STUDY PROTOCOL

A protocol to assess the risk of dementia among patients with coronary artery diseases using CAIDE score [version 1; peer review: 1 not approved]

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Abstract

Introduction: The impact of coronary artery disease (CAD) on the later development of dementia is not well studied globally. Therefore, this study aims to determine the long-term risk of dementia using a mobile application-based tool in addition to elucidating the contributing factors among CAD patients.

Protocol: This ongoing cross-sectional study is collecting data from 285 stable CAD patients admitted to the "Ibrahim Cardiac Hospital and Research Institute" for coronary revascularization from August 2019 to July 2020. The patients were recruited using a convenient sampling technique due to economic and logistical issues. Data were collected through a face-to-face interview using a pretested semi-structured questionnaire. Physical parameters (blood pressure and anthropometry) were measured while maintaining the adequate privacy of the patients. The biochemical parameters analyzed by the hospital lab were also collected. The next phase of this study involves the use of a mobile application-based tool, "The Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE)" risk score, to determine the risk factors associated with dementia. In addition, a descriptive statistical and inferential analysis will also be performed to determine the key contributing risk factors linked to the development of dementia.

Ethics and dissemination: The study has been reviewed and approved by the Ethical Review Committee of Bangladesh University of Health Sciences. The results will be actively disseminated through peer-reviewed journals, conference presentations, social media, online news portal, the internet, and various community/stakeholder engagement activities.

Conclusion: As a baseline study of the country, this study will fill a key knowledge gap in the pathway to the development of better

Open Peer Review

Approval Status ?

	1
version 3	
(revision)	
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version 2	?
(revision)	view
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Any reports and responses or comments on the article can be found at the end of the article.

interventions for dementia in Bangladesh. Outcomes from this study will also help with raising awareness on the association of mental health-related issues with cardiovascular diseases so that an improved cardiac rehabilitation program can be implemented in Bangladesh.

Keywords

Risk of dementia, coronary artery disease, CAIDE score, risk factors, Bangladesh

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Introduction

Dementia is one of the foremost reasons for disability and dependency among older people and affects approximately 50 million of the world's population. Among them, 60% are presently living in low-and middle-income countries^{1,2}. Future projections indicate that the cumulative number of people with dementia will reach 82 million by 2030 and 152 by 2050³. The prevalence of dementia among people over 65 years is roughly 5%, while 20–40% of the general population older than 85 years are affected by dementia⁴. Because of the demographic transition and decreased mortality rate, the number of older people is increasing worldwide and may exceed 1 billion by 2020⁵. As dementia is a disease of the geriatric population, many of these older populations are at risk of developing dementia in the future. Therefore, immediate initiatives are required to be developed to prevent, treat, and rehabilitate them.

Region-wide distribution of incidence indicates that the burden of dementia is generally higher in Asian countries (~50%) compared to Europe (25%), America (18%), and Africa (8%)⁶. In the Asia Pacific region, the number of people with dementia will increase from 23 million in 2015 to almost 71 million by 2050⁶. Bangladesh is an over-populated country (>160 million people) situated in the South-East Asia region where 12 million are over 60 years of age⁷. From 1974 to 2001, the number of elderly people in Bangladesh increased from 1.38 million to 7.59 million, with 37% within the age range of 60–64 and 63% over 65⁸. Like other countries in Asia, it has the same prevalence of dementia both in urban and rural settings and the prevalence of questionable dementia is 11.5% and definite dementia is 3.6%⁹. However, these numbers are slightly lower than in other regions of the world⁹.

Annually, 50 million patients with dementia all around the world cost US\$818 billion, indicating the allocation of 3% of the world's gross domestic product (GDP) for the treatment and care of dementia patients². However, it is difficult for a developing country like Bangladesh to allocate such an amount of GDP only for dementia care. Therefore, initiation of risk stratification and risk reduction strategies are of utmost importance to develop control measures to handle the current and upcoming surge of dementia in Bangladesh.

Although dementia is thought to be a disease of those above 60 years, individuals who have a history of myocardial infarction or other vascular diseases (e.g. stroke, peripheral artery disease, and invasive procedures, including coronary bypass surgery or carotid endarterectomy) can be affected prematurely by this¹⁰. People with coronary artery diseases (CADs) have a higher chance of developing dementia because they have already been exposed to some kind of vascular damage¹⁰. Numerous vascular risk factors like systolic hypertension and diabetes mellitus are already known to be associated with cognitive impairments¹¹. Systolic hypertension is an imperative modifiable risk factor for late-life cognitive impairment that can cause vascular dementia¹². People with dementia often have difficulty describing the pain caused by angina and heart attacks¹³. Moreover, they often lose self-possession and develop a dependency on others to lead their everyday life¹⁴. As dementia, depression,

and anxiety can happen simultaneously, it may aggravate social isolation and affect someone's interest in doing physical exercise. Dementia can make it hard for a person to remember his/her medication schedule even if they have been doing it for years to mitigate the effects of different health conditions¹³.

