to missing a protocol. In those RCTs where a protocol was available, it was judged as low in 11 RCTs (21 %) and as high in five RCTs (9 %).
Further limitations were included in the last category “other bias” here 19 RCTs (40 %) were judged as low risk and 26 RCTs (50 %) were classified as high risk, five RCTs (10 %) remained unclear. The detailed judgement of each RCT is available in the supplemental material (Table 3), an overview is presented in Figure 7.

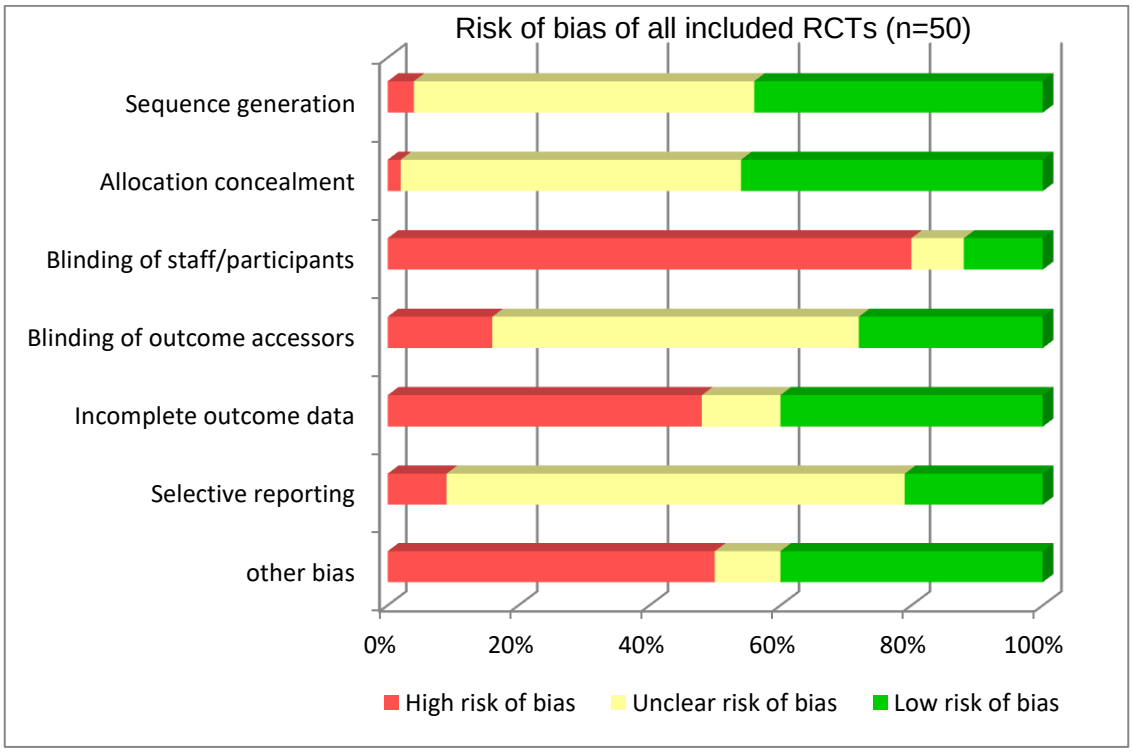


Figure 7: Overview on the judgement of the risk of bias of all included RCTs (n=50) on the basis of the Cochrane risk of bias tool in seven specific categories

5 Discussion

This review summarizes the available evidence for strategies to prevent, diagnose and treat diabetes in African countries.

50 RCTs conducted in Africa were identified, which were unequally distributed among the continent. Even though RCTs on prevention, diagnosis and treatment of diabetes were searched for, predominantly RCTs on treatment and on secondary or tertiary prevention and only a few on diagnosis and primary prevention were identified. Most of the RCTs were conducted in urban regions and only 9 out of 50 RCTs were conducted in a primary care setting. The quality of the included RCTs was limited, mainly due to low numbers of participants resulting in a limited precision of the results and non- or incomplete reported information. Still some promising interventions were identified, which could be useful for planning future research adapted to the local circumstances.

The fact, that the majority of the included RCTs were published within the last 5 years seems to indicate an increasing focus on diabetes research in some African countries.

Within the African continent, consisting of 54 countries, regional differences were observed: Most of the included RCTs were conducted in the North African region, especially in Egypt, followed by South Africa and Nigeria belonging to West Africa. Egypt is the country with the highest prevalence of diabetes of the African continent [12]. This might be related to economic expansion and urbanization, but also due to specific dietary issues (e.g. white bread, polished rice, trans fat), reduced physical activity due to prohibition of exercise in public places, shortage of exercise facilities, poor physical education in schools. Poor diet and physical inactivity are causing a high rate of overweight and obesity among the Egyptian population. Also the high rate of Hepatitis C infection might contribute to the comparatively high rate of diabetes in Egypt [82, 83]. Attention bias cannot be excluded as the prevalence of DM is high in Egypt but the rate of undiagnosed diabetes cases compared to the rest of Africa is less than the average [12, 84, 85].

All included RCTs on DM1 patients were conducted in Egypt except of one which was conducted in South Africa [40]. Those results are comparable to the statistics of the IDF [12]. The prevalence of diabetes seems to be higher in the North African region compared to the rest of Africa [84, 85]. Nevertheless the rate of undiagnosed patients with diabetes is estimated to be almost 45 % in North Africa compared to almost 60 % in rest of Africa [84, 85]. This distribution might be a result of a difference in social, economic, and genetic disparities [86]. The rate of undiagnosed diabetes cases may be related to the development level of the health care system and to a lack of awareness in the general population [87]. The high rate of undetected cases of diabetes signalize

a high need for research and implementation of diabetes screening strategies in the African context. Webb 2015 and Utz 2018 are RCT on screening for diabetes and diabetes related complications in primary care settings [34, 36, 37]. Only one RCT on primary prevention was identified, including people with prediabetes but the proportion of individuals progressing from pre-diabetes to diabetes has not been evaluated [39]. Interventions on primary prevention of diabetes, especially DM2, including strategies on lifestyle modification mostly require a long follow-up period and a rather high number of cases to analyze diabetes incidence [88]. In both cases including not only RCTs, but also other study types are needed [89].

The broad majority of included RCTs was conducted in urban settings, this is likely due to the better availability of research and health care infrastructure. The consequence is a limited generalizability of the results and a neglection of rural populations needs and a higher rate of undiagnoses diabetes [87]. Health care workers, including doctors and nurses seem to rather provide services in urban areas leading to an even higher deficit of health care access in rural areas and consecutively a lower life expectancy and poorer health status of the rural population [90, 91].

Africa is facing a shift from communicable to NCDs like diabetes resulting in a double burden for the whole continent [3, 6, 7]. However, strategies including nurse-doctor-teams which helped to cope with communicable disease like HIV may also be applicable to NCDs [92]. Nurse-led interventions, enhancing the primary healthcare capacity and the introduction of clinical guidelines and structured programs for detection and evidence based treatment of DM are needed to abolish the large undersupply [93, 94].

There is a strong need for context specific guidelines since eligible guidelines from high income countries may not be transferable to LMIC [95]. Steyn 2013, a cluster RCT from South Africa evaluated the introduction of a national guideline for diabetes care in nine community health care centers in South Africa [32]. After one year, the intervention had no impact on diabetes control. The staff criticized that these recommendations were rather idealistic and not realizable [32]. Modifying international guidelines to the socioeconomic context, human resources, especially well-trained health care professionals and infrastructure of Africa countries with a focus on clinical practicable strategies may be a better plan to improve diabetes care.

Education is the basis and essential to prevent or delay the manifestation of diabetes or diabetes related complications [96]. Patients empowerment being achieved through a good enlightenment may motivate each individual for a better control of their disease and is an essential component of the management of chronic diseases [97].

A couple of effective RCTs on education were included in the current work. Essien (2017) showed the efficacy of an intensive and systematic disease self-management education program in Nigeria improving the HbA1c value [77]. Amendezo 2017 succeeded in achieving clinical relevant results concerning glycemic control also by structured monthly lifestyle education sessions in Rwanda [59].

Tawfik 2016 also succeeded in showing the impact of communicating cardiovascular risk in patients with DM2 on HbA1c [68]. Debussche 2018 also analyzed structured culturally tailored education delivered by trained peer educators and proved a significant benefit for the interventional group concerning the HbA1c [54]. All studies had in common, that they were adapted on the local circumstances. Those interventions are potentially replicable at other levels of African health care systems and in other LMICs, where nurses can run respective programs. Further task-shifting to nurses and other health workers in primary health care management of NCDs such as diabetes, might improve health care effectiveness and efficiency [98]. In countries with a lack of doctors, the role of the nurses in NCD care should be expanded, especially in LMIC, not only for education as an intervention, but also for improving the diagnostic and for treatment of diabetes. Benefits of nurse-led care regarding clinical effectiveness and cost-effectiveness of chronic diseases in high income countries is well recognized [99–102], however evidence for LMICs is still limited [95, 103]. In total, three RTCs on nurse-led intervention were included and none of them evaluated the cost effectiveness, even though the economic aspect should be evaluated as well [29, 33, 61].

Adibe 2013 evaluated a structural self-care education program implemented by pharmacists with the cooperation of physicians and nurses and was successful in showing a benefit of incremental gain in QALYs and reduced costs compared with the control group after one year [51, 52]. More economic evaluations like this should be implemented in African countries to assess the efficacy of nurse-led care [104].

In times of growing digitalization also other sources should be evaluated. Takenga 2014 combined self-management of diabetes with telemedical approaches and stated a significant decrease of the HbA1c [67]. Information and communication technologies might also have great potential improve the accessibility of the African population to high quality health care services where the human resources are limited [67, 105]. Life-style focussed messages might be a low cost and effective option for keeping the patients motivated to adhere to a healthy lifesytle [105]. The number of people having access to mobile services is expected to rise during the next years [106]. The application of telemedicine in different parts of diabetes management has been evaluated in previous studies before and has shown promising results [107, 108]. Still,

the implementation of a digital health ecosystem is a complex process with many challenges to overcome [109, 110]. Currently the COVID-19 pandemic has forced all nations to implement alternative and more flexible strategies including for example telemonitoring and teleconsultation for continuing care of NCDs [111, 112].
This can indicate options or the need for assessing these approaches in the regional context.
Of the strategies to enhance physical activity, Fayehun 2018 managed to improve glycemic control by setting the goal to accumulate 10.000 steps per day, an intervention which does not require any cost intensive infrastructure and still managed to show significant decrease in HbA1c levels after 4 weeks [60].
Another important aspect is that originally pre-planned primary outcomes were mortality and quality of life, but study results are only available on quality of life in two RCTs [30, 31, 51, 52]. Mortality is not reported in any of the included RCTs. This could be due to the fact that overall surviving time with diabetes is higher than the follow up time of most of the RCTs. Nevertheless long-term glycemic control, being represented by the HbA1c value is one of the strongest clinical-outcome indicators of efficient diabetes management and health outcomes [113]. It is easy to measure and gives a good overview over individual's average blood glucose levels in the previous 3 months [113, 114]. Compared to mortality, which requires long follow up periods, the HbA1c value is more easily measured and therefore might explain why the majority of the included studies chose it as a primary outcome parameter.
Regarding the substance-based studies, it has to be noted that big international multicenter pharmacological studies with few centers in African countries were excluded, resulting in a rather small amount of included studies (Table 1). Several studies where metformin was tested during pregnancy were included. For example, Ashoush 2016 showed a significant result regarding the glycemic control in the interventional group using metformin plus if needed insulin vs. insulin only as a control group. Concerning the maternal hypoglycemia the results were also in favor of the intervention group with a prevalence of 6.3 % vs. 12.5 % [43]. Ibrahim 2014, a RCT conducted in Egypt including also patients with GDM or pre-existing DM2, demonstrated a significant better glycemic control and a significant lower rate of maternal hyperglycemia in the metformin group [45]. Both showed a benefit of metformin. Their results are similar to the findings of an international RCT, which showed a comparability of Metformin to Insulin during pregnancy without increasing perinatal complications and better results for Metformin in achieving a faster glycemic control and an overall lower weight gain during pregnancy [115]. Another meta-analysis proved that metformin is not associated with increased perinatal complications

compared with insulin [116]. Still long term outcome information is limited and this is the reason why insulin is still the first line therapy of diabetes in pregnancy [117].

Besides the identified studies, there are other approaches, which are very well established and likely can be transferred to an African setting. For example the disease management programs (DMPs), which intended to improve the quality of care of patients suffering from chronic disease [118]. Those structured programs might help to identify or even prevent the diabetes related complications at early stage through regular checkups. This would allow adjusting or adapting treatment strategies in time.

5.1.1 Strength and limitations

Systematic reviews and meta-analyses have become progressively important in health science [20]. Clinicians as well as researchers read them to get an overview on pre-existing information on a certain topic in order to conduct new studies as wells as to keep up with a certain field [20].

We strictly followed the PRISMA guidelines [20] in this project to guarantee a high standard of reporting. A protocol has been registered and published in the PROSPERO (CRD42019122785) prior to starting this work.

This systematic review includes RCTs as the gold standard for determining causal efficacy of medical interventions and their benefit assessment [119], without time constrictions, but language restrictions. Language bias was shown to be unlikely. Despite the high linguistic diversity on the African continent, the most spoken language besides English are Arabic and French [120]. Nevertheless, we did not exclude any studies due to their publication language.

Four databases were searched, but further African publications might only be listed in local databases that had not been searched for this review. The effect of this bias is assumed to be small since high quality studies are published in internationally indexed journals [21]. The ICTRP also includes the Pan African Clinical Trial Registry (PACTR) representing a local register which aims to be a comprehensive database of all planned, ongoing or completed clinical trials in African countries [121].

Concerning the risk of bias, often there was insufficient information on the different categories and thus this bias had to be often judged as “unclear”. The CONSORT statement aims to improve this in future RCTs [22].

The included entities of diabetes (DM1, DM2, GDM) cover more than 98 % of the patients with diabetes [122].

On the baseline data, it has to be noted that only the half of the studies reported information on duration of diabetes at baseline, but this is a major risk factor for developing diabetes related complication [123]. External validity might also be limited

by the focus on mainly urban areas. People living there have a better access to health care are more likely to be diagnosed at an early disease stadium. People living in rural ares are rather be diagnosed at an advanced state of disease and are more likely to already suffer from diabetes related mirco-and/or macrovascular complications [87]. The avoidance of risk factors, an early detection and an early treatment of diabetes have an enormous benefit on the course of disease and on the financal burden [10, 124].

6 Conclusion

This systematic review shows an increasing number of studies due to a rising prevalence and awareness of diabetes in African countries. But the number of RCTs to improve detection, treatment, adherence and prognosis of African patients with diabetic illnesses is still low. The majority of RCTs included in this review were interventions on the treatment of diabetes being part of secondary and tertiary prevention and not on the primary prevention or diagnostic. Both important aspects to control diabetes in LMIC like the countries in Africa with a special need of locally feasible interventions. Available RCTs might not be representative for all people in Africa, as there are focusing only on a few countries and a rather urban setting. More RCTs in rural settings are necessary, however especially there, a shortage of human resources like health care workers, nurses, basis technologies for diagnostic and medication is still a challenge for conducting research and implementing strategies on diabetes management.

It is crucial to plan and implement more RCTs on the effectiveness of different prevention and treatment strategies. One major implication for practice is the expanded role of doctors and nurses in primary health care to improve the diabetes care in Africa and the evaluation of digital health services to improve health care services in places, which are facing a shortage of professionals.

The empowerment of the patients as well as the whole population is urgent to achieve an increased awareness and understanding of the disease, leading to a higher willingness to change life style and overall adherence to the treatment and regular checks.

Health systems must ensure technical and financial resources to screen and care for patients with diabetes. An improvement in the prognosis of patients with diabetes in African countries requires the implementation of locally adapted guidelines aiming to identify diabetes and its complications as early as possible.

The identified RCTs offer effective strategies as a basis for local guidelines tested in African countries, including non-pharmacological strategies on education and lifestyle modification including nurse-led interventions, and pharmacological strategies with the particularities resulting from the wide diversity of the African population.

7 References

1. Jakovljevic MB, Milovanovic O. Growing Burden of Non-Communicable Diseases in the Emerging Health Markets: The Case of BRICS. Front Public Health. 2015;3:65. doi:10.3389/fpubh.2015.00065.
2. Beagley J, Guariguata L, Weil C, Motala AA. Global estimates of undiagnosed diabetes in adults. Diabetes Res Clin Pract. 2014;103:150–60. doi:10.1016/j.diabres.2013.11.001.
3. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018:1736–88. doi:10.1016/S0140-6736(18)32203-7.
4. World Health Organization. Diabetes | WHO | Regional Office for Africa. https://www.afro.who.int/health-topics/diabetes. Accessed 4 Mar 2020.
5. World Health Organization (WHO). Diabetes burden rising sharply in the African Region | WHO | Regional Office for Africa. https://www.afro.who.int/news/diabetes-burden-rising-sharply-african-region. Accessed 3 Aug 2020.
6. Misganaw A, Mariam DH, Araya T. The double mortality burden among adults in Addis Ababa, Ethiopia, 2006-2009. Prev Chronic Dis. 2012;9:E84. doi:10.5888/pcd9.110142.
7. Kushitor MK, Boatemaa S. The double burden of disease and the challenge of health access: Evidence from Access, Bottlenecks, Cost and Equity facility survey in Ghana. Plos one. 2018;13:e0194677. doi:10.1371/journal.pone.0194677.
8. Sustainable Development solutions Network, a global initiative for the United Nations. 3.4 by 2030 reduce by one-third pre-mature mortality from non-communicable diseases (NCDs) through prevention and treatment, and promote mental health and wellbeing – Indicators and a Monitoring Framework. https://indicators.report/targets/3-4/. Accessed 3 Aug 2020.
9. Internation Diabetes Federation. IDF Atlas 9th edn. Brussel, Belgium. 2019. https://www.diabetesatlas.org. Accessed 7 Aug 2020.
10. Mutyambizi C, Pavlova M, Chola L, Hongoro C, Groot W. Cost of diabetes mellitus in Africa: a systematic review of existing literature. Global Health. 2018;14:3. doi:10.1186/s12992-017-0318-5.
11. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care. 2019:13–28. doi:10.2337/dc19-S002.

12. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. Available at: https://www.diabetesatlas.org. Accessed 7 Aug 2020.
13. Beaglehole R, Epping-Jordan J, Patel V, Chopra M, Ebrahim S, Kidd M, Haines A. Improving the prevention and management of chronic disease in low-income and middle-income countries: a priority for primary health care. Lancet. 2008;372:940–9. doi:10.1016/S0140-6736(08)61404-X.
14. Gray N, Picone G, Sloan F, Yashkin A. Relation between BMI and diabetes mellitus and its complications among US older adults. South Med J. 2015;108:29–36. doi:10.14423/SMJ.0000000000000214.
15. Stupin JH, Arabin B. Overweight and Obesity before, during and after Pregnancy: Part 1: Pathophysiology, Molecular Biology and Epigenetic Consequences. Geburtshilfe Frauenheilkd. 2014;74:639–45. doi:10.1055/s-0034-1368486.
16. Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, Blonde L, Bush MA, DeFronzo RA, Garber JR, Garvey WT, Hirsch IB, Jellinger PS, McGill JB, Mechanick JI, Perreault L, Rosenblit PD, Samson S, Umpierrez GE. CONSENSUS STATEMENT BY THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY ON THE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM - 2020 EXECUTIVE SUMMARY. Endocr Pract. 2020;26:107–39. doi:10.4158/CS-2019-0472.
17. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42:S165-S172. doi:10.2337/dc19-S014.
18. Internation Diabetes Federation. IDF Atlas 9th edn. Brussel, Belgium. 2019. https://diabetesatlas.org/upload/resources/material/20191217_165723_2019_IDF_Advocacy_guide.pdf. Accessed 4 Mar 2020.
19. Gomez F, Hirbo J, Tishkoff SA. Genetic variation and adaptation in Africa: implications for human evolution and disease. Cold Spring Harb Perspect Biol. 2014;6:a008524-a008524. doi:10.1101/cshperspect.a008524.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos medicine. 2009;6:e1000097. doi:10.1371/journal.pmed.1000097.
21. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook. Accessed 3 Aug 2020.

22. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol. 2010:1-37. doi:10.1136/bmj.c869.
23. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin JA, Doré CJ, Parulekar WR, Summerskill WS, Groves T, Schulz KF, Sox HC, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200–7. doi:10.7326/0003-4819-158-3-201302050-00583.
24. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
25. Brinke R ten, Dekker N, Groot M de, Ikkersheim D. Lowering HbA1c in type 2 diabetics results in reduced risk of coronary heart disease and all-cause mortality. Primary Care Diabetes. 2008;2:45–9. doi:10.1016/j.pcd.2007.12.004.
26. Malek R, Ajili F, Assaad-Khalil SH, Shinde A, Chen JW, Van den Berg E. Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. Diabetes Metab. 2015;41:223–30. doi:10.1016/j.diabet.2014.11.002.
27. Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshmivenkataraman B, Assaad-Khalil SH. An RCT Investigating Patient-Driven Versus Physician-Driven Titration of BIAsp 30 in Patients with Type 2 Diabetes Uncontrolled Using NPH Insulin. Diabetes Ther. 2017:767–80. doi:10.1007/s13300-017-0268-1.
28. Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. J Am Coll Nutr. 2001:212–8. doi:10.1080/07315724.2001.10719034.
29. Labhardt ND, Balo JR, Ndam M, Manga E, Stoll B. Improved retention rates with low-cost interventions in hypertension and diabetes management in a rural African environment of nurse-led care: a cluster-randomised trial. Trop Med Int Health. 2011;16:1276–84. doi:10.1111/j.1365-3156.2011.02827.x.
30. Mash R, Kroukamp R, Gaziano T, Levitt N. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. Patient Educ Couns. 2015;98:622–6. doi:10.1016/j.pec.2015.01.005.

31. Mash RJ, Rhode H, Zwarenstein M, Rollnick S, Lombard C, Steyn K, Levitt N. Effectiveness of a group diabetes education programme in underserved communities in South Africa: pragmatic cluster randomized control trial. Diabet Med. 2014:987-93. doi:10.1111/dme.12475.
32. Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, Levitt NS. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: a randomised controlled trial. Glob Health Action. 2013:20796. doi:10.3402/gha.v6i0.20796.
33. Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, Bateman ED, Lund C, Cornick R, Faris G, Gaziano T, Georgeu-Pepper D, Zwarenstein M, Levitt NS. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Med. 2016;13:e1002178. doi:10.1371/journal.pmed.1002178.
34. Utz B, Assarag B, Smekens T, Ennassiri H., Lektal T. El Ansari N. et al. Detection and initial management of gestational diabetes through primary health care services in Morocco: An effectiveness-implementation trial. Plos one. 2018:e0209322. doi:10.1371/journal.pone.0209322.
35. Webb EM, Rheeder P, Van Zyl DG. Diabetes care and complications in primary care in the Tshwane district of South Africa. Prim Care Diabetes. 2015:147–54. doi:10.1016/j.pcd.2014.05.002.
36. Webb EM, Rheeder P, Roux P. Screening in Primary Care for Diabetic Retinopathy, Maculopathy and Visual Loss in South Africa. Ophthalmologica. 2016;235:141–9. doi:10.1159/000443972.
37. Webb EM, Rheeder P. A cluster-randomized trial to estimate the effect of mobile screening and treatment feedback on HbA1c and diabetes-related complications in Tshwane primary health care clinics, South Africa. Prim Care Diabetes. 2017:546-554. doi:10.1016/j.pcd.2017.05.010.
38. Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, and Mohamed MS. Metabolic effects of honey in Type 1 Diabetes Mellitus: A randomized crossover Pilot Study. J Med Food. 2013:66–72. doi:10.1089/jmf.2012.0108.
39. Krawinkel MB, Ludwig C, Swai ME, Yang RY, Chun KP, Habicht SD. Bitter gourd reduces elevated fasting plasma glucose levels in an intervention study among prediabetics in Tanzania. J Ethnopharmacol. 2018:1-7. doi:10.1016/j.jep.2018.01.016.

40. Van der Hoogt M, van Dyk JC, Dolman RC, Pieters M. Protein and fat meal content increase insulin requirement in children with type 1 diabetes – Role of duration of diabetes. J Clin Transl Endocrinol. 2017:15–21. doi:10.1016/j.jcte.2017.10.002.
41. El-Shamy FF, El-Kholy SS, Labib M, Kabel AM. Ameliorative potential of acupressure on gestational diabetes mellitus a randomized controlled trial. J Complement Integr Med. 2018:20180011. doi:10.1515/jcim-2018-0011.
42. Embaby H, Elsayed E, Fawzy M. Insulin Sensitivity nd Plasma Glucose Response to Aerobic Exercise in Pregnant Women at Risk for Gestational Diabetes Mellitus. Ethiop J Health Sci. 2016:409–414. doi:10.4314/ejhs.v26i5.2.
43. Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. J Obstet Gynaecol Res. 2016:640–7.
44. Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. Plos one. 2015;10:e0125712. doi:10.1371/journal.pone.0125712.
45. Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Arch Gynecol Obstet. 2014;289:959–65. doi:10.1007/s00404-013-3090-7.
46. Yan H, Prista A, Ranadive SM, Damasceno A, Caupers P, Kanaley JA, Fernhall B. Effect of Aerobic Training on Glucose Control and Blood Pressure in T2DDM East African Males. ISRN Endocrinol. 2014:864897. doi:10.1155/2014/864897.
47. Mohamad RH, Zekry ZK, Al-Mehdar HA, Salama O, El-Shaieb SE, El-Basmy AA, et al. Camel milk as an adjuvant therapy for the treatment of type 1 diabetes: verification of a traditional ethnomedical practice. J Med Food. 2009:461–5. doi:10.1089/jmf.2008.0009.
48. Maharaj SS, Nuhu J. M. Rebound exercise: A beneficial adjuvant for sedentary non‐insulin‐dependent type 2 diabetic individuals in a rural environment. Aust. J. Rural Health. 2016:123–9.
49. Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC Public Health. 2017;17:962. doi:10.1186/s12889-017-4973-5.
50. Abaza H, Marschollek M, Schulze M. SMS Education for the Promotion of Diabetes Self-Management in Low & Middle Income Countries: A Randomized Controlled

Trial in EgyptTrial in Egypt. Stud Health Technol Inform. 2017;245:1209. doi:10.3233/978-1-61499-830-3-1209.

51. Adibe MO, Aguwa CN, Ukwe CV. Cost-Utility Analysis of Pharmaceutical Care Intervention Versus Usual Care in Management of Nigerian Patients with Type 2 Diabetes. Value in Health Regional Issues. 2013;2:189–98. doi:10.1016/j.vhri.2013.06.009.
52. Adibe MO, Ukwe CV, Aguwa CN. The Impact of Pharmaceutical Care Intervention on the Quality of Life of Nigerian Patients Receiving Treatment for Type 2 Diabetes. Value in Health Regional Issues. 2013;2:240–7. doi:10.1016/j.vhri.2013.06.007.
53. Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian J Endocrinol Metab. 2016:189-194. doi:10.4103/2230-8210.176345.
54. Debussche X, Besançon S, Balcou-Debussche M, Ferdynus C, Delisle H, Huiart L, Sidibe AT. Structured peer-led diabetes self-management and support in a low-income country: The ST2EP randomised controlled trial in Mali. Plos one. 2018;13:e0191262. doi:10.1371/journal.pone.0191262.
55. Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U-500 regular insulin plus metformin. Endocr Pract. 2014:1143-1150. doi:10.4158/EP14067.OR.
56. El-Haggar SM, Farrag WF, Kotkata FA. Effect of ketotifen in obese patients with type 2 diabetes mellitus. J Diabetes Complications. 2015;29:427–32. doi:10.1016/j.jdiacomp.2015.01.013.
57. El-Sharkawy HM, Anees MM, van Dyke TE. Propolis Improves Periodontal Status and Glycemic Control in Patients With Type 2 Diabetes Mellitus and Chronic Periodontitis: A Randomized Clinical Trial. J Periodontol. 2016;87:1418–26. doi:10.1902/jop.2016.150694.
58. El-sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of l-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. Diabetes Metab Syndr. 2019:167–73.
59. Amendezo E, Walker Timothy D, Karamuka V, Robinson B, Kavabushi P, Ntirenganya C, Uwiragiye J, Mukantagwabira D, Bisimwa J, Uwintwali Marie H, Umulisa H, Niyomwungeri S, Ndayambaje B, Dusabejambo V, Bavuma C. Effects of a lifestyle education program on glycemic control among patients with diabetes

at Kigali University Hospital, Rwanda: A randomized controlled trial. Diabetes Res Clin Pract. 2017:129–137. doi:10.1016/j.diabres.2017.02.001.

60. Fayehun AF, Olowookere OO, Ogunbode AM, Adetunji AA, Esan A. Walking prescription of 10 000 steps per day in patients with type 2 diabetes mellitus: a randomised trial in Nigerian general practice. Br J Gen Pract. 2018:e139-e145. doi:10.3399/bjgp18X694613.
61. Hailu FB, Hjortdahl P, Moen A. Nurse-Led Diabetes Self-Management Education Improves Clinical Parameters in Ethiopia. Front Public Health. 2018:302. doi:10.3389/fpubh.2018.00302.
62. Muchiri JW, Gericke GJ, Rheeder P. Effect of a nutrition education programme on clinical status and dietary behaviours of adults with type 2 diabetes in a resourcelimited setting in South Africa: a randomised controlled trial. Public Health Nutr. 2016:142–55. doi:10.1017/S1368980015000956.
63. Nteleki B, Abrahamse H, Houreld NN. Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers. Semin Vasc Surg. 2015;28:172–83. doi:10.1053/j.semvascsurg.2016.02.001.
64. Rashad H, Metwally FM, Ezzat SM, Salama MM, Hasheesh A, Abdel Motaal A. Randomized double-blinded pilot clinical study of the antidiabetic activity of Balanites aegyptiaca and UPLC-ESI-MS/MS identification of its metabolites. Pharm Biol. 2017:1954–61.
65. Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. J Am Coll Nutr. 2003:316–21. doi:10.1080/07315724.2003.10719310.
66. Sodipo OO, Adedokun A, Olusola AA. Effect of self-monitoring of blood glucose on glycaemic outcome among type 2 diabetic patients. S Afr Fam Pract. 2017:208–13. doi:10.1080/20786190.2017.1340250.
67. Takenga C, Berndt RD, Musongya O, Kitero J, Molo K, Kazingufu B, Meni M, Vikandy M, Takenga H. An ICT-Based Diabetes Management System Tested for Health Care Delivery in the African Context. Int J Telemed Appl. 2014:437307. doi:10.1155/2014/437307.
68. Tawfik MY, Mohamed RA. The impact of communicating cardiovascular risk in type 2 diabetics on patient risk perception, diabetes self-care, glycosylated hemoglobin, and cardiovascular risk. J Public Health. 2016:153–164. doi:10.1007/s10389-016-0710-2.
69. Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, Tankeu AT, Katte JC, Dehayem MY, Bengondo CM, Sobngwi E. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1

study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health. 2018:28. doi:10.1186/s12903-018-0479-5.

70. Van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A1C in Black females with type 2 diabetes mellitus. Q J Med. 2004;97:343–51. doi:10.1093/qjmed/hch061.
71. Elbarbary NS, Ismail EAR, Zaki MA, Darwish YW, Ibrahim MZ, El-Hamamsy M. Vitamin B complex supplementation as a homocysteine-lowering therapy for early stage diabetic nephropathy in pediatric patients with type 1 diabetes: A randomized controlled trial. Clin Nutr. 2019:49-56. doi:10.1016/j.clnu.2019.01.006.
72. Elbarbary NS. Effectiveness of the low-glucose suspend feature of insulin pump during fasting during Ramadan in type 1 diabetes mellitus. Diabetes Metab Res Rev. 2016;32:623–33. doi:10.1002/dmrr.2781.
73. Elbarbary NS, Ismail EAR, El-Naggar AR, Hamouda MH, El-Hamamsy M. The effect of 12 weeks carnosine supplementation on renal functional integrity and oxidative stress in pediatric patients with diabetic nephropathy: a randomized placebo-controlled trial. Pediatric Diabetes. 2018;19:470–7. doi:10.1111/pedi.12564.
74. Salem MA, Aboelasrar MA, Elbarbary NS, Elhilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetol Metab Syndr. 2010:47. doi:10.1186/1758-5996-2-47.
75. Adjei DN, Agyemang C, Dasah JB, Kuranchie P, Amoah AG. The effect of electronic reminders on risk management among diabetic patients in low resourced settings. Journal of diabetes and its complications. 2015;29:818–21. doi:10.1016/j.jdiacomp.2015.05.008.
76. Asuako B, Moses MO, Eghan BA, Sarpong PA. Fasting plasma glucose and lipid profiles of diabetic patients improve with aerobic exercise training. Ghana Med J. 2017:120–7. doi:10.4314/gmj.v51i3.5.
77. Essien O, Otu A, Umoh V, Enang O, Hicks JP, Walley J. Intensive Patient Education Improves Glycaemic Control in Diabetes Compared to Conventional Education: A Randomised Controlled Trial in a Nigerian Tertiary Care Hospital. PLoS One. 2017:e0168835.
78. Ghoneim EM, Abd El Ghany AA. Behavior of intraocular pressure after intravitreal injection of triamcinolone acetonide among Egyptians. Ophthalmol Ther. 2013;2:121–30. doi:10.1007/s40123-013-0017-0.

79. Saeed AM. Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. Clin Ophthalmol. 2013:283-297. doi:10.2147/OPTH.S37781.
80. Somanah J, Aruoma OI, Gunness TK, Kowelssur S, Dambala V, Murad F, et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. Prev Med. 2012:90–7. doi:10.1016/j.ypmed.2012.01.014.
81. Yakoot M, Abdelatif M, Helmy S. Efficacy of a new local limb salvage treatment for limb-threatening diabetic foot wounds - a randomized controlled study. Diabetes Metab Syndr Obes. 2019;12:1659–65. doi:10.2147/DMSO.S210680.
82. Issaka A, Paradies Y, Stevenson C. Modifiable and emerging risk factors for type 2 diabetes in Africa: a systematic review and meta-analysis protocol. Syst Rev. 2018;7:139. doi:10.1186/s13643-018-0801-y.
83. Hegazi R, El-Gamal M, Abdel-Hady N, Hamdy O. Epidemiology of and Risk Factors for Type 2 Diabetes in Egypt. Ann Glob Health. 2015;81:814–20. doi:10.1016/j.aogh.2015.12.011.
84. Internation Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. 2019. https://diabetesatlas.org/data/en/region/2/afr.html. Accessed 21 Sep 2020.
85. Internation Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. 2019. https://diabetesatlas.org/data/en/region/4/mena.html. Accessed 21 Sep 2020.
86. Tekola-Ayele F, Adeyemo AA, Rotimi CN. Genetic epidemiology of type 2 diabetes and cardiovascular diseases in Africa. Prog Cardiovasc Dis. 2013;56:251–60. doi:10.1016/j.pcad.2013.09.013.
87. Asmelash D, Asmelash Y. The Burden of Undiagnosed Diabetes Mellitus in Adult African Population: A Systematic Review and Meta-Analysis. J Diabetes Res. 2019;2019:4134937. doi:10.1155/2019/4134937.
88. Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med. 2001;344:1343–50. doi:10.1056/NEJM200105033441801.
89. Colditz GA, Taylor P. R. Prevention trials: their place in how we understand the value of prevention strategies. Annu Rev Public Health. 2010;31:105–20. doi:10.1146/annurev.publhealth.121208.131051.

