**TEXTME-2**

**(Tobacco, Exercise, and Diet Messages for primary prevention of cardiovascular disease):   
A mobile Health primary prevention program**

*A single-blinded, randomised controlled trial to determine the impact of a program of semi-personalised lifestyle-focused text messages on multiple modifiable cardiovascular risk factors, in a population of high-risk individuals without documented coronary artery disease*

**STUDY PROTOCOL**

Version 2.0

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**INTRODUCTION AND RATIONALE**

Cardiovascular disease (CVD) includes coronary artery disease, stroke and peripheral vascular disease, and remains the largest cause of premature death and disability worldwide (1, 2). Multiple risk factors contribute to incident cases of cardiovascular disease, many of which are behavioural, and thus preventable, including smoking, physical inactivity and poor diet. Abnormal lipids, hypertension, smoking, excess alcohol consumption, physical inactivity, diabetes, abdominal obesity, psychosocial factors, and fruit/vegetable consumption accounts for over 90% of the risk of myocardial infarction worldwide (3).

In response to the CVD burden, in 2013 the World Health Organisation (WHO) developed a Global action plan on the prevention and control of cardiovascular disease (4). Whilst there is strong evidence supporting secondary cardiovascular prevention programs, there has been substantial underutilisation of existing cardiac preventative programs, mostly due to access barriers (5). Thus, high quality research into novel cost-effective and accessible prevention programs targeting high-risk individuals is needed in order to find ways to reduce the incident cases of CVD worldwide (6).

The use of mobile health (mHealth) technology has in recent years gained attention as a potential novel method of delivering health care. The Global Observatory for eHealth has defined mHealth as “medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices”(7). mHealth includes short messaging service (SMS), as well as more complex functionalities and mobile applications. Just under a third of the global population currently own and use a smartphone, and this is expected to increase to more than 50% by 2018 (8). Growth of mobile phone use has now seen low-income countries almost reach usage levels seen in middle- to high-income countries (9). Due to its ubiquity, this technology may reduce access block to healthcare and allow convenient community-based health assessment, support the exchange of health information, and encourage positive health behaviour (7, 10).

SMS-based interventions are an exciting growing development in healthcare delivery due to their low cost, ubiquity and potential for wide dissemination and equal accessibility across different cultures and geographical areas. Studies assessing the effects of text-messaging on cardiovascular risk factors have shown promise, however many studies are of short duration and/or use other modalities in conjunction with text messaging. Whilst short term adherence to text-messaging based programs has been demonstrated, long-term studies are important given the chronicity of cardiovascular disease. There is some evidence that programs targeting multiple risk factors may be more effective and more cost effective than treatment decisions based on individual risk factor targets (11).

The Australian Tobacco, Exercise and Diet Messages (TEXT ME) is a recent single-centre randomized controlled trial we conducted that assessed multiple cardiovascular risk factors in 710 patients with cardiovascular disease (12). The intervention arm consisted of a 6-month non-interactive semi-personalised text-message program in addition to usual care. The subjects received four messages per week that provided advice, motivation and support. Content covered smoking if relevant, diet, physical activity, and general cardiovascular information. At 6-month follow-up, participants in the intervention group compared to controls had modest reductions in LDL-C, blood pressure, BMI, significant increases in physical activity, and a significant reduction in smoking (12).

TEXTME 2 is a trial which builds on the work of TEXTME(12). The primary objective of the TEXT ME 2 study is to determine the impact of a program of lifestyle-focused text messages on multiple modifiable cardiovascular risk factors, in a population of high-risk individuals who have been referred to outpatient cardiology services for chest pain but without documented coronary artery disease (i.e. primary prevention cohort). In addition, this study will look at the effect of such a program on quality of life, health literacy, medication adherence and depression/anxiety scores.

**OBJECTIVES:**

1. To determine in a randomised controlled trial of patients of high cardiovascular risk who have been referred to outpatient cardiology services for chest pain but without documented coronary artery disease (i.e. primary prevention cohort), the effect of semi-personalised lifestyle-focused text message program sent via mobile phone on:

**(A) Primary outcomes:**

Change in the proportion of patients who have 3 or more uncontrolled modifiable risk factors at 6 months compared to standard care

**(B) Secondary outcomes:**

(i) Mean change in objective measures of risk (fasting LDL-C, systolic blood pressure, BMI, waist circumference, HbA1c for those with diabetes at baseline)

(ii) Lifestyle modifications - proportion achieving guideline recommendation vegetable and fruit intake, regular physical activity, and smoking cessation rates.

