Study Protocol and Statistical Analysis Plan

NCT01926041

The Effectiveness of Smoking Cessation in Prediabetic Smokers

Introduction

Post-cessation weight gain (PCWG) facilitates short-term type 2 diabetes (T2D) risk in prediabetic smokers in the absence of complementary measures. Little existing literature has explored the long-term effect of smoking cessation combined with PCWG restriction on T2D development. Primary care physicians should fight smoking and obesity together to prevent T2D and progression of its relevant comorbidities such as nonalcoholic fatty liver disease (NAFLD). This project pioneered the Fight Tobacco and Stay Fit (FIT2) program, which integrated smoking cessation therapy with individualized behavior coaching in diet and physical activity for PCWG restriction in prediabetic smokers.

Study Objectives

1. ***Glycemic***: *T*o investigate whether glycemic outcomes would be improved by the FIT2 program (combining smoking cessation therapy and PCWG restriction for a complete 16 weeks) and the post-program abstinence, respectively

   Aim 1-(1): To test the hypothesis that the FIT2 program would reduce long-term T2D risk determined in December 2020 (primary outcome) and at 10 years.

   Aim 1-(2): To test the hypothesis that maintaining post-program abstinence would reduce 10-year T2D risk.

   Aim 1-(3): To test the hypothesis that the FIT2 program would facilitate long-term probability of regression to normoglycemia determined in December 2020 and at 10 years.

   Aim 1-(4): To test the hypothesis that maintaining post-program abstinence would facilitate a 10-year probability of regression to normoglycemia.

   Aim 1- (5) To explore whether HbA1c changes at 6 and 12 months would be affected by FIT2 program and the post-program abstinence, respectively.

2. ***Extraglycemic***: *T*o explore whether extraglycemic endpoints would be improved by the FIT2 program and the post-program abstinence, respectively.

   Aim 2-(1): To test the hypothesis that the FIT2 program and maintaining post-program abstinence would reduce serial and 10-year NAFLD progression.

   Aim 2-(2): To test the hypothesis that the FIT2 program and maintaining post-program abstinence would reduce major adverse cardiac events at 10 years.

   Aim 2-(3): To test the hypothesis that the FIT2 program and maintaining post-program abstinence would reduce serial and 10-year chronic kidney disease progression.

   Aim 2-(4): To test the hypothesis that the FIT2 program and maintaining post-program abstinence would reduce malignancy incidence at 10 years.

   Aim 2-(5): To test the hypothesis that the FIT2 program and maintaining post-program abstinence would reduce all-cause mortality at 10 years.

Methods

Participants

We expect to recruit prediabetic smokers receiving medical care at two hospitals in Northern and Central Taiwan, where a systematic identification system has been applied to classify the tobacco addiction status of every patient in outpatient clinics.[1] This study invites identified current smokers to undergo screening tests between August 2013 to January 2017. **Included** are participants with prediabetes aged 30 to 75 years who have smoked ≥10 cigarettes per day for at least six months. Prediabetic participants are those who have repeated results for any of the following parameters: 1) plasma glucose levels 5.6–6.9 mmol/L (100–125 mg/dL) in the fasting state; 2) plasma glucose levels 7.8–11.0 mmol/L (140–199 mg/dL) two hours after a 75-g oral glucose load; and 3) glycated hemoglobin (HbA_{1c}) levels 39–46 mmol/mol (5.7–6.4%), in the absence of antidiabetic drugs.[2] **Excluded** are those with a pre-existing diagnosis of T2D; thyroid disease; an acute cardiac condition within three months; acute renal failure; chronic glomerulonephritis; polycystic kidney disease; decompensated liver disease; a mental health disorder ever diagnosed by psychiatrists; or malignancy; as well as those with alcohol consumption exceeding 70 g per week for women or 140 g per week for men; women who were pregnant or breast-feeding; or those currently taking antidiabetic drugs, smoking cessation medications, steroids, lithium or antipsychotics. Information about tobacco use, alcohol consumption, physical activity, depression, sleep quality, personal medical histories, and current medications is collected through standardized personal interviews and medical records. The study protocol has been approved by the National Taiwan University Hospital Research Ethics Committee (No. 201303041RINB). All participants should provide written informed consent. This study is conducted according to the Declaration of Helsinki and has been pre-registered at ClinicalTrials.gov (NCT01926041).