90. Strasser R, Kam SM, Regalado SM. Rural Health Care Access and Policy in Developing Countries. Annu Rev Public Health. 2016;37:395–412. doi:10.1146/annurev-publhealth-032315-021507.
91. Anyamele OD. Urban and rural differences across countries in child mortality in sub-Saharan Africa. J Health Care Poor Underserved. 2009;20:90–8. doi:10.1353/hpu.0.0199.
92. Mendelsohn AS. Empowering patients, empowering clinicians: How the lessons of HIV can inform chronic disease management across the primary healthcare system. South Afr J HIV Med. 2017;18:692. doi:10.4102/sajhivmed.v18i1.692.
93. Mehring M, Donnachie E, Bonke FC, Werner C, Schneider A. Disease management programs for patients with type 2 diabetes mellitus in Germany: a longitudinal population-based descriptive study. Diabetol Metab Syndr. 2017;9:37. doi:10.1186/s13098-017-0236-y.
94. Stock S, Drabik A, Büscher G, Graf C, Ullrich W, Gerber A, Lauterbach KW, Lüngen M. German diabetes management programs improve quality of care and curb costs. Health Aff (Millwood). 2010;29:2197–205. doi:10.1377/hlthaff.2009.0799.
95. Owolabi MO, Yaria JO, Daivadanam M, Makanjuola AI, Parker G, Oldenburg B, Vedanthan R, Norris S, Oguntoye AR, Osundina MA, Herasme O, Lakoh S, Ogunjimi LO, Abraham SE, Olowoyo P, Jenkins C, Feng W, Bayona H, Mohan S, Joshi R, Webster R, Kengne AP, Trofor A, Lotrean LM, Praveen D, Zafra-Tanaka JH, Lazo-Porras M, Bobrow K, Riddell MA, Makrilakis K, Manios Y, Ovbiagele B, COUNCIL Initiative. Gaps in Guidelines for the Management of Diabetes in Low- and Middle-Income Versus High-Income Countries-A Systematic Review. Diabetes Care. 2018;41:1097–105. doi:10.2337/dc17-1795.
96. Haas L, Maryniuk M, Beck J, Cox CE, Duker P, Edwards L, Fisher EB, Hanson L, Kent D, Kolb L, McLaughlin S, Orzeck E, Piette JD, Rhinehart AS, Rothman R, Sklaroff S, Tomky D, Youssef G, 2012 Standards Revision Task Force. National standards for diabetes self-management education and support. Diabetes Care. 2013:100-108. doi:10.2337/dc13-S100.
97. Gómez-Velasco DV, Almeda-Valdes P, Martagón AJ, Galán-Ramírez GA, Aguilar-Salinas CA. Empowerment of patients with type 2 diabetes: current perspectives. Diabetes Metab Syndr Obes. 2019;12:1311–21. doi:10.2147/DMSO.S174910.
98. Laurant M, Harmsen M, Wollersheim H, Grol R, Faber M, Sibbald B. The impact of nonphysician clinicians: do they improve the quality and cost-effectiveness of health care services? Med Care Res Rev. 2009;66:36–89. doi:10.1177/1077558709346277.

99. Baker E, Fatoye F. Clinical and cost effectiveness of nurse-led self-management interventions for patients with copd in primary care: A systematic review. Int J Nurs Stud. 2017:125-138. doi:10.1016/j.ijnurstu.2017.03.010.

100. Daly B, Tian CJL, Scragg RKR. Effect of nurse-led randomised control trials on cardiovascular risk factors and HbA1c in diabetes patients: A meta-analysis. Diabetes Res Clin Pract. 2017;131:187–99. doi:10.1016/j.diabres.2017.07.019.

101. Carrington MJ, Jennings GL, Harris M, Nelson M, Schlaich M, Stocks NP, Burrell, LM, Amerena J, de Looze FJ, Swemmer CH, Kurstjens NP, Stewart S. Impact of nurse-mediated management on achieving blood pressure goal levels in primary care: Insights from the Valsartan Intensified Primary carE Reduction of Blood Pressure Study. Eur J Cardiovasc Nurs. 2016;15:409–16. doi:10.1177/1474515115591901.

102. Shaw RJ, McDuffie JR, Hendrix CC, Edie A, Lindsey-Davis L, Nagi A, Kosinski AS, Williams JW Jr. Effects of nurse-managed protocols in the outpatient management of adults with chronic conditions: a systematic review and meta-analysis. Ann Intern Med. 2014;161:113–21. doi:10.7326/M13-2567.

103. Checkley W, Ghannem H, Irazola V, Kimaiyo S, Levitt NS, Miranda JJ, Niessen L, Prabhakaran D, Rabadán-Diehl C, Ramirez-Zea M, Rubinstein A, Sigamani A, Smith R, Tandon N, Wu Y, Xavier D, Yan LL, GRAND South Network, UnitedHealth Group/National Heart, Lung, and Blood Institute Centers of Excellence. Management of NCD in low- and middle-income countries. Glob Heart. 2014;9:431–43. doi:10.1016/j.gheart.2014.11.003.

104. Carrington MJ, Zimmet P. Nurse health and lifestyle modification versus standard care in 40 to 70 year old regional adults: study protocol of the Management to Optimise Diabetes and mEtabolic syndrome Risk reduction via Nurse-led intervention (MODERN) randomized controlled trial. BMC Health Serv Res. 2017;17:813. doi:10.1186/s12913-017-2769-z.

105. Haider R, Sudini L, Chow CK, Cheung NW. Mobile phone text messaging in improving glycaemic control for patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes research and clinical practice. 2019;150:27–37. doi:10.1016/j.diabres.2019.02.022.

106. The Mobile Economy. The Mobile Economy Sub-Saharan Africa 2019. https://www.gsma.com/mobileeconomy/sub-saharan-africa/. Accessed 31 Aug 2020.

107. Lee JY, Chan CKY, Chua SS, Paraidathathu T, Lee KK, Tan CSS, Nasir N, Lee SWH. Using telemedicine to support care for people with type 2 diabetes mellitus:

a qualitative analysis of patients' perspectives. BMJ Open. 2019;9:e026575. doi:10.1136/bmjopen-2018-026575.

108. Tchero H, Kangambega P, Briatte C, Brunet-Houdard S, Retali GR, Rusch E. Clinical Effectiveness of Telemedicine in Diabetes Mellitus: A Meta-Analysis of 42 Randomized Controlled Trials. Telemed J E Health. 2019;25:569–83. doi:10.1089/tmj.2018.0128.

109. Federal Ministry for Economic Cooperation and Development. Digital Health Ecosystem for African countries.

110. Working Group on Digital Health - Broadband Commission for Sustainable Development. The Promise of Digital Health: Addressing Non-communicable Diseases to Accelerate Universal Health Coverage in LMICs.

111. Rodriguez T. Telemedicine for Diabetes Management During the COVID-19 Pandemic and Beyond - Endocrinology Advisor. 2020. https://www.endocrinologyadvisor.com/home/topics/diabetes/telemedicine-for-diabetes-management-update-and-interviews/. Accessed 7 Aug 2020.

112. Tchero H, Kangambega P, Briatte C, Brunet-Houdard S, Retali GR, Rusch E. Clinical Effectiveness of Telemedicine in Diabetes Mellitus: A Meta-Analysis of 42 Randomized Controlled Trials. Telemed J E Health. 2019;25:569–83. doi:10.1089/tmj.2018.0128.

113. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. Biomark Insights. 2016;11:95–104. doi:10.4137/BMI.S38440.

114. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus Abbreviated Report of a WHO Consultation. Geneva: WHO; 2011.

115. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–15. doi:10.1056/NEJMoa0707193.

116. Butalia S, Gutierrez L, Lodha A, Aitken E, Zakariasen A, Donovan L. Short- and long-term outcomes of metformin compared with insulin alone in pregnancy: a systematic review and meta-analysis. Diabet Med. 2017;1:27–36. doi:10.1111/dme.13150.

117. Schäfer-Graf UM, Gembruch U, Kainer F, Groten T, Hummel S, Hösli I, Grieshop M, Kaltheuner M, Bührer C, Kautzky-Willer A, Laubner K, Bancher-Todesca D. Gestational Diabetes Mellitus (GDM) - Diagnosis, Treatment and Follow-Up. Guideline of the DDG and DGGG (S3 Level, AWMF Registry Number

057/008, February 2018). Geburtshilfe Frauenheilkd. 2018;78:1219–31. doi:10.1055/a-0659-2596.

118. Fuchs S, Henschke C, Blümel M, Busse R. Disease management programs for type 2 diabetes in Germany: a systematic literature review evaluating effectiveness. Dtsch Arztebl Int. 2014;111:453–63. doi:10.3238/arztebl.2014.0453.

119. Lange S, Sauerland S, Lauterberg J, Windeler J. The Range and Scientific Value of Randomized Trials. Dtsch Arztebl Int. 2017;114:635–40. doi:10.3238/arztebl.2017.0635.

120. Matshego L. How Many Languages of Africa Are There? https://africa.com/many-african-languages/. Accessed 3 Aug 2020.

121. World Health Organization (WHO). WHO | Pan African Clinical Trial Registry (PACTR). https://www.who.int/ictrp/network/pactr/en/. Accessed 4 Aug 2020.

122. World Health Organization (WHO). Classification of diabetes mellitus. Geneva 2019. https://www.who.int/publications/i/item/classification-of-diabetes-mellitus. Accessed 6 Sep 2020.

123. Zoungas S, Woodward M, Li Q, Cooper ME, Hamet P, Harrap S, Heller S, Marre M, Patel A, Poulter N, Williams B, Chalmers J, ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia. 2014;57:2465–74. doi:10.1007/s00125-014-3369-7.

124. Zhang Y, Dall TM, Mann SE, Chen Y, Martin J, Moore V, Baldwin A, Reidel VA, Quick WW. The economic costs of undiagnosed diabetes. Popul Health Manag. 2009;12:95–101. doi:10.1089/pop.2009.12202.

Theses

1. This systematic review implicates an increased awareness of diabetes in African countries during the last years, as the majority of the included RCTs had been published within the last 5 years.
2. The number of RCTs, which improve detection, treatment, adherence and prognosis of African patients with diabetic illnesses is still low. A total of 50 RCTs with all together 9331 patients were included.
3. Apparently, there seems to be a lack of evidence of Eastern and Central Africa. The included RCTs were set in 15 of the 54 African countries with a focus on the Northern and Southern African region, especially Egypt and South Africa.
4. The broad majority of included RCTs were conducted in urban settings, stating an underrepresentation of RCTs in rural settings.
5. It is necessary to integrate the patient in disease-associated decisions. Interventions to strengthen the empowerment on the basis of an improved knowledge, motivation and capacity to take control of their disease seem to be very promising.
6. A strong collaboration of doctors and nurses is necessary to improve diabetes care. Moreover, the tasks of the nurses could be redefined and expanded in countries with a comparably few physicians as a measure for improvement of detection, treatment, adherence and prognosis of patients with diabetic illnesses.
7. In times of growing digitalization, information and communication technologies might also have great potential to improve the accessibility of the African population to high quality health care services, where the human resources are limited.
8. An improvement in the prognosis of patients with diabetes in African countries requires the implementation of locally adapted guidelines aiming to lower the rate of undiagnosed diabetes, leading to earlier detection and effective actions to prevent or delay the onset of diabetes and its consecutive complications.

Supplementary Material

Search strategies

Medline (Ovid)

Search on 19.11.2018, 1470 references

Nr.	Searches
1.	exp Diabetes Mellitus/
2.	Diabetes.tw
3.	**or/1-2**
4.	Africa.tw
5.	Exp Africa/
6.	Algeria$.tw or exp Algeria/
7.	Angol$.tw or exp Angola/
8.	Benin$.tw or exp Benin/
9.	Botswan$.tw or exp Botswana/
10.	Burkina Faso.tw or exp Burkina Faso/
11.	Burund$.tw or exp Burundi/
12.	Cameroon$.tw or exp Cameroon/
13.	Cape Verde.tw or exp Cape Verde/
14.	Central African Republic$.tw or exp Central African Republic/
15.	Chad$.tw or exp Chad/
16.	Comoros$.tw or exp Comoros/
17.	Cote d'Ivoire.tw or exp Cote d'Ivoire/
18.	Democratic Republic of Congo.tw or exp Democratic Republic of Congo
19.	Djibout$.tw or exp Djibouti/
20.	Egypt$.tw or exp Egypt/
21.	Equatorial Guinea$.tw or exp Equatorial Guinea/
22.	Eritrea$.tw or exp Eritrea/
23.	Ethiop$.tw or exp Ethiopia/
24.	Gabon$.tw or exp Gabon/
25.	Gambia$.tw or exp Gambia/
26.	Ghana$.tw or exp Ghana/
27.	Guinea$.tw or exp Guinea/
28.	Guinea-Bissau.tw or exp Guinea-Bissau/
29.	Kenya$.tw or exp Kenya/
30.	Lesoth$.tw or exp Lesotho/
31.	Liberia$.tw or exp Liberia/
32.	Libya$.tw or exp Libya/

Nr.	Searches
33.	Madagascar$.tw or exp Madagascar/
34.	Malawi$.tw or exp Malawi/
35.	Mali.tw or exp Mali/
36.	Mauritania$.tw or exp Mauritania/
37.	Mauritius$.tw or exp Mauritius/
38.	Morocc$.tw or exp Morocco/
39.	Mozambique$.tw or exp Mozambique/
40.	Namibia$.tw or exp Namibia/
41.	Niger.tw or exp Niger/
42.	Nigeria$.tw or exp Nigeria/
43.	Rwanda$.tw or exp Rwanda/
44.	(Sao Tome and Principe).tw
45.	Senegal$.tw or exp Senegal/
46.	Seychell$.tw
47.	Sierra Leone.tw or exp Sierra Leone/
48.	Somalia$.tw or exp Somalia/
49.	South Africa$.tw or exp South Africa.de
50.	South Sudan.tw or exp South Sudan/
51.	Sudan$.tw or exp Sudan/
52.	Swaziland$.tw or exp Swaziland/
53.	Tanzania$.tw or exp Tanzania/
54.	Togo$.tw or exp Togo/
55.	Tunisia$.tw or exp Tunisia/
56.	Uganda$.tw or exp Uganda/
57.	Zambia$.tw or exp Zambia/
58.	Zimbabwe$.tw or exp Zimbabwe/
59.	Somaliland$.tw or exp Somaliland/
60.	Sahrawi Arab Democratic Republic.tw.
61.	or/4-60
62.	3 and 61
63.	randomized controlled trial.pt.
64.	controlled clinical trial.pt.
65.	randomized.ab.
66.	placebo.ab.
67.	randomly.ab.
68.	trial.ab.
69.	groups.ab.
70.	or/63-69
71.	exp animals/ not humans.sh.

Nr.	Searches
72.	70 not 71
73.	62 and 72

CENTRAL

Search on 14.01.2019, 439 results

1	Africa, explode all trees
2	Algeria* or Angol* or Benin* or Botswan*
3	(Burkina Faso) or Burund* or Cameroon* or (Cape Verde) or (Central African Republic)
4	Chad* or Comoros* or Cote d'Ivoire or Congo*
5	Djibout* or Egypt* or (Equatorial Guinea*) or Eritrea*
6	Ethiop* or Gabon* or Gambia* or Ghana* or Guinea* or Guinea-Bissau
7	Kenya* or Lesoth* or Liberia* or Libya* or Madagascar* or Malawi*
8	Mali* or Mauritania* or Mauritius* or Morocc* or Mozambique* or Namibia* or Niger*
9	Nigeria* or Rwanda* or (Sao Tome and Principe) or Senegal* or Seychell*
10	Sierra Leone or Somalia* or (South Africa) or (South Sudan*) or Sudan* or Swasiland
11	Tanzania* or Togo* or Tunisia* or Uganda* or Zambia* or Zimbabwe* or Somaliland or (Sahrawi Arab Democratic Republic)
12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor Diabetes, this term only
14	MESH descriptor Diabetes mellitus, explode all trees
15	Diabetes near 3 gestation*
16	Latent autoimmune diabetes in adults
17	Prediabetes
18	Insulin resistan*
19	Hyperglycaemia or hypoglycaemia
20	HBA1C
21	Diabet* near 3 (angiopath* or foot orfeet or retinopath*)
22	Diabet* near 3 (cardiomyopathy* or coma or ketoacido* or neuropath*)
23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
32	#12 and #23

CINAHL

Search on 07.01.2020, 19 results

(Africa$ or Africa$ or Algeria$ or Angol$ or Benin$ or Botswan$ or (Burkina Faso) or Burund$ or Cameroon$ or (Cape Verde) or (Central African Republic) or Chad$ or Comoros$ or Cote d'Ivoire or Congo$ Djibout$ or Egypt$ or (Equatorial Guinea$) or Eritrea$ or Ethiop$ or Gabon$ or Gambia$ or Ghana$ or Guinea$ or Guinea-Bissau or Kenya$ or Lesoth$ or Liberia$ or Libya$ or Madagascar$ or Malawi$ or Mali$ or Mauritania$ or Mauritius$ or Morocc$ or Mozambique$ or Namibia$ or Niger$ or Nigeria$ or Rwanda$ or (Sao Tome and Principe) or Senegal$ or Seychell$ or Sierra Leone or Somalia$ or (South Africa) or (South Sudan$) or Sudan$ or Swasiland or Tanzania$ or Togo$ or Tunisia$ or Uganda$ or Zambia$ or Zimbabwe$ or Somaliland or (Sahrawi Arab Democratic Republic)) in Abstract
AND
diabetes in Abstract
AND
randomized or rct or randomized in Abstract
AND
In English
AND
Peer-reviewed
And
Humans

International Clinical Trials Registry Platform

Search on 9.-10.10.2019

http://apps.who.int/trialsearch/AdvSearch.aspx

1. Africa or African in the Title and diabetes or diabetic or HbA1c in the condition, Recruitment status: all**:** 90 records for 90 trials (9.10.2019)
2. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Algeria or Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Central African Republic or Chad or Congo or Cite D'ivoire: 96 record for 63 trials
3. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all

Countries of recruitment: Democratic Republic of Congo or Djibouti or Egypt or Equatorial Guinea or Eritrea or Ethiopia: 292 records for 159 trials

4. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Gabon or Gambia or Ghana or Guinea or Guinea-Bissau or Kenya or Lesotho or Liberia or Lybia: 22 records for 22 trials
5. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Madagascar or Malawi or Mali or Mauritania or Mauritius or Morocco or Mozambique: 96 records for 34 trials
6. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Nigeria: 13 records for 13 trials
7. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Namibia or Niger or Rwanda or (Sao Tome and Principe) or Senegal or Seychelles or Sierra Leone or Somalia or South Sudan or Sudan or Swaziland:
   11 records for 11 trials
8. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: South Africa: 1528 records for 429 trials:
9. diabetes or diabetic or HbA1c in the condition
   Recruitment status: all
   Countries of recruitment: Togo or Tunesia or Ujanda or Zambia or Zimbabwe: 129 records for 50 trials

List of included studies

Abaza 2017

Abaza H, Marschollek M. SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt. BMC Public Health. 2017;17:962. doi:10.1186/s12889-017-4973-5.

