Assessing type 2 Diabetes Associated NeuroCognitive impairment using an e-screening tool in a South African population

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Thesis

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Declaration

I know the meaning of plagiarism and declare that all of the work in the thesis, save for that which is properly acknowledged, is my own.

Signed by candidate

K Bobrow

26 March 2018

Acknowledgements

The material in this thesis is my own work. I was responsible for the study design, data collection strategy, analysis, and writing of the manuscript. The study is a sub-study in a large multi-centre trial and as such a number of people contributed to its success. I would like to thank Andrew Farmer for allowing me to conduct this sub-study and for his guidance with the analysis. I would like to thank Sr Carmen Delport, Didi Gobile and the entire StAR2D field team for their help, and for the study participants without whom this project would not have been possible. I also thank Rueben Robbins for allowing me to use the tool he has developed in a new study population and for providing technical support as well as assisting with data extraction and guidance with the analysis and editing the manuscript. I would also like to thank Hetta Gouse and Naomi Levitt for their supervision, assistance with training and support of the field team and their valuable guidance on data analysis and editing of the manuscript. I am also extremely grateful to Leslie London for his insights and sharing his work in this area with me and to my departmental supervisor Virginia Zweigenthal for her support and guidance in the writing up of this thesis.

Abstract

Assessing type 2 Diabetes Associated NeuroCognitive impairment using an e-screening tool in a South African population

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Background: Type 2 diabetes has been found to be associated with cognitive impairments in planning, problem solving, organization, and working memory and also with an increased risk of dementia. Neurocognitive impairment may impact self-care and other health behaviours increasing the risk of poor health outcomes in this patient population. Detection of neurocognitive impairment in low and middle-income settings is challenging; there is a lack of validated screening tools suitable for local use in primary care and outpatient settings and access to formal neuropsychological testing services is limited. The inability to easily identify people with type 2 diabetes with neurocognitive impairments is constraining the development of context appropriate interventions to improve the care and outcomes in this sub-group of patients.

Aim: The aim of the current analysis is to explore associations between neurocognitive function and measures of diabetes control (HbA1c, disease duration, type of blood glucose lowering treatment) at baseline in a population of people with type 2 diabetes participating in a clinical trial of treatment adherence support using SMS-text messages.

Materials and Methods: SMS supporting treatment Adherence foR for type 2 Diabetes (StAR2D) is a randomised clinical trial testing if a system of SMS-text messages to support treatment adherence is more effective than usual care for controlling blood sugar among people with type 2 diabetes in sub-Sahara Africa (ISRCTN70768808). We have embedded neurocognitive assessment sub-studies into the Cape Town trial site. At baseline participants in the StAR2D trial complete a novel mobile-device based cognitive assessment, NeuroScreen, assisted by a field research assistant. The assessment contains 9 variants of tests found in the gold-standard neuropsychological test battery that have been adapted and normed for use in South Africa. It is available in English or isiXhosa. The assessment takes between 20 to 40 minutes depending on participant error rate. This cross-sectional analysis of baseline data uses linear and logistic regression models to explore associations between neurocognitive function and measures of diabetes control.

Results: Six hundred participants eligible for enrolment in the StAR2D trial were recruited from the Cape Town trial site; 499 participants completed the baseline neurocognitive screening assessment (20 to 40 minutes to complete); 101 participants did not complete the assessment (commonly due to eyesight, hearing or motor difficulties e.g. hemiplegia due to previous stroke or technical difficulties.) We found differences in the scores in some but not all the neuropsychological tests. Using cut points suggested by an earlier validation study of NeuroScreen tool more than half of study participants would be scored as having at least mild neurocognitive impairment. HbA1c, duration of disease, type of blood glucose lowering treatment were not significantly associated with individual or overall neuropsychological test scores or odds of neurocognitive impairment.

Conclusions: The prevalence of neurocognitive impairment may be substantial in this patient population. A novel tablet based neurocognitive screening tool was broadly feasible and acceptable to lay researchers and trial participants. There was no evidence that HbA1c, duration of disease, or type of blood glucose lowering treatment (oral agents alone or insulin containing regimens) was significantly associated with individual or overall neuropsychological test scores or odds of neurocognitive impairment. Validating this tool for this patient population and optimising its role in routine clinical care need further study.

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Note on structure of this thesis

This thesis is divided in to four parts as instructed in the University of Cape Town MMed (minor dissertation) guidelines for Public Health Medicine. Part A is the research protocol as approved by the Departmental Research Committee and Faculty Research Ethics Committee. The research protocol describes two sub-studies. For the purposes of this dissertation I report on the baseline analysis from sub-study 2 only. Part B is a structured review of the literature; Part C presents the results of the baseline analysis from sub-study 2: *Pilot cohort study to explore the prevalence of and associations with neurocognitive impairment among adults with type 2 diabetes in primary care.* Part D contains the official ethics approval letter from the Faculty Research Ethics Committee, the author guidelines for PLOS and for ease of reference a copy of the multimedia appendix from Robbins et al, (1) *A Mobile App to Screen for Neurocognitive Impairment: Preliminary Validation of NeuroScreen Among HIV-Infected South African Adults* for a complete description of each test used in the assessment.

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Assessing type 2 Diabetes Associated NeuroCognitive impairment using an e-screening tool in a South African population (DANCes); validation and pilot cohort study

October 2016 – December 2018

Ethics Reference:

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Investigator: Dr Kirsty Bobrow

Degree: Master in Medicine

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Contents

Background

Type 2 diabetes is major global public health concern. (2) Low- and middle-income countries are disproportionally affected by the substantial and growing burden of premature morbidity and mortality associated with chronically elevated blood glucose levels. (3,4) For example, in South Africa the estimated prevalence of type 2 diabetes is about 9%; the condition is also a top 10 cause of premature mortality and morbidity. (5,6)

A key component of health care for people with diabetes is self-care and management. (6) Most people with type 2 diabetes will require the use of one of more blood glucose lowering agent in addition to a package of lifestyle modifications across many domains which often require ongoing negotiation in their daily lives. Planning, problem solving, organization, and working memory are just some of the higher order cognitive functions required for adequate self-care. (7) Self-care activities have been shown to be associated with improved treatment adherence, blood glucose control, and disease outcomes in people with type 2 diabetes. (8)

Type 2 diabetes is a multi-system disease. Well known are the increase in risk of cardio- and cerebrovascular events, impaired renal function, and peripheral neuropathies and association with long term blood glucose control. Increasingly results from epidemiological research shows that type 2 diabetes may also be associated with neurocognitive impairment (NCI) (impairments in motor function, verbal memory, executive function, visual memory, processing speed, and attention and concentration) and an increased risk of dementia. (9–13) Vascular, metabolic, and neuroendocrine factors have all been shown to contribute to type 2 diabetes associated NCI. (14) Epidemiological studies suggest that NCI may be a potential cause and consequence of variable blood glucose control. (15) Such findings suggest that NCI and abnormal blood glucose levels (high or low) may act in concert to increase the risk of poor long-term outcomes associated with the condition.

Detection and management of NCI among people with type 2 diabetes in low and middle-income settings is challenging. In high income settings there is generally wider availability of skilled professionals and validated tools to screen for NCI in people with diabetes and other chronic conditions. In lower income settings to formal neuropsychological testing services is limited. There is also a lack of validated screening tools suitable for local use to screen for NCI. As a result, to date little research has been done in low and middle-income countries to describe the burden of NCI among people with type 2 diabetes, and its association with long term blood glucose control and treatment adherence.

In high income settings screening tools such as the Montreal Cognitive Assessment (MoCA) have been used to identify patients with type 2 diabetes and NCI and who may benefit from additional treatment support. (16) In these settings such support is often made available through interventions in the formal health care system with specialist diabetes care providers. (6) In low- and middle-income settings support for people with type 2 diabetes is based more on a volunteer-based peer support model with care provided by generalist health care providers. (15) The inability to easily identify people with type 2 diabetes needing additional support as a result of NCI in lower income settings has constrained the development of context appropriate interventions to improve the care and outcomes among this subset of patients.

New developments in computerised neuropsychological testing combined with mobile communications technology have potential to improve the detection of NCI in people with type 2 diabetes that is scalable, low-cost and suitable to be used by non-specialist health care workers. (17) Mobile devices are already being used to deliver brief messaging and other interventions to health care providers and individuals to support treatment adherence

in people with chronic conditions including type 2 diabetes in low and middle-income settings. (17–19)

NeuroScreen is a tablet based health application that has been validated to screen for neurocognitive impairment in people living with HIV.(20) This simple tool which can be used by lay health workers has the potential to be an important screening tool for a range of chronic conditions which may be associated with neurocognitive impairment. Validation studies are required to validate this tool in different patient populations, and to assess the relative contribution of conditions in patients with multi-morbidity.

We are proposing to, (1) validate NeuroScreen comparing it to a gold standard battery of neurocognitive tests, and (2) assess the burden and severity of neurocognitive dysfunction in a population of people with type 2 diabetes within an existing study; the SMS supporting treatment Adherence foR people with type 2 diabetes (StAR2D) trial.

StAR2D is a pragmatic individual randomised trial testing whether treatment adherence support delivered by SMS-text message is more effective than usual care for controlling blood sugar among people with type 2 diabetes in diverse operational settings in sub-Sahara Africa. The trial will recruit participants from a general adult population of people with type 2 diabetes receiving primary care from outpatient facilities in Cape Town, Johannesburg, and Lilongwe. The main trial offers an established platform for methodological advances in measurement tools, and exploration of further factors which may influence treatment adherence.

Study aim and objectives

The overall aim of this project is to improve the assessment of neurocognitive function in people with diabetes at a wide-scale to (1) validate NeuroScreen, a tablet based neurocognitive screening tool for use in people with type 2 diabetes, and (2) to assess the burden and severity of NCI in a population of people with type 2 diabetes, and (3) identify potential interventions to assist those with NCI in their self-care and management.

This will be achieved through the following specific objectives:

- Test the sensitivity and specificity of NeuroScreen to detect NCI in people with type 2 diabetes compared to a gold standard battery of neurocognitive tests.
- Explore the association between NeuroScreen results at baseline and 12-month follow-up and biological markers of blood glucose control and measures of treatment adherence.
- Use sub-group analysis of main trail results stratified by neurocognitive function to explore differences in response to the trial intervention and to generate hypotheses about potential future interventions in this sub-group of people

Study design

Parent Study

StAR2D is a pragmatic individual randomised trial testing if a system of SMS-text messages to support treatment adherence is more effective than usual care for controlling blood sugar among people with type 2 diabetes in diverse operational settings in sub-Sahara Africa. The specific trial objectives are to; evaluate the effectiveness of SMS messages in improving overall diabetes control and supporting adherence to diabetes medicines

compared with usual care, determine the factors (including individual, health system and broader contextual factors) influencing the intervention impact as well as uptake, maintenance, scaling-up and potential for long-term engagement with the technology using both quantitative and qualitative methods, and to examine the incremental cost and cost-effectiveness of introducing a new SMS-text messaging programme into an existing health service setting. The trial will recruit participants from a general adult population of people with type 2 diabetes receiving primary care from outpatient facilities in Cape Town, Johannesburg, and Lilongwe.

We propose leveraging the platform of the main trial for a set of sub-studies at the Cape Town site to validate NeuroScreen and to assess the burden and severity of neurocognitive dysfunction in people with type 2 diabetes.

Sub-study 1: Validation of NeuroScreen to detect NCI in people with type 2 diabetes

The aim of this cross-sectional study component is to assess sensitivity and specificity for NeuroScreen in adult patients with type 2 diabetes managed in primary care.

Participants

Inclusion and exclusion criteria

Enrolled in the StAR2D trial and willing and able to provide consent to participate in this sub-study. StAR2D inclusion and exclusion criteria apply,

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Able to communicate in one of the predominant indigenous African languages in the South African provinces (e.g. English, Afrikaans Xhosa, Zulu and Sesotho), and in Malawi, the Chichewa language
- Male or female, aged 18 years or above.
- A diagnosis of type 2 diabetes.
- Taking oral glucose lowering treatment
- Has access to a cell-phone
- Knows how to use SMS (it is okay if participant needs help to send or retrieve SMS)
- Currently lives in the community served by the clinic and plans to live there for the next 18 months

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Within three months of a hospital admission for hyperglycaemia or hypoglycaemia
- Pregnant or within three months post-partum by self-report or with plans to become pregnant in the next 12-months
- A terminal medical condition
- Another member of the household already recruited to the trial
- Participation in the formative work for the intervention

In addition to the StAR2D exclusions participants who self-report the presence of a current psychotic disorder, significant current suicidal ideation, and or recent hospital admission for hypoglycaemia will be excluded from participation in the validation sub- study. Trial participants who do not know their HIV status will be excluded from the validation study. Trial participants who self-report a head injury that has led to more than 30 minute loss of consciousness or overnight hospitalisation, previous central nervous system disorders, for

example stroke and epilepsy, depression and substance abuse disorders will also be excluded from the validation sub-study.

Setting

Participants will be recruited from the main StAR2D trial site at Vanguard Community Health Centre, Cape Town, South Africa. NeuroScreen will be administered at this site. Formal neuropsychologocal testing will be done at the Department of Psychiatry and Mental Health at Groote Schuur Hospital.

Measurements

NeuroScreen

NeuroScreen is a tablet-based neurocognitive screen that consists of 9 neuropsychological tests. These types of tests are sensitive to the NCI associated with type 2 diabetes - learning, memory, executive functioning, attention/concentration, processing speed, and motor functioning. (14) All the neuropsychological tests embedded in the app are novel variants of those found in the gold-standard neuropsychological test battery that have been adapted and normed for use in South Africa for English or isiXhosa speakers (see "Gold-Standard Neuropsychological Battery" below). Raw scores from each test will be totalled and transformed into Z-scores based on the full sample results.