History of the illness, cognitive function testing with brain imaging, and blood testing are the key parameters that are commonly used for dementia identification and diagnosis. Screening the mass population for dementia diagnosis is not recommended and feasible¹⁵. Therefore, the development of a predictive tool for determining dementia risk that could allow health providers to take preventive measures is important¹⁶. According to the previous Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) study, patients with heart disease are more likely to develop dementia in their later stages of life¹⁷. However, this observation seems to be controversial and the relative importance of heart disease in the development of dementia may vary from population to population with different risk profiles¹⁷. In Bangladesh, there is a lack of data regarding dementia and thus the policymakers are unable to take an initiative to address this issue. Again, no dementia risk prediction tool has been applied and tested yet for the Bangladeshi population to generate baseline evidence for future research on this progressive disorder. As there is a lack of sufficient resources and healthcare access to the general population, the development of a cost-effective dementia risk assessment tool is extremely important. Therefore, this study aims to predict the risk of developing dementia in established CAD patients using a mobile application-based risk prediction tool; the CAIDE risk score. In addition to this, we are also planning to evaluate the factors that influence later life dementia among patients with established CAD.

Protocol

Study design

This is an ongoing cross-sectional study planned from August 2019 to July 2020. [Figure 1](#) shows the study procedure that started from the literature review through to the end of dissemination. Different study objectives are described below.

Study objectives

Primary objective 1: Dementia risk prediction— we are categorizing the study subjects as per CAIDE risk score of dementia as low, mild, moderate, high and very high risk.

Primary objective 2: Burden related to dementia

- Assess the burden of sociodemographic risk factors (age, sex, marital status, education level, occupation, economic background) among the study subjects
- Evaluate the distribution of behavioral risk factors (tobacco use in the form of smoke and oral consumption, inadequate fruits and vegetable intake, physical inactivity) among the study subjects
- Assess the personal and family history of chronic diseases (hypertension, diabetes, CAD, stroke, chronic kidney disease, dementia or Alzheimer's disease) among the study subjects

Figure 1. Timeline of the study. Here month and duration-wise description of overall study procedure is illustrated.

- Determine the burden of anthropometric risk factors (overweight and obesity) among the CAD patients
- Assess how these risk factors distribute in different risk categories of CAIDE score
- Explore the biochemical and other diagnostic profile of the study population

Secondary objective: Identify the influencing factors

- Evaluate the association of cardiac biomarkers with the risk of dementia development
- Identify the factors that influence the risk of dementia among CAD patients
- Identify the relationship between the number of coronary vessels involved and the risk of developing dementia among the study subjects

Study setting

The study is being conducted in Ibrahim Cardiac Hospital and Research Institute (ICHRI), a tertiary level cardiac hospital in Dhaka, Bangladesh. It is one of the eight affiliated institutes of the Diabetic Association of Bangladesh (BADAS) that has the objective to improve both preventive and curative cardiac care with quality services at an affordable cost. At the initial stage, it was conceived as an extension of the cardiac outdoor facility of another affiliated hospital, Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), which is the World Health Organization Collaborating Centre on Diabetes, Endocrine and Metabolic Disorders, the only one of its kind in Asia. However, thereafter it was agreed that the project would best achieve its objectives from a stand-alone specialized cardiac hospital supported by the multidisciplinary hospital of BIRDEM for treatment of cardiac patients

concurrently suffering from other medical conditions. It is a 150-bedded specialized cardiac hospital that has a cardiac emergency, inpatient, and outpatient services.