Abaza H, Marschollek M, Schulze M. SMS Education for the Promotion of Diabetes Self-Management in Low & Middle Income Countries: A Randomized Controlled Trial in EgyptTrial in Egypt. Stud Health Technol Inform. 2017;245:1209. doi:10.3233/978-1-61499-830-3-1209.

Abdulrhman 2013

Abdulrhman MM, El-Hefnawy MH, Aly RH, Shatla RH, Mamdouh RM, Mahmoud DM, and Mohamed MS. Metabolic effects of honey in Type 1 Diabetes Mellitus: A randomized crossover Pilot Study. J Med Food. 2013:66–72. doi:10.1089/jmf.2012.0108.

Adibe 2013

Adibe MO, Aguwa CN, Ukwe CV. Cost-Utility Analysis of Pharmaceutical Care Intervention Versus Usual Care in Management of Nigerian Patients with Type 2 Diabetes. Value in Health Regional Issues. 2013;2:189–98. doi:10.1016/j.vhri.2013.06.009.

Adibe MO, Ukwe CV, Aguwa CN. The Impact of Pharmaceutical Care Intervention on the Quality of Life of Nigerian Patients Receiving Treatment for Type 2 Diabetes. Value in Health Regional Issues. 2013;2:240–7. doi:10.1016/j.vhri.2013.06.007.

Adjei 2015

Adjei DN, Agyemang C, Dasah JB, Kuranchie P, Amoah AG. The effect of electronic reminders on risk management among diabetic patients in low resourced settings. Journal of diabetes and its complications. 2015;29:818–21. doi:10.1016/j.jdiacomp.2015.05.008.

Amendezo 2017

Amendezo E, Walker Timothy D, Karamuka V, et al… effects of a lifestyle education program on glycemic control among patients with diabetes at Kigali University Hospital, Rwanda: A randomized controlled trial. Diabetes Res Clin Pract. 2017:129–137.doi:10.1016/j.diabres.2017.02.001.

Anderson 2001

Anderson RA, Roussel AM, Zouari N, Mahjoub S, Matheau JM, Kerkeni A. Potential antioxidant effects of zinc and chromium supplementation in people with type 2 diabetes mellitus. J Am Coll Nutr. 2001:212–8. doi:10.1080/07315724.2001.10719034.

Roussel AM, Kerkeni A, Zouari N, Mahjoub S, Matheau JM, Anderson RA. Antioxidant effects of zinc supplementation in Tunisians with type 2 diabetes mellitus. J Am Coll Nutr. 2003:316–21. doi:10.1080/07315724.2003.10719310.

Anyanwu 2016

Anyanwu AC, Fasanmade OA, Odeniyi IA, Iwuala S, Coker HB, Ohwovoriole AE. Effect of Vitamin D supplementation on glycemic control in Type 2 diabetes subjects in Lagos, Nigeria. Indian J Endocrinol Metab. 2016:189-194. doi:10.4103/2230-8210.176345.

Ashoush 2016

Ashoush S, El-Said M, Fathi H, Abdelnaby M. Identification of metformin poor responders, requiring supplemental insulin, during randomization of metformin versus insulin for the control of gestational diabetes mellitus. J Obstet Gynaecol Res. 2016:640–7.

Asuako 2017

Asuako B, Moses MO, Eghan BA, Sarpong PA. Fasting plasma glucose and lipid profiles of diabetic patients improve with aerobic exercise training. Ghana Med J. 2017:120–7. doi:10.4314/gmj.v51i3.5.

Beyuo 2015

Beyuo T, Obed SA, Adjepong-Yamoah KK, Bugyei KA, Oppong SA, Marfoh K. Metformin versus Insulin in the Management of Pre-Gestational Diabetes Mellitus in Pregnancy and Gestational Diabetes Mellitus at the Korle Bu Teaching Hospital: A Randomized Clinical Trial. Plos one. 2015; 10:e0125712. doi:10.1371/journal.pone.0125712.

Chraibi 2017

Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshmivenkataraman B, Assaad-Khalil SH. An RCT Investigating Patient-Driven Versus Physician-Driven Titration of BIAsp 30 in Patients with Type 2 Diabetes Uncontrolled Using NPH Insulin. Diabetes Ther. 2017:767–80. doi:10.1007/s13300-017-0268-1.

Debussche 2018

Debussche X, Besançon S, Balcou-Debussche M, Ferdynus C, Delisle H, Huiart L, Sidibe AT. Structured peer-led diabetes self-management and support in a low-income country: The ST2EP randomised controlled trial in Mali. Plos one. 2018;13:e0191262. doi:10.1371/journal.pone.0191262.

Distiller 2014

Distiller LA, Nortje H, Wellmann H, Amod A, Lombard L. A 24-week, prospective, randomized, open-label, treat-to-target pilot study of obese type 2 diabetes patients with severe insulin resistance to assess the addition of exenatide on the efficacy of U

500 regular insulin plus metformin. Endocr Pract. 2014:1143-1150. doi:10.4158/EP14067.OR.

Elbarbary 2016

Elbarbary NS. Effectiveness of the low-glucose suspend feature of insulin pump during fasting during Ramadan in type 1 diabetes mellitus. Diabetes Metab Res Rev. 2016;32:623–33. doi:10.1002/dmrr.2781.

Elbarbary 2018

Elbarbary NS, Ismail EAR, El-Naggar AR, Hamouda MH, El-Hamamsy M. The effect of 12 weeks carnosine supplementation on renal functional integrity and oxidative stress in pediatric patients with diabetic nephropathy: a randomized placebo-controlled trial. Pediatric Diabetes. 2018;19:470–7. doi:10.1111/pedi.12564.

Elbarbary 2019

Elbarbary NS, Ismail EAR, Zaki MA, Darwish YW, Ibrahim MZ, El-Hamamsy M. Vitamin B complex supplementation as a homocysteine-lowering therapy for early stage diabetic nephropathy in pediatric patients with type 1 diabetes: A randomized controlled trial. Clin Nutr. 2019:49-56. doi:10.1016/j.clnu.2019.01.006.

El-Haggar 2015

El-Haggar SM, Farrag WF, Kotkata FA. Effect of ketotifen in obese patients with type 2 diabetes mellitus. J Diabetes Complications. 2015;29:427–32. doi:10.1016/j.jdiacomp.2015.01.013.

El-Shamy 2018

El-Shamy FF, El-Kholy SS, Labib M, Kabel AM. Ameliorative potential of acupressure on gestational diabetes mellitus a randomized controlled trial. J Complement Integr Med. 2018:20180011. doi:10.1515/jcim-2018-0011.

EL-Sharkawy 2016

El-Sharkawy HM, Anees MM, van Dyke TE. Propolis Improves Periodontal Status and Glycemic Control in Patients With Type 2 Diabetes Mellitus and Chronic Periodontitis: A Randomized Clinical Trial. J Periodontol. 2016;87:1418–26. doi:10.1902/jop.2016.150694.

El-Sheikh 2019

El-sheikh HM, El-Haggar SM, Elbedewy TA. Comparative study to evaluate the effect of l-carnitine plus glimepiride versus glimepiride alone on insulin resistance in type 2 diabetic patients. Diabetes Metab Syndr. 2019:167–73.

Embaby 2016

Embaby H, Elsayed E, Fawzy M. Insulin Sensitivity nd Plasma Glucose Response to Aerobic Exercise in Pregnant Women at Risk for Gestational Diabetes Mellitus. Ethiop J Health Sci. 2016:409–414. doi:10.4314/ejhs.v26i5.2.

Essien 2017

Essien O, Otu A, Umoh V, Enang O, Hicks JP, Walley J. Intensive Patient Education Improves Glycaemic Control in Diabetes Compared to Conventional Education: A Randomised Controlled Trial in a Nigerian Tertiary Care Hospital. PLoS One. 2017:e0168835.

Fairall 2016

Fairall LR, Folb N, Timmerman V, Lombard C, Steyn K, Bachmann MO, Bateman ED, Lund C, Cornick R, Faris G, Gaziano T, Georgeu-Pepper D, Zwarenstein M, Levitt NS. Educational Outreach with an Integrated Clinical Tool for Nurse-Led Non-communicable Chronic Disease Management in Primary Care in South Africa: A Pragmatic Cluster Randomised Controlled Trial. PLoS Med. 2016;13:e1002178. doi:10.1371/journal.pmed.1002178.

Fayehun 2018

Fayehun AF, Olowookere OO, Ogunbode AM, Adetunji AA, Esan A. Walking prescription of 10 000 steps per day in patients with type 2 diabetes mellitus: a randomised trial in Nigerian general practice. Br J Gen Pract. 2018:e139-e145. doi:10.3399/bjgp18X694613.

Ghoneim 2013

Ghoneim EM, Abd El Ghany AA. Behavior of intraocular pressure after intravitreal injection of triamcinolone acetonide among Egyptians. Ophthalmol Ther. 2013;2:121–30. doi:10.1007/s40123-013-0017-0.

Hailu 2018

Hailu FB, Hjortdahl P, Moen A. Nurse-Led Diabetes Self-Management Education Improves Clinical Parameters in Ethiopia. Front Public Health. 2018:302. doi:10.3389/fpubh.2018.00302.

Ibrahim 2014

Ibrahim MI, Hamdy A, Shafik A, Taha S, Anwar M, Faris M. The role of adding metformin in insulin-resistant diabetic pregnant women: a randomized controlled trial. Arch Gynecol Obstet. 2014;289:959–65. doi:10.1007/s00404-013-3090-7.

Krawinkel 2018

Krawinkel MB, Ludwig C, Swai ME, Yang RY, Chun KP, Habicht SD. Bitter gourd reduces elevated fasting plasma glucose levels in an intervention study among prediabetics in Tanzania. J Ethnopharmacol. 2018:1-7. doi:10.1016/j.jep.2018.01.016.

Labhardt 2011

Labhardt ND, Balo JR, Ndam M, Manga E, Stoll B. Improved retention rates with low-cost interventions in hypertension and diabetes management in a rural African

environment of nurse-led care: a cluster-randomised trial. Trop Med Int Health. 2011;16:1276–84. doi:10.1111/j.1365-3156.2011.02827.x.

Maharaj 2016

Maharaj SS, Nuhu J. M. Rebound exercise: A beneficial adjuvant for sedentary non-insulin-dependent type 2 diabetic individuals in a rural environment. Aust. J. Rural Health. 2016:123–9.

Malek 2015

Malek R, Ajili F, Assaad-Khalil SH, Shinde A, Chen JW, Van den Berg E… Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. Diabetes Metab. 2015;41:223–30. doi:10.1016/j.diabet.2014.11.002.

Mash 2014

Mash RJ, Rhode H, Zwarenstein M, Rollnick S, Lombard C, Steyn K, Levitt N. Effectiveness of a group diabetes education programme in underserved communities in South Africa: pragmatic cluster randomized control trial. Diabet Med. 2014:987-93. doi:10.1111/dme.12475.

Mash R, Kroukamp R, Gaziano T, Levitt N. Cost-effectiveness of a diabetes group education program delivered by health promoters with a guiding style in underserved communities in Cape Town, South Africa. Patient Educ Couns. 2015;98:622–6. doi:10.1016/j.pec.2015.01.005.

Mohamad 2009

Mohamad RH, Zekry ZK, Al-Mehdar HA, Salama O, El-Shaieb SE, El-Basmy AA, et al. Camel milk as an adjuvant therapy for the treatment of type 1 diabetes: verification of a traditional ethnomedical practice. J Med Food. 2009:461–5. doi:10.1089/jmf.2008.0009.

Muchiri 2016

Muchiri JW, Gericke GJ, Rheeder P. Effect of a nutrition education programme on clinical status and dietary behaviours of adults with type 2 diabetes in a resourcelimited setting in South Africa: a randomised controlled trial. Public Health Nutr. 2016:142–55. doi:10.1017/S1368980015000956.

Nteleki 2015

Nteleki B, Abrahamse H, Houreld NN. Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers. Semin Vasc Surg. 2015;28:172–83. doi:10.1053/j.semvascsurg.2016.02.001.

Rashad 2017

Rashad H, Metwally FM, Ezzat SM, Salama MM, Hasheesh A, Abdel Motaal A. Randomized double-blinded pilot clinical study of the antidiabetic activity of Balanites aegyptiaca and UPLC-ESI-MS/MS identification of its metabolites. Pharm Biol. 2017:1954–61.

Saeed 2013

Saeed AM. Combined vitrectomy and intravitreal injection versus combined laser and injection for treatment of intractable diffuse diabetic macular edema. Clin Ophthalmol. 2013:283-297. doi:10.2147/OPTH.S37781.

Salem 2010

Salem MA, Aboelasrar MA, Elbarbary NS, Elhilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetol Metab Syndr. 2010:47. doi:10.1186/1758-5996-2-47.

Sodipo 2017

Sodipo OO, Adedokun A, Olusola AA. Effect of self-monitoring of blood glucose on glycaemic outcome among type 2 diabetic patients. S Afr Fam Pract. 2017:208–13. doi:10.1080/20786190.2017.1340250.

Somanah 2012

Somanah J, Aruoma OI, Gunness TK, Kowelssur S, Dambala V, Murad F, et al. Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. Prev Med. 2012:90–7. doi:10.1016/j.ypmed.2012.01.014.

Steyn 2013

Steyn K, Lombard C, Gwebushe N, Fourie JM, Everett-Murphy K, Zwarenstein M, Levitt NS. Implementation of national guidelines, incorporated within structured diabetes and hypertension records at primary level care in Cape Town, South Africa: a randomised controlled trial. Glob Health Action. 2013:20796. doi:10.3402/gha.v6i0.20796..

Takenga 2014

Takenga C, Berndt RD, Musongya O, Kitero J, Molo K, Kazingufu B, Meni M, Vikandy M, Takenga H. An ICT-Based Diabetes Management System Tested for Health Care Delivery in the African Context. Int J Telemed Appl. 2014:437307. doi:10.1155/2014/437307.

Tawfik 2016

Tawfik MY, Mohamed RA. The impact of communicating cardiovascular risk in type 2 diabetics on patient risk perception, diabetes self-care, glycosylated hemoglobin, and cardiovascular risk. J Public Health. 2016:153–164. doi:10.1007/s10389-016-0710-2.

Tsobgny-Tsague 2018

Tsobgny-Tsague NF, Lontchi-Yimagou E, Nana ARN, Tankeu AT, Katte JC, Dehayem MY, Bengondo CM, Sobngwi E. Effects of nonsurgical periodontal treatment on glycated haemoglobin on type 2 diabetes patients (PARODIA 1 study): a randomized controlled trial in a sub-Saharan Africa population. BMC Oral Health. 2018:28. doi:10.1186/s12903-018-0479-5.

Utz 2018

Utz B, Assarag B, Smekens T, Ennassiri H., Lektal T. El Ansari N. et al. Detection and initial management of gestational diabetes through primary health care services in Morocco: An effectiveness-implementation trial. Plos one. 2018:e0209322. doi:10.1371/journal.pone.0209322.

van der Hoogt 2017

van der Hoogt M, van Dyk JC, Dolman RC, Pieters M. Protein and fat meal content increase insulin requirement in children with type 1 diabetes – Role of duration of diabetes. J Clin Transl Endocrinol. 2017:15–21. doi:10.1016/j.jcte.2017.10.002.

van Rooijen 2004

van Rooijen AJ, Rheeder P, Eales CJ, Becker PJ. Effect of exercise versus relaxation on haemoglobin A1C in Black females with type 2 diabetes mellitus. Q J Med. 2004;97:343–51. doi:10.1093/qjmed/hch061.

Webb 2015

Webb EM, Rheeder P, Van Zyl DG. Diabetes care and complications in primary care in the Tshwane district of South Africa. Prim Care Diabetes. 2015:147–54. doi:10.1016/j.pcd.2014.05.002.