Standard Comparator

The Gold-Standard Neuropsychological Test Battery is a paper-and-pencil test battery that assesses individuals across seven cognitive domains using tests that have been shown to be sensitive with NCI seen in type 2 diabetes: learning and memory (Hopkins Verbal Learning Test-Revised and the Brief Visuospatial Memory Test-Revised); executive functioning (Color Trails Test 2, Stroop Color Word Test, and the Wisconsin Card-Sorting Test); attention/concentration (Mental Alteration, Mental Control and Digit Span); processing speed (Trail Making Test, Part A, and Digit Symbol Coding); language (semantic fluency of animals, fruits and vegetables), and motor functioning (finger tapping and grooved pegboard.) (14,16) This particular paper-and-pencil battery has been used by the UCT team for several other studies, and has been normed and validated for use with isiXhosa-speakers. (21,22) Data will include (1) raw test scores, (2) scaled scores; (3) age, education, gender and/or language adjusted T-scores; (4) individual domain deficit scores; and (5) global deficit scores. Demographic information (e.g., age and education) will be available from the StAR2D trial and will be controlled for in the predictive model (see Statistical Analysis below).

Procedures

Recruitment

After StAR2D assessment is completed participants who meet study criteria for the validation arm will be invited to participate in the sub-study. They will be given a study information sheet and time to consider whether they wish to participate. If they decide to participate a booking will be made for them to have the gold-standard battery of neuropsychiatric tests performed at Groote Schuur Hospital within two weeks of completing the NeuroScreen assessment.

Informed consent

The parent study informed consent process includes the NeuroScreen assessment at baseline and 12-month follow-up Informed consent procedures in the parent study (StAR2D) include completing the NeuroScreen at baseline and 12-month follow-up. Participants will consent for the parent study (StAR2D) and those participants who are eligible and willing to

participate in the enrolled in the validation study will provide additional written informed consent. Participant information leaflets and informed consent procedures will conform to the Helsinki Declaration and local HREC requirements.

Study procedures

The NeuroScreen questionnaire will be added to the baseline assessment of StAR2D trial patients enrolled at the Cape Town site. Trained psychometrists will administer and score the gold-standard battery, and enter the data into the database, within 7 days of the NeuroScreen assessment. Participants and lay health care workers will also be asked to complete a short survey on the acceptability of the NeuroScreen questionnaire. At the end of the formal assessment a per diem which may include money for transport costs will be provided to the participant.

Dr. Gouse, a neuropsychologist, will review the results of the Gold Standard Battery and calculate the global deficit score (GDS) for each patient, and we will use this GDS to identify those who have impairment and those who do not. The GDS is a robust method of summarizing neuropsychological battery scores to determine presence and severity of neurocognitive impairment.(23) Individual test *T*-scores are converted to a deficit score from 0 (no impairment) to 5 (severe impairment); deficit scores are averaged across all tests to create the GDS. The GDS considers number and severity of impairments, assigning less weight to unimpaired performance and overcoming the disadvantage of averaging absolute performance, which gives equal weight to unimpaired and impaired scores. (9,13,24) The GDS method detects mild NCI (GDS≥0.5) across varying impairment patterns in different neurocognitive domains. (9,13,23,25) We will set the threshold of GDS ≥ 0.5 as indicative of NCI.

Statistical Analysis

We will review the data for each variable we will explore graphically and formally test normal distribution assumptions.

We will compute the sensitivity (i.e., proportion of participants with impairment, among those who satisfied the criterion) and specificity (i.e., proportion of participants without impairment, among those who did not satisfy the criterion) of the NeuroScreen tool. Positive and Negative predictive values will also be calculated to truly define those with or without impairment. The area under the curve and the goodness of fit for the data will be assessed via the Receiver Operator Curve and the C-statistic respectively while considering the set threshold pf GDS≥0.5.

To assess the validity of the NeuroScreen tool we will calculate the sensitivity and specificity, positive and negative predictive values, the area under the receiver operating characteristic (AUC) curve and C-statistic as compared to GDS ≥ 0.5. (26,27) Using the strategy suggested by Bland and Altman we will enrol 100 participants in the validation sub-study. (26)

Sub-study 2: Pilot cohort study to explore the prevalence of and associations with NCI among adults with type 2 diabetes in primary care

The aim of this component is to explore associations between neurocognitive function and blood glucose control and treatment adherence, and to explore change in score over time.

Participants

Inclusion and exclusion criteria

All participants enrolled in the StAR2D trial recruited from the Cape Town site. StAR2D inclusion and exclusion criteria apply, After StAR2D enrolment and baseline assessment is

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Able to communicate in one of the predominant indigenous African languages in the South African provinces (e.g. English, Afrikaans Xhosa, Zulu and Sesotho), and in Malawi, the Chichewa language
- Male or female, aged 18 years or above.
- A diagnosis of type 2 diabetes.
- Taking oral glucose lowering treatment
- Has access to a cell-phone
- Knows how to use SMS (it is okay if participant needs help to send or retrieve SMS)
- Currently lives in the community served by the clinic and plans to live there for the next 18 months

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Within three months of a hospital admission for hyperglycaemia or hypoglycaemia
- Pregnant or within three months post-partum by self-report or with plans to become pregnant in the next 12-months
- A terminal medical condition
- Another member of the household already recruited to the trial
- Participation in the formative work for the intervention

Setting

Participants in this sub-study are a sample of participants from the main StAR2D trial from the Cape Town site, Vanguard Community Health Centre. The NeuroScreen questionnaire will be part of the baseline and follow-up assessment for all trial participants recruited at the Cape Town site.

Measurements

The NeuroScreen mobile-device based questionnaire consists of 10 tests sensitive to the NCI associated with type 2 diabetes: learning, delayed recall (memory), executive functioning, attention/concentration, processing speed, and motor functioning. (14)

Procedures

Recruitment

The NeuroScreen questionnaire questionnaire will be part of the baseline and follow-up assessment for all StAR2D trial participants recruited at the Cape Town site.

Informed consent

Participants provide written informed consent to participate in the parent study (StAR2D.) Participant information leaflets and informed consent procedures will conform to the Helsinki Declaration and local HREC requirements.

Study procedures

StAR2D participants have the NeuroScreen questionnaire administered as part of their baseline and final follow-up assessments for the trial. This sub-study will leverage the infrastructure, participant pool, and biomedical and behavioural outcome data of the StAR2D

trial in Cape Town (Vanguard Community Health Centre.) Demographic, medical (including HbA1c, lipid profile and blood pressure), and adherence data are collected at baseline (pre-intervention), and at 12 months follow-up in the StAR2D trial.

Statistical Analysis

We will review the data for each variable we will explore graphically and formally test normal distribution assumptions. We will conduct cohort analyses exploring for associations between baseline blood glucose control and NCI at 12-months controlling for various factors; exploratory analysis of change in NCI score between baseline and 12-months by blood glucose level.

The prevalence of cognitive impairment in adults with diabetes ranges from 2.2% in a population of people newly diagnosed with diabetes (in outpatient care) to 26.1% in a population based survey of adults older than 65 years. (11,28) In a small local study of a specialist hospital in-patient population of people with diabetes found a prevalence of 52%. (29) Prevalence could be lower or higher depending on the proportion of the sample with recently diagnosed diabetes, level of blood glucose of control, and co-morbid conditions. Thus if we assume a prevalence of this outcome to be about 32% then our sample size is sufficient to detect the prevalence of cognitive impairment as low as 26% and as high as 35% with 80% power at 5% significance.

Risks and benefits

Although participating in the study is low risk participants may feel distressed if they perceive their neurocognitive functioning is poor. Participants may also disclose substance use or mental health issues that necessitate referral. Participants in the validation study may experience distress at the idea of being 'tested' and may perceive the tests to indicate intelligence rather than function. In addition, the formal gold-standard battery of tests takes about 2 hours and this may result in mental fatigue for the participants.

Participants in the StAR2D trial will not be incentivised for their participation in the text message programme. Where additional travel to clinics may be required, they will be offered reimbursement of travel costs and provide an incentive that will cover the cost of a small meal. Eligible participants who decide to participate in the validation sub-study will also be offered reimbursement of travel costs for additional visit for the neuropsychological evaluation at the hospital and an incentive to compensate for time for the neuropsychological evaluation and lost earning potential.

Privacy and confidentiality

Data collected as part of this study will conform to the requirements and standards of the parent study. Please see the StAR2D data management plan.

Discontinuation/Withdrawal of Participants from Study

Participants who withdraw from the StAR2D trial will automatically be withdrawn from the DANCes sub-study. In addition participants in the main trial who withdraw from the validation study will continue to participate in the StAR2D trial without any effect on their participation, follow-up or standards of clinical care they receive.

What happens at the end of the study?

The end of the study is defined as the end of the final interview with the trial participant. When data analysis is complete, the findings will be shared as per the StAR2D reporting requirements.

Quality assurance procedures

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Ethical and regulatory considerations

Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Finance and insurance

Funding

This study is self-funded through the CDIA network.

Publication policy

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

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Appendix1. Copy of participant information leaflet and informed consent form for sub-study 1

PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE MAIN RESEARCH PROJECT: ***SMS supporting treatment Adherence foR for type 2 Diabetes (StAR2D)***

TITLE OF SUB-STUDY: ***Assessing type 2 Diabetes Associated NeuroCognitive impairment using an e-screening tool in a South African population***

PRINCIPAL INVESTIGATOR: Professor Naomi Levitt (Dr Kirsten Bobrow – clinical coordinator)

ADDRESS: Chronic Diseases Initiative for Africa (CDIA) J-47, J-floor, Old Main Building Groote Schuur Hospital, Observatory 7925 Cape Town. Tel: +27 21 406 6140

You have entered the StAR2D study and have just completed your last study visit for it. We would like to invite you to take part in another linked study. Please take some time to read over the information about this new study. You do not have to enter this new study – it is your choice whether you want to or not. Your participation is **entirely voluntary.** If you say no, this will not affect you negatively in any way. It will not affect your participation in the StAR2D study or services you are receiving at this clinic. You are also free to withdraw from the study at any point, even if you do agree to take part.

If you have any questions or are confused about anything, please ask the study staff or doctor any questions about any part of this new study that you do not fully understand. It is very important that you feel fully satisfied in your understanding of what participating in this study requires.

This study has been approved by the **Human Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town (UCT HREC 820/2016)**. This study will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

What is this research study all about?

- People living with type 2 diabetes often experience memory, thinking, attention, and concentration problems, as well as problems with coordination (known as cognitive problems). These problems can interfere with daily life and put individuals at risk for developing more severe cognitive problems.
- Knowing if people are experiencing cognitive problems is challenging, and a new tool that can be used by health care workers has been developed to help screen for cognitive problems among people living with type 2 diabetes.
- This study will be conducted at the study site to see how well the new tool can detect cognitive problems compared to the original tests. The study will include up to 100 participants who have completed the StAR2D study.

- In this study, you will be asked to complete a brief assessment of your mental health and a neuropsychological test battery that will take 2-3 hours. The neuropsychological battery will also ask you to remember things, drawing lines with your finger, and do other game-like activities that will assess your cognitive abilities. You will be able to complete this on the same day as you complete your StAR2D visit, or within 7 days of the visit.
- The study will not offer special treatment or medication. You will be provided with transport to the study site, a meal, and a small stipend when attend your visit.

What will your responsibilities be?

- If you agree to take part in this study, you will sign this form.
- You will be administered a short series of neuropsychological tests on a smartphone, which consist of remembering some words, tapping buttons on a smartphone, repeating number sequences, and using your finger or a stylus to connect dots on the smartphone screen.
- Then, the study counsellor will administer the screening tool on the tablet to you, which consists of remembering some words, tapping buttons, repeating number sequences, and using your finger to connect dots on the tablet screen.
- You will also be asked to answer some questions about your experience using computers and mobile deceives, and what it was like to use the tablet device.
- Then, you will be asked to complete the longer assessment that will take 2-3 hours. You can complete it today or come back within 7 days to complete it.
- The longer assessment will ask you questions about how you've been feeling in the past month, and ask you to remember things, draw, tap your finger, put pegs in holes, repeat number sequences, and solve problems.
- Your name will not be attached to any of the forms and results: they will only be identified with a study identification number.
- As part of this research project, the researchers will collect your unique StAR2D study number and get the following information from your StAR2D research record: your demographic information (age, gender, race, ethnicity, years of education, handedness), information about your diabetes medications, medical information, such as your HbA1C levels. All other information (your age, whether you are male or female, date of birth, whether you are taking medicines, the measurements made by the blood pressure machines and the blood test results) will not have your name on, and will just have a code so that the results could not be linked back to you.

Will you benefit from taking part in this research?

- You will not personally benefit from participating in this new study. Participation could possibly help researchers and scientists understand if the new screening tool works accurately, and this could lead to improved health for people like you.

Are there any risks involved in your taking part in this research?

- During the testing, you may experience emotional upset, embarrassment, or discomfort. If you request it and if you agree, the tests and interview will be stopped and rescheduled. Referral to appropriate counselling or support services can be made if you wish.
- There always exists the potential for loss of private information; however, there are procedures in place to minimize this risk.

If you do not agree to take part, what alternatives do you have?

- Participation in the study is voluntary. You may withdraw from the study at any time. There are no alternatives to participation. You are free not to participate or to withdraw at any time during the study. Your treatment will not be affected in any way, nor will your participation in the StAr2D study. You may continue to attend your clinic. It would be helpful for the study team to let us know why you have decided not to take part, but you are free to not give a reason.

Can you be dismissed from the study for any reason?

- Once you begin study participation, study staff may ask you to leave the study before you complete it. This is rare. There are several reasons this could happen such as becoming so medically or mentally sick you cannot attend study visit. If this happens, the study staff will refer you to appropriate health services. If you get better and wish to continue in the study, you may contact the study staff.