Sample Size Estimation, Recruitment, Assignment, Follow-up, and Analytic Design

We estimated to recruit at least 596 prediabetic smokers, 33% (199) of whom join the FIT2 program, to reach 90% power and a two-sided 95% CI for the detection of a 50% risk reduction, assuming 30% as the risk of incident T2D during follow-up in the usual care group.[3] The assignment of this trial is based on shared decision-making (**Figure 1**). At baseline, all eligible prediabetic smokers are asked if they would like to join the FIT2 program or just receive usual care. Beginning at enrollment, the smoking status, breath carbon monoxide levels, anthropometric indices, and blood tests are recorded every six months. The *intention-to-treat* analysis is performed to compare the FIT2 program participants with those receiving usual care. The *modified per-protocol* analysis is adopted to compare participants with documented abstinence at prespecified study ends (e.g., December 2020 or 10 years)

with the controls.

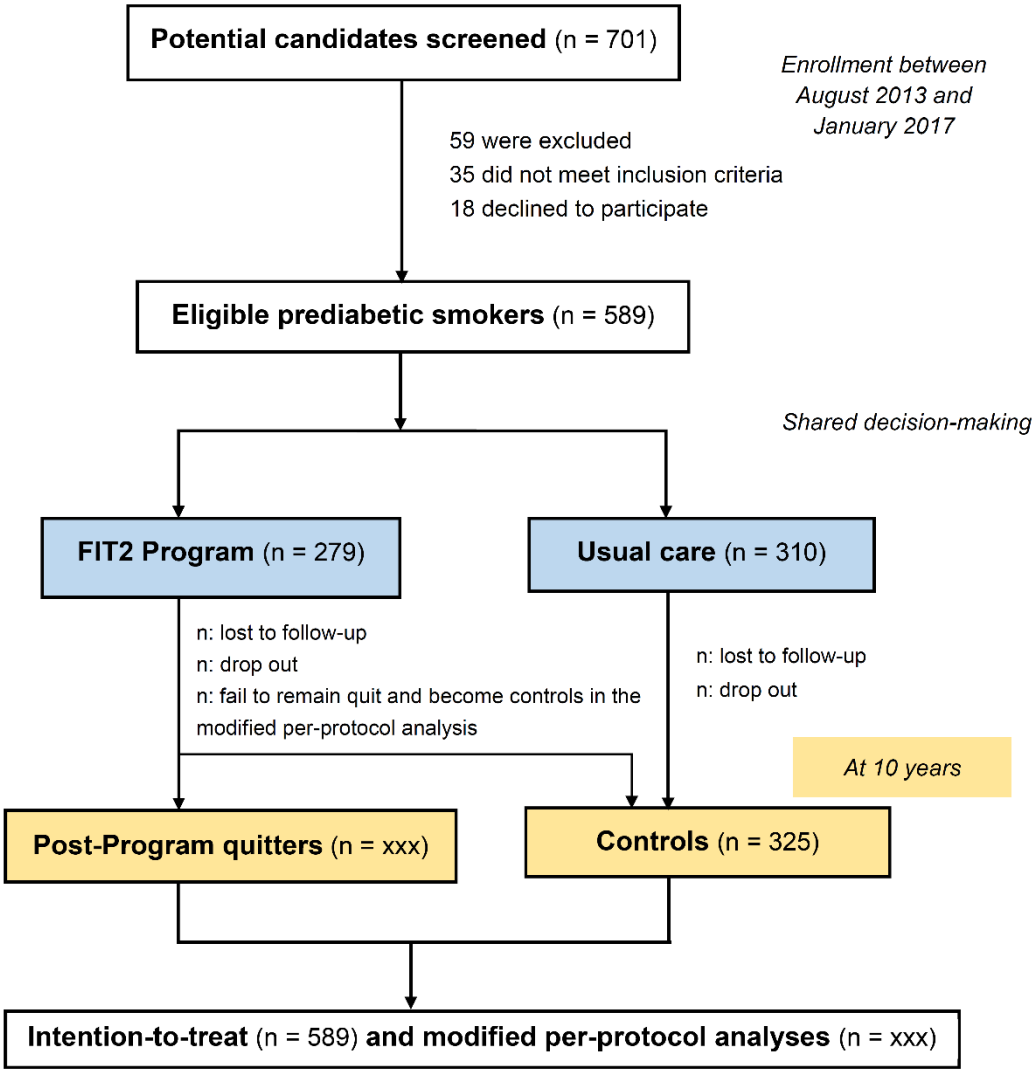

Figure 1. Study flowchart

The Fight Tobacco and Stay Fit (FIT2) program was a 16-week program including smoking cessation therapy with individualized behavior coaching in diet and physical activity for PCWG restriction. Post-program quitters are those who quit successfully after the intervention and maintain their non-smoking status at 10 years.