Webb EM, Rheeder P, Roux P. Screening in Primary Care for Diabetic Retinopathy, Maculopathy and Visual Loss in South Africa. Ophthalmologica. 2016;235:141–9. doi:10.1159/000443972.

Webb EM, Rheeder P. A cluster-randomized trial to estimate the effect of mobile screening and treatment feedback on HbA1c and diabetes-related complications in Tshwane primary health care clinics, South Africa. Prim Care Diabetes. 2017:546-554. doi:10.1016/j.pcd.2017.05.010.

Yakoot 2019

Yakoot M, Abdelatif M, Helmy S. Efficacy of a new local limb salvage treatment for limb-threatening diabetic foot wounds - a randomized controlled study. Diabetes Metab Syndr Obes. 2019;12:1659–65. doi:10.2147/DMSO.S210680.

Yan 2014

Yan H, Prista A, Ranadive SM, Damasceno A, Caupers P, Kanaley JA, Fernhall B. Effect of Aerobic Training on Glucose Control and Blood Pressure in T2DDM East African Males. ISRN Endocrinol. 2014:864897. doi:10.1155/2014/864897.

Characteristics of included studies

Table 2: Overview on characteristics of included studies

Study name Design	**Setting**	**Population**		**Intervention vs. Control**	**Outcomes**	**Results**
	Place, environmental/ health care setting (primary vs. other care) and time	Inclusion / Exclusion criteria	Randomized participants, gender, age, type and length of diabetes, diagnostic criteria, BMI, co-morbidities	Description (n=), Duration	primary and secondary	Longest follow-up period with intervention effects: Intervention (IG) vs. Control (CG), intervention effect (95%-CI, p-value)
Abaza 2017 [49, 50] RCT	Egypt, urban, tertiary care, 03/2015 - 05/2013	DM2, mobile phone, capable to read SMS or live with someone who could read	n=73 gender: 56 % females age (yrs): 51.5±9.2 HbA1c (%): 9.7±2.7 random Blood glucose (mg/dl): 88.1±16 the majority had had diabetes for > 1 yr hypertension: 41.1 % on insulin: 19.2 % suffer diabetes complication: 80.8 %	MUST diabetes awareness program paper-based educations material IG (n=34): daily messages and weekly reminders addressing various diabetes care categories vs. CG (n=39): paper-based educations material Duration: 12 wks.	Primary: change in Hba1C Secondary: Random blood glucose levels, body weight, adherence of treatment and medication, diabetes self-efficacy and knowledge, rate of hospital/ER visits, frequency of measurements, regular exercise, patients confidence in healthcare provider and satisfaction, healthcare provider's reputation	After 12 weeks: HbA1c (%): • No differences: 8.73 ±1.98 vs. 8.84±2.40 (p=0.838) • MDa: 0.290 (-0.402 to 0.983; p = 0.406) • Benefit for IG: 47 vs. 15 % achieved the targeted 1% drop (p = 0.003) Random blood glucose (mg/dl): • 181±65 vs. 201±87 (p=0.288) Treatment adherence: • SCI: Benefit for IG: 3.42±0.48 vs. 2.52±0.49 (p<0.001) • Morisky: Benefit for IG: 3.76±0.55 vs. 2.74±1.07 (p<0.001) no hospital /ER admission (%): No differences: 100 vs. 89.7 (p=0.118)
Abdulrhman 2013 [38] Cross-over RCT	Egypt, urban, tertiary care,	DM1, age > 2 yrs, HbA1c< 10 % no renal or hepatic impairment, coexisting	n=20 gender:50% females age (yrs): 11.3 ± 4.3 HbA1C (%):7.21 %±	IG to CG (n=10): Honey consumption (0.5 ml/kg body weight per day) vs.	Primary: serum lipids, c-peptide Secondary: anthropometric measures (e.g. BMI),	After 12 weeks: (IG/CG vs. CG/IG): HbA1c (%): • better with CG/IG: 6.7±0.9 vs. 5.9±0.8 (p<0.01) • no differences in change in

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
	01/2010 - 10 / 2011	diseases or therapies that may affect body weight or serum lipids	0.76 fasting glucose (mg/dl): 154.5±22.5 duration of diabetes (yrs): 4.7±4.5	CG to IG (n=10): changed after 12 wks and received than honey Duration: 24 wks.	fasting and 2h-postprandial serum glucose, HBA1c, serum lipid profile	period 1: -5.83 ± 13.66 vs. 2.94±8.82 (p=0.105) Fasting serum glucose (mg/dl): • better with CG/IG: 142.7 ±26.6 vs. 116.7±19.4 (p<0.01) • better with IG/CG in period 1-21.51 ± 10.84 vs. -0.08±5.14 (p=0.001)
Adibe 2013 [51, 52] RCT	Nigeria, urban, tertiary care	DM2, age≥ 18 yrs with oral hypoglycemic and / or insulin therapy no pregnancy	n=220 gender: female 58 % age (yrs): 52.6±7.9 duration of diabetes (yrs): 4.7±2.5, 60.5% with diabetes > 5 yrs on insulin: 13.6 % hypertension: 60.5 %	IG (n=110): structured self-care education and training program by pharmacists and nurses vs. CG (n=110): usual / conventional care Duration: 12 months	Primary: incremental cost-utility ratio, net monetary benefit Other: quality of life	After 12 months: Quality of life: • improved QoL: 0.86 ± 0.12 vs. 0.64 ± 0.10 (p=0.0001) improved single attributes except "hearing" functioning of the patients Costs: • benefit of $0.7625±0.15 vs. $0.6425± 0.15 QALY per patient per year (MD: $ 0.12 (0.07to0.16) • incremental cost-utility ratio of $571 per QALY gained
Adjei 2015 [75] RCT	Ghana, urban	DM	n=200 gender: 64.5% female age (yrs): < 50 yrs: 63 % > 50 yrs: 37 % fasting glucose (mmol/l): 10.4±3.8	IG: (n=100): electronical reminder for clinical appointments of patients + alert system for abnormal laboratory results vs. CG: (n=100): usual diabetes care, paper based method Duration: 6 months	Primary: Compliance with appointment dates Other: metabolic risk factors (SBP, DBP, pulse rate, FBG), BMI	After 6 months: Adherence to appointment schedules (%) • Benefit for IG: 97.8 vs. 89.4, p=0.010 FBG (mmol/l): • Benefit for IG: 8.04±2.14 vs. 8.85±2.63; MD 0.4 (-0.593 to -0.365, p=0.022)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
Amendezo 2017 [59] RCT	Rwanda, urban, tertiary care	DM2>3mth, age>21yrs no pregnant or pat. with severe co-morbid illnesses.	n=251 gender: 69.3% females age (yrs): 50.9 (±10.9) HbA1c (%): 8.98 (8.6-9.3) fasting glucose (mmol/L): 8.97 BMI (kg/m²): 27.9 (27.0-28.5) duration of diabetes : <10 yrs 73.7%, >10yrs: 16.3%	IG (n=115): standard of care plus monthly lifestyle education sessions of 45 min duration vs. CG (n=108): standard care Duration: 12 months	primary: difference in HbA1c secondary: fasting glucose, systolic and diastolic blood pressure, BMI	after 12 months: HbA1c (%): • Benefit for IG with median reductions by 1.70 (-2.09 to-1.31) vs. 0.52 (-0.95 to -0.10); MD: -0.72 (-1.14 to -0.30; p< 0.001) Fasting glucose (mmol/L): • 6.9 (6.45 to 7.36) vs. 9.02 (8.18 to 9.87) (p<0.001)
Anderson 2001 [28, 65] RCT	Tunesia, urban, other care	DM2 ≥ 5y, age< 65 yrs, fasting glucose > 8 mmol/l and HbA1C > 7,5 % no pregnant or lactating women, receiving trace element supplements in past 3 months, with gastric or diuretic treatment, acute renal, acute infection or recent surgery	n=110 age (yrs): 53.2 ±1.62 HbA1c (%):8.82±0.31 fasting glucose (mmol/l): 11.45±0.08 BMI (kg/m²): 29.15±0.15 duration of diabetes (months): 73.6±6.3	IG 1 (n=27): 30 mg Zinc /d vs. IG 2 (n=27): 400 µg Chromium/d vs. IG 3 (n=27): 30 mg Zinc + 400 µg Chromium /d vs. CG (n=29): placebo Duration: 6 months	Not specified: HbA1C, fasting glucose plasma concentrations of zinc, copper, selenium, urinary chromium and zinc, Plasma thiobarbituric acid reactive substances, copper-zinc-superoxid dismutase, selenium - glutathione peroxidase	Change over 6 months: HbA1c (%): • 7.7±0.3 vs. 7.4±0.26 vs. 8.1±0.3 • CG: not reported
Anyanwu 2016 [53] RCT .	Nigeria, urban, other care	DM2, age 35-65 yrs on oral antidiabetics with vitamin D deficiency and poor glycemic control (HbA1c > 6.5 %) no patients on insulin, pregnancy, renal insufficiency, chronic	n=42 gender: 57.6 % female age (yrs): 51.8±2.05 HbA1c (%): 7.88 fasting glucose (mg/dl): 152.8±56.5	IG (n=21): Vitamin D3 supplements (3000 IU daily) vs. CG(n=21): placebo Duration: 12 weeks	Primary: HbA1c Other: fasting glucose, levels of serum Vitamin D, calcium, albumin, phosphate, creatinine, and alanine transaminase	Changes over 12 wks: HbA1c (%): • MD (IG vs. CG): -0.66 (-0.161 to 0.29) vs 0.38 (-0.08 to 0.84); • MD: -1.04 (-2.09 to 0.01) • change from poor glycemic control (HbA1c>6.5 %) to normal HbA1c (%): benefit for IF: 33.3 vs. -9.1 (p<0.05)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		liver disease or alanine transferase > 5 times upper reference limit, tuberculosis, diarrheal, or malabsorption state				fasting glucose (mg/dl): • 137.2±33.6 vs. 154±67.5 patient adherence (tablet counts, %): 62.2 vs. 59.9
Ashoush 2016 [43] RCT	Egypt, urban, tertiary care, 01/2014-11/2014	mothers with 26–32-week GDM (oral 2-h 75 G glucose tolerance test) singleton pregnancies, failure of satisfactory glycemic control despite adequate diet and exercise for ≥ 1 wk no fetal anomalies on ultrasonography, other pregnancy complications, known intolerance to metformin or risk factors for lactic acidosis	n=95 gender: 100% female age (yrs): 31.85±3 HbA1c (%): 5.75 ± 0.55 75g OGTT(mg/dl) • fasting: 106.05±4.6 • 1h:310.25±11.6 • 2h:176.65±9.4 BMI (kg/m²): 31.2±1.4	IG (n = 47): metformin (initial total dose 1000 mg/d with meals, increase by 500 or 850 mg every 1 or 2 wks toward target or up to a maximum dose of 2500 mg/d until delivery, addition of insulin if needed vs. CG (n = 48): regular insulin + neutral protamine Hagedorn (3:7), starting dose of 0.7 units /kg / day, adjusted to achieve adequate glycemic control at increments of 1 unit/10 mg glucose higher than the desired cut-off, short action insulin whenever needed	primary: successful maternal glycemic control Secondary: maternal BMI, glycemic control parameters, maternal weight gained during pregnancy, side effects to metformin, mode of delivery, gestational age at delivery, neonatal birthweight, macrosomia, neonatal hypoglycemia, neonatal death, congenital anomalies, admission to neonatal intensive care unit	fasting glucose during treatment (mg/dl): • during the last wk: 78±3.1 vs. 79.9±3.7 (p=0.008) • during the last 2 wks: 78.9±3.5 vs. 80.8±4.7 (p=0.029) maternal hypoglycaemia (%): 6.25 vs. 12.5 (p=0.254) neonatal hypoglycaemia (%): 12.8 vs. 14.6 (p= Maternal weight gain (Kg): 4.4 ± 0.6 vs. 5.1 ± 0.8 (p=0.001) neonatal congenital anomalies (%): 2.1 vs. 2.1 p= 0.747 headache (%): 27.3 (metformin+insulin) vs. 5.6 (metformin monotherapy) vs. 0% (insulin monotherapy) neonatal ICU admission (%): 8.5 vs. 10.4 (p= 0.514) Costs (Egyptian pounds): 89.66±0.96 vs. 174.9±11.1 (for monotherapies)
Asuako 2017 [76] RCT	Ghana, urban, tertiary care, 08/2015-03/2016	DM, age: 20-68 yrs, ambulant patients, without diabetes complications with < 150 minutes /wk of moderate physical activity no SBP > 140 or DBP> 90 mmHg, bilateral or	n=12 gender: 83% female age (yrs): 83% were btw. 46-55 yrs. fasting glucose (mmol/l):9.33 ± 5.7 BMI	IG (n=7): walking aerobic exercise sessions without treadmills (3/week) vs. CG (n=5):	FPG, Lipid profile, body weight, BMI	Change over 8 wks: FPG (mmol/l): Benefit for IG: 6.27 ± 0.91 vs. 8.00 ± 0.96; MD 1.73 (-1.88 to -1.59; p<0.001)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		unilateral lower or upper limbs amputation, use of insulin pump	(kg/m²):25.4±4.5 type of diabetes: • DM1: 17 % • DM2: 83 % duration of diabetes (yrs): • 1-5 yrs: 25 % • 6-10 yrs: 50 % • 10 yrs: 25 %	only activity of daily living Both continued regular medical/clinical routines Duration: 8 weeks		
Beyuo 2015 [44] RCT	Ghana, urban, other care 01/2013-12/2013	pregnant women with DM2 or GDM (plasma glucose ≥7 mmol/l after an overnight fast or plasma glucose concentration ≥11.1 mmol/l 2 hours after a 75 g glucose drink), 20-30 wks gestation, age: 18-45yrs, eligible for insulin therapy no T1DM, DM2 who have previously failed to achieve glycemic control on metformin monotherapy, allergies to metformin	n= 104 gender: 100% female age (yrs): 33.3±4.6 fasting glucose (mmol/l): 8 2HPG (mmol/l): 10.5 BMI (kg/m²):33.1±6.6 type of diabetes: • GDM:65.9% • DM2: 34.0%	IG (n=52): metformin, starting with 500 mg / d, gradually increase over 2 wks to a maximum dose of 2500 mg/d, insulin was added if necessary vs. CG (n=52): insulin treatment (daily dose 0.3 IU/kg), titrated to achieve the glycemic targets, if necessary admission to the ward and therapy with soluble insulin until delivery	Primary: 2-hour post prandial blood glucose (2HPG) Secondary: FBG, 1HPG, maternal weight gain, pregnancy outcome and feto-neonatal outcomes.	Change from enrollment to delivery: Glycemic control (mmol/l): • FBG: 6.42±0.98 vs. 6.62±1.57 (p=0.928) • 1HPG: 8.95±1.27 vs. 9.62±1.44 (p=0.078) • 2HPG: 7.84±1.43 vs. 9.05±1.89 (p=0.004)
Chraibi 2017 [27] RCT	Egypt, Indonesia, Morocco, Saudi Arabia, Vietnam 05/2012-	DM2 with diagnosis ≥ 12 months, age≥18 , currently being treated with NPH) Insulin for ≥ 3 months + metformin(1000-1500 mg) for ≥ 2 months, HbA1c ≥ 7.0% ≤10%, BMI ≤ 40.0 kg/m^2	n=155 gender: 74.9 % female age (yrs): 54.5 ±10.0 HbA1c (%):8.6 ±0.83 fasting glucose:	IG (n=76): patient driven titration of BIAsp 30 (Biphasic insulin aspart 30) twice daily, 3 clinic visits vs. CG (n=79): physician driven	Primary: change in HbA1c Secondary: proportion of patients achieving the ADA target of HbA1c <7.0 % and the HbA1c target of <6.5 % after 20 weeks, FPG	Change to week 20: HbA1c (%): • Decreased in both arms with non-inferiority between groups: MD -0.23 (-0.54 to 0.08) • More patients in IG reached HbA1c (<7.0%: 40.8 vs. 29.1 %,

Study name Design	**Setting**	**Population**		**Intervention vs. Control**	**Outcomes**	**Results**
	07/2015	no treatment with thiazolidinedione, glucagon-like peptide-1 receptor agonists, pramlintide within the last 3 months , >1 IU/kg NPH insulin daily; previous use of premixed or bolus insulin, > 1 severe hypoglycemic episode during the previous 12 month, impaired kidney or hepatic function, proliferative retinopathy or maculopathy requiring treatment	8.45±3.2 mmol/l, 152.6±56.6 mg/dl BMI (kg/m²):29.05±4.9 duration of diabetes (yrs): 9.5±5.8 African patients: • Egypt: 25.75 % • Morocco: 27.7 % Diabetic nephropathy / neuropathy / retinopathy (%): 3.2 / 16.1 / 3.2 Macroangiopathy: 5.2	titration twice daily, 6 clinic visits Titration in both arms was performed according to the titration protocol and was based on self-measured plasma glucose values, measured twice daily on 3 preceding days, telephone contact whenever deemed necessary Duration: 20 weeks	changes, hypoglycemic episodes,	RR: 1.79 (0.87 to 3.65), <6.5%: 25 vs. 19 %; RR: 1.52 (0.67 to 3.46) • More patients in IG reached target HbA1c levels without severe or minor hypoglycemic episodes (<7.0%: 38 vs. 27.8 %, RR: 1.52 (0.61 to 3.79), <6.5%: 18 vs. 14.8 %; RR 1.13 (0.36 to 3.52)) FPG (mmol/l): • Decreased in both arms • 0.95±0.28 vs. 0.67±0.28; MD: -0.28 (-1.07 to 0.52) Costs • clinic visits to healthcare professionals were less frequent in IG 4.8±0.65 vs. 7.5±1.42 visits/patient mean total number of BG strips used per patient was moderately higher in IG: 37.5 ±15.22 vs.31.3±20.33 per patient Complications: • hypoglycemic episodes: 608.4 vs. 789.2 per 100 patient-years (RR: 0.74 ; 95 %-CI 0.44; 1.23) of exposure • treatment-emergent AEs: 324.2 vs. 302.2 events per 100 patient-years of exposure
Debussche 2018 [54] RCT	Mali, urban, secondary care, 07/2011-02/2013	DM2, age 30-80 yrs, HbA1c ≥ 8 %, no DM1, severe diabetes complications or concomitant illnesses that threatened their functional	n=151 gender: 76.2% female age (yrs): 52.5±9.8 HbA1c (%):10.7±1.8 BMI	IG (n=76): peer-led structured patient education received culturally tailored structured patient education (3 courses of 4 sessions)	Primary: HbA1c Secondary: evolution of HbA1c levels, differences in anthropometric indicators (weight and BMI, waist	Change to 12 months HbA1c (%): Benefit in IG: MD 1.05 % (95 %-CI -1.54;-0.56) vs. -0.15 % (95 %-CI -0.56; 0.26), p = 0.006.

