The Effect of Communicating Genetic Risk of Type 2 Diabetes and Wearable Technologies On Wearable-Device-Measured Behavioral Outcomes in East Asians: Analysis plan of a Randomized Controlled Trial

Hin Sheung Ho, Ziyuan Chen, Job Godino, Michael Multhaup, King Chung, Derwin Chan, Shiu Lun Au Yeung, Shan Luo, Hon Yin, Brian Chung, Simon Griffin, Youngwon Kim

Submitted to: JMIR Research Protocols
on: August 05, 2024

Table of Contents

The Effect of Communicating Genetic Risk of Type 2 Diabetes and Wearable Technologies On Wearable-Device-Measured Behavioral Outcomes in East Asians: Analysis plan of a Randomized Controlled Trial

Hin Sheung Ho[1*]; Ziyuan Chen[1*]; Job Godino[2] PhD; Michael Multhaup[3] PhD; King Chung, Derwin Chan[4] PhD; Shiu Lun Au Yeung[1] PhD; Shan Luo[1] PhD; Hon Yin, Brian Chung[5] MBBS; Simon Griffin[6] PhD; Youngwon Kim[1*] PhD

[1]School of Public Health, Li Ka Shing Faculty of Medicine The University of Hong Kong Hong Kong HK
[2]Herbert Wertheim School of Public Health & Human Longevity Science University of California San Diego La Jolla US
[3]Exai Bio Palo Alto US
[4]Department of Early Childhood Education The Education University of Hong Kong Hong Kong HK
[5]Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine The University of Hong Kong Hong Kong HK
[6]MRC Epidemiology Unit, School of Clinical Medicine University of Cambridge Cambridge GB
[*]these authors contributed equally

Corresponding Author:
Youngwon Kim PhD
School of Public Health, Li Ka Shing Faculty of Medicine
The University of Hong Kong
Room 301D 3/F, Jockey Club Building for Interdisciplinary Research, 5 Sassoon Road, Pokfulam, Hong Kong
Hong Kong
HK

Abstract

Background: Evidence suggests that the dissemination of type 2 diabetes (T2D) genetic risk alone has displayed limited effectiveness on facilitating behavioral changes amongst individuals of European descent. Although the usage of physical activity surveillance systems such as wearable devices, have been associated with changes in behavior, the effects of combining personalized precision medicine with wearable devices on T2D prevention remains unclear. This study aims to assess the novel effects of T2D genetic risk communication and wearable device functions on objectively measured physical activity (PA) time amongst overweight and obese East Asian individuals.

Objective: There are two specific objectives in this study. To investigate 1) the effects of communicating T2D genetic risk, and 2) the effects of combining T2D genetic risk communication with wearable device functions such as step-goal setting and activity prompts on objectively measured MVPA time within overweight and obese East Asians.

Methods: The study is conducted as a parallel group, randomized controlled trial. 355 overweight or obese East Asians aged between 40 to 60, are allocated into one of three groups: 1 control and 2 intervention groups. All participants are instructed to wear a Fitbit device throughout the study. Blood samples are used for estimation of T2D genetic risk and tested for metabolic risk markers. T2D genetic risk is estimated based on 113 SNPs associated with T2D in East Asians using an established method. Both intervention groups are provided with T2D genetic risk reports together with lifestyle advice leaflets on a weekly basis using whatsapp and on a monthly basis using email. Additional Fitbit wearable functions such as step-goal setting and prompt functions have been activated in one of the intervention groups. The primary outcome is moderate-to-vigorous physical activity (MVPA) time, which is objectively measured with the in-built accelerometer of the Fitbit Inspire 3 and will be assessed at baseline, immediately post-intervention, 12-months post intervention and post follow up. Secondary outcomes include other parameters measured by the wearable device, such as sedentary time, body mass index, systolic and diastolic blood pressure, five metabolic risk markers, hand grip strength, sleep, self-reported PA, self-reported fruit and vegetable consumption, smoking status and other psychological variables.

Results: The intervention started in May 2023 and will continue until February 2024.