What if you decide you no longer want to participate in the study?

- Your participation is completely voluntary. You may withdraw from the study at any time. If you do, you will not lose any benefits to which you are otherwise entitled. Withdrawal will not affect the services provided to you by the clinic.

Who will have access to your medical records?

- The information collected about you will be treated as confidential and protected. If we write about this work, we will not identify you personally. Only the research study team will have full access to the information. Other researchers may have access to this data only in a securely anonymised form. Information you provide may be stored by the project team for a period of time after the project ends. Any personal information about you will be destroyed at the end of the study.

Is the information you provide confidential?

- All research study staff are instructed to keep all of your study information secret. They are not allowed to discuss it with the clinic staff. They are only allowed to discuss it with the research study staff. All study information will be identified by unique ID numbers and will be kept in locked file drawers. These records will only be available to research study staff. Institutional personnel may access it as part of routine audits. A list matching participant names with ID numbers will be kept in a separate locked file drawer. This information will only be available to research study staff. Study results will be reported only as a group. This way, no individual participant can be identified.

Will you be paid to take part in this study and are there any costs involved?

- You will be reimbursed for your transport costs and time to complete the study procedures. You will receive R200.00 when you complete all of the study questions and evaluations for the validation sub-study.
- The maximum compensation is R200.00.

What if you get injured as a direct result of participating in this study?

- Free essential medical treatment is available to you only if you are injured because of your participation in this study. You will not receive any money as compensation for injury.

In case of an emergency or if you feel you need to contact one of the study doctors, you can do so by phoning

Professor Naomi Levitt or Dr Kirsten Bobrow at tel no 021-6505351

- You can also contact the Human Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by study staff.

Information and Consent Summary

Ensure that each participant clearly understands each of the following points:

- You are being asked to partake in a research study linked to the StAR2D study because you already in the StAR2D study.
- As a participant in the study, you have already completed the NeuroScreen on a tablet device, **at one study visit** at the field site, you will:
  - Allow the study psychometrist to administer a comprehensive neuropsychological battery to you.
- Everything you share during the visits is confidential. Only those people involved in this research study will see your answers to the questions. The clinic staff will not have access to your answers.
- Your participation in this study is completely voluntary.
- Your participation or decision not to participate in the study WILL NOT affect your care at the clinic.
- You can withdraw from the study at any time without negative consequences and you can continue receiving care at this clinic.

DECLARATION BY PARTICIPANT

PARTICIPATION IN RESEARCH STUDY

By signing below, I _____ agree to take part in a research study entitled: "*Assessing type II Diabetes Associated NeuroCognitive impairment using an e-screening tool in a South African population (DANCes); a validation study"*

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan as agreed.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature/Fingerprint of participant

DECLARATION BY INVESTIGATOR/STUDY COORDINATOR

I *(name)* _____declare that:

- I explained the information in this document to _____
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above.

Signed at (*place*) _____ on (*date*) _____ 20____.

_____

Signature of investigator/study coordinator

Part B: Structured literature review on the relationship between cognitive function and self-care and related health behaviours in adults with type 2 diabetes mellitus

Contents

Introduction

Background

Type 2 diabetes is major global public health concern. (2) Low- and middle-income countries are disproportionally affected by the substantial and growing burden of premature morbidity and mortality associated with the condition. (3,4) In South Africa the estimated prevalence of type 2 diabetes is about 9% and it is a top 10 cause of premature mortality and morbidity. (5,6)

Type 2 diabetes is a progressive multi-system disease. Published results from epidemiological studies suggest that type 2 diabetes may also be associated with and increased risk of neurocognitive impairment and dementia. (14,30,31) Well known are the increase in risk of cardio- and cerebrovascular events, impaired renal function, and peripheral neuropathies in people with type 2 diabetes and the association between event risk and long-term blood glucose control. (9–13)

Although results observational epidemiological studies have consistently shown an association between type 2 diabetes and cognitive impairments and dementia there remains no unifying theory of the underlying mechanism. The neuropathological processes are likely multi-factorial and may occur in parallel. Vascular, metabolic, and neuroendocrine factors have all been shown to contribute to risk neurocognitive impairment and dementia in people with type 2 diabetes. (14)

Imaging and post-mortem studies show that cortical grey matter volumes are reduced, and there is a high burden of vascular disease in this population.(32,33) Pre-clinical, pathological, and imaging studies in have shown associations between type 2 diabetes and disruptions in the blood-brain-barrier, neuronal insulin resistance and impaired signalling, abnormal mitochondrial function and a pro-inflammatory state which may increase the presence of abnormal proteins (like amylin) or decrease clearance of amyloid and tau. (33–36) There is some evidence for gene-environment interactions with people who are Apoe4 allele carriers and who have diabetes at even greater risk for dementia.(33) Finally, more research is needed to clarify the role of treatments including exogenous insulin in mediating or mitigating pathophysiological process.(10,37)

Most people with type 2 diabetes will require the use of one of more blood glucose lowering agent in addition to a package of lifestyle modifications across multiple domains including diet and physical activity. Ongoing modification of lifestyle and adoption of diabetes related health behaviours (foot care, timing of medication and meals, attending clinic appointments on-time) is achieved through daily self-care and management activities. (38) Planning, problem solving, organization, and working memory are just some of the higher order cognitive functions required to successfully navigate these behavioural tasks. (39) Self-care activities have been shown to be associated with improved treatment adherence, blood glucose control, and disease outcomes in people with type 2 diabetes. (38,40)

Objectives

The objective of this structured literature review is to summarise the available published evidence on the nature of the relationship between cognitive function and self-care and related health behaviours in adults with type 2 diabetes mellitus. Attention will be given to identification of specific cognitive domains (and specific tests) which may be particularly affected in adults with type 2 diabetes, and their association with self-management and other health related behaviours and outcomes.

Methods

A literature search was conducted in July and August 2016 and up-dated in January 2018.

Search terms

Search terms were grouped under the themes: type 2 diabetes, self-management and health behaviours, and cognitive functions and impairment. (See table 1.)

Table 1 Search themes and terms used in to search published literature

Primary Search Terms	Key words / associated terms Information
Type 2 diabetes mellitus	Type 2 diabetes mellitus
Self-management and health behaviours	Self-management; self-care; treatment adherence
Cognitive functions and impairment	Diabetes; brain; cognition; cognitive; cognitive performance; executive function; neuropsychological test; mild cognitive impairment (MCI); cognitive impairment; cognitive dysfunction; risk factor;

Data bases

Peer-reviewed published literature from 01/01/1990 to 31/12/2017 was searched using search engines PubMed, Web of Science, OVID, CINHAL and the Cochrane library. Searches were restricted to studies in humans, no language restrictions were set.

A hand search of references from studies included in the review was also performed.

1.1. Inclusion and exclusion criteria

Studies were included if,

- Study population human adults (> 18 years of age)
- Observational (cross sectional or longitudinal) or intervention studies
- Contained people with type 2 diabetes (self-report, medical record review, measured using international guidelines for measurement and interpretation of short or long term blood glucose levels.)
- Objective measure of neurocognitive function using validated and reliable tests (not limited to specific tests)
- Objective measure of self-care or health behaviour (either self-care scale or one of the criteria from ADA statement on Self-Management and Support Education; diabetes pathophysiology and treatment options, healthy eating, physical activity, medication usage, monitoring and using patient-generated health data, preventing, detecting, and treating acute and chronic complications, healthy coping with psychosocial issues and concerns, problem solving) (38)

Studies were excluded if,

- Small studies (<100 participants with type 2 diabetes)
- Did not report measurement of cognitive function (i.e. reported only diagnosis of dementia or cognitive impairment)
- Did not report measurement of self-care or health behaviour
- Did not control for gender
- Did not control for age
- Did not control for education
- ***Figure 1 Flow diagram describing how studies selected for review***

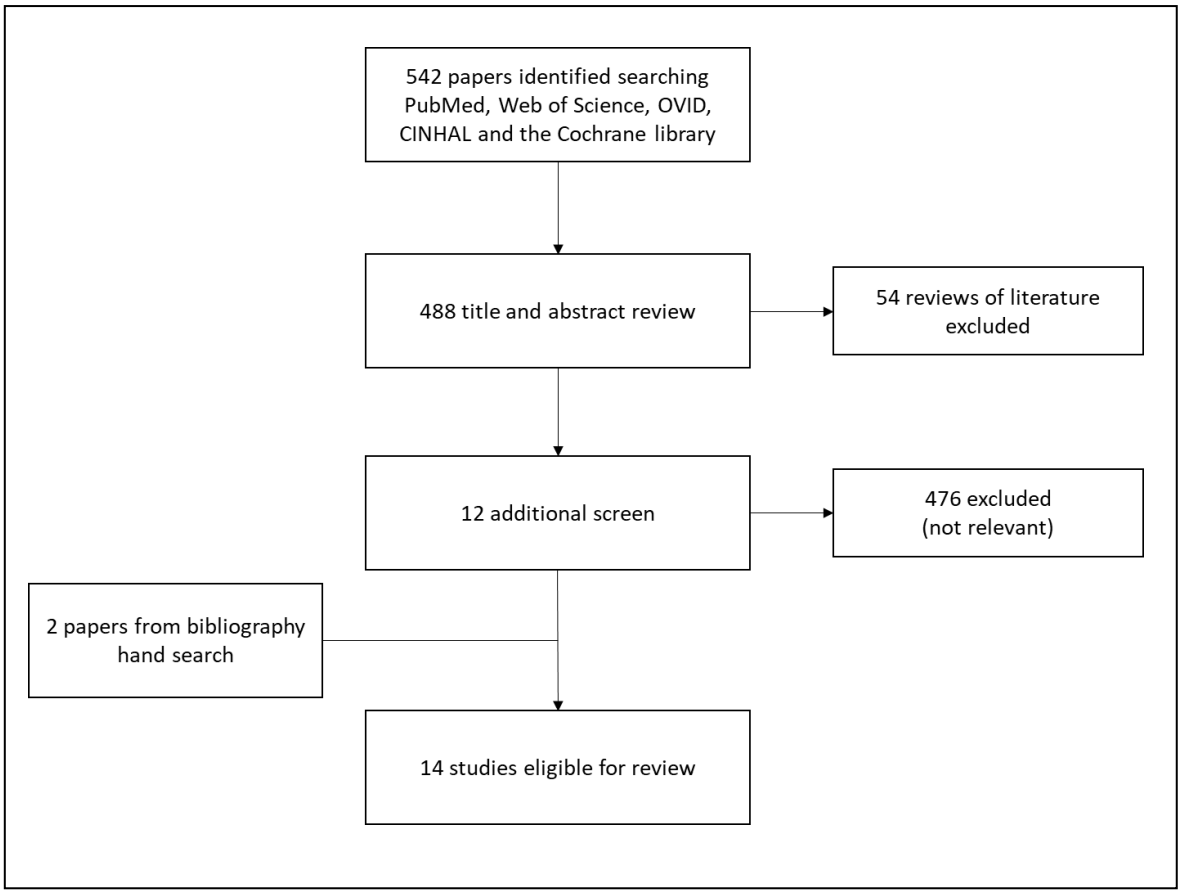

Figure 2 Flow diagram describing how studies selected for review

Results

542 records were retrieved from the various databases for title and abstract review. 54 studies which were reviews of the literature were excluded (the bibliographies were searched for additional relevant studies.) Duplicates were removed as were studies which did not meet inclusion and exclusion criteria. Twelve studies were eligible for final review. A hand search of references from studies included in the review was also performed. The final number of studies included was fourteen.(41–54)

Study and sample characteristics

Tables 2a and 2b show study design, sample size and location, main study aims, and how type 2 diabetes was diagnosed, neuropsychological and self-management measures for the selected studies. Of the selected studies most were observational; cross sectional design (11), case control (1); cohort (3). One study used data from a cluster randomised trial. Sample sizes ranged from 112 participants to 27 271. No studies came from low income

settings; fourteen studies were conducted in high income countries; one study was conducted in China (upper middle-income.) The primary aim of most studies was to explore the association between cognitive function or impairment and some measure of self-management among adults with type 2 diabetes. In six studies it was a secondary aim or studies included sufficient information on neurological function testing and self-management to be included in the review.

The studies included 45 586 participants. Table 2 shows selected participant characteristics from the included studies. Although the mean age of participants in most of the studies (10 of 16) was 70 years or older (in two it was over 80 years of age) the mean age of most of the individual participants was 62 (SD 11) years. Most of the studies enrolled more women than men; calculating a weighted average 63% of all the participants were women. Level of education was variously reported making it difficult to compare across studies. All studies included education in their models even if they did not present this variable in the results. Few studies reported the ethnicity of study participants again making it difficult to compare across reported.

Diagnosis of Type 2 Diabetes and measures of glycaemia

Studies included adults with either prevalent or screen diagnosed type 2 diabetes. Three studies included participants who self-reported a physician diagnosis of type 2 diabetes; Tran et al used self-report alone as a binary variable i.e. did not report measure of glycaemia.(47) Jagielski et al used data from the Guangzhou Biobank Cohort Study (GBCS) self-report of physician diagnosis and use of blood glucose lowering treatments and measured fasting blood glucose levels; categorised as normal (<5.6 mmol/l), impaired (≥5.6–<7.0 mmol/l), and type 2 diabetes (≥7.0 mmol/l.) They did not report the number of screen detected cases of type 2 diabetes. Demakakos et al used data from the English Longitudinal Study of Aging (ELSA) which supplemented self-report data with biennial blood sampling for HbA1c levels; 90% of participants took part in the second wave of data collection which included blood sampling.(55,56) The remaining studies used record reviews and laboratory testing of HbA1c levels.