Study population

Ongoing data collection of this study involves patients with stable CAD who are admitted to ICHRI for revascularization at the inpatient department. A total of 285 patients (age range 40 to 59 years) are selected using a convenient sampling technique due to economic and logistical issues. As this is a Master's thesis that has a pre-defined period, this non-probability sampling method will enable us to achieve the desired sample size in a relatively fast and cost-effective way. All the registered and eligible patients under the cardiac surgery department were invited to take part in the study. For this, the researchers counseled both the patient and their caregivers about the potential benefit of screening the future risk of dementia and the importance of their participation. The researchers also informed that the participation is voluntary and they have the right to withdraw themselves or refuse to answer any question. Before enrollment, patients are being screened as having "no cognitive impairment" based on the Bangla adaptation of mini-mental state examination (BAMMSE), a self-reported statement, and documented clinical history. The sample size is determined using the prevalence of vascular dementia among the Indian population (11.4%) extracted from published literature¹⁸, with a precision of 4% at a 95% confidence interval. The final sample size is adjusted considering 15% non-response rate. Thus, a total of 285 patients were selected for the study. Exclusion criteria include patients with a history of cognitive impairment, congenital heart diseases, clinically unstable, pregnant, and refusal to participate in the study.

Questionnaire development

A semi-structured questionnaire is being used to collect data¹⁹. The questionnaire was prepared based on the study objectives and the conceptual framework (Figure 2). The questionnaire has

Figure 2. Conceptual framework of the study. In this framework, interaction of different factors on the risk of dementia is illustrated. Here, risk of dementia is outcome variable and the factors are independent variables. CAD, cardiovascular disease; S. creatinine, serum creatinine; LVEF, left ventricular ejection fraction; HbA1c, haemoglobin A1C; FBG, fasting blood glucose; RBG, random blood glucose.

five components: (1) sociodemographic information (age, gender, marital status, educational status, occupation, monthly household income); (2) behavioral information (tobacco use-smoking and oral consumption, dietary servings of fruits and vegetables and work-related physical activity); (3) personal history of chronic diseases and medication (hypertension, CAD, diabetes, chronic kidney disease); (4) family history of chronic diseases (Alzheimer's disease, hypertension, CAD, stroke, chronic kidney diseases); (5) measurement (anthropometric - height, weight and body mass index [BMI]; blood pressure - systolic and diastolic; and investigation parameters - blood glucose, creatinine, troponin-I, HbA1C, lipid profile, angiogram, echocardiogram, and electrocardiogram). The behavioral part is comprised of relevant questions adapted from the STEPwise approach to Surveillance (STEPS) of Noncommunicable diseases risk factors questionnaire (version 3.2) of the World Health Organization

(WHO) with appropriate modification²⁰. The English questionnaire was translated into the Bengali language to maintain cultural sensitivity and understandability by the participants. Then the translated questionnaire was pre-tested to detect any inconsistency, unclear wording, or unusually long time taken to administer. To pre-test, ten men and ten women patients with stable CAD within the pre-selected age group were recruited randomly and interviewed by the trained data collectors (one-on-one, in-person, and face-to-face) in the cardiothoracic department of ICHRI. Before this, the objective and importance of pre-testing were explained to the participants and the invitation followed the similar approach mentioned in the previous section. To maintain consistency among the interviewers and the pretest sessions, we used a pretest answer sheet to note verbal and nonverbal responses to the translated questionnaire. The collected responses were analyzed and interpreted based on the following

parameters: trends in responses; fundamental flaws with the design or format; attractiveness; comprehension; acceptance; and relevance.

Data collection procedures

The data is collected by the research student with the help of a male and female assistant in the inpatient department of ICHRI. Data collection is taking place in three steps covering the five components of the questionnaire. In the first step, a face-to-face interview is organized to gather information on sociodemographic background, behavioral risk factors, and personal and family history of chronic diseases. In the second step, physical measurements are conducted with adequate privacy. Anthropometric measurements (height and weight) are carried out following a standard method described in “Noncommunicable disease risk factors survey Bangladesh 2010”²¹ and values are recorded in the checklist. Generalized obesity is determined by BMI according to the international guidelines of BMI²² and calculated as weight in kg/height in m². Blood pressure is measured using an aneroid sphygmomanometer on the right arm in a sitting position with their hand in resting on the handle of the chair or some objects. Following resting for at least 15 minutes the first reading is taken, followed by a second reading after three minutes of resting interval. Systolic and diastolic measurements were taken in mmHg. The mean of the two measurements is used to determine the final value of blood pressure. In the third step, all the investigation (biochemical, angiogram, echocardiogram, and electrocardiogram) data is collected from the patient’s record file. The coronary angiogram report is used to determine the number of vessels involved in the disease process. The echocardiogram report is used to assess the left ventricular ejection fraction.