(iii) Quality of life, depression/anxiety scores

(iv) Effect on medication adherence

(v) Effect on cardiovascular health literacy

(vi) Major cardiovascular events and mortality

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| Achieving Guideline Levels of Risk Factors: LDL-C <2 mmol/L, Blood pressure <140/90 mm Hg, Exercising regularly, Nonsmoker, BMI <25, diet according to guideline recommendations |
| Systolic Blood pressure (BP) – *3 digital recordings of resting, sitting BP, mean of last 2 readings (using office automated BP)* |
| Low density lipoprotein (LDL) cholesterol/high density lipoprotein (HDL) cholesterol/Total Cholesterol/Triglycerides – *fasting blood sample* |
| Body mass index (BMI) - weight/height2– *measured by research assistant blinded to treatment allocation* |
| Waist circumference -  *measured by research assistant blinded to treatment allocation* |
| HbA1c and fasting BSL - *both* *measured at baseline, and HbA1c at the 6-month follow-up visit.* |
| Smoking rate, quitting attempts – *self report* |
| Physical activity – *Global Physical Activity Questionnaire* (GPAQ) |
| Medical adherence –*Self-report of use over last 7 and 30 days* |
| Diet – *Self-report fruit and vegetable consumption over last 7 days* |
| Quality of life – *EQ-5D-5L* |
| Depression - *The Patient Health Questionnaire-9 (PHQ-9). Mean score and proportion* |
| Anxiety *- Generalised Anxiety Disorder – 7-item (GAD-7). Mean score and proportion* |
| Health literacy – *BRIEF questionnaire for general health literacy and Cardiovascular Knowledge Survey. Mean score.* |
| Inpatient readmissions, clinical events and use of other health services (GP, specialists, hospitals, community services – *self report, hospital records)* |

2. To determine the cost effectiveness of the intervention

3. To determine the acceptability and utility of the intervention among participants

**MAIN HYPOTHESIS:**

The main hypothesis is that a program of lifestyle-focused text messages delivered to a high-risk primary prevention cohort who have experienced chest pain will improve cardiovascular risk profile compared to standard care. This is an opportunistically identified cohort of high cardiovascular risk patients that were referred for assessment of chest pain and subsequently found to have no coronary artery disease (as defined by no documented myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or 50% or greater stenosis in at least 1 major epicardial vessel on invasive coronary angiography).

**METHODS AND ANALYSIS:**

**Study design and population**

TEXTME-2 is a single-blinded randomized controlled trial. Recruitment will occur over 12 months. The TEXTME-2 program will be delivered over 6 months.

The study population will consist of patients referred to an outpatient cardiology clinic for chest pain within a 12-month period, at high cardiovascular risk *WITHOUT* documented coronary artery disease.

**Inclusion criteria:**

* 1. Referred to an outpatient cardiology clinic for assessment of chest pain *or* have other symptoms leading to investigation for ischaemic heart disease AND
  2. Framingham absolute cardiovascular risk calculation of ≥10%

**Exclusion criteria:**

1. No active mobile phone
2. Unable to understand a language TEXTME-2 is provided in
3. Unable to provide informed consent
4. Documented coronary artery disease (documented prior myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or 50% or greater stenosis in at least 1 major epicardial vessel on invasive coronary angiography)

Asymptomatic individuals will not be eligible for TEXTME-2 as it is hypothesized that at risk individuals who have experienced chest pain are most likely to adhere to lifestyle preventative measures.

Enrolment and baseline assessment

July 2017 to June 2018

**Participant eligibility**

* Referred to outpatient clinic for chest pain
* Framingham absolute risk calculation ≥ 10%
* NO documented CAD\*
* Have an active mobile telephone and speak in language TEXTME-2 is provided in

**Randomisation (n~ 246)**

* Collection of baseline data including biomedical risk factors, lifestyle and psychosocial questionnaires
* Computer-generated randomization sequence with uniform 1:1 allocation

**TEXT ME-2 intervention (n~ 123)**

* Text messaging program over 6 months providing lifestyle advice plus standard care

**Standard care (n~123)**

* Standard care for lifestyle change and medications

**Follow up at 6 months**

* Face-to-face visits at 6 months
* Risk factors assessed by clinical research assistant blinded to treatment allocation
* SMS program terminates at 6 months for treatment arm
* Acceptability/follow-up questionnaire completed by both arms at 6 months

Intervention

July 2017– Dec 2018

Follow-up and analysis

Jan 2018 to June 2019

**Figure 1: Study design.** eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; RAC, Rapid Access Cardiology.

\* CAD defined as documented prior myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, or 50% or greater stenosis in at least 1 major epicardial vessel on coronary angiography.

**Randomisation**

Eligible participants will be randomized into either the treatment arm (texting program) or standard care. Randomisation will occur via a computerized randomization program that will be accessed through a secure web interface that will be accessible by study staff with username and password. The random allocation sequence will be in a uniform 1:1 allocation ratio with a block size of 8 and will be concealed from study personnel. To maintain blinding of study personnel, patients will be informed of their allocation in a text message sent after leaving the outpatient cardiology clinic. Prior to any follow-up appointments patients will also receive a text message to ask them not to reveal their allocation status to study personnel or clinicians.

**Intervention**

The text-messaging bank will be developed for 5 modules: diet, physical activity, smoking, general cardiovascular health, and medication adherence. The message bank will include many of the questions included in TEXTME, however the refined message bank will remove questions specific to a cohort with established cardiovascular disease, and add an additional module on medication adherence. Examples text messages include: “Did you exercise today?”, “The Heart Foundation recommends at least 30 minutes of exercise most days of the week”, “Is there a low fat option? Most products have low fat options. Check the markings on the back”. There will be some personalization of text messages based on age, smoking status, sex, and physical disability. For example, only smokers will receive messages regarding smoking cessation, and patients with limited mobility will not be sent messages regarding strenuous activities such as jogging.