The studies by Tran et al and Demakakos et al used presence or absence of type 2 diabetes to classify study participants and did not report measures of glycaemia. In the remaining studies all except Rodríguez-Pascual et al and GBCS used HbA1c as a continuous measure of glycaemia in their models. In Rodríguez-Pascual et al percentage HbA1c was summarised into a binary variable indicating metabolic control (good or not) by age[1]; in the GBCS fasting blood glucose was treated as a categorical variable (see above).(50) The mean weighted HbA1c for studies of people with prevalent type 2 diabetes was 7.25%. HbA1c results for individual studies are presented in table 3.

Cognitive domains and neuropsychological tests

Studies reported testing various cognitive domains using a variety of neuropsychological tests. (See tables 2 and 3.) Cognitive domains and tests mapped to them were not reported in a standardised manner. Appendix 1 contains list of cognitive domains and neuropsychological tests adapted from NHI Health Brain Project. Most commonly studies used the Mini Mental Status Exam or another combined measure of mental status with or without additional individual tests as a measure of cognitive function and to classify participants as impaired or not (9 of 15.) Use of combined measures may lead to misclassification of cognitive impairment sub-types. For example, risk of dementia is known to be increased in people with type 2 diabetes and people with early stage disease may have similar MMSE scores to those with diabetes associated cognitive impairment. Of the studies using the MMSE only two reported excluding participants with prevalent dementia (49) however all studies required written informed consent making it unlikely people with

[1] Glycosylated haemoglobin: patients without high comorbidity or associated disability ≤7% if under 80 years, and <8% if 80 or more years. In patients with high comorbidity or functional impairment <8% if under 80 years old, and <8.5% if in 80s or over.(44)

severe dementia would be included; participants with early stage dementia may have been included in the studies and may have been misclassified.

Individual neuropsychological tests reported most commonly by the included studies were, RAVLT or other word recall test (n=4), Stroop (n=3), Trails A, B (n=2), Clock (n=2), Digit Symbol Coding or Substitution (n=2). Lack of uniform testing and reporting make it difficult to compare across studies. For example, three studies used mean MMSE scores (41,47,52), two used MMSE as a binary variable with cut point of ≤24 to indicate impairment (50,57) although Jagielski et al defined cognitive impairment using a Delayed Word Recall Test score <4 (mean = 5.36; SD = 1.42).(50) Five studies presented raw test scores, (44,45,53,54,58) four standardised their scores calculating t, z, or g-scores. (42,43,46,59) Three studies used physician review and diagnostic criteria to classify participants as impaired or not. (48,49,51)

A recent systematic review explored the effect size for individual neuropsychological tests frequently reported in the literature on cognitive impairment in adults with type 2 diabetes. (14) The authors reported that the domains most commonly tested were verbal and visual memory, attention/concentration, processing speed, and executive function.

Table 2 Characteristics of observational studies included in this review

Authors	Study Design (sample size)	Location	Aim of study	Diabetes diagnosis	Neuropsychological tests	Self-help or other health behaviour measures
Sinclair et al, 2000 (41)	Case control (n=789)	UK (Wales)	Explore association between cognitive impairment and changes in self-care behaviour, use of health and social services in adults with and without type 2 diabetes	Record review or physician diagnosis	Mini Mental State Exam (MMSE) Clock Drawing Test	Barthel Index and the Extended ADL Scale
Kazlauskaite et al, 2009 (42)	Cross sectional (n=115)	USA	Determine prevalence of inaccurate SMBG and predictors of inaccurate reporting in adults with diabetes	Record review or physician diagnosis	Digit Symbol Coding Test (DSCT) Rey Auditory Verbal Learning Test (RALT) Trail Making Tests A, B (TMT-A,B)	Blood glucose self-monitoring (glucose diary accurate; meter with at least 10 readings in past 60 days)
Primozic et al, 2010 (43)	Cross sectional (n=114)	Slovenia	Explore association between cognition and emotion self-management in patients with type 2 diabetes	Record Review or physician diagnosis	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Tower of London (ToL) Stroop Colour and Word Test	Diabetes Self-Care Activities (SDSCA) measure
Rodríguez-Pascual et al, 2011 (44)	Cross sectional (n=112)	Spain	To describe characteristics, level of metabolic control, and health related quality of life in older people with type 2 diabetes	Record Review or physician diagnosis	Pfeiffer abbreviated questionnaire	EuroQol 5-Dimensions (EQ-5D) Red Cross ADLS IADLS
Feil et al, 2012 (45)	Cross sectional (n=1 398)	USA	To examine relationships between cognitive impairment and diabetes self-care ability	Laboratory (HbA1c)	Telephone Interview for Cognitive Status (modelled after MMSE)	Taking diabetes medication, exercising regularly; following a recommended eating plan; checking blood glucose level; and checking feet for wounds or sores.
Munshi et al 2012 (46)	Cross sectional (n=145)	USA	Association between executive function variously measured with glycaemic control in type 2 diabetes	Record Review or physician	Clock-in-a-box Phonemic verbal fluence Trails A,B	Dysexecutive questionnaire; Activities of Daily Living (ADLS); Instrumental Activities of Daily Living (IADLS); Falls
Tran et al, 2014 (47)	Cross sectional (n=252)	USA	Explore association between cognitive impairment and type 2 diabetes, health-related behaviours; health services utilisation.	Self-report of physician diagnosis	MMSE Behavioral Dyscontrol Scale (BDS)	Oral hygiene (frequency of brushing and frequency of flossing) IADLs (total IADLs, medication, and meal planning) SAILS (incl. medication)

Table 2 Continued

Authors	Study Design (sample size)	Location	Aim of study	Diabetes diagnosis	Neuropsychological tests	Self-help or other health behaviour measures
Gorska-Ciebiada et al, 2014 (48)	Cross sectional (n=276)	Poland	To estimate the prevalence of cognitive impairment, depressive mood, and its comorbidities and risk factors	Record Review or physician	Montreal Cognitive Assessment (MoCA) Geriatric Depression Scale (GDS-30)	Katz Basic Activities of Daily living (BADL) Lawton Instrumental Activities of Daily Living (IADL)
Koekkoek et al, 2015 (49)	Cross sectional (n=225)	Netherlands	Explore differences in health status and depressive symptoms between patients with type 2 diabetes with and without undiagnosed cognitive impairment.	Record Review or physician	Test Your Memory (TYM) Self-Administered Gerocognitive Examination(SAGE) MMSE	Short Form-36 (SF-36) EQ-5D EuroQol Visual Analogue Scale (EQ-VAS)
Jagielski et al, 2015 (50)	Cross sectional (n=27 271)	China	Explore association between type 2 diabetes and cognitive impairment	Self-report of physician diagnosis, measured fasting blood glucose (FBG)	MMSE Delayed Word Recall Test (DWRT)	Self-rated health status
Bruce et al 2009 (51)	Cohort (n=302)	Australia	Explore associations between hypoglycaemia and cognitive status	Laboratory (HbA1c)	MMSE	Hypoglyaemic episodes (self-report, medical record review, linkage to health service data)
Verny et al 2015 (52)	Cohort (n=987)	France	Study factors associated with cognitive decline in adults with type 2 diabetes	Record Review or physician	Global function	ADLS, IADLS
Demakakos et al, 2017 (53)	Cohort (n=10 524)	UK	Associations between baseline diabetes and elevated depressive symptoms and trajectories of cognitive function over a 10-year follow-up.	Self-report, laboratory measures biennially (HbA1c)	Semantic verbal fluency test 10-word immediate and delayed recall test	ADLS

Table 3 Characteristics of interventional studies included in this review

Authors	Study Design	Location	Aim of study	Diabetes diagnosis	Neuropsychological tests	Self-help or other health behaviour measures
Punthakee et al, 2012 (54)	RCT (n=2 956)	USA, Canada	To assess the effect of baseline cognitive function on subsequent risk of severe hypoglycaemia, and risk for severe hypoglycaemia, and whether intensive versus standard glycaemic control strategies affect these relationships.	Laboratory	MMSE DSST 4 questions on ability to manage diabetes RAVLT Stroop test Patient Health Questionnaire (PHQ)	Hypoglycaemia severe enough to require medical assistance by self-report

Few studies reported on motor function. Commonly reported tests and their associated effect size measured using Cohen's delta are shown in table 5. The effect size for most tests was small to moderate. The individual tests with the largest effect size were the Grooved Peg Board (both hands), Trail Making Test B, RAVLT (immediate), and the delayed Rey Osterrieth Complex Figure. None of the studies included in this review used the Groove Peg Board or the Rey Osterrith Complex Figure tests and only Kazlauskaite et al and Munshi et al used Trail Making Tests.(42,46)

Table 4 Selected participant characteristics of included studies

Authors	Age (years,SD)	Sex (% Female)	Level of education (Years, SD or %)	Ethnicity (%, Reported)	Measure of glycaemia (% HbA1c, SD or as reported]
Sinclair et al, 2000 (41)	74.9 (7)	96	65% (schooled to 14)	Not adequately reported (NAR)	7.8 (3)[2]
Kazlauskaite et al, 2009 (42)	56 (11)	63	40% High school or less	60% Black African American	8 [6.1 – 116.6]
Primozic et al, 2010 (43)	63.7 (9.9)	51	11.2 years	91% Slovene	7.7 (1.3)
Rodríguez-Pascual et al, 2011 (44)	81.4 (5.7)	70	85% Primary school only	NAR	7.4
Feil et al, 2012 (45)	70 (7.4)	53	33% less than high school	79% White	7.2 (2.5)[1]
Munshi et al 2012 (46)	77 (5)	52	15 years (3)	NAR	7.3 (1.2)
Tran et al, 2014 (47)	71.8 (6.7)	59	10.3 years (3.5)	64% Hispanic	NA
Gorska-Ciebiada et al, 2014 (48)	73.6 (4.8)	54	11.3 years (2.4)	NAR	7.2 (0.7)
Koekkoek et al, 2015 (49)	76.8 (5)	40	NAR	NAR	7 (3)
Jagielski et al, 2015 (50)	61 (6.9)	72	40% Primary school or less	NAR	5.2 (2.6)[1]
Bruce et al 2009 (51)	76 (6)[1]	52	NAR	NAR	7[1]
Verny et al 2015 (52)	77 (5.7)[1]	52	55% Less than high school	NAR	7.6 (1.3)[1]
Demakakos et al, 2017 (53)	65 (9.9)	47	38% no qualifications	NAR	NA
Punthakee et al, 2012 (54)	62.5 (5.8)	47	39% High school or less	70% Non-Hispanic white	8.3 (1.0)

Self-management and health care behaviours

Studies also reported a variety of self-care or health behaviours. (See table 1.) Most studies measured either Activities of Daily Living (ADLS) or Instrumental Activities of Daily Living (IADLS). (41,44,46–48,52,53) Studies also reported blood glucose measuring, oral health, falls, and hypoglycaemia which may be important individual aspects of self-care in people with type 2 diabetes. (42,46,47,51,54) Three of the included studies measured a more

[2] Calculated from published data

comprehensive set of diabetes specific behaviours; taking diabetes medication, exercising regularly;, following a recommended eating plan, checking blood glucose level, and checking feet for wounds or sores. (43,45,46) Feil et al reported individual scores whereas the other two reported composite scores in their models and it was not possible to explore whether one or more diabetes specific behaviours was associated with a measure of cognitive function.

***Table 5 Cognitive domains most commonly thought to be being tested by specific named tests adapted from Palta et al.* (14)**

Cognitive domain	Test or instrument		Pooled Cohen's *d* effect size from Palta et al. (14)
Verbal memory	Rey Auditory Veral Learning Test (RAVLT) – Immediate	Immediate	-0.40 (-0.53 to -0.28)
		Delayed	-0.33 (-0.47 to-0.19)
	Wechsler Memory Scale (WMS), Logical Memory	Immediate	-0.13 (-0.55 to 0.30)
		Delayed	-0.18 (-0.66 to 0.30)
	California Verbal Learning Test (CVLT)	Immediate	-0.19 (-0.49 to 0.12)
		Delayed	-0.27 (-0.45 to -0.09)
Visual memory	Rey Osterrieth Complex Figure	Immediate	-0.33 (-0.52 to -0.15)
		Delayed	-0.38 (-0.54 to -0.21)
	WMS-Visual Reproduction	Immediate	-0.18 (-0.55 to 0.20)
		Delayed	-0.11 (-0.38 to 0.15)
Attention/Concentration	Weschler Adult Intelligence Scale (WAIS)	Forward	-0.18 (-0.27 to -0.08)
		Backward	-0.12 (-0.22 to -0.02)
	Stroop	Part I	-0.28 (-0.45 to -0.11)
		Part II	-0.26 (-0.42 to -0.10)
Processing speed	WAIS	DSST	-0.33 (-0.45 to -0.20)
	Trail Making Test	A	-0.34 (-0.44 to -0.24)
Executive function	Trail Making Test	B	-0.39 (-0.52 to -0.27)
	Stroop	Part III	-0.26 (-0.39 to -0.12)
	Wisconsin Card Sorting Test	Categories	-0.35 (-0.70 to 0.00)
Motor function	Grooved peg board	Dominant hand	-0.60 (-0.90 to -0.31)
		Non-dominant hand	-0.51 (-0.81 to -0.22)
	Finger tapping	Dominant hand	-0.17 (-0.32 to -0.02)
		Non-dominant hand	-0.23 (-0.39 to -0.08)

Association between type 2 diabetes and cognitive impairment

Four of the included studies included a comparison population without type 2 diabetes. (41,47,50,53) Reported findings from both the cross-sectional GBC study and the three cohort studies showed that adults with type 2 diabetes performed worse on global and individual neuropsychological tests than adults without type 2 diabetes. All models were adjusted for age, sex, education, depression score as well as other potential confounders.