Dementia risk prediction using CAIDE score

CAIDE risk score, a mobile application-based risk prediction tool, will be used to assess the long term risk (20 years later) of dementia using all the collected data. This is the first evidence-based tool to predict dementia risk in individuals in their late-life²³. The tool uses the risk score model to predict the risk of developing dementia in the future among middle-aged and elderly people²³. It was developed by the European Institute of Innovation and Technology (EIT) from a multi-mode project. The project partners were Karolinska Institute (Sweden), Research Institutes of Sweden (Sweden), Imperial College London (UK), PracSaitariSant Joan de Deu (Spain), and Erasmus University Medical Centre Rotterdam (the Netherlands). This tool has been externally validated to predict late-life dementia risk²⁴ and was incorporated into the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial. The CAIDE score application has also been found to motivate participants into mitigating their risk factors²⁵.

The application includes a series of questions, concerning their lifestyle and medical condition, and then calculates a dementia risk score based on the answers. There are a total of 15 points against all of the variables and there is the flexibility of skipping cholesterol level and blood pressure measurements wherever appropriate. The tool then generates the percentage of risk and categorizes risk as low, mild, moderate, high risk, and very high.

The CAIDE risk score has never previously been applied within the Bangladeshi population and hence we will pre-test it in a sample of CAD patients before the final application. The variables of the tool are incorporated in the semi-structured questionnaire and pre-tested among the patients described earlier in the ‘Questionnaire development’ sub-section. When data collection will be completed, tool-specific information will be inputted and analyzed to detect any inconsistency. The research student will entry the necessary data using an android (version 7.0) mobile phone where the application (CAIDE risk tool) will be downloaded from the Google play store.

Definitions of key variables

Stable CAD patients— defined as admitted patients with myocardial infarction or ischemic cardiomyopathy who are hemodynamically stable, free from acute symptoms, and ready for prescribed revascularization.

Cognitive impairment— defined according to BMMSE in which any score < 24 points (out of 30) indicates cognitive impairment.

Current tobacco user— those who have smoked or consumed tobacco orally in the past 30 days are considered to be a ‘current’ user²¹.

Inadequate fruit and vegetable intake— consumption of less than five servings of fruits and/or vegetables in a day is considered inadequate²¹.

Low physical activity—we define it as per STEPS protocol and for that, we convert all the work-related physical activities in minutes per day (metabolic equivalent of task or MET-minute) as follows:

- One minute in sedentary position (sitting quietly) = 1 MET-minute
- One minute in moderate activities = 4 MET-minutes
- One minute in vigorous activities = 8 MET-minutes

Then all the MET-minutes will be added together to get the cumulative physical activity in MET-minutes. Based on the cumulative MET-minutes participants will be categorized as low, moderate, and high as follows: ≥ 3000 MET-minutes per week = highly active; 600–3000 MET-minutes per week = moderately active. The respondents who do not fall within the moderately active group will be categorized in the low activity group²¹.

Overweight and obesity—we classify overweight and obesity as BMI 25.0 - 29.9 kg/m² and BMI ≥ 30.0 kg/m², respectively²².

Hypertension—it will be diagnosed based on “Seventh Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)” criteria when systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or known case of hypertension or on antihypertensive drugs²⁶.

Diabetes mellitus—it will be diagnosed as fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl) or 2-h plasma glucose ≥ 11.1 mmol/L (200 mg/dl) or a known case of diabetes or on anti-diabetic drugs²⁷.

Quality assurance

To maintain quality, a quality control panel is formed by the researchers who are acting in different levels of study. The panel is comprised of a research student who is the principal investigator, three senior public health specialists with expertise in prevention and control of chronic diseases, and a cardiothoracic surgeon. The cardiothoracic surgeon and the student together assessed and will recruit stable CAD patients as per inclusion and exclusion criteria. The questionnaire will be filled, checked, and entered into the database by the student herself. The group of three public health specialists are monitoring the overall patient recruitment and data collection procedure. Besides them, an external monitoring panel of two researchers from other institutions was recruited to evaluate the overall procedures and comment on the performance. To prevent bias, the monitoring panel is being anonymized for the data collectors. The overall performance at the end of the study will be categorized as satisfactory based on three parameters: (1) mode of measurement; (2) maintenance of data collection environment; and (3) mode of administration of the questionnaire. In addition, to assure the quality of the study, we are also maintaining and following specific protocol: (1) pre-testing of the questionnaire and the tool; (2) use of the standard method of measurement as per the STEPS survey of Bangladesh 2010; (3) use of show cards for a better understanding of dietary servings and intensity of physical activities; (4) maintenance of adequate privacy during physical measurements; (5) ensuring the use of robust equipment for physical and biochemical measurements.