Conclusions: This study will be the first randomized controlled trial using a combination of T2D genetic risk communication with wearable device functions in any population. Novel findings will be used to inform future lifestyle modification strategies for T2D prevention. We plan to provide a comprehensive report on this study by publishing this analysis plan before the

completion of data collection. Clinical Trial: ClinicalTrials.gov, NCT05524909. https://register.clinicaltrials.gov/ (30 Aug 2022)

(JMIR Preprints 05/08/2024:65012)
DOI: https://doi.org/10.2196/preprints.65012

Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.
Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

Original Manuscript

The Effect of Communicating Genetic Risk of Type 2 Diabetes and Wearable Technologies On Wearable-Device-Measured Behavioral Outcomes in East Asians: Analysis plan of a Randomized Controlled Trial

Abstract

Background: Evidence suggests that the dissemination of type 2 diabetes (T2D) genetic risk alone has displayed limited effectiveness on facilitating behavioral changes amongst individuals of European descent. Although the usage of physical activity surveillance systems such as wearable devices, have been associated with changes in behavior, the effects of combining personalized precision medicine with wearable devices on T2D prevention remains unclear. This study aims to assess the novel effects of T2D genetic risk communication and wearable device functions on objectively measured physical activity (PA) time amongst overweight and obese East Asian individuals.

Objective: There are two specific objectives in this study. To investigate 1) the effects of communicating T2D genetic risk, and 2) the effects of combining T2D genetic risk communication with wearable device functions such as step-goal setting and activity prompts on objectively measured MVPA time within overweight and obese East Asians.

Methods: The study is conducted as a parallel group, randomized controlled trial. 355 overweight or obese East Asians aged between 40 to 60, are allocated into one of three groups: 1 control and 2 intervention groups. All participants are instructed to wear a Fitbit device throughout the study. Blood samples are used for estimation of T2D genetic risk and tested for metabolic risk markers. T2D genetic risk is estimated based on 113 SNPs associated with T2D in East Asians using an established method. Both intervention groups are provided with T2D genetic risk reports together with lifestyle advice leaflets on a weekly basis using whatsapp and on a monthly basis using email. Additional Fitbit wearable functions such as step-goal setting and prompt functions have been activated in one of the intervention groups. The primary outcome is moderate-to-vigorous physical activity (MVPA) time, which is objectively measured with the in-built accelerometer of the Fitbit Inspire 3 and will be assessed at baseline, immediately post-intervention, 12-months post intervention and post follow up. Secondary outcomes include other parameters measured by the wearable device, such as sedentary time, body mass index, systolic and diastolic blood pressure, five metabolic risk markers, hand grip strength, sleep, self-reported PA, self-reported fruit and vegetable consumption, smoking status and other psychological variables.

Results: The intervention started in May 2023 and will continue until December 2024.

Conclusions: This study will be the first randomized controlled trial using a combination of T2D genetic risk communication with wearable device functions in any population. Novel findings will be used to inform future lifestyle modification strategies for T2D prevention. We plan to provide a comprehensive report on this study by publishing this analysis plan before the completion of data collection.

Trial Registration: ClinicalTrials.gov, NCT05524909. https://register.clinicaltrials.gov/ (30 Aug 2022)

Keywords: Type 2 diabetes, Physical activity, Genetic risk, Wearable technology, Randomized controlled trial, Movement behavior, Statistical analysis plan

Introduction

Trial background and rationale

Currently around 500 million individuals live with diabetes worldwide, of whom 90% are diagnosed as type 2 diabetes (T2D),[1] The prevention of T2D is recognized as a public health priority across the globe. Recent epidemiological data has revealed that individuals aged 40-60 accounted for 40% of T2D incident cases in Hong Kong,[2] signaling a necessity for innovative strategies aimed towards middle-aged adults.

The defining characteristic of T2D is the decline of pancreatic beta cell functions, caused primarily by chronic insulin resistance. Although research has uncovered a plethora of risk factors implicated in T2D progression, such as age, diet, physical inactivity, alcohol consumption, body mass index (BMI), and family history,[3] the multi-factorial nature of T2D would render singular procedures challenging in accurately screening and predicting disease risk in at-risk individuals.