The FIT2 Program and Post-Program Abstinence

The FIT2 program is a 16-week program that combined pharmacotherapy for smoking cessation with individualized counseling focused on both smoking cessation and weight-control techniques. Behavioral counseling in tobacco cessation techniques is delivered to every FIT2 participant involving one session per week.[4] The pharmacotherapy in the FIT2 program is a 16-week varenicline course, which conforms to real-practice government regulations in Taiwan. The varenicline is subsidized by the tobacco health welfare surcharge and its prescription adheres to manufacturer's directions and regulations by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan (www.hpa.gov.tw). It is initiated at 0.5 mg once daily for the first three days, increased to 1 mg once daily from day 4

to day 7, and then increased to 1 mg varenicline twice daily from day 8 to the end of 16 weeks. After 16 weeks, varenicline is no more administered. During the therapy course, physicians could adjust the varenicline dosages according to tolerability. Participants joining the FIT2 program are encouraged either to set their quit day 8 days after starting the varenicline; or to freely choose quit day at any time between Days 8 and 35. Nicotine replacement therapies are prohibited during the study period.

In addition to varenicline prescription and smoking cessation counseling covered in conventional smoking cessation services, the FIT2 program also offers individualized weekly diet and physical activity coaching to restrict PCWG. The counseling sessions allow opportunities to identify obstacles to lifestyle change and to discuss approaches with a professional panel of dietitians and certified personal trainers. The dietitians instruct the FIT2 participants to choose minimally processed, whole grains, vegetables, whole fruits, nuts, healthful sources of protein, and plant oils; rather than sugared beverages, refined grains, potatoes, red and processed meats, and other highly processed foods. The FIT2 participants are also encouraged to do at least 150 minutes of moderate-intensity (3.0-6.0 metabolic equivalents) aerobic physical activity throughout the week. Emphasis is placed on checking the weekly diary for body weight, food, and physical activity through protected cellphone messages between participants and the assigned panel professionals. For those who gain weight, more intensive ways of calorie restriction and physical activity (at least 300 minutes of moderate-intensity aerobic physical activity per week) will be instructed.

Post-program abstinence status is recorded weekly during the first 16 weeks and then every 6 months until 10 years by self-reported 7-day point prevalence of abstinence and a breath carbon monoxide level of less than 6 ppm. Post-program quitters are those who quit successfully at 16 weeks after the FIT2 program and maintain their non-smoking status at prespecified study ends (e.g., December 2020 or 10 years) (achieving post-program abstinence). For the *modified per-protocol* analysis, participants who fail to keep quit after the FIT2 program are reassigned to the control group.

Usual Care and Control

Usual care is provided for prediabetic smokers who decide not to join the FIT2 program. Usual care comprises interpretation of laboratory results and encouragement to quit smoking and initiate a therapeutic lifestyle change for T2D prevention at each visit. In the *modified per-protocol analysis*, the control group contains participants joining the FIT2 program who fail to achieve post-program abstinence and all participants receiving usual care, including those who quit smoking on their own (**Figure 1**).

Outcome Measures (refer to the section "Study Objectives")

The primary outcome is new-onset T2D through December 2020, defined as random plasma glucose ≥11.1 mmol/L (200 mg/dL) with hyperglycemic symptoms or repeated results in at least one of the following parameters: 1) plasma glucose levels ≥7.0 mmol/L (126

mg/dL) in the fasting state; 2) plasma glucose levels ≥11.1 mmol/L (200 mg/dL) two hours after a 75-g oral glucose load; 3) HbA_{1c} levels ≥48 mmol/mol (6.5%) [2]; or currently taking medications for physician-diagnosed T2D. The other prespecified glycemic outcome is new-onset T2D at 10 years (determined between 2022 and 2026). We also determine the probability of regression to normoglycemia in December 2020 and at 10 years (between 2022 and 2026). Participants who regress to normoglycemia should meet all the following conditions for more than six months and maintain such status until the prespecified study end: 1) plasma glucose levels <5.6 mmol/L (100 mg/dL) in the fasting state; 2) plasma glucose levels <7.8 mmol/L (140 mg/dL) two hours after a 75-g oral glucose load; or 3) HbA_{1c} levels <39 mmol/mol (5.7%), in the absence of antidiabetic drugs. The investigators also explore whether HbA1c changes at 6 and 12 months would be affected by FIT2 program and the post-program abstinence, respectively.