In studies with only participants with type 2 diabetes Feil et al, Koekoek et al, and Primozic et al did not find evidence that HbA1c or duration of disease was significantly associated with cognitive impairment. (45,49) In contrast, Kazlauskaite et al, and Gorska-Ciebiaa et al,

showed that HbA1c and duration of disease were significantly associated with cognitive impairment. (42,48) The effect sizes were small. Reviewing the findings for associations between type of blood glucose lowering treatment were similarly mixed; some but not all studies showed that insulin containing regimens were associated with worse performance on neuropsychological tests. Some but not all the studies found that people with both type 2 diabetes and symptoms of depression had lower neuropsychological test and self-care scores.

Association between cognitive impairment and self-care

We used the Capability Opportunity Motivation – Behaviour (COM-B) model for characterising and changing behaviours to develop a theoretical model of how cognitive function and dysglycaemia in type 2 diabetes interact with self-management activities. (60) This model is slightly different to the one suggested by Feil et al (45) – it doesn't conceive of the relationship as cyclical i.e. poor glycaemic control leads to poor cognitive function leads to poor self-care which exacerbates poor control etc. Rather, it highlights the mediating role that an individual's capability (physical and psychological), motivation (autonomic and reflexive), and opportunity (social and physical) may play in the relationship and the bidirectional relationship of the interactions.

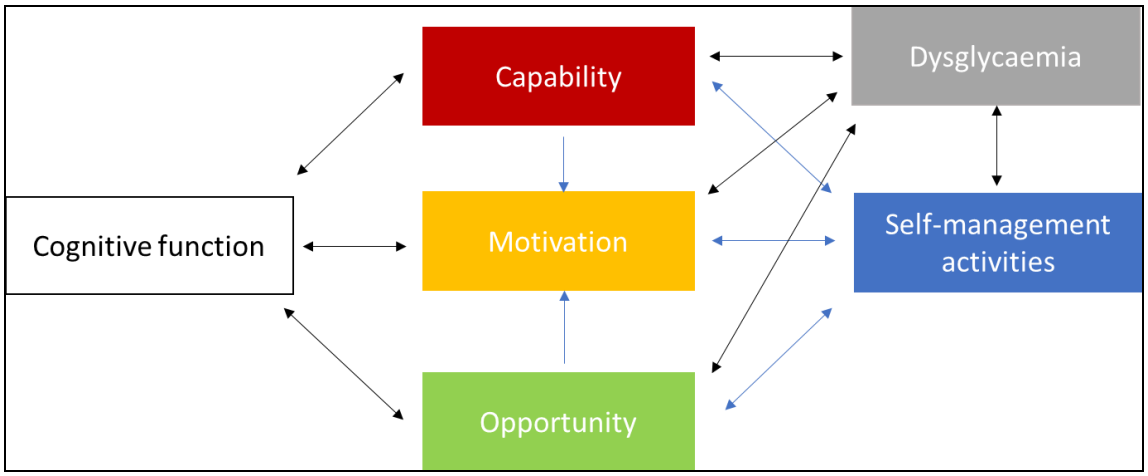

Figure 3 Hypothesised model characterising the relationship between type 2 diabetes, cognitive function and self-management activities using the COM-B model.

All the studies included in this review found an association with some if not all their reported measures of self-care. For example, Feil et al (45) sampled adults in the community and found that the percentage of participants who reported being able to adhere to each diabetes related self-care task decreased with worse neuropsychological test scores; the self-care tasks most likely to be affected were following a recommended eating plan and participating in regular physical activity. Results in Tran et al also showed worse test scores to be associated with decrease in self-reported meal, medication management, and activities of daily living scores. (47) Meal planning and preparation is a complex often social activity where aspects of opportunity (for example whether a person is living independently or in a care facility), motivation (for example finding and selecting healthful ingredients), and capability (for example negotiating meal selection with partners or family) dynamically interact with cognitive function and self-management activities. (61)

Discussion

In this structured review of literature on the relationship between cognitive function and impairment on self-care and related health behaviours in adults with type 2 diabetes mellitus we found evidence that type 2 diabetes is associated with cognitive impairment and with measures of self-management. There is evidence that people with type 2 diabetes have worse cognitive function than those without and that those with impaired cognitive function have evidence of poorer self-management. These findings are similar to those reported in a recent small systematic review. (39)

We have proposed a model to potentially explain how type 2 diabetes dysglycaemia, cognitive function, and self-management synergistically act on each other through mediators of capability, motivation, and opportunity. We think it is plausible that the relationship is dynamic and shifts over time. This model also allows for multi-morbidity to be accounted for (again through capability, motivation, and opportunity as mediators.)

Of concern is that none of the trials to date have showed benefit of glycaemic control in preventing or treating cognitive decline associated with type 2 diabetes. (31) This may suggest that targeting other aspects of the relationship are required to improve outcomes in this group. For example, providing additional treatment adherence support to people with cognitive impairment (with special focus on supporting eating as recommended and being physically active.)

This review has several limitations to be noted. We found few studies explicitly tying the outcomes of neuropsychological tests to important clinical and health behaviours. Of the studies included none were from low or middle-income settings and none were from Africa. We found two studies exploring the association between type 2 diabetes and cognitive function in hospital outpatient populations. (62,63) Results from both studies showed cognitive impairment to be common in these populations. It is likely that the associations noted between impaired cognition and poorer self-care in this review may be found in these populations as well.

The studies included reported a wide variety in how people with type 2 diabetes were identified (self-report, medical record review, biochemical measurements), how cognitive function was measured (global or specific domains measured, face-to-face interview or telephone interview) and scored (raw or transformed), and which confounders were measured and adjusted for in models. This variety made it difficult to directly compare results across studies. Also, most of the studies included in this review were cross-sectional which limits inferences on the role of chronic hyperglycaemia as well whether cognitive impairment is static or dynamic over time; and whether shifts in cognitive impairment vary across domains.

While there is a growing body of epidemiological evidence of the association between type 2 diabetes and cognitive impairment in diverse study populations there is much less published evidence on the clinical relevance of small to moderate differences in neuropsychological test scores. Researchers could meaningfully focus on standardising the neuropsychological tests used to measure cognitive function in people with type 2 diabetes (specific attention should be given to measuring those domains thought to be important based on known pathophysiology) and on standardising the self-management measures of importance. Attention should also be given to conducting research in settings where type 2 diabetes is highly prevalent as it is in many low and middle-income settings. Lastly, there is probably sufficient evidence of an association between cognitive impairment and self-management in adults with type 2 diabetes to warrant intervention studies focused on behavioural and

complex interventions beyond glycaemic control and which are suitable for implementation in low and middle-income settings.

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Appendix 2. List of Cognitive Measures adapted from NHI Healthy Brain Project (64)

Learning and memory	
Verbal learning and memory	**Nonverbal learning and memory**
Wechsler Memory Scale - Revised (WMS-R) Selective Reminding Test (SRT) Cued Selective Reminding Test Fuld Object Memory Test Rey Auditory Verbal Learning Test (AVLT) California Verbal Learning Test (CVLT) Delayed Word Recall Test New York University Memory Test Rivermead Behavioral Memory Test	Visual Reproduction subscale of Wechsler Memory Scale - Revised Benton Visual Retention Test (VRT) Benton Visual Retention Test, Multiple Choice (VRT-MC) Rey-Osterrieth Complex Figure Test Delayed Recognition Span Test (DRST)

Executive function abilities[3]	***Language***
Trail Making Test (TMT) Ravens Progressive Matrices Wisconsin Card Sorting Test / Modified Wisconsin Card Sorting Test Stroop Color-Word Interference Test Visual-Verbal Test WAIS-R Similarities subtest Gorham Proverb Interpretation Test	Aphasia screening battery Halstead-Wepman Aphasia Screening Test Confrontation naming Boston Naming Test Verbal fluency Controlled Oral Word Association Test (FAS) Isaacs Set Test (IST) Comprehensive batteries to assess linguistic skill Boston Diagnostic Aphasia Examination (BDAE) Multilingual Aphasia Examination (MAE)

Visuospatial abilities	***Sustained Attention***
WAIS-R Performance subtests Clock Drawing Task Figure copying Figure matching	Digit Span from WAIS-R Mental Control subtest from WMS-R Attention/Concentration Index from WMS-R Continuous Performance Test (CPT) The "A" Test

Brief mental status tests	***Intelligence Tests***
Short Portable Mental Status Questionnaire (SPMSQ) Mini-Mental State Exam (MMSE) Modified Mini-Mental State Exam (3MS) Cognitive Abilities Screening Test (CASI) East Boston Memory Test (EBMT) Blessed Information, Memory, Information and Concentration Test (BIMC) Neurobehavioral Cognitive Status Examination (NSCE) 7 Minute Screen Geriatric Mental State Examination Telephone Interview for Cognitive Status (TICS)	Wechsler Adult Intelligence Scale - Revised (WAIS-R) National Adult Reading Test (NART) Primary Mental Abilities

[3] concept formation, abstraction, set shifting, set maintenance, planning, self-monitoring, divided attention

Part C: Journal manuscript

Burden and severity of neurocognitive impairment in adults with type 2 diabetes in primary care in South Africa: a cross-sectional analysis using a novel screening tool

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[4] For readability, figures and tables are inserted into the text. Text, tables and figure numbering are formatted to align with dissertation.

Background: Type 2 diabetes has been found to be associated with cognitive impairments in planning, problem solving, organization, and working memory and also with an increased risk of dementia. Neurocognitive impairment may impact self-care and other health behaviours increasing the risk of poor health outcomes in this patient population. Detection of neurocognitive impairment in low and middle-income settings is challenging; there is a lack of validated screening tools suitable for local use in primary care and outpatient settings and access to formal neuropsychological testing services is limited. The inability to easily identify people with type 2 diabetes with neurocognitive impairments is constraining the development of context appropriate interventions to improve the care and outcomes in this sub-group of patients.

Aim: The aim of the current analysis is to explore associations between neurocognitive function and measures of diabetes control (HbA1c, disease duration, type of blood glucose lowering treatment) at baseline in a population of people with type 2 diabetes participating in a clinical trial of treatment adherence support using SMS-text messages.

Materials and Methods: SMS supporting treatment Adherence foR for type 2 Diabetes (StAR2D) is a randomised clinical trial testing if a system of SMS-text messages to support treatment adherence is more effective than usual care for controlling blood sugar among people with type 2 diabetes in sub-Sahara Africa (ISRCTN70768808). We have embedded neurocognitive assessment sub-studies into the Cape Town trial site. At baseline participants in the StAR2D trial complete a novel mobile-device based cognitive assessment, NeuroScreen, assisted by a field research assistant. The assessment contains 9 variants of tests found in the gold-standard neuropsychological test battery that have been adapted and normed for use in South Africa. It is available in English or isiXhosa. The assessment takes between 20 to 40 minutes depending on participant error rate. This cross-sectional analysis of baseline data uses linear and logistic regression models to explore associations between neurocognitive function and measures of diabetes control.

Results: Six hundred participants eligible for enrolment in the StAR2D trial were recruited from the Cape Town trial site; 499 participants completed the baseline neurocognitive screening assessment (20 to 40 minutes to complete); 101 participants did not complete the assessment (commonly due to eyesight, hearing or motor difficulties e.g. hemiplegia due to previous stroke or technical difficulties.) We found differences in the scores in some but not all the neuropsychological tests. Using cut points suggested by an earlier validation study of NeuroScreen tool more than half of study participants would be scored as having at least mild neurocognitive impairment. HbA1c, duration of disease, type of blood glucose lowering treatment were not significantly associated with individual or overall neuropsychological test scores or odds of neurocognitive impairment.

Conclusions: The prevalence of neurocognitive impairment may be substantial in this patient population. A novel tablet based neurocognitive screening tool was broadly feasible and acceptable to lay researchers and trial participants. There was no evidence that HbA1c, duration of disease, or type of blood glucose lowering treatment (oral agents alone or insulin containing regimens) was significantly associated with individual or overall neuropsychological test scores or odds of neurocognitive impairment. Validating this tool for this patient population and optimising its role in routine clinical care need further study.

Introduction

Type 2 diabetes (T2DM) is major global public health concern. (2) Low- and middle-income countries are disproportionally affected by the substantial and growing burden of premature morbidity and mortality associated with chronically elevated blood glucose levels. (3,4) For example, in South Africa the estimated prevalence of type 2 diabetes is about 9%; the condition is also a top 10 cause of premature mortality and morbidity. (5,6)

A key component of health care for people with diabetes is self-care and management. (6) Most people with type 2 diabetes will require the use of one of more blood glucose lowering agent in addition to a package of lifestyle modifications across many domains which often require ongoing negotiation in their daily lives. Planning, problem solving, organization, and working memory are just some of the higher order cognitive functions required for adequate self-care. (7) Self-care activities have been shown to be associated with improved treatment adherence, blood glucose control, and disease outcomes in people with type 2 diabetes. (8)

Type 2 diabetes is a progressive multi-system disease. Type 2 diabetes has been found to be associated with cognitive impairments in planning, problem solving, organization, and working memory and also with an increased risk of dementia in populations in several high-income settings. (65) There is less published evidence on the burden or severity of neurocognitive impairment in adults with type 2 diabetes in low and middle-income settings. Studies from Nigeria and China suggest cognitive impairment in people with type 2 diabetes may be very common in clinical and community settings (40% and 60% respectively.) (66,67) Vascular, metabolic, and neuroendocrine, chronic immune activation and inflammation are some of the factors that been shown to contribute to the risk neurocognitive impairment and dementia in people with type 2 diabetes. (14) Neurocognitive impairment may impact self-care and other health behaviours increasing the risk of poor health outcomes in this patient population.(68–72)

Currently the detection of neurocognitive impairment (NCI) in low and middle-income settings is challenging; there is a lack of validated screening tools suitable for local use in primary care and outpatient settings, and access to formal neuropsychological testing services is limited. The inability to easily identify people with type 2 diabetes with neurocognitive impairments is constraining the development of context appropriate interventions to improve the care and outcomes in this sub-group of patients.