Owing to advances in fields of genomics and precision medicine, the technology for assessing genetic predisposition to non-communicable diseases has become more accessible over time. Coupled with recent genome-wide association studies, they have enabled the discovery of genetic variants that exhibit significant associations with T2D in East Asian populations. With such advancements, accurate genomic sequencing can facilitate the adoption of genetic risk communication for T2D on an unprecedented magnitude. This could provide researchers with potential insights on the impact of communication of T2D genetic risk on behavioral changes in East Asians.

However, evidence from multiple studies indicated that communication of genetic risk has limited impact on behavioral changes,[4] raising concerns regarding the overall effectiveness of this technique. Nonetheless, these studies share similar limitations; for example, 1) the dissemination of genetic risk was carried out without considering behavioral change theories; 2) physical activity as a primary outcome was often measured with report-based measures; 3) genetic risk of polygenic diseases was calculated with singular genetic variants; 4) a predominant focus on individuals of European descent, thus limiting the general applicability of findings to East Asian populations.

We, herein, provide detailed data analysis plans for the first East-Asian focused, randomized controlled trial utilizing wearable device functions in conjunction with genetic risk communication to facilitate changes in physical activity (PA). The wearable device (Fitbit Inspire 3 tracker) used in the trial has a built-in accelerometer, providing researchers with objectively measured activity data. Fitbit functions such as activity goal-setting and activity prompts would be central to promoting and sustaining healthy lifestyle behaviors as demonstrated by previous intervention studies using wearables.[5] Through combining personalized precision medicine with wearable device functions, the trial will provide novel insights on lifestyle modification strategies for T2D prevention.

Trial objectives and hypothesis

The main objectives of this trial include: 1) investigating the impact of T2D genetic risk communication, and 2) examining the effects of combining T2D genetic risk communication with theory-based wearable device functions (e.g., step-goal setting and prompt functions commonly found in consumer-based wearables) on wearable-device measured MVPA time amongst overweight or obese East Asian middle-aged adults.
It is hypothesized that T2D genetic risk communication alone will lead to minimal increases in objectively measured MVPA time. Combining T2D genetic risk communication with wearable-device functions will significantly increase MVPA time not only post-12-month intervention but also at 6-month follow-up.

Methods

Recruitment

Participants were recruited across various communities in Hong Kong primarily via flyer distribution, local minibus advertisements, emails and word of mouth. Recruitment materials contained the title, research question, brief information of study (e.g. study period, duration, particulars), participant incentives, inclusion and exclusion criteria, sign-up methods and contact information of the research team.
Flyers were distributed alongside pull-up banners within local communities, and minibus advertisements were placed on the back of local minibus seats. Recruitment emails were circulated in local organizations and community centers. Any interested participant was asked to complete an online screening form when signing up.

Trial design

This trial is a parallel-group randomized controlled trial, which commenced on 11th May 2023 and aims to involve a sample of 355 participants. We randomly allocate each participant into one of three groups: one control group and two intervention groups (Intervention group 1st arm and 2nd arm). All participants are asked to wear a Fitbit device throughout the study period.
The 1st arm receives a Fitbit device, T2D genetic risk estimates and a lifestyle e-leaflet. Participants in the 2nd arm also receive and have their Fitbit devices calibrated such that their Fitbit step goal will be 10% higher than their baseline step count, as well receiving activity prompts, in addition to the T2D genetic risk estimate and e-leaflet. The control group only receives a Fitbit device.

Intervention

T2D genetic risk estimates along with a lifestyle e-leaflet are delivered on a weekly basis via Whatsapp alongside monthly emails. The genetic risk estimates are presented as a dichotomized genetic risk category in comparison to the average population risk of T2D: "increased genetic risk" and "no increased genetic risk". The e-leaflet contains detailed information such as the definition and health impacts of T2D, as well as lifestyle advice on four major T2D risk factors (physical activity, diet, weight management and smoking) as recommended by the World Health Organization.