The following extraglycemic endpoints are also secondary outcomes (determined between 2022 and 2026). The steatohepatitic outcome is serial and 10-year NAFLD progression. Each participant is evaluated using FIB-4 scores, BARD scores, liver stiffness measurement (LSM) at baseline, every six months, and at 10 years. TE (FibroScan) for liver LSM is performed in fasting condition.[5-7] The measurement depth is between 25 and 65 mm using the M-probe (standard probe) and between 35 and 75 mm using the XL-probe. LSM is stopped when 10 valid measurements are recorded with the result (kilo Pascal, kPa) expressed as the median of these valid measurements. The same machine can be used to determine whether steatosis is present after the CAP value is determined. We will also obtain FIB-4 scores (www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis) and BARD scores (www.mdcalc.com/bard-score-nafld-fibrosis) at 10 years for every participant, as described in the Introduction section. In addition, a low 10-year composite score is defined as simultaneously reaching a FIB-4 score <1.45, a BARD score 0-1, and LSM <7 kPa. The cardiovascular outcome is major adverse cardiac events at 10 years, defined as events of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke diagnosed by specialists according to medical records. The renal outcome is serial and 10-year chronic kidney disease progression, defined as progression to macroalbuminuria [urinary albumin-to-creatinine ratio (UACR), >300 mg of albumin per gram of creatinine] for ≥ 3 months, or decrease in estimated glomerular filtration rate (eGFR) to <60mL/min/1.73 m2 for ≥ 3 months, as calculated by the four-variable Modification of Diet in Renal Disease (MDRD) formula, and incident albuminuria for ≥ 3 months. Incident malignancies based on medical records are accessed at 10 years, confirmed by national cancer registry system. All-cause mortality is ascertained at 10 years by computer linkage to the national death registry (death certificates were created by the Ministry of Health and Welfare, Taiwan) using ID numbers and these death certificates have been validated.

Interview, Anthropometric Indices, Laboratory Tests, Covariates, and Confounders

We review the medical records after getting informed consent. Through standardized

personal interviews, the investigators collect information about tobacco use, alcohol consumption, eating habits, physical activity levels, depression scale, circadian rhythm, sleep quality, and current medications. Body height and weight are measured using a standard stadiometer, and body mass index is calculated. Blood pressure is measured with an electronic sphygmomanometer while the patient is seated after resting for at least five minutes. Hypertension is defined as a history of hypertension according to medical records or repeatedly having office blood pressure ≥140/90 mmHg or home blood pressure ≥135/85 mmHg. Each participant undergoes laboratory testing after fasting for at least ten hours. The blood tests are performed every 6 months by the central lab of a tertiary center. The items include plasma glucose and HbA_{1c} levels, serum fasting insulin levels, complete blood count (CBC & platelet), ferritin, ALT, AST, total/direct bilirubin, LDL-C, HDL-C, TG, high sensitivity C-Reactive Protein (hs-CRP), urine albumin to creatinine ratio (UACR), and creatinine levels. The estimated glomerular filtration rate is calculated using the four-variable version of the Modification of Diet in Renal Disease Study equation for Chinese Patients.[8] Dyslipidemia is defined as the presence of at least one of the following conditions: a plasma triglyceride level ≥1.70 mmol/L (150 mg/dL), a serum low-density lipoprotein level ≥3.37 mmol/L (130 mg/dL), a serum high-density lipoprotein level <1.04 mmol/L (40 mg/dL) in men or <1.29 mmol/L (50 mg/dL) in women, or history of dyslipidemia according to medical records. Insulin resistance scores are determined by the homeostasis model assessment of insulin resistance (HOMA-IR),[9] as calculated by the following formula: HOMA-IR score = fasting insulin (μIU/mL) × fasting glucose (mg/dL)/405. Participants are categorized as insulin resistant if the HOMA-IR was 2.5 or higher.[10,11] The triglyceride glucose (TyG) index is calculated by the logarithm of fasting triglyceride × fasting glucose/2 to account for a surrogate marker of insulin resistance.[12] Serological tests include serum hepatitis B surface antigen, serum antibody to hepatitis C virus, and hepatitis B e antigen, determined via a microparticle enzyme immunoassay (Abbott Laboratories, Illinois, USA).