The SMS supporting treatment Adherence foR for type 2 Diabetes (StAR2D) is a randomised clinical trial testing if a system of SMS-text messages to support treatment adherence is more effective than usual care for controlling blood sugar among people with type 2 diabetes in sub-Sahara Africa (ISRCTN70768808). We have embedded a set of sub-studies into the Cape Town, South Africa site of the trial which aim to improve the assessment of neurocognitive function in people with type 2 diabetes at wide scale in low resource settings using a novel mobile-device based cognitive screening tool, NeuroScreen, for use in this patient population. NeuroScreen is a cogntive assessment tool developed for use by lay health care workers in low- and middle-income (LMIC) settings. (1)

Using data from the baseline assessment we report here on the associations between neurocognitive function measured using the screening tool and selected disease characteristics (HbA1c, disease duration, and type of blood glucose lowering treatment) adjusting for important potential confounders.

Materials and methods

Setting and participants

Participants for the NeuroScreen sub-study were recruited from the Cape Town site of the StAR2D trial; Participants were eligible for inclusion in the main trial if they were (1) adults (≥ 18 years) and (2) willing and able to give informed consent for participation in the study, (3) able to communicate in one of the predominant indigenous African languages in the Western Cape province (e.g. English, Afrikaans Xhosa), (4) had previously been diagnosed with type 2 diabetes by a health care worker and (5) were taking oral glucose lowering treatment (could also be taking insulin), (6) had access to a mobile phone and knows how to use SMS (help to send or receive messages allowed), and (7) was currently living in the community served by the clinic and planned to live there for the next 18 months. Participants were excluded if they had (1) a recent hospital admission for hyperglycaemia or hypoglycaemia (within three months), (2) were currently pregnant or within three months post-partum by self-report or with plans to become pregnant in the next 12-months, (3) self-reported a terminal medical condition. Participants were also excluded if (4) another member of their household was already participating or (5) if they had participated in the formative work to develop the trial intervention.

Study design

This is a cross-sectional study of associations between cognitive function and type 2 diabetes disease characteristics at baseline. Cognitive function measured using NeuroScreen a mobile-device (tablet) based neurocognitive screening tool that assesses individuals across cognitive domains sensitive to NCI associated with type 2 diabetes (novel variants of 10 research validated neuropsychological tests that have been adapted and normed for use in South Africa.) (1)

Procedures

Recruitment

The NeuroScreen questionnaire was administered as part of the baseline assessment for all StAR2D trial participants recruited at the Cape Town site unless a participant opted out of the assessment.

Informed consent

People interested and eligible provided written informed consent to participate in the parent study (StAR2D) which included completing baseline and follow-up NeuroScreen questionnaires. Participant information leaflets and informed consent procedures conformed to the Helsinki Declaration and the University of Cape Town Human subjects Research Ethics Committee requirements. Participants could decline completing the NeuroScreen assessment (i.e. opt out) without affecting their participation in the parent trial or access to any routine clinical care.

Study procedures

NeuroScreen was administered by a trained research assistant as part of the baseline assessment for the parent study. See Multimedia Appendix 1[5] in Robbins et al, *A Mobile App to Screen for Neurocognitive Impairment: Preliminary Validation of NeuroScreen Among HIV-Infected South African Adults* for a complete description of each test used in the assessment. (1)

[5] For ease of reference this has been included in Part D as Appendix 5.

Measures

Data collection

Trained research assistants used a modified from the questionnaire (used previously and harmonised with data collection tools from other GACD funded projects on diabetes mellitus) (73,74) to collected information on sociodemographic factors (education, employment and finances), medical history (previous clinician diagnoses of hypertension, cardiovascular disease, depression, HIV, and other chronic illnesses), current medication (for diabetes, hypertension and other chronic illnesses), medication adherence (5-item Medication Adherence Report Scale, MARS-5),(75) lifestyle (physical activity, diet, alcohol consumption and smoking), and health status (EuroQol Group 5-Dimension Self-Report Questionnaire,EQ-5D),(76) and satisfaction with treatment and care. Questionnaires were available in English, isiXhosa and Afrikaans.

Anthropometry and blood pressures were measured using standardised procedures. A venepuncture sample was collected at the study site by a trained research nurse for measurement of HbA1c. The blood samples were transported on the same day to a clinical trials laboratory for processing using an immunoassay on the Roche cobas c501 (Tina-quant HbA1c Gen. 2, Roche Diagnostics, Indianapolis, IN, USA). The laboratory participated in internal quality control (exchanging samples between sites for repeat testing) and external quality control processes.

The NeuroScreen assessment consists of 10 tests to briefly assess across six neuropsychological domains: learning (two trials, five words), memory (5-minute delayed recall), processing speed (two Trail Making Test sequences, two visual discrimination tasks, and a number input task), attention (Number Span forward and backward), executive function (alternating trail making test sequence), and motor function (Finger-Tapping task.) (65) See Appendix 1 for a complete description of each test.(77) The interviewer is required to read standardized test instructions or play videos that provide audio-visual instructions, is prompted at appropriate points to offer practice trials on selected tests and is prompted to move on to the next test, thus sequencing through all the tests. NeuroScreen was administered in English or isiXhosa by trained research assistants using Android tablet devices.

Definitions

We calculated disease duration from self-reported time lived with type 2 diabetes in years and months; we grouped this into less than 5 years, between 5 and 10 years, and 10 or more year. We categorised diabetes control using measured HbA1c (%) level into tertiles; reasonable (mean 6.72%, 95% CI 5.4% to 7.8%), average (8.98, 8.1 to 10.0), poor (11.74,10.3 to 14.) We collected information on the type of diabetes medication prescribed from participants clinic prescribing records. We grouped these into oral medications (metformin, glibenclamide, gliclazide), insulin (actrapid, actraphane, protaphane), or both. We also collected information on use of anti-hypertensive agents and statins.

We defined overweight as BMI of 25·0–29·9 kg/m2 and obesity as BMI of 30·0 kg/m2 or more. Multimorbidity was defined as the presence of diabetes mellitus plus either hypertension or obesity (not including overweight.) We defined hypertension as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or current antihypertensive medication use. Education was calculated from the total number of years participants reported they spent in school or full-time study.

Data management

All participant trial data were captured at the study site and uploaded to OpenMRS (OpenMRS version 1.6.1, OpenMRS Limited, Michigan) using Sana Mobile (Sana, MIT, Massachusetts), an open-source Android platform. NeuroScreen data were uploaded to a secure server and stored in a study specific data base. Data from the parent study and the sub-study were linked using study specific identifiers.

Statistical analysis

The main outcome for this cross-sectional baseline analysis is neurocognitive function. We summarised global neurocognitive function using two composite z-scores: (1) sum of all individual test scores and total errors from the trail making and number speed tests (z-score I), and (2) sum of four tests (Visual Discrimination 1 and 2, Trail Making 1, and Number Span total; z-score II). All raw scores were converted to z scores using the entire sample and timed tests were reverse scored so that higher scores indicated better performance. We defined neurocognitive impairment using 2 cut points suggested by an earlier validation study of NeuroScreen tool in a group of 102 HIV-positive black South African adults aged 18 to 56 years.(1) Two cut points were used: 0.21[6] and 0.18[7]. We compared the z-scores of individual tests between groups with and without impairment as defined using the cut-points above. (1)

The main exposure variables were percentage HbA1c treated as a continuous variable, duration of diagnosis of type 2 diabetes (continuous), and type of blood glucose lowering medication (categorical variable). Type 2 diabetes is a progressive disease and HbA1c will tend to increase with longer duration of disease, the type of medication regimen selected is also related to HbA1c and indirectly to duration of disease and other patient level factors (for example, metformin is not used in the presence of renal impairment which is a complication that is more common with longer disease duration and higher HbA1c levels.) The relationship between duration of diagnosis of type 2 diabetes, medication regimen and HbA1c was explored. Student t-tests were used to explore associations between these and the exposure and outcome variables. χ^2 likelihood ratio tests were used to assess heterogeneity by disease duration and medication regimen, and, where observed we present stratified analyses.

The following potential confounders were included in statistical models for the main analyses: age, sex, years of formal education, systolic and diastolic blood pressures (mmHg), and blood total and HDL cholesterol levels (mmol/l); all treated as continuous variables.

Data were explored visually and with Shapiro-Wilk tests to check underlying distribution assumptions. Univariate and bivariate analyses of the outcome and exposure variables were performed using two-by-two tables and t-tests. Linear regression was used to estimate the mean change in global neurocognitive score associated with increasing HbA1c (%) with

[6] In the validation study the AUC for a cut point of 0.21 was 86 (95% CI 0.78-0.94) and the Youden index maximal sensitivity was 81.48% (95% CI 61.92%-93.70%) and specificity was 81.33% (95% CI 70.67%-89.40%). The PPV was 61.11% and the NPV was 92.42%.)

[7] In the validation study the AUC for cut point of 0.18 was 0.87 (95% CI 0.80-0.94) and the Youden index NeuroScreen predicted NCI cut-score of 0.18 maximized sensitivity at 92.59% (95% CI 75.71%-99.09%) and specificity at 70.67% (95% CI 59.02%-80.62%). The PPV was 53.19% and the NPV was 96.36%.

adjustment for all the factors listed above. T-tests and logistic regression analyses were used to estimate the odds ratios of neurocognitive impairment defined using the two global summary tests (z-score I and z-score II) and cut points described above associated with change in HbA1c (%) adjustment for all the factors listed above. All analyses were done in STATA SE version 14.2 for Windows (Stata Corp, 2018). *P* values were two sided and $p<0.05$ was regarded as significant.

Role of funding

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participant characteristics

Six hundred participants enrolled in the parent study between November 8, 2016 and August 5, 2017 were assessed for enrolment in the sub-study, of whom 499 (83%) completed a baseline NeuroScreen assessment and were eligible for this analysis (see Figure 3 for a flow diagram of participants and reasons for drop out of 101 participants.) Assessment of neurocognitive function using NeuroScreen as part of trial enrolment procedures was broadly feasible and acceptable to lay researchers and trial participants. Most commonly trial participants were unable to complete the baseline assessment because of sensory (uncorrected sight or hearing difficulties) or motor (hemiplegia as a result of previous stroke) difficulty (48% of exclusions, 8% of total assessments.) Technical problems (device freezing or data transfer problems) resulted in missing data or incomplete assessments at a rate of about 7% of total assessments. These data were excluded.

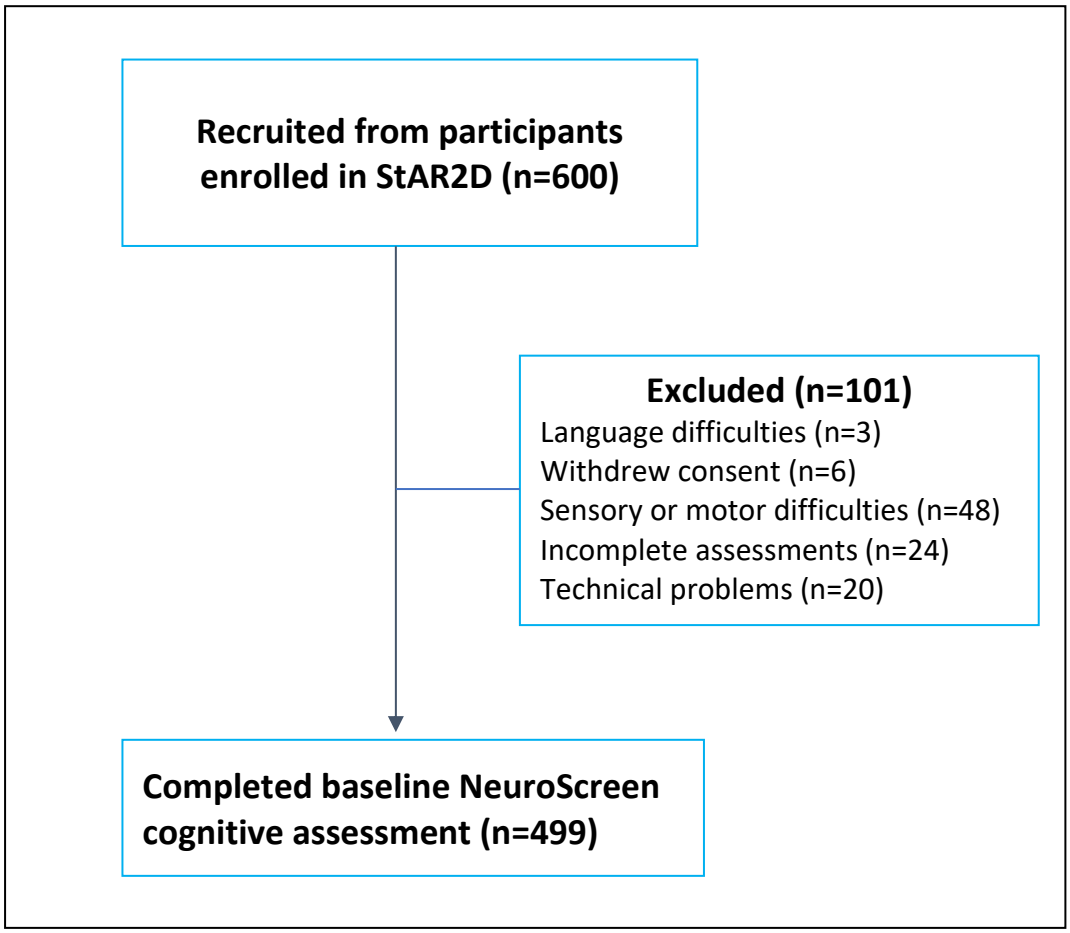

Figure 4 Flow diagram of participants recruited from StAR2D parent trial and enrolled into the NeuroScreen sub-studies

Table 6 shows characteristics of study participants by sex. 76% of participants were women. The mean age of participants was 58.5 (SD 11.7) years. The sex distribution was similar among participants who did not complete the baseline assessment, although they were older (61.3, SD 11.8 years), reported fewer years of education (7.6, SD 3.4), and had a lower BMI

(mean BMI 31.7, s.d 5.4.) There was no material difference in duration of T2DM, HbA1c blood pressure, or type of blood glucose lowering agents used.