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		or vital prognosis	(kg/m²):28.6±5.4	delivered in the community by five trained peer educators vs. CG (n=75): conventional care alone Duration:1 yr	circumference), SBP, DBP, anti-diabetic and anti-hypertensive treatment, knowledge score, and dietary practices	
Distiller 2014 [55] RCT	South Africa	DM2 for ≥ 1 year with total insulin requirement of >200 U/d for ≥ 3 months, BMI > 30 kg/m^2, HbA1c> 7,5 %, on long-term metformin therapy (1.7–2.5 g/d) no pregnant or with childbearing potential, endocrinopathy, chronic inflammatory or systematic autoimmune disorder, CVD, active carcinoma, chronic illness, renal dysfunction, gastroparesis, no corticosteroids, DPP-4 inhibitors, exenatide, liraglutide, no anticipated change in other concomitant medication or insulin resistence	n=28 gender: 50% female age (yrs): 51.7 (36-71) HbA1c (%): 8.95 (7.6-11.3) BMI (kg/m²): 40.8 (31.2-47)	IG (n=14): 500 U/ml regular Insulin + metformin + exenatide (5 µg orally twice a day for 1 month and titrated to 10 µg) vs. CG (n=14): U500+metformin Duration: 6 months	Primary: HbA1c Secondary: Body weight, insulin dose, hypoglycemia	Change to 6 months: HbA1c (%): Significant improvement in both groups 8.7→7.7(p=0.002) vs. 9.2→7.5 (p=0.0001) With no difference between groups (MD: 0.28; p=0.80) Complications: Mild hypoglycaemia: 5 vs. 2 persons with 20 vs. 5 events (p ≤ 0.001)
Elbarbary 2016 [72] RCT	Egypt, urban, 06/2014-07/2014	DM1, adolescents and adults who wished to fast the month of Ramadan with insulin pump for ≥6 months and attending the whole education session 2 months before fasting and committed to follow-up the	n=73 gender: 68.3% female age (yrs): 15.6±2.7 HbA1c (%): 7.65±0.9 BMI (kg/m²): 24.56±3.5 duration of diabetes	Insulin pump therapy during Ramadan fasting IG (n=25): sensor with low glucose suspension activation vs. CG (n=35):	Primary: hypoglycaemia Other: glucose value, number of 'full fasted days', emergency hospital visit for diabetes-related problem	After 1 months: Glucose value (mg/dl): 152.5±17.3 vs. 141±33.8 (p=0.9) Complications: Number of hypoglycaemic excursions: 3.68±1.62 vs. 6.7±2.1 (p=0.001) Number of hyperglycaemic excursions: 17.0±4.0 vs. 23.0±7.6

Study name Design	**Setting**	**Population**		**Intervention vs. Control**	**Outcomes**	**Results**
		given instructions no diabetic ketoacidosis, episodes of severe hypoglycaemia or symptoms of uncontrolled diabetes in the last 6 months, diabetic microvascular complications or macrovascular disease, pregnant women	(yrs): 5.8±2.9 pat. on pump therapy for 1.73±0.99 yrs	sensor without low glucose suspension activation Duration:1 month		(p=0.001) No severe hypoglycaemic events, no episodes of diabetic ketoacidosis, no hyperglycaemic events associated with ketosis no deaths or device-related SAE
Elbarbary 2018 [73] RCT	Egypt, urban, other care	DM1, age: 9 - 18 yrs, ≥ 5 yrs disease duration, active diabetic nephropathy in the form of microalbuminuria, HbA1c ≤ 8.5 % no infection, renal impairment due to other causes other than diabetes, other diabetic complications, hypersensitivity to carnosine	n=90 gender: 52.3 % female age (yrs): 12.85±3.1 HbA1c (%):7.85±1.95	IG (n=45): 1 g/d carnosine vs. CG (n=45): control/placebo group Patients in both groups received oral ACE-Is captopril 25 mg Duration: 12 wks	Primary: change in tubular damage marker Secondary: urinary albumin excretion (UAE), oxidative stress markers Safety: any AE	After 12 wks: HbA1c (%): • Benefit for IG: 7.4 ±1.3 vs. 8.3±2.4 • change -9.88±7.12 vs. 3.89±2.28 (p=0.005) No adverse reactions were reported
Elbarbary 2019 [71] RCT NCT03594240	Egypt, urban, 03/2017-03/2018	DM1 on insulin therapy with > 5 yrs of disease duration, 12-18 yrs, active nephropathy, HbA1c< 8.5 %, no infections, renal impairment due to other causes than diabetes, other diabetic complications , elevated liver enzymes, hyper-or	n=80 gender:55% female age (yrs): 15.4 ± 1.6 HbA1c (%):7.95±0.5 FBG (mg/dl): 114.5±21.8 duration of diabetes (years): 8.65 ± 2.65	IG (n=40) oral vitamin B complex (B1,B6,B12) once daily CG (n=40): placebo both groups received oral angiotensis-converting-enzyme inhibitors (captopril) duration: 12 weeks	primary: Cystatin C secondary: glycaemic control, urinary albumin excretion, lipid profile	after 12 weeks HbA1c (%): Benefit for IG: 7.5±0.6 vs. 8.0±0.6 FBG (mg/dl): 107.7±14.1 vs. 116.4±17 (p=131)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		hypothyroidism, hypertension, neoplasm, taking any vitamins or food supplements within 1 months before study start				
El-Haggar 2015 [56] RCT	Egypt, urban, other care 01/2013-04/2014	DM2, age: 45-55 yrs, obese (BMI⩾30 kg/m^2), with duration 5-10 yrs, treated with glimepiride alone no Inflammatory disease, severe hepatic or renal disease, epilepsy pregnant/lactating females	n=48 gender: 79 % female age (yrs): 50.1±4.6 HbA1c (%): 7.83±0.87 % fasting glucose (mg/dl): 193±50 BMI (kg/m²): 37.6±4.6 duration of diabetes (yrs): 7.7 ±2.6	IG1 (n=16): glimepiride 3 mg/d + ketotifen 1 mg twice daily vs. IG2 (n=16): glimepiride 3 mg/d + ketotifen 1 mg once daily vs. CG (n=16): glimepiride 3 mg/d alone Duration: 12 weeks	not specified: glycemic markers, metabolic markers, adiponectin, interleukin-6, leukotriene B4, mast cell tryptase, lipid panel, BMI	Changes over 12 weeks: HbA1c (%): • Highest benefit for IG1: 7.1±0.86 vs. 8.2±0.82 vs. 8.7±0.93 FBG (mg/dl): • 147.9±39.3 vs. 199±38 vs. 207.7± 47.6
El-Shamy 2018 [41] RCT	Egypt, urban, other care, 12/2016-05/2017	GDM, age: 20-30 yrs, gestational age: 24-26 wks, BMI ≤ 30 kg/m², singleton live fetus no high risk pregnancy, bad obstretric situations or diseases, smoking, oral sedatives	n=30 gender: 100% female age (yrs): 24.2±2.8 75 g OGTT (mg/dl): • fasting glucose: 129.05±0.,6 • 2h postprandial: 146±1.65 BMI (kg/m²): 27±1.5	IG: (n=15): acupressure + standard antenatal care vs. CG (n=15): standard antenatal care only Duration: 12 weeks	Primary: glycemic control, requirement for insulin, insulin resistance Secondary: neonatal outcomes	Change over 12 wks: 75 g OGTT (mg/dl): Fasting: 116.1±0.1 vs. 118.2 ± 0.7 2h postprandial: 125.3±1.2 vs. 127.3 ± 0.9 Complication (%): 5-min Apgar-Score < 7: 6.7 vs. 6.7 %
El-Sharkawy 2016 [57] RCT NCT027945	Egypt, urban, 06/2014-03/2015	DM2 >5 yrs, >20 teeth, chronic moderate or severe periodontitis with probing depth and clinical attachment level >5 mm, bleeding by probing, on oral hypogylcemic drug	n=50 gender: 34% female age (yrs): 50.5 ± 7.4 (38 to 63) HbA1c (%): 8.66 ±0.73	IG(n=24): scaling and root planning (SRP)+ 400mg oral Propolis once daily CG(n=26) scaling and root planning (SRP)+Placebo	primary: HbA1c secondary: FPG, serum N-(carboxymethyl) lysine, periodontal parameters	after 6 months HbA1c (%) Benefit for IG 7.75± 0.48 vs.8.5±0.73 (p<0.01) FPG(mg/dl) Benefit for IG

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
06		therapy > 6 months, no smoking, use of antibiotics, non steroidal or anti-inflammatory drugs within the last 3 months, periodontal therapy ≤ 1 year, retinopathy grade 3/4, pregnancy, no contraceptive drugs	FPG (mg/dl): 183.5 ±12.547 BMI (kg/m²): 26.9± 3.1 duration of diabetes (yrs): 8.1 ± 3.9 hypertension: 4.5% neuropathy: 1.5% retinopathy: 0.5% nephropathy: 0%	 Duration: 6 months		
El-Sheikh 2019 [58] RCT	Egypt, urban, other care	DM2 on glimepiride alone, age ≥30 yrs no insulin sensitizers, steroids, NSAIDs, warfarin or lipid lowering medications, thyroid hormones, valproic acid or suffered from: acute or chronic inflammatory diseases, end-stage renal disease undergoing dialysis, hypothyroidism epilepsy, pregnant and breast-feeding women	n= 72 gender: 67 % female age (yrs): 50.6±8.7 HbA1c (%):9.76±1 fasting glucose (mg/dl):194.84±20.8 BMI (kg/m²):34.4±5.45	IG (n=38): glimepiride 2 mg twice daily + L-carnitine 1 gm twice daily vs. CG (n=34): glimepiride dose 2 mg twice daily Duration: 6 months	HbA1c, FBG, PPBG, fasting insulin, extracellular part of insulin regulated aminopeptidase, tumor necrosis factor-alpha, visfatin and lipid panel, BMI and homeostasis model assessment of insulin resistance	Change over 6 months: HbA1c (%): Benefit for IG: 7.41±0.5 vs. 9.5±0.78 (p<0.001) FBG (mg/dl): Benefit for IG: 179.6±9.3 vs. 192.41±27.4 (p=0.018)
Embaby 2016 [42] RCT	Egypt, urban, other care, 07/2014-02/2015	at increased risk for GDM due to obesity (BMI ≥ 30 kg/m^2), age:> 25 yrs, 20-24th gestational wks, multigravida, physically active with ≥ 1 of the following 3 characteristics: history of macrosomia, abnormal glucose tolerance during previous pregnancy or first grade relative with DM2	n=40 gender: 100% female age (yrs): 29.2±3.8 fasting glucose (mmol/l): 6-5±0.9 BMI (kg/m²):28.7±1.3	IG: aerobic exercise program (walking on treadmill) three times weekly until the end of 37 wks of gestation + diet control. vs. CG: diet control with usual care given by obstetricians and midwives.	Fasting plasma glucose, Insulin level	Change to 37th week of gestation: FPG (mmol/l) Benefit for IG: 4.26±0.67 vs. 5.07±0.54 (p=0.0001) Fasting insulin (IU/l): Benefit for IG: 10.59±1.10 vs. 12.43±1.44 (p=0.0001)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		no hypertension, GDM, medications that affects insulin secretion, serious pulmonary disease , cardiac, renal impairment and malignancy		Duration: appr. 4 months		
Essien 2017 [77] RCT	Nigeria, urban, tertiary care, 09/2013-05/2014	DM1 or DM2, age: ≥ 18 yrs, HbA1c> 8.5 %, able to engage in moderate exercise, no eye disease that would limit the ability to read	n=118 gender: 60.2 % female age (yrs): 52.7±10.5 HbA1c (%):10.7±1.6 BMI (kg/m²): 28.9±7.5 type of diabetes • DM1: 14.4% • DM2: 85.6%	IG: (n=59): intensive and systematic disease self-management education programme (invitation and encouragement by clinical staff to attend 12 structured teaching sessions) vs. CG (n=59): conventional disease-self-management education Duration: 6 months	Primary outcome: HbA1c no secondary outcomes	After 6 months: HbA1c (%): 8.4 (8 to 8.9) vs. 10.2 (9.8 to 10.7); (MD_a: -1.8 (-2.4 to -1.2; p < 0.0001))
Fairall 2016 [33] Cluster-RCT	South Africa , urban/rural , primary care, 03/2011 – 11 / 2011	age ≥ 18 yrs , clinics providing service for NCD Patients with DM, hypertension, chronic respiratory disease or depression, with self-reported hypoglycaemic (in case of DM)	n= 38 public sector primary care clinics, 4393 patients, n=1842 with DM gender: 73 % female age (yrs):median, IQR): 52 (42-61) vs. 52 (44-62) HbA1c (%):9 (4-17) in DM-pat.: HbA1c≥ 7%: 77% BMI (kg/m²): 30±8	IG (n=2166, 851 with DM): Nurses were trained to use a primary care programme to support and expand nurses`role in NCD care and contains a clinical management tool with enhances prescribing provisions vs. CG (n=2227, 991 with DM): Nurses continued to use the Lung Health	Primary (for DM): treatment intensification (addition or increase in dose of metformin and/or sulphonylurea, insulin, ACE-inhibitor, aspirin, statin	over 14 months HbA1c (%): • <7 %: 41 vs. 38 %; RR 1.08 (0.77 to 1.52; p=0.638) • 7-10 %: 69 vs. 55 %; RR 1.30 (1.16 to 1.47; p<0.001) • >10 %: 71 vs. 73 %; RR 0.97 (0.81 to 1.16; p=0.703) Treatment intensification rates* (%): • 57% vs. 50%, RRa: 1.11; 95 %-CI 0.99-1.26 (p=0.083) *results for patients with DM