The 2nd arm receives two unique Fitbit features: 1) Step-goal setting and 2) Activity prompts, in addition to the T2D genetic risk estimate and e-leaflet. Each participant's step-goal is set by staff 10% higher than their baseline step counts (the average of the 7-day pre-intervention Fitbit data). The "Reminders to move" function is used as a prompt to break up prolonged periods of sedentary time. When the wearer has not accumulated more than 250 steps within an hour, the device vibrates and displays a reminder message. We have specified an operation period for this function and the device reminds participants 10 minutes before every hour between 9am to 10pm. All unique Fitbit functions can only be accessed and modified by researchers via the Fitbit online dashboard system.

Randomization

A block randomization approach has been adopted. The randomization list has been generated from a computer program, by a staff member without prior knowledge of participant information. The list consists of blocks of six that contain two of each of the three groups per block.
Group allocation has been concealed from study staff until the 7-day pre-intervention period, whereby staff had already prepared the corresponding intervention materials for participants. The participants will be initially blinded to the randomization assignment, but it would be impossible to blind them once the intervention is delivered. It should be noted that staff responsible for data analysis will analyze de-identified data and will continue to be blinded to participant randomization assignment.

Sample size

To ensure sufficient statistical power, we intend to recruit 355 overweight or obese East Asian participants. An over-sampling strategy has been adopted, with approximately 35% of the full sample (n=87) consisting of individuals at a higher genetic risk for T2D within the population (n=248; 87/35%). The required number of participants (n=87) for sub-sample analysis was based on the desired medium effect size F of 0.3085, derived from a three-group comparison. The control group's average wearable device-measured MVPA time was 80 minutes/day, the intervention group receiving genetic risk information alone had minimal changes (intervention group 1st arm; 85 minutes/day), and the other intervention group that would receive combined genetic risk information and wearable functions would have a 23% difference in MVPA time (intervention group 2nd arm; 105 minutes/day, [(105-85)/85*100%]; corresponding to a 23% MVPA time difference compared previous Fitbit interventions).[6]
Our sample size calculation assumes an alpha level of 5%, a power level of 80%, and a correlation of 0.70 among three repeated measures. A total of 355 participants are recruited to ensure inclusion of an analysis sample of 248, while factoring in an expected attrition rate of

20% (n=71; 355*20%) and an anticipated 10% Fitbit-data-missing rate considering instances of insufficient battery life or device loss(n=36; 355*10%).

Framework

We adopt a superiority hypothesis testing framework for this trial, examining whether combining T2D genetic risk communication with theory-based wearable device functions will lead to significant increases in objectively measured MVPA time and if such changes will be sustained over 6-month follow up. Each of the intervention groups (Intervention 1st Arm and Intervention 2nd Arm) will be compared separately with the control group.

Interim analysis and stopping guidance

No planned interim analysis is planned for this study, as the intervention effects are not harmful towards participants to warrant ending the trial prematurely based on safety concerns.

Timing of outcome assessments

Time-points for outcome measurements during the trial are listed in Table 1.

Table 1. Schedule of assessments.

Time point	Baseline	t_0 (Immediate post-intervention)	t_{+12M} (post-12-month intervention)	t_{+18M} (6-month follow up)	$t_{-endpoint}$ - (post-follow up)
MVPA time (minutes)	x	x	x		x
Steps	x	x	x		x
Sedentary time (minutes)	x	x	x		x
Sleep time (minutes)	x	x	x		x
Lightly active time (minutes)	x	x	x		x
Psychological variables of genetic risk communication	x	x	x	x	
PA and sitting time	x	x	x	x	
Fruit and vegetable consumption	x	x	x	x	
Smoking status	x	x	x	x	
Blood biomarkers	x			x	

Height (cm)	x			x	
Weight (kg)	x			x	
Hand grip strength (kg)	x			x	
Systolic/ diastolic blood pressure (mmHg)	x			x	
Resting heart rate (BPM)	x			x	

Timing for final statistical analysis

Statistical analysis listed will be performed upon completion of the trial.