Among participants, men and women differed in mean BMI, measures of HbA1c and blood pressure; women had higher BMIs and higher mean HbA1C levels but lower mean blood pressures. Women were more likely to be taking oral blood glucose lowering agents and insulin, and to have been prescribed high blood pressure lowering medications than men. Statin prescribing was slightly more than 80% among both.

Table 6 Selected participant characteristics

CHARACTERISTICS	ALL	FEMALE	MALE
N	499	382	117
AGE (MEAN, SD)	58.5 (11.7)	58.5 (11.8)	58.3 (11.4)
YEARS OF EDUCATION (MEAN, SD)	8.8 (3.3)	8.9 (3.2)	8.5 (3.7)
LANGUAGE*			
ENGLISH (N,%)	345 (69.1%)	268 (70.2%)	77 (65.8%)
ISIXHOSA (N,%)	125 (25.0%)	91 (23.8%)	34 (29.1%)
YEARS WITH TYPE 2 DIABETES (MEAN, SD)	8.87 (8.4)	9.06 (8.6)	8.25 (7.6)
BODY MASS INDEX (MEAN, SD)≠	33.0 (7.6)	34.1 (7.8)	29.8 (6.1)
SYSTOLIC BLOOD PRESSURE (MEAN, SD)	130.2 (17.6)	129.0 (17.1)	134.3 (18.6)
DIASTOLIC BLOOD PRESSURE	76.6 (11.0)	75.0 (10.5)	81.7 (11.1)
HBA1C (%, SD)	9.13% (2.2)	9.20% (2.3)	8.89% (2.2)
CHOLESTEROL			
TOTAL (MEAN, SD)	4.6 (1.1)	4.7 (1.1)	4.4 (1.1)
HDL (MEAN, SD)	1.2 (0.4)	1.2 (0.4)	1.0 (0.3)
PRESCRIBED MEDICATIONS (N, %)			
ORAL	323 (68%)	237 (66%)	86 (77%)
ORAL AND INSULIN	148 (31%)	123 (34%)	25 (22%)
BLOOD PRESSURE MEDICATIONS	399 (80%)	316 (83%)	83 (71%)
STATIN	407 (81%)	312 (82%)	95 (81%)

**Totals do not sum to 100% - 30 participants reported Afrikaans as their preferred home language; ≠ 6 people do not have BMI recorded because of physical problems obtaining measurements for either weight or height including being in a wheelchair*

Raw scores from selected individual tests

Table 7 shows raw scores from individual tests included in the NeuroScreen assessment. Raw scores did not materially differ between men and women except for a small but significant difference for Finger Tapping with the non-dominant hand (results not shown.) Participants were able to learn 7.66 (SD 1.85) words across two learning trials

(same five words per trial) and recall 2.18 (SD 1.8) words after a 5-minute delay. The mean total finger taps for both the dominant and nondominant hand was 363.88 (SD 114.66) taps across five trials. The mean total correct responses on Visual Discrimination 1 was 8.34 (maximum 33) and 17.78 on Visual Discrimination 2 (maximum 47). Trail Making Tests were reverse score with slower times indicting worse performance. On average the total time taken to complete the assessment was 28:31 (SD 9:41) minutes although a few participants took substantially longer.

Table 7 Selected raw scores from NeuroScreen

RAW SCORES	Mean (SD)	Min	Max
FINGER TAPPING BOTH HANDS	363.88 (114.66)	67	723
VISUAL DISCRIMINATION 1 TOTAL CORRECT	8.34 (4.27)	1	33
VISUAL DISCRIMINATION 2 TOTAL CORRECT	17.78 (10.27)	1	47
NUMBER SPAN TOTAL (FORWARD AND BACKWARD)	6 (1.74)	1	11
VERBAL LEARNING TOTAL CORRECT	7.66 (1.85)	2	10
DELAYED VERBAL RECALL TOTAL CORRECT	2.18 (1.8)	2	5
TRAIL MAKING 1 COMPLETION TIME (SECONDS)[A]	-14.80 (10.36)	-120.00	0
TRAIL MAKING 2 COMPLETION TIME (SECONDS) [A]	-34.53 (12.71)	-120.00	0
TRAIL MAKING 3 COMPLETION TIME (SECONDS) [A]	-13.20 (4.92)	-62.77	0
NUMBER SPEED COMPLETION TIME (SECONDS) [A]	-53.41 (25.88)	-173.75	0
FULL BATTERY COMPLETION TIME (MINUTES)	28:31 (9:41)	4:03	130:21

[a]Indicates reverse scored (slower time=worse performance).

Exploring the association between HbA1c, disease duration, and type of blood glucose lowering medicine on global cognitive function score

Table 8 shows the estimated change in global cognitive function using composite z-score I (sum of all individual test scores and total errors from the trail making and number speed tests) associated with HbA1c, duration of type 2 diabetes in a linear regression model. Univariate or unadjusted results are shown (Model A) as well as with adjustment for age, sex, and education (Model B.) Model C shows the results with additional adjustment for HbA1c, duration of diabetes diagnosis, type of blood glucose lowering medicine, blood pressure, blood cholesterol, and BMI (add in use of BP meds and statins).

In the univariate analyses, both duration of disease and type of blood glucose lowering medication showed small but significant changes in the composite z-score I. These associations were no longer significant after adjusting for age, and years of education. In the final model only, age and years of education had small but significant effects on the composite z-score I; each additional year of age decreased z-score I by -0.02 (95% CI -0.03 to -0.01), each additional year of education increased z-score I by 0.04 (95% CI 0.01 to 0.07.) This analysis was repeated on composite z-score II as well as individual z-scores with similar results. There was no evidence of interaction between HbA1c, type of blood glucose lowering medicines, and duration of disease (each combination individually tested using likelihood ratio test.)

Table 8 Change in global cognitive function using composite z-score I by HbA1c, duration of disease, and type of blood glucose lowering medication in linear regression models variously adjusted

Selected characteristics	Model A (unadjusted)	Model B (age, sex, education)	Model C (fully adjusted)*
HbA1c (β, 95%CI)	0.03 (-0.01 to 0.07)	0.02 (-0.03 to 0.05)	0.02 (-0.02 to 0.07)
Duration diabetes (β, 95%CI)	-0.02 (-0.03 to -0.01)**	0.01 (-0.03 to 0.05)	-0.01 (-0.02 to 0.00)
Type of medication (β, 95%CI)┘	-4.11 (-7.84 to -0.37)**	-0.14 (-0.33 to 0.04)	-0.17 (-0.38 to 0.05)

**Model B plus adjustment for HbA1c, duration of diabetes diagnosis, type of medicine, blood pressure, blood cholesterol, and BMI ; **P<0.05; ┘Oral agents only as reference category and compared to regimens containing insulin*

Nature and pattern of neurocognitive impairment in this study population

Using a score of 0.21 as the cut point to define neurocognitive impairment 54.3% of participants would be classified as having impaired cognitive function using composite score 1 and 58.5% using composite score 2. In comparison using a score of 0.18 as the cut point 50.9% and 57.7% of participants would be classified as having impaired cognitive function using the respective composite scores.

Table 9 shows the means of individual raw scores in participants with a global composite z-score I (sum of all individual test scores and total errors from the trail making and number speed tests) using 0.21 as the cut point to classify individuals as impaired or not. Means were compared using t-test statistics. All the individual test scores except trail making 3 completion time were significantly different between the two groups. Participants with a global composite z-score I less than 0.21 had lower raw scores and longer completion times for the tests. The tests with the largest difference in mean scores were Finger Tapping Both Hands (mean difference 86.31, 95% CI 67.53 to 105.10), Number Span total forward and backward (-18.40, 95%CI -23.79 to13.01) Visual Discrimination 2 total correct (6.79, 95% CI 5.08 to 8.50), Trail Making 1 (-6.14, 95% CI -9.48 to -2.81), Trail Making 2 (-4.20, 95% CI -8.96 to 0.55 with p 0.04) and the total time to complete the assessment (4.22, 95% CI 23:54:58 to 23:58:11.) Visual Discrimination 1 had a mean difference of 1.87 (95% CI 1.13 to 2.60.) The mean differences in raw scores for the remaining tests was less than one.

Table 9 Means of raw scores in participants with a global composite z-score I of less than and greater than 21 with compared using t-test statistic

NEUROSCREEN RAW SCORES	< .21(Mean, SD)	≥0.21(Mean, SD)
FINGER TAPPING BOTH HANDS*	324.4 (117.3)	410.8 (91.7)
VISUAL DISCRIMINATION 1 TOTAL CORRECT*	7.5 (4.1)	9.4 (4.3)
VISUAL DISCRIMINATION 2 TOTAL CORRECT*	14.7 (9.5)	21.5 (9.9)
NUMBER SPAN TOTAL (FORWARD AND BACKWARD)* ┘	5.9 (1.8)	6.1 (1.7)
VERBAL LEARNING TOTAL CORRECT*	7.5 (1.9)	7.8 (1.8)
DELAYED VERBAL RECALL TOTAL CORRECT*	1.9 (1.7)	2.5 (1.8)
TRAIL MAKING 1 COMPLETION TIME (SECONDS) ≠*	17.2 (13.7)	23.4 (22.3)
TRAIL MAKING 2 COMPLETION TIME (SECONDS) ≠*	37.8 (24.9)	42.0 (28.5)
TRAIL MAKING 3 COMPLETION TIME (SECONDS) ≠	17.2 (10.1)	17.3 (14.5)
NUMBER SPEED COMPLETION TIME (SECONDS) ≠*	75.0 (34.1)	56.6 (25.6)
FULL BATTERY COMPLETION TIME (MINUTES) ≠*	30:15 (12:00)	25:53 (5:32)

**T-test for difference in means <0.05; ┘ Driven by difference in scores in number span backwards ≠ reverse scored, slower time is worse*

Risk factors for neurocognitive impairment in this study population

Tables 10 shows the odds of being classified as impaired using 0.21 cut point and global composite z-score I associated with HbA1c, duration of disease, and type of blood glucose lowering medicines. Likelihood ratio tests did not show an interaction with the above variables for composite z-score I but did with the more limited composite z-score II.

In these logistic regression analyses HbA1c, disease duration, and type of blood glucose lowering treatment did not significantly influence the odds of being classified as impaired using 0.21 cut point and global composite z-score I. Participant age was the only variable significantly associated with the odds of being classified as impaired (OR 1.04, 95%CI 1.02 to 1.06.) Years of education was protective but not significant in this model (OR 0.95, 95%CI 0.89 to 1.00.)

Table 10 Odds of associated with HbA1c, duration of disease, and type of blood glucose lowering agents

SELECTED CHARACTERISTICS	Model A (unadjusted)	Model B (age, sex, education)	Model C (fully adjusted) *
HBA1C (OR, 95%CI)	0.95 (0.87 to 1.02)	0.98 (0.90 to 1.10)	0.95 (0.87 to 1.04)
DURATION DIABETES (OR, 95%CI)	1.04 (1.01 to 1.06)	1.02 (0.99 to 1.04)	1.02 (0.99 to 1.05)
TYPE OF MEDICATION (OR, 95%CI)┘	1.35 (0.93 to 1.96)	1.29 (0.88 to 1.90)	1.29 (0.83 to 2.01)

**Model B plus adjustment for HbA1c, duration of diabetes diagnosis, type of medicine, blood pressure, blood cholesterol, and BMI ; **P<0.05; ┘ Oral agents only as reference category and compared to regimens containing insulin*

Discussion

Summary of findings

In this analysis of the cognitive function of 499 adults with type 2 diabetes being managed in an outpatient primary care setting in a middle-income country or LMIC using a novel tablet-based screening tool we found differences in scores in some but not all the neuropsychological tests. Using cut points suggested by an earlier validation study of NeuroScreen tool more than half of study participants would be scored as having at least mild neurocognitive impairment. None of the diabetes related variables explored (HbA1c, duration of disease, type of blood glucose lowering treatment) was significantly associated with individual or overall neuropsychological test scores nor odds of neurocognitive impairment. There was no evidence of interaction between these variables in the main models.

Limitations

It is important to note the limitations of this study and this analysis. This is a cross-sectional analysis of baseline characteristics for a population enrolled in a randomised clinical trial. The study population may not be representative of the total population with type 2 diabetes because of trial inclusion criteria (including being able to provide written informed consent.) Although the study population is quite similar in age and sex structure to that seen in primary care facilities it is not representative of the known age and sex distribution for prevalent type 2 diabetes in South Africa (prevalence of type 2 diabetes is similar in men and women). (5,78) The number of people who were unable to complete the assessment because of either uncorrected sensory difficulty (poor eyesight or hearing) or motor deficit (hemiplegia) was larger than anticipated (8%), and is perhaps greater in the general outpatient population with type 2 diabetes. This is an important sub-group of patients who may be at increased risk of developing cognitive impairment or dementia; hearing loss is a risk factor for dementia and many patients with stroke suffer post-stroke decline in cognitive function. (79) It would be an operational challenge if screening for neurocognitive impairment became part of routine care to ensure that people who could not complete one type of assessment be offered another type.