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
				and HIV/AIDS approach with usual training Duration: 14 months		
Fayehun 2018 [60] RCT	Nigeria, urban, other care, 06/2014-11/2014	DM2, age 18-64 yrs, Diagnosed ≥ 12 months, non-insulin dependent, on dietary control ± hypoglycemic agents, able to walk without limitations no pregnant women, smokers, prescription of medications that might impair ability to walk	n= 46 gender: 63% female age (yrs): 54±7.7 (33-64) HbA1c (%): 6.6 (5.3-9.0) BMI (kg/m²): 22.4±3.35 duration of diabetes (yrs): <7yrs: 70%, >7 yrs 30 %	IG (n=23): Goal to accumulate 10000 steps per day vs. CG (n=23): normal activity habits Duration: 10 weeks	Primary: HbA1c Secondary: step count	Change over 10 weeks: HbA1c (%): • Lower in IG: 6.26 (6.19 to 6.33) vs. 6.82 (6.19 to 6.33); MDa -0.74 (-1.32 to -0.02; p=0.015)
Ghoneim 2013 [78] RCT	Egypt, 03/2010-03/2012	DM,duration ≥ 15yrs, bilateral diabetic macula edema (≥ 6 months) no prior treatment with intravitreal corticosteroids, peribulbar steroid injection within ≤ 6 months, pars plana vitrectomy, history of glaucoma or steroid induced IOP elevation, ischemic maculopathy, foveal tracted, IOP≥ 23 mmHg	n=19 (38 eyes) gender: 89.5 % female age (yrs): 52.3±11.4	IG (n=19): one eye with 8 mg triamcinolone acetonide vs. CG (n=19): other eye with4 mg of triamcinolone acetonide Duration: 6 months	Primary: Visual acuity Others: Intraocular pressure (IOP), IOP lowering drugs, complications	after 6 months: Complications: • no eyes with retinal detachment, vitreous hemorrhage, intraocular reaction or endophthalmitis. • one eye in IG developed posterior subcapsular cataract.
Hailu 2018 [61] RCT	Ethiopia, urban, 02/2016-10/2017	DM2, age > 18 yrs no DM1 or GDM, pregnant women, severe cognitive or physical impairment, and terminally ill people	n=220 gender: 33 % female age (yrs):54.5±10 HbA1c (%):10.5±4 BMI (kg/m²):25±4	IG (n= 116): Nurse-led disease-management education: 6 sessions, supported with illustrative pictures handbooks and fliers,	Primary: patients with target HbA1c (≤ 7 %) secondary: systolic and diastolic blood pressure, fasting blood sugar, BMI, waist	Change over 9 months: HbA1c (%): • 45 % vs. 50 % with target values (p=0.21) • No difference in MD: 2.88% (-3.85 to -1.92) vs. 2.57% (-3.47 to -1.67)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
				customized to local conditions, delivered by trained nurses vs. CG (n=104): usual follow-up care Duration: 9 months	circumference	FBS (mg/dl): • 36 % vs.25 % with target values • Benefit for IG: MD: -27 (-45 to -9; p=0.003)
Ibrahim 2014 [45] RCT	Egypt, urban, other care, 08/2011-04/2012	GDM or pre-existing DM, gestational age 20-34 wks with insulin resistance No DM1, secondary diabetes or liver or renal impairment	n=90 gender: 100% female age (yrs): 29.8 ± 5.4 BMI (kg/m²):31.83 ± 3.23 Gestational age: 28.7 ± 3.7 wks GDM: 43.3 % Pre-existing DM : 56.7 % with median duration of 4 (1-15) yrs	IG (n=46): Metformin (1500 mg, raised to 2000 mg) without increasing insulin dose Patients switched to CG if treatment was not successful to control blood glucose concentrations CG (n=44): insulin dose was increased according to the standard protocol	Primary: maternal gylcemic control (FBG ≤ 95 mg/dl and 2-HPG ≤ 120 mg/dl) Secondary: maternal bouts of hypoglycemia, need for another hospital admission for uncontrolled diabetes during pregnancy, gestational age at delivery, mode of delivery, birth weight, birth trauma, congenital anomalies, Apgar score, neonatal hypoglycemia, need for neonatal intensive care unit admission, adverse neonatal outcomes	gylcemic control: • 76.1 vs. 100 % reached glycemic control (p=0.001) • 13 vs. 18.2 % had readmission for poor glycemic control • 6.5 vs. 22.7 % had bouts of maternal hypoglycaemia Complications: • 23.3 vs. 30.8 % had fetal macrosomia • 1 newborn in each group had congenital malformations • 7 vs. 38.5 % had neonatal hypoglycaemia • 18.6 vs. 41 % had NICU admission • 0 vs. 5.1 % had stillbirths • 11.6 vs. 25.6 % with respiratory distress syndrome
Krawinkel 2018 [39] Crossover-RCT	Tanzania, urban, 10/2013-03/2014	Individuals with prediabetes age (yrs): 30 -65, FPG 5.6-6.9 mmol/l (100–125 mg/dL) on 2 days or on one day + HbA1c 5.7-7.5 %, BMI 27–35 kg/m^2, BP 90/60-160/110 mmHg, waist circumference	n=52 gender: 55% female age (yrs): 47.5±8.7 HbA1c (%):5.85±0.43 FPG: (mmol/l): 5.34±0.49 BMI (kg/m²):29.6±2.2	IG/CG (n=30): started with bitter gourd supplementation (2,5 g) over 8 wks, followed by placebo over 8 wks vs. CG/IG (n=31): first placebo over 8 wks, followed by bitter	Primary: FPG Secondary: HbA1c, Insulin, SBP, DBP, lipids	after 8 wks FPG (mmol/l): Benefit for IG/CG: MD 0.31 (0.08-0.54) HbA1c: (%): No differences (MD 0.05)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		> 80/90 cm for women / men No chronic disease, taking regular intake of medication, identified glucose-6-phosphatase-dehydrogenase deficiency, heavy alcohol consumption, pregnancy, lactation		gourd over 8 wks washout period: 4 wks Duration 8 weeks		
Labhardt 2011 [29] Cluster-RCT	Cameroon rural, primary care, 08/2008-02/2010	newly detected adult patients with DM2 and⁄or hypertension in the catchment area of nurse-led health centres, staffed, equipped and trained to care for DM2 and hypertension	n=33 facilities, 221 patients gender: 64% females age (yrs): 59.8±12.7 diabetes: 15.4 % Overweight (BMI 25-29.9 kg/m^2): 28.5 % Obesity (BMI> 30 kg/m^2): 20.4 %	IG 1 (11 centres, n=55): incentive group free treatment for 1 months for patients who regularly attended follow up visits vs. IG 2 (11 centres, n=77): letter group: reminder letters in case of a missed follow-up visit vs. CG (11 centres, n=89): no additional intervention Duration: 12 months	Primary: Patient retention at 1 yr (≥ 12 follow-up visits within 12 months) Secondary: Adherence with timely attendance of follow-up visit schemes and changes in blood pressure and blood glucose levels.	After 12 months: Retention rates (%): • Benefit for IG1+IG2 vs.CG: 60 vs. 65 vs. 29 %; MD 34(21 to 46), but no differences between IG1 and IG2 MD -5 (-22 to 12) • HR of loss to follow-up was lower for IG IG1 vs. CG: HR 0.44 (0.27 to 0.72; p< 0.001), IG2 vs. CG: HR 0.38 (0.24 to 0.61; p<0.001) with adjustments for cluster Adherence (%): • Benefit for IG1+IG2 vs. CG: 38 vs. 35 vs. 10; MD 26 (14 to 42), IG1 vs CG: MD 28(13 to 37); IG2 vs. CG: MD 25(13 to 37) • no difference between IG1 and IG2: MD 3(-14 to 20) FPG: • No differences between groups
Maharaj 2016 [48] RCT	Nigeria, rural, other care, 07/2013-06/2014	DM2, non- insulin dependent, blood glucose levels 6 -13 mmol/l no cardiac, abdominal or spinal surgery ≤ 6 months, history of fractures of lower limbs, spine, weakness,	n=90 gender: 52 % females age (yrs): 39.4 ± 8.6 (30-58) HbA1c (%):8.79±2.11 BMI	IG (n=45): rebound exercise 3 times/week for 20-30 min, moderate intensity of 40-60 % of heart rate maximum CG (n=45): watched videos and	Primary: HbA1c , FPG, BMI Other: Heart and respiratory rates, blood pressure, oxygen saturation	After 9 weeks HbA1c (%): Benefit for IG: 7.12±1.19 vs. 8.36±1.25; MDa: 0.904 (0.832 to 0.984; p=0.017) FPG (mmol/l): Benefit for FPG: 6.92±1.21 vs. 8.73±1.23; MD_a: 0.787 (0.7345-

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		deformities, loss of sensation in the feet, retinopathy, nephropathy	(kg/m²):27.72±5.77 type of diabetes duration of diabetes (yrs): 2.54±2.13	read health magazines Duration: 9 weeks		0.841; p=0.002)
Malek 2015 [26] RCT	Egypt, Algeria, Tunesia, South Africa, 03/2010-05/2012	DM2, age ≥ 18 yrs, currently treated with suboptimal dose pf oral anti-diabetic drugs; HbA1c 7-11 % (under metformin-monotherapy) and ≤ 10 % (under combination therapy), BMI≤40 kg/m^2 no allergies or contraindications to the product, pregnant or breastfeeding, impaired hepatic or renal function, cardiovascular history, uncontrolled hypertension, proliferative retinopathy, macular oedema	n=403 age (yrs): 52.8±9.6 59.8 % female HbA1c (%): 8.65 BMI (kg/m^2): 29.7±4.5 duration of diabetes (yrs): 7.5±5.1	Stepwise individual insulin intensification of IG (n=200): basal-bolus insulin analogues (insulin detemir +Insulin aspart) vs. CG2 (n=203): thrice daily biphasic insulin aspart (n=203) depending on HbA1c-values over 50 wks	Primary: HbA1c Secondary: patients achieving HbA1c < 7.0 %, prandial plasma glucose	Change over 50 weeks: HbA1c (%): Non-inferiority: 7.4 vs. 7.3; MD 0.1 (-0.1 to 0.3 (full-analysis set), MD 0.2 (-0.1 to 0.4 (per protocol) 40.3% and 44.9% achieved HbA1c<7.0% Hypoglycaemia (events/patient year): 9.4 vs. 9.8 Serious adverse events: 6.5 vs. 3.4 % with 1 treatment-related SAE in CG Adverse events: 58.5 vs. 63.1%
Mash 2014 [30, 31] Cluster RCT	South Africa, urban, primary care, 12/2010 -12/2012	DM2 with any therapy attending community health centres in the working class areas of Cape Town Metropole no DM1, dementia, mental illness or acute illness	n=34 public sector community health centres, 1570 patients gender: 73.8% females age (yrs): 56.1±11.6 HbA1c (%): 9.1±2.3	IG (17 health centres, n=710): 4 monthly sessions lasting 60 min with group education about diabetes topics (understanding diabetes and medication, living a healthy lifestyle and preventing complications), delivered by a health promotion officer vs. CG (17 health centres,	Primary: improvement of diabetes self-care activities (5 % weight loss, and a 1 % reduction in HbA1c level) Secondary: improved diabetes specific self-efficacy, locus of control, mean blood pressure, mean weight loss, mean waist circumference, mean HbA1c, mean total cholesterol levels,	After 12 months: HbA1c (%): 8.4±2.0 vs. 8.8±2.2; MDa: 0.01 (-0.27 to 0.28; p=0.967) Adherence (self-care activities): No differences in scores of physical activity, use of diet plan or medication, foot care or frequency of smoking Quality of life: No differences in physical functioning, role or social functioning, mental or general health and pain Costs: Incremental Cost effectiveness

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
				n=860): usual care: ad hoc advice during consultations and occasional educational talks in waiting room Duration: 12 months	quality of life	Ratio: 1862 Dollar/ QALY gained
Mohamad 2009 [47] RCT	Egypt, urban, other care	DM1, age 17 to 20 yrs no acute metabolic complications like diabetic ketoacidosis, hypoglycaemia, cardiovascular events, renal or acute infections	n=64 gender: 30 % female age (yrs): 19.9±6.8 HbA1c (%): 9.52±2.08 FBS (mg/dl): 228.7±13.5 BMI (kg/m²): 18.82±3.01	IG (n=27): 500 ml camel milk +usual care vs. CG (n=27): usual care for diabetes (i.e. diet, exercise, insulin mixtard) Duration: 16 weeks	Not specified: HbA1c, human C-peptide, lipid profile, serum insulin, anti-insulin antibodies, creatinine clearance, albumin extraction in 24 h urine, BMI, Diabetes QoL score, fasting blood sugar	After 16 wks HbA1c (%): Benefit for IG: 7.16±1.84 vs. 9.59±2.05 FBG (mg/dl) benefit for IG: 227.2±17.7 vs. 98.9±16.2
Muchiri 2015 [62] RCT	South Africa, rural, primary care, 04/2010-11/2011	DM2, age 40-70 yrs attending community health centres, HbA1c≥ 8 %, blood sugar levels ≥ 10 mmol/l, duration of diabetes ≥ 1 yr no insulin therapy, pregnant women, full time employed	n=82 gender: 86.6 % female age (yrs): 59±7.4 HbA1c (%): 11.1±2.0 BMI (kg/m²):30.9±6.9 duration of diabetes (yrs): 6	IG (n=41): education materials+ 8 weekly group educational sessions about diabetes and nutrition, follow-up sessions+vegetable gardening CG (n=41): education materials Duration: 12 months	Primary: HbA1c Secondary: other clinical outcomes (BMI, blood pressure and blood lipids), HbA1c, dietary behaviours	over 12 months HbA1c (%): • 9.8±1.92 vs. 10.4±1.92; MD −0.63 (-0.26 to 1.50; p=0.16)
Nteleki 2015 [63] RCT	South Africa, urban, other care	DM2 with neuropathic or mixed (venous and arterial) ulcers; lower extremity ulcer; stable or worsening ulcer that has been present for ≥ 4 weeks	n=7 with 14 lower extremity ulcers gender: 85 % male age (yrs): 62 duration of diabetes (yrs): 16.7	standard podiatric management and IG1 (n=2): phototherapy to the regional lymphatic nodes and ulcer(s) vs.	healing rate (area and perimeter of the ulcer)	after 12 wks Healing: • The rate of healing increased in all three groups, • 67% of ulcers received some form of phototherapeutic intervention, 40% of those ulcers

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		no acute cellulitis, osteomyelitis, or gangrene, renal, hepatic, hematologic, neurologic, or immune disease not related to diabetes; presence of malignant disease not in remission for > 5 years; use of oral or parenteral corticosteroids, immunosuppressive, or cytotoxic agents; known infection with human immunodeficiency virus or presence of AIDS; other leg ulcers		IG2 (n=3): phototherapy on the ulcer vs. CG (n=2): placebo phototherapy Duration: 12 weeks		resolved completely over 8 weeks no adverse effects.
Rashad 2017 [64] RCT	Egypt, urban, other care	DM2, 50-62 yrs no insulin medication, allergies, recent thromboses or uncontrollable hypertension	n=34 gender: 43.3 % female age (yrs): 55.5±6.15 HbA1c (%):6.75±1.2 fasting glucose (mmol/l): 8.5±1.4 postprandial plasma glucose(mmol/l): 15.6±3.3 BMI (kg/m^2):28.55±4 type of diabetes duration of diabetes (yrs): 6.1 ± 2.2	IG (n=17): 400mg of BE (Balanites aegyptiaca extract) vs. CG: (n=17) placebo capsules (potato maltodextrin) Duration: 8 wks	glycemic markers, lipid profile, FPG	Change over 8 wks: 2h postprandial plasma glucose: benefit for IG :26.88% decrease vs. CG 2.6% increase FPG (mmol/l): benefit for IG: 7.8 ± 0.9 vs. CG: 8.5 ± 1.1
Saeed 2013 [79]	Egypt, urban, other care,	intractable diffuse diabetic macular edema without vitreomacular traction.	n= 34, 34eyes gender: 50% female age (yrs): 55.5 ± 8.9	IG1 (n=15): pars plana vitrectomy with removal of the	primary: best-corrected visual acuity (BCVA), central foveal thickness	Changes over 12 months Complications: • Changes in BCVA and central

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
RCT	11/2010-07/2012	central foveal thickness ≥300 µm no vitreomacular traction, active neovascularization of proliferative diabetic retinopathy, an enlarged foveal avascular zone on fluorescein angiography, neurosensory detachment on optical coherence tomography, treatment for diabetic macular edema within ≤ 3 months, previous vitreoretinal surgery, other major ocular surgery within the previous 6 months, YAG capsulotomy within ≤2 months, macular pathology	duration of diabetes (yrs): 24±5.4	posterior hyaloid was performed, and at the end of the procedure, IVTA 0.1 mL (40 mg/mL) +bevacizumab 1.25 mg were injected IG2 (n=15); macular grid laser photocoagulation was performed 2 weeks after the same intravitreal injection combination as used in IG Duration: 12 months		foveal thickness at 3, 6, and 12 *(P*< 0.01), better mean BCVA in IG2 at 12 months. • Better mean central foveal thickness in IG2 at 12 months. Major adverse events: development of cataracts (6/15 vs. 3/15) and elevation of intraocular pressure (2/15 vs. 7/15)
Salem 2010 [74] RCT	Egypt, urban, other care, 02/2009-11/2009	DM1 for ≥3 years, 12-18 years, HbA1c ≥7.5 % for ≥6 months no significant diabetic complications limiting exercise like, uncontrolled hypertension, diabetic keto-acidosis, severe hypoglycemia within the past 3 months, patients on lipid lowering therapy	n=196 gender: 61.7 % female age (yrs): 14.78 ± 2.31 HbA1c (%): 8.7±1.7 duration of diabetes (yrs): 4.6 ± 1.9	IG 1(n=75): attended exercise sessions once times/week vs. IG2:(n=73): attended exercise sessions three times/week vs. CG (n=48): no exercise Duration: 6months	glycemic control, plasma lipids values, blood pressure, severity and frequency of hypoglycemia, anthropometric measurements and insulin dose	Change over 6 months: HbA1c (%): Improvement in both intervention groups: 7.8 ± 1.0 vs. 8.1 ± 1.1 vs. 8.9 ± 1.3% (p=0.2)
Sodipo 2017 [66] RCT	Nigeria, primary care, 03/2013-11/2013	DM2 ≥ 18 yrs. on antidiabetic medication no patients with emergencies, chronic complications such as	n=120 gender: 50% female age (yrs): 59±10.95 HbA1c (%): 8.7±2.45 FBG (mg/dl):	IG (n=60): Self-monitoring of blood glucose before and after meals 3 days a week for 12 weeks CG (n=60); non SMBG	HbA1C, FBG	after 12 wks: HbA1c (%): No difference: 7.2±2.0 vs.7.7±2.0 (p= 0.174) FBG (mg/dl): No difference: 123.2±35.1 vs.