Planned analysis

Data will be analyzed using the Statistical Package for Social Science (SPSS) version 20.0 for Windows (SPSS, Inc. Chicago, IL, USA). All estimates of precision will be presented at a 95% confidence interval (CI) in the tables. In this study, the *p*-value (two-sided) will be considered statistically significant at the threshold of $p < 0.05$. Analyses are planned based on study objectives.

Descriptive statistics. To address the primary objective 1 and primary objective 2, a descriptive analysis will be conducted using mean, standard deviation (SD), median with interquartile range (IQR), frequencies and percentages where appropriate.

Exploratory data analysis. To address the secondary objectives, an in-depth exploratory analysis will be applied. For normally distributed variables, the correlation between biochemical parameters and dementia risk percentages will be assessed using the Pearson correlation coefficient or the Spearman correlation otherwise. For continuous, normally distributed variables, we will use a *t*-test while comparing two variables and one-way analysis of variance (ANOVA) while comparing more than two variables. For continuous variables not normally distributed, we will use non-parametric tests: the Mann-Whitney

U test to compare two groups, and the Kruskal-Wallis test to compare three or more groups.

To identify the relationship between the numbers of coronary vessels involved and the risk of dementia among the study subjects, we will employ the χ^2 test or Fisher's exact test, depending on the number of observations obtained in each considered category. Similar statistical analysis will also be applied initially to assess the association of different risk factors with the risk of developing dementia among CAD patients. Moreover, we will identify the influencing factors that are associated with increasing the long-term risk of dementia development using multivariate analysis. For this purpose, univariate analysis will be used to select variables according to the *p*-value obtained ($p \leq 0.25$) to include in the multivariate analyses^{28,29}. For the multivariate analyses, we will run multinomial logistic regression considering "dementia risk categories" as the dependent variable and the "low risk" as reference. We will also calculate odds ratios (OR), and 95% CI for each independent variable. In the regression table, predictors with OR > 1 will be presented. To ensure the presence of no multicollinearity, we will use the variance inflation factor (VIF) before the regression analysis. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines will be used to report the results of our study.

Ethics and dissemination

The purpose of the study and data safety issues will be explained to the participants. All the participants will provide their informed written consent for inclusion in the study¹⁹. The study will be conducted following the Declaration of Helsinki, and the protocol has been approved by the Ethical Review Committee of Bangladesh University of Health Sciences (identification number: BUHS/BIO/EA/19/208). The permission of data collection has been provided by the appropriate authority of ICHRI. No personally identifiable information will be collected to maintain the anonymity of the participants. Patients have not been involved in the setting of the research question or outcome measures. They had no role in designing or implementing this work or interpretation of the results.

This study will bring no direct and immediate benefits to the patients. Indirect benefits include a contribution to understanding the underlying risk of dementia among patients with CAD. This will eventually increase the awareness around the importance of early lifestyle modification and the integration of mental health in the cardiac rehabilitation program. No important risk is foreseen as a direct result of the study.

We will apply a comprehensive strategy to disseminate the findings of the study. The strategy will use various communication platforms to reach out to a diverse range of beneficiaries: CAD patients, caregivers, cardiologists, psychiatrists, researchers, journalists, etc. We will use academic media (i.e., peer-reviewed journal articles, national and international conference presentations), social media (i.e., Facebook), online news portal, other platforms in the internet (i.e., links to study reports on the university website) and electronic mail (i.e., posting of study findings to participants and stakeholders) to disseminate the

outcomes from this study. The study data will be made available publicly through an online repository using CC0 license.

Study status

It remains ongoing (permanently closed to additional enrollment but subjects continue to undergo research-related activities like checking for consistency, completeness, coding, analysis).

Conclusion

Studies on dementia risk and its associated factors is scarce in Bangladesh. To the best of our knowledge, this is the first study that is addressing the long-term risk of dementia to determine different associated factors among people with CAD in Bangladesh. This study will act as a baseline to introduce a cognitive screening program to the local healthcare system. CAIDE scoring could be beneficial in the selection of high-risk patients for prompt and early intervention studies and for other uses of bespoke treatment. As it is a cross-sectional study, we would not be able to draw a definitive conclusion, however, this study is exploratory in nature. Further, large-scale studies are required to find out the effectiveness of the CAIDE risk tool. Clinicians can use the CAIDE risk tool to guide their assessments

in terms of clinical consideration and cognitive screening after its validation in the Bangladesh context.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Zenodo: A protocol to assess the risk of dementia among patients with coronary artery diseases using CAIDE score. <http://doi.org/10.5281/zenodo.4033006>¹⁹.