Participants randomized to the intervention group will, in addition to standard care, receive text messages up to 4 times a week, on different days and at different times between 0800 and 1800. Control participants will receive standard lifestyle change advice and medication care only.

Participants will not be informed not to respond to the text messages at time of enrolment. All participants will be provided with contact details (a telephone number) of the research staff if they want to ask questions.

**Study outcomes**

The primary outcome is percent change in the proportion of patients who have 3 or more **uncontrolled** modifiable risk factors **(LDL-C > 2.0mmol/L, systolic blood pressure > 140mmHg (average of 3 readings), body mass index (BMI) > 24.9, physical activity (less than the equivalent of 150 minutes of moderate intensity each week), smoking status)**.

Secondary outcomes are mean change in fasting LDL-C, systolic blood pressure, BMI, waist circumference according to sex (high risk is >102cm in men and >88cm in women), proportion achieving guideline recommendation vegetable (≥ 5 serves) and fruit (≥ 2 serves) intake, proportion exercising equivalent of 150 minutes of moderate intensity exercise each week, and smoking cessation rates. HbA1c will be recorded at the 6 months follow-up and mean values calculated. The diagnosis of new diabetes will be made if two consecutive HbA1c levels measured at baseline are ≥6.5%, two consecutive baseline fasting plasma glucose levels are ≥7.0mmol/L, or if both the baseline HbA1c and fasting plasma glucose are above their diagnostic thresholds as per current Australian recommendations.(13) Quality of life, depression/anxiety scores, medication adherence, and general and cardiovascular health literacy will also be assessed. Six-month hospital readmissions/representations will be assessed from time of enrolment and measured at the 6-month face-to-face follow-up visit as described below.

There will be a face-to-face visit at time of registration and at 6 months (see figure 2 for details). At both time points LDL-C, systolic blood pressure, smoking quantity and quit attempts if applicable, self-reported diet, BMI/waist circumference will be measured, HbA1c, and fasting plasma glucose level. In addition, questionnaires regarding physical activity (GPAQ (14)), quality of life (EQ-5D-5L(15)), depression/anxiety scores (GAD-7(16), PHQ-9(17)), medication adherence, and health literacy (BRIEF health literacy(18) survey at time of registration and cardiovascular health literacy at 6 months(19)) will be conducted. At baseline for those who have cardiovascular risk factors (such as diabetes, hypertension, and/or hyperlipidaemia), treatment, duration of treatment, and time since diagnosis will be recorded. Any diabetic microvascular and macrovascular complications will also be recorded.

At the end of the SMS program (6 months), participants will complete a questionnaire of a series of Likert responses about their experiences of being sent health text messages. Questions will address the tolerability of the text messages, asking which the participants liked or disliked, perceived utility, and intrusiveness.

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| **Box 1: Primary and secondary outcomes** | |
| **Primary** | * Percent change in the proportion of patients who have 3 or more uncontrolled modifiable risk factors |
| **Secondary** | * Fasting LDL-C * Systolic blood pressure (average of three readings) * BMI and Waist circumference * Change in HbA1c (for those with diabetes) * Global Physical Activity Questionnaire (GPAQ) (14) * Self-reported smoking rate (cigarettes per day) and quit attempts (if relevant) * Servings of vegetables and fruit consumed each day (self-reported) * Quality of life as assessed by the EQ-5D-5L Health Survey(15) * Depression score as assessed by Patient Health Questionnaire- 9 (PHQ-9)(17) * Generalised Anxiety Disorder 7-item (GAD-7) score(16) * Cardiovascular Health literacy(19) * Medication adherence – self reported * Hospital readmissions/representations (self-report, medical records) |

**Figure 2: Study timeline of measured clinical outcomes.** FTF, Face-to-Face; BMI, Body Mass Index; GPAQ, Global Physical Activity Questionnaire; PHQ-9, Patient Health Questionnaire 9-item; GAD-7, Generalised Anxiety Disorder 7-item.

**Statistical analyses**

During a 12-month enrolment period, based on our current referrals of high-risk patients without documented CAD (as defined by Framingham risk greater than or equal to 10%, age greater than 74, and/or presence of chronic kidney disease), and assuming 10% loss to follow-up rate, our estimated possible sample size would be 246. Using existing local control data we found that 62% of a primary prevention cohort attending an outpatient cardiology clinic had 3 or more risk factors. We estimated that with 90% power and two-sided α at 0.05, a sample size of 246 (123 in each group) would be able to detect a 33% decrease in the proportion of people with 3 or more uncontrolled modifiable risk factors.

**CONCLUSIONS**

This study will be the first to evaluate the effectiveness of a systematic high-risk primary prevention program utilizing novel mobile health technology on multiple cardiovascular risk factors. To date, evidence regarding the effectiveness of primary prevention programs on cardiovascular health is limited.(20) However, none have targeted symptomatic high-risk individuals who maybe more likely to adhere to primary prevention practices compared to asymptomatic individuals.

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