Statistical principles

Confidence intervals and P values
95% confidence intervals with adjusted marginal means will be presented for comparison of differences between groups at measurement time points (at baseline, immediately post-intervention, 12 post-12-month intervention and at 6-month follow-up); results for the interaction term will also be presented. Pairwise between-group comparisons will be performed with Bonferroni adjustment. A level of statistical significance will be set at $\alpha = 0.05$.

Adherence and protocol deviations

This study grants researchers a high level of control over protocol adherence and deviations. Given that intervention materials are mainly delivered weekly via Whatsapp messages, and only researchers have full control over Fitbit wearable functions, there is minimal possibility of protocol deviation. Participant are told to feel free to request to drop out at any phase of the study.
To investigate the effects of adherence and device wear time, a post-hoc analysis will be conducted by comparing individuals across all groups with consistent wear time against those that did not.

Analysis populations

Primary outcome analysis will be conducted according to the intent-to-treat principles. Participants with missing outcome data at 6-month follow-up will be excluded.

Trial population

Screening data

No screening data are collected. Participants' eligibility are assessed on site.

Eligibility criteria

Participants are accessed during the baseline assessment according to the following criteria:

- 40-60 years of age
- East Asian ancestry
- BMI ≥ 23 kilograms/meters^2 (according to the WHO BMI-defined cut-offs for Asians)
- Able to comprehend English or Chinese language
- Able to perform daily-life physical activities (determined by Physical Activity Readiness Questionnaire)
- Currently using a smartphone
- No prior experience with consumer-directed genetic testing
- Not diagnosed with any form of diabetes
- Not currently participating in any exercise-related intervention studies

Recruitment

We will report:

- Number of participants eligible for baseline assessment
- Number of participants randomized to each group
- Number of participants who completed 6-month follow-up
- Number of participants included in the main analysis (recording any exclusion with reasons)

Withdrawal and loss to follow-up

Participants are free to request withdrawal from the study without providing any reasons. The number of participants that report withdrawing due to reasons such as serious adverse events, safety concerns, and development of health conditions or symptoms is reported within each randomized group across each timepoint for outcome measurements.

Baseline characteristics

The following baseline characteristics will be recorded and summarized for the full sample and by trial arm:

- Age
- Sex
- Educational level
- Body weight and height
- BMI
- Non-dominant hand
- Blood pressure (systolic/ diastolic)
- Hand grip strength (Left and right hand)
- Estimated next 10 years and remaining lifetime genetic risk
- Blood biomarkers such as total cholesterol, HbA1c, HDL, LDL, and triglycerides

For categorical variables, we will present the proportion and total number of participants within each category. For continuous variables, means and standard deviations will be presented. Medians as well as 25^{th} and 75^{th} percentiles will be presented instead if data are skewed.

Analysis

Primary outcome

Moderate-to-vigorous PA (MVPA; sum of ‘Fairly active minutes’ and ‘very active minutes’) measured by the Fitbit tracker will be presented as the primary outcome of this study. The primary outcome will be measured during baseline, immediately post-intervention, post-12-month intervention and at 6-month follow-up.

Secondary outcomes

All measurements of secondary outcomes will be conducted during baseline, immediately post-intervention, 12 months post-intervention and at 6-month follow-up. Secondary outcomes include the following:

Lab assessment variables:

- BMI (kilograms/meters^2; derived from height and weight measurements)
- Systolic and diastolic blood pressure (mmHg; measured with OMRON HEM-907 Digital Automatic Blood Pressure Monitor)
- Resting heart rate (BPM; measured with OMRON HEM-907 Digital Automatic Blood Pressure Monitor)
- Hand grip strength (kg; measured using the Jamar Hydraulic Hand Dynamometer)

Metabolic risk blood biomarkers:

- Hemoglobin A1c (HbA1c) (%)
- Total cholesterol (mmol/L)
- High-density lipoproteins (HDL) (mmol/L)
- Low-density lipoprotein (LDL) (mmol/L)
- Triglycerides (mmol/L)

Fitbit tracker variables:

- Steps
- 'Sedentary minutes' (minutes)
- 'Lightly active minutes' (minutes)
- 'Calories burnt'(kcal)
- Sleep time (minutes)