This project contains the following extended data within the file 'Extended data file.pdf':

- Consent form (English & Bengali Version)
- Interview questionnaire (English & Bengali Version)

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Shireen Sindi

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This protocol describes an exploratory study that aims to assess the risk of dementia among patients with coronary artery diseases (CAD) using the validated CAIDE score. The project will describe a sample of CAD patients and their CAIDE score. It will further measure different demographic, behavioral, and comorbidity risk factors for dementia. It will also assess the associations between various lab parameters with the risk score. This study is novel and unique for the Bangladeshi setting, and will better inform health care providers on the levels of dementia risk, including individual risk factors, which can support when planning dementia prevention initiatives. This project is also the basis for a Master's thesis.

I have the following questions/comments:

INTRODUCTION

- In the sentence "Systolic hypertension is an imperative modifiable risk factor for late-life cognitive impairment that can cause vascular dementia¹²". When describing dementia risk factors, I suggest that the authors use the terminology "increase the risk for" instead of "cause".
- The fourth paragraph can benefit from restructuring. It starts by describing vascular risk factors for dementia, but then switches to describing pain experienced by individuals who already have dementia. Then it moves on to describing depression, anxiety, isolation and lack of exercise. It ends with describing adherence to medication schedules. What is the goal of the paragraph? What idea is it trying to portray? What is the connection between these different components in this context? This would clarify the message to the reader.
- Is the observation of an association between heart disease and dementia really "controversial" as it is described? Even if it varies according to risk profiles? Please clarify or rephrase.
- Specifically, which "mobile application-based risk prediction tool; the CAIDE risk score." are

the authors referring to? A search on App Store and Google Play does not show that such an App currently exists. If this App was used in the past, the exact name needs to be provided, as well as the dates when it was accessed/used.

PROTOCOL

- Study Design: How is this considered “an ongoing cross-sectional study”, when it was completed July 2020? Since it has been completed, can the authors present the study baseline data?
- Primary objective 1: This is a description of what is done, not necessary an actual objective. Can this be rephrased into an objective?
- Primary objective 2: What is meant by “biochemical and other diagnostic profile”: Please clarify.
- Secondary objective: Which cardiac biomarkers are you referring to?
- Please provide more information regarding this objective: “relationship between the number of coronary vessels involved and the risk of developing dementia”.

Study population:

- The text states: “As this is a Master’s thesis that has a pre-defined period, this non-probability sampling method...”. Can you please add more information about the pre-defined period?
- Was it a requirement to have a ‘caregiver’ to participate? Please clarify.
- Regarding verb tenses, if the study or a component of the study is complete, I suggest writing the descriptions in the past tense. For example it states “Before enrollment, patients are being screened as having”.
- It is unclear what this statement is referring to “a self-reported statement, and documented clinical history”. Can you please clarify?
- Why is the sample size based on vascular dementia prevalence, when this is a short-term cross-sectional study among middle-aged adults, with no measurements of dementia development?
- Why is depression not included among the comorbid conditions?
- Why does the behavioral information not include other dietary factors? E.g. fish consumption, consumption of meat, refined sugars?
- A more detailed description is needed for these parameters: “parameters: trends in responses; fundamental flaws with the design or format; attractiveness; comprehension; acceptance; and relevance.”
- This statement is inaccurate “This tool has been externally validated to predict late-life dementia risk²⁴ and was incorporated into the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial.”. The EIT project (which took place later after the FINGER trial primary outcome results were published) included risk scores for late-life dementia. However, for the FINGER trial, the original midlife CAIDE Dementia risk score was used (not those for late-life)¹.

PLANNED ANALYSIS

- It states “To identify the relationship between the numbers of coronary vessels involved and the risk of dementia among the study subjects, we will employ the X^2 or Fisher’s exact test”. Why would X^2 be used if both are continuous variables?

ETHICS

- Were some participants illiterate? If yes, how did they provide informed consent? Please clarify.

References

1. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, et al.: Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *The Lancet Neurology*. 2006; **5** (9): 735-741 [Publisher Full Text](#)

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, dementia, lifestyle interventions, dementia risk scores, clinical trials, stress, sleep

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 18 Jan 2021

Lingkan Barua

Thanks a lot for your valuable comment on our protocol. Here we have added our responses.

Comments on Introduction

Comment 1: In the sentence "Systolic hypertension is an imperative modifiable risk factor for late-life cognitive impairment that can cause vascular dementia¹²." When describing dementia risk factors, I suggest that the authors use the terminology "increase the risk for" instead of "cause".

Response 1: Thank you for your valuable feedback, and we have changed it accordingly in the manuscript.