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		nephropathy, neuropathy etc., those already using glucometer	152±60.9 duration of diabetes (yrs): 50%> 3yrs	Duration: 12 wks		137.6±50.1 (p=0.087)
Somanah 2012 [80] RCT	Mauritius, urban/rural, other care, 11/2010-03/2011	newly diagnosed DM, age 25–60 yrs FBG range: 5.1–5.9 mmol/L no secondary complications, non-smoker or stopped for > 6 months , alcoholic consumption < 2 standard drinks/day, post-menopausal women without hormone replacement treatment, no glucose-lowering, cholesterol-lowering or anti-hypertension treatment	n=127 gender:47% female age (yrs): range 25–60 HbA1c (%): 5.99±0.4 FBG (mg/dL): 93.,2±8.,0 BMI (kg/m$^{2)}$: 26.6 ± 3.7	IG (n≥44): 6g/day supplementation of a fermented papaya preparation for 12 wks dissolved in half flass of warm warter twice daily, followed by a 2 week wash out period with the same amount of water vs. CG (n≥56): consumed an equivalent amount of water Duration: 14wks	HbA1C, FBG, Lipid profile, diet score, blood pressure, alanine aminotransferase; aspartate aminotransferase, Ferritin, c-reactive protein, uric acid, microalbumin/urinary creatinine ratio	After 14 wks: HbA1c (%): no difference (p=0.448) FBG (mg/dL): • remained relatively unchanged in boths genders: • males: 96.2±17.0 vs. 87.6±11.7 • females: 95.6±15.8 vs. 94.3±5.0
Steyn 2013 [32] Cluster-RCT	South Africa, urban, primary care, 1999-2000	public sector primary health care clinics (CHC) with ≥ 25 diabetes and ≥ hypertension patients age ≥15yrs, a documented attendee at the particular CHC with ≥ 4 visits during the previous year for hypertension or diabetes who received treatment for these conditions at each visit no patients being unable to answer a questionnaire	18 community health centres with n=1096 patients, of them n= 456 diabetic pat. age (yrs): 58.3 ± 11 gender:74 % females HbA1c (%): 8.85% HbA1C>7%: 62.85% BMI (kg/m$^{2)}$: 30.7 ± 6.2 Type of Diabetes: • DM1: 5.8%	IG (9 clinics, n=545pat., 229 diabetics): introduction of structured clinical record with guidelines prompts after training of doctors in their use and suggestions to incorporate them in regular patient records, contact over 1 year vs. CG (9 clinics, n=541pat, 227 diabetics): usual care	primary: HbA1C in the diabetes group secondary: uncontrolled glycaemia (HbA1c ≥7%) in the diabetes group.	After 12 months: HbA1c (%): IG: 8.8% vs. 8.8%; MDa -1.0 (-1.1 to -0.9) HbA1c ≥7% (%): no relevant difference: 64.1 vs. 62.6; MD 0.90 (0.53 to 1.53)

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
			• DM2: 91.35% • uncertain DM Typ: 2.85%	with passively disseminated guidelines Duration: 1 year		
Takenga 2014 [67] RCT	Congo, urban	DM2, 35-75 yrs	n=40 gender: 20 % females age (yrs): 53.3 ± 10.1 HbA1C (%): 8.63	IG (n=20): self-management of diabetes with Mobil DIAB (telemedical approach) CG(n=20):conventional therapy without the use of telemedice system Duration: 60 days	primary: HbA1c	after 60 days HbA1c (%): Benefit for IG: 6.73±1.59 vs. vs. 8.6±1.35 (MD -1.87 (-2.91 to -0.83)
Tawfik 2016 [68] RCT	Egypt, urban, primary care, 05/2015-09/2015	DM2 for ≥ 1 yr, 40-79 yrs attending an outpatient clinic no patients who were already using a similar medication chart, severe or terminal health conditions, or patients with behavioral health issue that could make it difficult to understand the communication	n=255 gender: 53.7 % females age (yrs): 55.7±8.35 HbA1c (%): 8.14±1.3 duration of diabetes (yrs): 8.3±1.3	IG (n=127): comprehensive cardiovascular risk communication vs. CG (n=128): standard usual care Duration: 3 months	primary: HbA1c secondary: Cardiovascular risk perception, diabetes self-care, cardiovascular risk scores	After 3 months: HbA1c (%): Benefit for IG: 7.5±0.8 vs. 8.12±0.9; MD -0.62 (-0.85 to -0.39) controlled HbA1c (%): 32.7 vs. 29.9
Tsobgny-Tsague 2018 [69] RCT	Cameroon, urban, tertiary care, 12/2014-05/2015	DM2, >11teeth, severe chronic periodontitis according to the 2012 CDC-AAP classification, no peridontal treatment, alteration of DM treatment 6 mths prior to the study, onset of systemic diseases	n=34 (30analyzed) gender: 56% female age (yrs): 51.4 ± 8.8 HbA1c (%):9.3 ± 1.3 BMI (kg/m²): 28.3± 5.4 duration of diabetes (months): 55.5 ±	IG (n=17): immediate ultrasonic scaling, scaling and root planning +subgingival 10% povidone iodine irrigation CG(n=17): periodontal treatment 3 months later	primary: change in HbA1c secondary: Plaque index, gingival bleeding index, pocket depth, clinical attachment loss	Change over 3 months: HbA1c (%): Better with IG: 6.7 ± 2.0 % vs. 8.1 ± 2.6 %, MD: 2.2 (p=0.029) adverse events: 1 /15 patient reported tongue irritation following chlorhexidine moth rinse in IG

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
		or an acute condition, use of immunosuppressive medications or others drugs or presence of conditions able to alter periodontitis clinical features	42.6 complications: neuropathy: 40% nephropathy7% retinopathy: 7% diabetic foot: 3%	Duration: 3months		
Utz 2018 [34] Cluster-RCT NCT02979756	Marocco, urban / rural, primary care, 11/2016-02/2018	Health centres with ≥ 30 monthly antenatal care consultations and all pregnant women with newly diagnosed GDM no DM2, DM1	20 health centers n= 215 (210 analysed) age (yrs):27.6±6.6 urban(%):38,5 rural (%): 61.5 primipara: 33%	20 clinics were randomized→ 10 in each group IG (n=120) first screening for GDM→positive tested women received counselling on nutrition and exercise CG (n=95) routine practice	Primary: birthweight Secondary: maternal weight gain, glucose control, pregnancy complications.	Changes to post partum follow up FBG (g/l) No difference: 0.92 ±0.13 vs. 0.94 ±0.15; MD: -0.02 (-0.09 to 0.05;p= 0.480) Glucose control (%) No difference: 93.2 vs. 86.8; OR 2.62 (0.80 to 8.62; p=0.08) Macrosomia (birthweight>4000 g): 3.5 vs. 18.4 % (p<0.001)
van der Hoogt 2017 [40] cross-over RCT	South Africa	DM1, age 4-17 yrs on insulin pump therapy, HbA1c>9,6% for ≥3months, BMI/age z.score -1 to < 3, total daily insulin use of >0,5 u/kg no remission of diabetes, smoking, coeliac disease, cystic fibrosis, diseases or medication that are associated with delayed gastric emptying or altered digestation, glucocorticoids, oral diabetic drugs, no acute illnesses	n=32, gender: 41% female age (yrs): 10.4±4.0 HbA1c (%):8.2±0.8 duration of Diabetes (yrs): 3.5 (1.5-8.0)	IG1 (n=22): 1 home-based low fat and protein meal vs. IG2 (n=22): 1 high fat and protein meal with identical carbohydrate content two meals were consumed at dinner time (18:00) under parental supervision at least 1 day apart within one month Duration: 3months	primary: peak sensor glucose value post-meal, time to peak sensor glucose, time of first and largest correction bolus ,total correction insulin, total meal insulin, additional insulin required ,area under the sensor glucose response curve (AUC) (≥ 8 mmol/L), duration of elevated post-prandial glucose	Change over 12 weeks Occurance of hypoglycaemic events: 7 (32 %) vs. 1 patients after IG1 vs. IG2
van Rooijen	South	black women with DM2,	n=158	IG (n=80):	primary: HbA1c, BMI	Change over 12 weeks:

Study name Design	Setting	Population		Intervention vs. Control	Outcomes	Results
2004 [70] RCT	Africa, urban, other care, 03/2002-11/2002	age 40-65yrs, duration of DM ≥1 y no chest pain on effort, possible previous myocardial infarction and intermittent claudication, cerebro-vascular incidents, arthritis, retinopathy	gender:100 % females age(yrs): 54-55 years HbA1c (%): 9.35	education+ incremental daily home exercise, use of daily physical activity records+6 fortnightly supervised aerobic exercise classes vs. CG(n=77): education+ relaxation exercise Duration: 12wks	secondary: walking distance (6 min walk)	HbA1c (%): no difference: MD -0.39 (-0.89 to 0.02) vs. -0.97 (-1.38 to 0.55) (p=0.052)
Webb 2015 [35–37] Cluster RCT NCT01275040	South Africa, urban, primary care, 06/2010-03/2011	primary health care clinics, patients with clinical diagnosis of DM2 or DM1 for ≥5yrs, age ≥ 18 yrs	n= 12 primary health care clinics, 599 pat. gender:68.5 % female age (yrs): 57.8±10.5 HbA1c (%): 8.73±2.3 HbA1c ≥ 7 %: 73 % BMI (kg/m$^{2)}$: 30.8±6.7 Typ of diabetes: • DM1: 3.7 %, • DM2: 70.3 % • unknown: 26 % duration of Diabetes: • < 5 yrs: 47.3 % • 5-10 yrs: 22.0 % • > 10 yrs: 20.2 %	IG (n=328): mobile screening team visits primary care clinic and provides education and active screening for diabetic complications (foot, kidney, cardiac and renal complications) vs. CG(n=273): no mobile screening team, routine care with similar education for patients. and health care workers Duration: 1 yr	primary: HbA1c, detected neuropathy, nephropathy and retinopathy, HbA1c categories secondary: detected complications, referred patients for complication assessment or care, blood pressure and lipid control, costs, LDL cholesterol, creatinine	after 1 yr HbA1c (%): no difference: 8.54±2.11 vs. 8,76 ±2.2, MD-0.22 (-0.64, 0.20) screening rate for complications: in IG 60% increase of screening in all complication indicator groups, in both groups testing of HbA1c and renal complications (serum-creatinine) increased , but no significant difference , screening for eye complications, only increased significantly in IG no significant difference in the proportion of actions taken beweend IG and CG (p=0.83)
Yakoot 2019 [81] RCT	Egypt, urban, other care,	Adult DM2 or DM1 patients, limb-threatening diabetic foot ulcerations no life-threatening	n=119 gender:44.5% female age (yrs): 54.7 ±8.4 type of diabetes:	IG (n=61): local application of Pedyhair CG (n=58): lokal application of Panthenol	primary: complete healing; secondary: reduction of infection in the ulcer site, al reaction that	after 12 months rate of complete healing (%): Benefit for IG: 32.4% vs. 12%; p=0.034

Study name Design	**Setting**	**Population**		**Intervention vs. Control**	**Outcomes**	**Results**
NCT01531517	07/2011-07/2013	extensive gangrenous lesions that needed immediate amputations; bad general condition; shock or unstable vital signs; critically ill with severe organ/system dysfunctions or advanced malignancy.	• DM1: 22.9% • DM2: 86.2%	both groups first received conservative debridement of necrotic tissue and irrigation with warm normal saline Duration: 12months	may be due to study drug	
Yan 2014 [46] RCT	Mozambique, urban	DM2, male, age 40-70 yrs, diagnosis for ≥ 12 months no known diseases other than DM2 and hypertension, no diagnosed cardiovascular diseases	n=41 gender: 100% male age(yrs):54±2.5 HbA1c: 8.6±0.7 plasma glucose (mmol/l): 9.65±1.2 BMI ($kg/m^{2)}$: 27.1 ± 1.0	IG (n=31) low or vigorous intensity exercise 3-5 times/week vs. CG(n=10): walked 1 hour per day as part of their daily lifestyle Duration:12 wks	plasma glucose, HbA1c	Change over 12 wks: HbA1c (%): reduction in both groups with no differences between groups: 7.7±0.4 vs. 7.7±0.8 Plasma glucose (mmol/l): 9.6 ± 0.7 vs. 11.1 ± 1.3

ADA: American Diabetes Association; aRR: adjusted Relative Risk; BMI: Body mass index; CG: Control group; C/I: crossover from CG to IG; CI: confidence interval; CHC: community health center; DBGP: designed breakfast glucose profile, DBP: diastolic blood pressure; DM: diabetes mellitus; DM1: type 1 diabetes; DM2: type 2 diabetes; ER: emergency room; FBS: fasting blood sugar; FPG: fasting plasma glucose; GDM: gestational diabetes; HbA1c: hemoglobin A1c; 2HPG: 2-hour post prandial blood glucose; HDL: high density lipopreotein, I/C: cross over from IG to CG; IG: intervention group; LDL: low density lipoprotein; LILT: low-intensity laser therapy; n: number of participants; NCD: Non-communicable disease; NPH: neutral protamine Hagedorn; MD: mean difference; MDa: adjusted mean difference; OGTT: Oral glucose tolerance test; Pat: patients; RCT: randomized controlled trial; RRa: adjusted relative risk; SBP: Systolic blood pressure; SAE: Serious adverse events; SBP: Systolic blood pressure; SCI: Diabetes Self-Care Inventory; SMBG: self-monitoring of blood glucose;; wks: weeks; yrs: years

Risk of bias judgement

Table 3: Overview on risk of bias judgement per study

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Abaza 2017 [49, 50]	☺	☺	☹	☺	☹	☺	☺
Abdulrhman 2013 [38]	☺	😐	☹	☺	☺	☹	😐
Adibe 2013 [51, 52]	☺	☺	☹	☹	☹	😐	☺
Adjei 2015 [75]	😐	😐	☹	☺	☺	😐	☹
Amendezo 2017 [59]	😐	😐	☹	☺	☹	😐	☹
Anderson 2001 [28, 65]	😐	😐	☺	☺	😐	😐	☺
Anyanwu 2016 [53]	😐	😐	☹	😐	☹	😐	☺
Ashoush 2016 [43]	☺	☺	☹	😐	☺	😐	☺
Asuako 2017 [76]	😐	☺	☹	😐	☺	😐	☹
Beyuo 2015 [44]	😐	☺	☹	😐	☹	☹	☹
Chraibi 2017 [27]	😐	😐	☹	😐	☹	☺	☹
Debussche 2018 [54]	☺	☺	☹	😐	☺	☺	☺
Distiller 2014 [55]	😐	☺	☹	😐	☹	😐	☺
Elbarbary 2016 [72]	😐	😐	☹	😐	☹	😐	☹
Elbarbary 2018 [73]	☺	☺	☺	😐	☺	☺	☺
Elbarbary 2019 [71]	☺	☺	☺	☺	☺	☹	😐
El-Haggar 2015 [56]	😐	😐	☹	😐	😐	😐	☹
El-Shamy 2018 [41]	☹	☹	😐	😐	☺	😐	☺
El-Sharkawy 2016 [57]	☺	☺	☺	☺	☺	☺	☹
El-Sheikh 2019 [58]	😐	😐	☹	😐	☹	😐	☹
Embaby 2016 [42]	😐	😐	☹	😐	☹	😐	☹
Essien 2017 [77]	☺	☺	😐	☺	☹	😐	☺
Fairall 2016 [33]	😐	☺	😐	😐	☺	☺	☺
Fayehun 2018 [60]	😐	☺	☹	☹	☺	☹	☺
Ghoneim 2013 [78]	☺	😐	☹	😐	😐	😐	☹
Hailu 2018 [61]	☺	😐	☹	☺	☹	😐	☹
Ibrahim 2014 [45]	☺	😐	☹	😐	☹	☺	☹
Krawinkel 2018 [39]	☺	😐	☹	☹	☹	☺	☺
Labhardt 2011 [29]	☺	☺	☹	😐	☺	☺	☺
Maharaj 2016 [48]	😐	😐	☹	☺	😐	😐	☹
Malek 2015 [26]	😐	😐	☹	😐	☺	😐	😐
Mash 2014 [30, 31]	☺	😐	☹	☹	☹	☺	☺
Mohamad 2009 [47]	😐	😐	☹	😐	😐	😐	☹
Muchiri 2015 [62]	☺	☺	☹	☺	☺	😐	☹

Study	Sequence generation	Allocation concea-lment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other risk of bias
Nteleki 2015 [63]	☹	😐	☹	😐	☺	😐	☹
Rashad 2017 [64]	☺	☺	☺	☺	☹	😐	☹
Saeed 2013 [79]	😐	😐	☹	☹	☹	😐	☹
Salem 2010 [74]	😐	😐	☹	☹	😐	😐	☹
Sodipo 2017 [66]	☺	😐	☹	😐	☹	😐	☺
Somanah 2012 [80]	😐	😐	☹	😐	☹	☹	☹
Steyn 2013 [32]	☺	😐	☹	😐	☹	😐	☺
Takenga 2014 [67]	😐	😐	☹	😐	☺	😐	☹
Tawfik 2016 [68]	😐	☺	☺	☺	☹	😐	☺
Tsobgny-Tsague 2018 [69]	☺	😐	☹	☺	☹	☹	☺
Utz 2018 [34]	☺	☺	☹	☺	☺	☹	☹
Van der Hoogt 2017 [40]	😐	😐	☹	😐	☹	😐	☹
Van Rooijen 2004 [70]	☺	☺	☹	☺	☺	😐	☹
Webb 2015 [35–37]	😐	😐	😐	☺	☹	😐	😐
Yakoot 2019 [81]	😐	☺	☹	☹	☺	☹	☹
Yan 2014 [46]	😐	😐	☹	😐	☺	😐	☹

☺: low, 😐: unclear, ☹: high risk of bias

Appendix

Declaration under oath

I declare under oath that this thesis is my own work entirely and has been written without any help from other people. I met all regulations of good scientific practice and I used only the sources mentioned and included all the citations correctly both in word or content.

Declaration of previous attempts at doctoral application

I declare that I have not completed or initiated a doctorate procedure at any other university.

Declaration concerning the truth of information given

I declare that all information given is accurate and complete. The thesis has not been used previously at this or any other university in order to achieve an academic degree.

Acknowledgements

At this point, I would like to thank all persons supporting me in the past years.

First, I want to express my special thanks to my supervisors, PD. Dr. rer. nat. habil. Susanne Unverzagt for her outstanding support and Prof. Dr. med. Thomas Frese, the director of the Institut of General Medicine, Faculty of Medicine at the Martin Luther University of Halle-Wittenberg for his great advice in the implementation of the entire work.

Secondly, I want to thank my family and dedicate this work to my father, Prof. Hagen Sandholzer for supporting me with great advice and encouraging me. You are an excellent father, mentor and instructor.

Furthermore, I want to say thank you to my brother, Dr. Maximilian Sandholzer and my mother, Dr. Ute Sandholzer, for their patience. I also want to thank my host father, Doug Spencer for his proofreading and advice on the English language in academic papers.

Finally yet importantly, I thank my fiance, Hasan Yilmaz for his unconditional support, constant encouragement and his patience while studying and working on this dissertation.

I am deeply greatful to be surrounded by such wonderful people.