Moreover, self-reported variables will be assessed via a series of questionnaires, which will include:

- Physical activity and sitting time
- Fruit and vegetable consumption
- Smoking status
- Psychological variables to determine the effects of genetic risk communication

Analysis methods

Primary outcome

We will perform primary outcome analysis according to the intent-to-treat principles, which will include a series of linear mixed-effects models with fixed effects of time, group and interaction between time and group for objectively measured MVPA time for repeated measures on each participant, together with adjustments for potential confounders such as age, sex and BMI. Adjusted marginal means along with 95% confidence intervals will also be presented to compare any differences between study groups throughout the assessment time points.

The analysis model will adopt a longitudinal data analysis model, which will examine any patterns of differences over assessment time points, study groups and group x time point interactions. Results for the interaction term for group and time will be included.

The effect modification will also be investigated according to the level of T2D genetic risk, which will be further categorized based on the average T2D genetic risk estimate of the sample. Such post hoc categorization can allow us to examine the intervention effects within each group of genetic risk. To ensure fair randomization between the randomized groups, we will examine between-group differences in the primary outcome data collected, using analysis of variance (ANOVA) test or Kruskal-Wallis test, should the data not meet parametric assumptions.

Secondary outcome

Analysis of continuous secondary outcomes will be conducted in a manner similar to the method for the primary outcome. For continuous variables such as metabolic risk biomarker blood variables, additional Fitbit measured variables and lab assessment variables, we will perform analysis of variance (ANOVA) test or Kruskal-Wallis test, should the data not meet parametric assumptions. For differences in categorical variables, such as the smoking status and psychological variables for T2D genetic risk communication, we will conduct Chi-square tests.

Sensitivity analysis and missing data

We will conduct two sets of sensitivity analyses: 1) without adjusting for confounders, and 2) by an iterative Markov chain Monte Carlo (MCMC) multiple imputation procedure to handle massing data at post-12-month intervention and follow-up time points. This procedure assumes that the missing data is at random (MAR) within each group. For any missing values, five imputations for each missing value will be carried out, such as sex, age, education level, body mass index, blood pressure and hand grip strength at baseline.

Safety data

This is a low-risk trial and will not pose any major adverse effects on participants' health. No adverse events would arise from following any one of the interventions; as such there should be no formal monitoring of adverse events. However, it may be possible for participants to exhibit some degree of discomfort, distress, and/or psychological concerns regarding their genetic risk for T2D. To accommodate for this potential issue, we aim to assess participants' psychological responses to genetic risk communication via web-based questionnaires, which will be administered at all 4 measurement time points. It should be noted that all participants are informed of the full scope and content of the study prior to participation, and that they can withdraw from the study at any phase of the study without providing any reason

References

1. Ogurtsova K, Guariguata L, Barengo NC, Ruiz PL-D, Sacre JW, Karuranga S, Sun H, Boyko EJ, Magliano DJ. IDF diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021. Diabetes Res Clin Pr. 2022;183:109118.
2. Luk AOY, Ke C, Lau ESH, Wu H, Goggins W, Ma RCW, Chow E, Kong APS, So W-Y, Chan JCN. Secular trends in incidence of type 1 and type 2 diabetes in Hong Kong: A retrospective cohort study. PLoS medicine. 2020;17(2):e1003052.
3. Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. Plos One. 2018;13(3):e0194127.
4. Hollands GJ, French DP, Griffin SJ, Prevost AT, Sutton S, King S, Marteau TM. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. Bmj. 2016;352:i1102.
5. Brickwood KJ, Watson G, O'Brien J, Williams AD. Consumer-Based Wearable Activity Trackers Increase Physical Activity Participation: Systematic Review and Meta-Analysis. JMIR Mhealth Uhealth. 2019;7(4):e11819.
6. Cadmus-Bertram LA, Marcus BH, Patterson RE, Parker BA, Morey BL. Randomized Trial of a Fitbit-Based Physical Activity Intervention for Women. American journal of preventive medicine. 2015;49(3):414-8.