Previously it was "Systolic hypertension is an imperative modifiable risk factor for late-life cognitive impairment that can cause vascular dementia"

Now it is "Systolic hypertension is an imperative modifiable risk factor for late-life cognitive impairment that can increase the risk of vascular dementia" (Page number-3)

Comment 2: The fourth paragraph can benefit from restructuring. It starts by describing vascular risk factors for dementia but then switches to describing pain experienced by

individuals who already have dementia. Then it moves on to describing depression, anxiety, isolation, and lack of exercise. It ends by describing adherence to medication schedules. What is the goal of the paragraph? What idea is it trying to portray? What is the connection between these different components in this context? This would clarify the message to the reader

Response 2: Good observation, and we have revised the manuscript as per the comments. However, here actually, we were trying to say if CAD patients somehow develop dementia, then what will be the after-effects. This is true that not all who will achieve risk score will develop dementia. But somehow if they develop then how negatively it will impact the overall situation of both disease conditions was the matter of focus. For making the concept reader-friendly, we have discarded the lines. However, we have discarded those lines as those lines are not that to the readers. (Page number-3)

Comment 3: Is the observation of an association between heart disease and dementia really “controversial” as it is described? Even if it varies according to risk profiles? Please clarify or rephrase.

Response 3: We have discarded these lines (page number-3)

Comment 4: Specifically, which “mobile application-based risk prediction tool; the CAIDE risk score.” are the authors referring to? A search on App Store and Google Play does not show that such an App currently exists. If this App was used in the past, the exact name needs to be provided, as well as the dates when it was accessed/used.

Response 4: Thank you for the valuable comment. We use the searchable tool named “Dementia Risk Tool” instead of “mobile application-based risk prediction tool; the CAIDE risk score.” as per your suggestion to find out quickly in the Google play store. We have attached the link reference (<https://pubmed.ncbi.nlm.nih.gov/16914401/>) of the mobile app tool for your kind reference. But after December this tool is not displayed at Google Play store anymore, but we have completed the assessment through this tool)

(B). Comment on protocol

Study Design:

Comment 1: How is this considered “an ongoing cross-sectional study”, when it was completed in July 2020? Since it has been completed, can the authors present the study baseline data?

Response 1: We have submitted the protocol in June 2020. Moreover, this protocol is based on an MPH thesis work, which we submitted in June 2020, and the duration was one year. Due to COVID Pandemic, all the thesis works were postponed due to different restrictions of the Government of Bangladesh. However, now again, we are working on it.

Comment 2: Primary objective 1: This is a description of what is done, not necessarily an actual objective. Can this be rephrased into an objective?

Response 2: We have assessed the level of future dementia risk and categorize them as low, moderate, and high using the CAIDE risk score

Now it is “*Primary objective 1: Dementia risk prediction—* to assess the level of dementia risk of the study subjects as per CAIDE risk score and categorize as low, moderate and high” (Page number-4)

Comment 3: Primary objective 2: What is meant by “biochemical and other diagnostic profile”: Please clarify

Response 3: By biochemical profile, we meant the laboratory investigations of the respondents that were based on blood samples. We have evaluated the ECG findings, echocardiogram, and angiographic findings of the respondents, and as these are the tests that are a basis of a diagnosis of CAD patients, so we mentioned them as a diagnostic profile. However, we changed it to an investigation profile in the manuscript which would be more appropriate.

Now the line is “Explore the biochemical and other investigation profiles (Echocardiogram, angiogram, electrocardiogram, etc. will also be included) of the study population” (Page number-5)

Comment 4: Secondary objective: Which cardiac biomarkers are you referring to?

Response 4: We are collecting the reports of Brain Natriuretic Peptide (BNP) and N-terminal pro-B-type Natriuretic Peptide (NT-pro-BNP) as a cardiac biomarker of the respondents which is our secondary objective. (Page number-5)

Comment 5: Please provide more information regarding this objective: “relationship between the number of coronary vessels involved and the risk of developing dementia”.

Response 5: We will explore the relationship between cardiac vessel involvements with dementia risk by applying multivariate analysis. Normally cardiac vessel involvement can be of single-vessel disease (SVD), Double vessel disease (DVD), and Triple vessel disease (TVD). We will find out if there is any variation in the risk category for vessel involvement.

Now it is “Identify the relationship between the number of coronary vessels involved (Single vessel disease (SVD), double vessel disease (DVD) and triple vessel diseases (TVD)) and the level of dementia risk of the study subjects” (page number-5)

Study Population

Comment 6: The text states: “As this is a Master’s thesis that has a pre-defined period, this non-probability sampling method...” Can you please add more information about the predefined period?