Due to the timing of this analysis we had access to a limited number of key variables, additional socio-demographic, clinical and self-management variables will be available for analysis once the trial is complete (end 2018.) Although we do not expect the additional variables to change the results it will be important for us to review our models with additional adjustment for mental health status, HIV status and alcohol and tobacco use as these are known to be important potential confounders. It will be important to investigate the relationship between self-management behaviours and treatment adherence and cognitive function. Although we asked about current and past mental illness we did not screen for depression, we also did not measure blood glucose at the time of assessment though it is unlikely that people who were symptomatically hyper- or hypoglycaemic would have completed the assessment.

The NeuroScreen tool is in process of being validated in our study population so cut points used in these analyses may need to be revised and the individual tests used in composite summary scores may change. Normative performance data are still to be established for various South African language groups. We did not formally assess language fluency, for either English or isiXhosa. Participants were asked for their language preference by the research assistant. NeuroScreen is not yet available in other languages commonly spoken in South Africa for example Afrikaans meaning that some people who may have preferred to take the test in Afrikaans were assessed in a language they were less familiar with. Also, any neurocognitive impairment we may have detected in this study may or may not be due to type 2 diabetes; low education, head injuries and comorbid illness are just some of the common factors known to cause or contribute to impaired cognitive function.

Strengths

Strengths of this study include the adequate sample size of adult patients being managed in an outpatient primary care setting (our sample size is sufficient to detect the prevalence of cognitive impairment as low as 26% with 80% power at 5% significance.) The study population is broadly representative of clinic demographics in local context. (80) Whilst there were sex-specific differences in individual measures, in general participants in this study tended to have poorly controlled blood sugar levels (mean HbA1c 9.13%, SD 2.2) and to be overweight or obese (mean BMI 33 kg/m^2, SD 7.6.) Systolic and diastolic blood pressures and serum total and HDL cholesterol levels were around the treatment targets suggested by local guidelines.(81) (ref SEMSDA 2017.) Over two thirds of study participants were prescribed oral agents alone to control their blood glucose (women 66%, men 77%.) Most but not all participants had blood pressure lowering agents (80%) and statins (82%) as part of their prescribed treatment, again men and women differed with fewer men being prescribed blood pressure lowering agents (71% compared to 83%.)

Another strength is the wide range of socio-demographic, clinical, health and self-management variables being collected in the parent trial and being linked to objectively measured outcomes data (HbA1c, treatment adherence) which can be used in future analyses.

The mobile-device based capture of data was feasible and acceptable in a general outpatient setting using research assistants the equivalent of lay health workers administering the assessment. Although some studies have reported failure rates of zero industry reports suggest failure rates can be as high as 27% for some Android devices. (82,83) We consider the technical failure rate of about 7% acceptable for technology being deployed by non-technical experts and limited in-the-field technical and engineering support.

Other literature and findings in context

NeuroScreen was developed to enable lay health care workers in a primary care setting to screen for NCI among adults with HIV. The cognitive domains thought to be particularly affected in HIV associated neurocognitive impairment (HAND) are broadly similar to those in type 2 diabetes. The tool has been validated in populations in the USA and South Africa.(77,1) Compared to these our study population were similarly aged to the study population in the USA (58.5, SD 11.7 compared to 53.4, SD 7 years) and older than the one in South Africa (33.3 SD 7.5.) Our study population completed fewer years of education than participants in these studies (8.8, SD 3.3 compared to 11.8, SD 2.4 and 11.3, SD 2.0.) Black African ancestry was the most common self-reported ethnicity in all three studies. Participants in the current study had raw scores materially different from both USA and South African studies for Finger Tapping both hands (about 80 fewer taps overall i.e. evidence of slower motor speeds) and Trail Making Trials (longer) and Visual Discrimination 1 (4 or more.) Number Span, Delayed Verbal Recall, and Visual Discrimination 2 were similar to the South African study scores and either better or worse than the scores from the participants in the USA study. Differences in age profile and years of education may explain some of the differences but some may be as a result of either inflammation related to chronic disease processes in general (non-specific) or disease specific pathophysiology. Although these groups differ comparing how scores are similar or different between groups may provide some insight into which domains are broadly affected by many chronic disease processes and which may be somewhat disease specific.

Using the cut points to compare the results of individual neuropsychological tests between people who performed better and worse we found the largest difference in means scores with finger tapping both hands, number span total, visual discrimination 2, trail making 1 and 2. The abridged version of the score we also explored based on the South African validation study among adults with HIV included four tests: visual discrimination 1 and 2, trail making 1, and number span total. Further validation work is required to explore whether to adapt selected summary scores for different patient population groups. Using these cut points 54.3% of participants would be classified as having impaired cognitive function using composite score 1 and 58.5% using composite score 2. This is similar to the findings from a small cross-sectional study among adults with type 2 diabetes attending an outpatient tertiary referral diabetes clinic in Cape Town, South Africa. (62) The study results showed evidence of impairment in executive function in 52% of participants using a short battery of tests (three item registration, three item delayed recall, executive clock drawing task part 1, verbal fluency, and numeric problem solving.) Although the researchers reported an association between level of glycaemic control and neuropsychological test scores it was not clear which confounders had been accounted for.

Prevalence estimates for impaired neurocognitive function among adults with type 2 diabetes vary and may depend on the age of the study population as well as the tests and cut points used to define impairment. For example, in a French cohort of people over the age of 70 years with type 2 diabetes and using the MMSE and a score of less than 24/30 to indicate impairment 28.8% of the study population were impaired.(84) In a cross-sectional study in Nigeria among a hospital outpatient diabetes clinic population also using MMSE and a score cut point of 24, 40% were classified as having some form of cognitive impairment; in this study there was a sizeable difference in the prevalence in men (48%) as compared to women (30%.) (67) In contrast in a population based cross-sectional study of adults (average age 72 year) in China 62% of those with type 2 diabetes fulfilled Petersen's diagnostic standard on mild cognitive impairment.(85)

Some but not all studies have shown an association between HbA1c, disease duration, and type of blood glucose lowering treatment and scores on neuropsychological tests. In a case-control study of 246 participants in China researchers found that longer disease duration, higher HbA1c, and insulin treatment were associated with worse tests results using Mini Mental State Exam (MMSE), trails B, digit span, and block design. (86) The GERODIAB cohort showed a small but significant difference in HbA1c (0.3, SD 0.1) between the groups.(84) In contrast findings from another Chinese study, a cross sectional study of 1174 adults (average age 70.1 years, 50% women, average years of schooling 11) which used MMSE and the Montreal – Cognitive Assessment (MoCA) found that while in initial models 1% increase in HbA1c was associated with small but significant decreases in the scores for both tests, this association was no longer significant once models were adjusted for age, sex, education, duration of disease, prevalent cardiovascular disease, and alcohol and tobacco exposure.(85) Similarly results from baseline cognitive assessment of participants in the ACCORD-MIND trial using the Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test (RAVLT), Stroop and MMSE showed that after adjusting for age, sex, education, depression, diabetes duration, race, and language there remained a small significant effect of a 1% change of HbA1c on DSST results (-0.57, -1.01 to -.012) only.(87) In addition a recent systematic review of the effect of the treatment of Type 2 diabetes mellitus on the development of cognitive impairment and dementia did not find evidence that improving glycaemic control prevented or delayed cognitive impairment.(88)

Taken together this evidence suggests that individual measures of HbA1c (i.e. at a single time point) probably have a very small association if any at all with neuropsychological test scores. Chronically elevated blood glucose levels may affect neuropsychological test scores, type 2 diabetes is progressive disease and disease duration is perhaps in part a proxy for at least periods of what was chronically elevated blood glucose. Results from several studies have shown an association between disease duration and lower neuropsychological test scores. (86,89,90) However, disease duration may be confounded by other factors like age at diagnosis and diagnostic criteria. Similarly type of blood glucose lowering therapy may also be a proxy measure for disease control or disease progression.

Conclusion

This study of a large outpatient population of adults with type 2 diabetes managed in primary care showed that the prevalence of neurocognitive impairment may be substantial in this patient population. It also showed that use of a novel tablet based neurocognitive screening tool was broadly feasible and acceptable to lay researchers and trial participants. There was no evidence that current HbA1c, duration of disease, or type of blood glucose lowering treatment (oral agents alone or insulin containing regimens) was significantly associated with individual or overall neuropsychological test scores nor odds of neurocognitive impairment. Validating this tool for this patient population and optimising its role in routine clinical care need further study.

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Appendix 3 NeuroScreen tests from Robbins et al (77)

Learning and memory

Verbal learning and delayed memory are assessed via a 5-item word list with two learning trials and a 5-minute delayed recall. Words are prerecorded and played via the smartphone speaker. Every administration of the NeuroScreen word list is exactly the same – each word is spoken at a 2-second interval in a clear, enunciated male voice. After the words are played, the patient is asked to say the words back in any order. The test administrator, viewing the screen, sees buttons with the five words from the list, as well as an “other” button. The administrator taps the buttons that correspond to the words the patient says. In the case of an intrusion, the administrator taps the “other” button. Learning is scored by totaling the number of correctly recalled words across both learning trials. The minimum score is 0 and the maximum score is 10.

The delay recall test automatically gets queued to be administered approximately 5-minutes after the last learning trial is completed. The time limit is approximate because if it is reached during another test, NeuroScreen will not interrupt the currently administered test. Rather, the program waits for the current test to be completed and then forces the administrator to complete the delayed recall trial. The administrator reads the instructions to the patient to say as many words that can be remembered from the list. The administrator taps the buttons that correspond to the words the patient says. In the case of an intrusion, the administrator taps the “other” button. Delayed recall is scored by totaling the number of correctly recalled words. The minimum score is 0 and the maximum score is 5.

Working memory

Working memory is assessed via a number span test (forwards and backwards). Participants hear pre-recorded digit strings starting with a string of 3 digits with a max of 9 digits. Each number of each string is spoken at a 1-second interval in a clear, enunciated male voice. If participants do not get the number span correct, they are given another trial of the same span. After two incorrect responses, the task moves on to the number span backwards portion. The backwards span begins with a sequence of 3 digits and has a maximum of 8. Like the forwards test, participants get two trials per sequence, but if they get both incorrect, the test ends. The test records the longest forwards and backwards span repeated and is scored by summing the number of digits in each of those spans. For example, if the longest forward span correctly repeated had 6 digits and the longest backwards span correctly repeated had 4 digits, the score for this test would be 10.

Processing speed

Processing speed is assessed by two timed visual discrimination tasks, as well as a number input test. The first visual discrimination task requires patients to match a target shape to its correct number by tapping the number on the screen. This task is similar to Digit Symbol Coding of the WAIS-III (Wechsler, 1997) and Symbol Digit Modalities (Smith, 1982). The second task requires patients to determine if one of two symbols matches an array of symbols and is similar to the Symbol Search subtest of the WAIS-III (Wechsler, 1997). Both tests lasts 45-seconds and participants receive a practice trial with feedback. The first discrimination task has a total of 61 items. The second discrimination task has a total of 150 items. Each test is scored by summing the total number of correctly answered items.

On the number input test, participants see a keypad on the screen and a target number. They are asked to enter the target number as quickly as possible. Participants see the target numbers turn green as they enter the correct numbers. If an incorrect number is pressed, the corresponding number in the target number turns red and the participant must correct it by using a back button. After a target number is entered correctly, they move on to a longer number. The test starts with a five digit number and proceeds in one digit increments up to a ten digit number. Participants must complete all six trials. The smartphone records the completion time for each trial, as well as the number of errors made while inputting the number. Participants receive a practice trial to become familiar with the keypad. This test is scored by summing the completion times (in seconds) for each of the five trials. The maximum completion time allowed is 75-seconds.

Motor speed

Motor speed is assessed via a finger tapping test. Patients have to tap a virtual button on the screen as fast as they can. Each trial lasts 10-seconds. Participants have three trials with their dominant hands, three trials with their nondominant hands, then two more trials with the dominant, then nondominant hands. Handedness is entered into the patient information section of NeuroScreen and the patient is automatically presented with trials based on their handedness. This test is scored by summing the total number of taps completed by each hand across the 5 trials.

Executive functioning

Executive functioning is assessed via a trail making type test similar to the Trail Making Test Parts A and B (Partington & Leiter, 1949; Reitan, 1958). Trail 1 has users use their finger to draw a line between numbered circles (1 – 8). The smartphone automatically times how long it takes to complete the trial, as well as systematically records any errors. If an error is made, users see a pop-up screen telling them to go back to the last correct circle. The test is discontinued at 35-seconds with all discontinued tests recorded as the maximum completion time. Trail 2 requires users to draw a line between numbered and lettered circles in an ascending order (letter, number, letter, number, etc.) The smartphone automatically times how long it takes to complete, as well as records any errors. Preceding each trial, users are given an abbreviated practice test. Scores for this test are completion times (in seconds). The test is discontinued at 40-seconds with all discontinued tests recorded as the maximum completion time.

Part D: Supporting documents

Appendix 4 Official Ethics approval letter from the Faculty Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
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16 January 2017

HREC REF: 820/2016

Prof N Levitt
Division of Diabetic Medicine & Endocrinology
J-Floor
OMB

Dear Prof Levitt

PROJECT TITLE: ASSESSING TYPE 2 DIABETES ASSOCIATED NEUROCOGNITIVE IMPAIRMENT USING AN E-SCREENING TOOL IN A SOUTH AFRICAN POPULATION (DANCes); VALIDATION AND PILOT STUDY-(MMED-Candidate Dr K Bobrow) Sub-study linked to 126/2015 and 596/2014

Thank you for your response letter dated 09 January 2017, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 JANUARY 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, Dr K Bobrow will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

signature removed to avoid exposure online

PROFESSOR M BLUCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

HREC:820/2016

Part C: journal ready manuscript

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