Response 6: Master’s thesis needs to be complete by a one-year duration, and in the case of this study, we have the period from July 2019 to August 2020. By this time, protocol development, pre-testing, data collections all need to be completed. However, due to the COVID 19 situation, our study is also compromised (university authority allows us six months more) like the rest of the world.

Comment 7: Was it a requirement to have a ‘caregiver’ to participate? Please clarify.

Response 7: No, it was not a requirement but based on the patients' disease severity; we sometimes took help from the caregivers.

Comment 8: Regarding verb tenses, if the study or a component of the study is complete, I suggest writing the descriptions in the past tense. For example, it states, “Before enrollment, patients are being screened as having”

Response 8: Thank you for the valuable suggestion, and we revised the manuscript accordingly (Page number-5)

Comment 9: It is unclear what this statement is referring to as “a self-reported statement, and documented clinical history”. Can you please clarify?

Response 9: We have gone through the participants' interviews (self-reported statement) and have gone through their clinical history, written by a certified physician (documented clinical history), with appropriate permission from the physician.

Comment 10: Why is the sample size based on vascular dementia prevalence, when this is a short-term cross-sectional study among middle-aged adults, with no measurements of dementia development?

Response 10: We consider this prevalence for the following reasons- a. There is a lack of dementia prevalence study at Bangladesh b. Available prevalence study is not representative to such group of population c. Our study population is more exposed to develop vascular dementia as they already have such risk factors d. We selected the urban area of our neighboring country as the food habit, lifestyles are almost similar.

Comment 11: Why is depression not included among the comorbid conditions?

Response 11: For the diagnosis of clinical depression, we need to use a few specific scales, which was not possible in those settings.

Comment 12: Why does behavioral information not include other dietary factors? E.g. fish consumption, consumption of meat, refined sugars?

Response 12: Study populations are from a very sensitive group, and they were getting prepared for bypass surgery, and many of them had restrictions of too much talking, movement. Taking all these into the ground, we tried to keep the questionnaire as short as possible. So, these dietary habits were not explored. However, we included the risk factors (included fruits and vegetable intake) of chronic diseases that are usually used by the STEPwise approach to Surveillance (STEPS) of the Noncommunicable diseases risk factors questionnaire (version 3.2) of the World Health Organization.

Comment 13: A more detailed description is needed for these parameters: “parameters: trends in responses; fundamental flaws with the design or format; attractiveness; comprehension; acceptance; and relevance.”

Response 13: By ‘trends in responses,’ we mean whether the participants respond in the same pattern or do it vary from participant to participant?

By ‘fundamental flaws with the design or format,’ we mean whether the data quality match with the study design or not?

By ‘attractiveness,’ we mean, do the questionnaire materials attract the audience?

By ‘comprehension,’ we mean, are the materials properly understood by the target participants?

By ‘acceptance,’ we mean, is there anything in the questionnaire which is not sensitive or unfitting?

By ‘relevance,’ we mean the facts we are talking about ever faced by the participants.

We have elaborated them appropriately on page number-7

Comment 14: This statement is inaccurate “This tool has been externally validated to predict late-life dementia risk²⁴ and was incorporated into the Finnish Geriatric Intervention

Study to Prevent Cognitive Impairment and Disability (FINGER) trial.". The EIT project (which took place later after the FINGER trial primary outcome results were published) included risk scores for late-life dementia. However, for the FINGER trial, the original midlife CAIDE Dementia risk score was used (not those for late-life

Response 14: We have corrected those lines

Now the line is "This tool has been externally validated to predict mid-life dementia risk ²⁴ and was incorporated into the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial"

(C). Comment on PLANNED ANALYSIS

Comment 1: It states "To identify the relationship between the numbers of coronary vessels involved and the risk of dementia among the study subjects, we will employ the X2 or Fisher's exact test". Why would X2 be used if both are continuous variables?

Response 1: We will categorize the vessel involvement as SVD, DVD, and TVD and categorize the dementia risk as low, moderate, and high. After that, we will apply for X2.

Now the line is "To identify the relationship between the numbers of coronary vessels involved (SVD, DVD, and TVD) and the level of dementia risk among the study subjects, we will employ the χ^2 test or Fisher's exact test" (Page Number-9)

(D). Comment on Ethics

Comment 1: Were some participants illiterate? If yes, how did they provide informed consent? Please clarify

Response 1: We found none of the respondents as illiterate. Hence, we did not face any problem to take consent.

Competing Interests: No competing interests.

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