The investigators collect the parameters of physical activity level, depression scale score, and sleep quality at baseline. The physical activity level within the last week is calculated as the average daily energy expenditure in Kcal/day by the following formula: Sum of 7-day task-specific metabolic equivalent values (MET, Kcal/kg/hour; 1 for sleeping, 1.5 for light-intensity activities, 4 for moderate-intensity activities, 6 for vigorous-intensity activities, and 10 for very-vigorous-intensity activities) multiplied by task-specific hours multiplied by body weight (kg) and then divided by 7 days.[13] Being physically active is determined if the energy expenditure was over the third quartile. The depression score for one week is obtained using the Center for Epidemiologic Studies Depression Scale,[14] Chinese version (20 sub-items; '0', '1', '2', and '3' for each sub-item; summed global score from 0 to 60). Depressive disorder is suspected if the score ≥16, and the patient was referred to a psychiatrist. The sleep quality score for one month is obtained using the Pittsburgh Sleep Quality Index,[15] Chinese version [7 components; '0 (no difficulty)' to '3 (severe difficulty)' for each component; summed global score from 0 to 21]. Sleep disturbance is considered if the score was six or higher.

Statistical analyses

For the descriptive analyses, values are presented as either numbers (percentages) or mean ± standard deviations. For the univariate analyses, categorical data are compared by the χ^2 test or Fisher's exact test. Continuous variables are compared using the two-sample Student's *t*-test. Statistical significance levels were determined by two-tailed tests ($P<0.05$).

We will perform Cox proportional hazards regression and logistic regression analyses to explore the associations of the FIT2 program with development of all prespecified outcomes in *intention-to-treat analyses*. Kaplan-Meier failure plots of T2D risks of the two groups are drawn. We assumed missing values over time were missing at random and performed listwise deletion. We will test the assumption of proportional hazards. Logistic regression via GEE approach is utilized to evaluate the serial associations of the FIT2 program with NAFLD and CKD progression. In *modified per-protocol analyses*, the associations between achieving post-program abstinence and glycemic and extraglycemic outcomes will be explored using multiple logistic regression models. All of the abovementioned statistical analyses summarized in **Table 2** and will be performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 2. Statistical strategies for glycemic and extraglycemic outcomes in this study

Outcomes	Cox regression	Logistic regression
T2D risk: ITT analysis	Actual time	At 10 years
T2D risk: modified PP analysis	N/A	At 10 years
Regression to normoglycemia: ITT analysis	Actual time	At 10 years
Regression to normoglycemia: modified PP analysis	N/A	At 10 years
NAFLD progression: ITT analysis	N/A	Serially (GEE) and at 10 years
NAFLD progression : modified PP analysis	N/A	At 10 years
Major adverse cardiac events: ITT analysis	Actual time	At 10 years
Major adverse cardiac events: modified PP analysis	N/A	At 10 years
CKD progression: ITT analysis	Actual time	Serially (GEE) and at 10 years
CKD progression: modified PP analysis	N/A	At 10 years
Incident malignancies: ITT analysis	Actual time	At 10 years
Incident malignancies: modified PP analysis	N/A	At 10 years
All-cause mortality: ITT analysis	Actual time	At 10 years
All-cause mortality: modified PP analysis	N/A	At 10 years

ITT, intention-to-treat; PP, per-protocol.

References

1. Adams JM. Smoking Cessation-Progress, Barriers, and New Opportunities: The Surgeon General's Report on Smoking Cessation. *JAMA.* 2020;323(24):2470-2471.
2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care.* 2021;44(Suppl 1):S15-s33.
3. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346(6):393-403.
4. Krist AH, Davidson KW, Mangione CM, et al. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation Statement. *JAMA.* 2021;325(3):265-279.
5. Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol.* 2016;65(3):570-578.
6. Castera L, Friedrich-Rust M, Loomba R. Noninvasive Assessment of Liver Disease in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology.* 2019;156(5):1264-1281.e1264.
7. Serra-Burriel M, Graupera I, Toran P, et al. Transient elastography for screening of liver fibrosis: Cost-effectiveness analysis from six prospective cohorts in Europe and Asia. *J Hepatol.* 2019;71(6):1141-1151.
8. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol.* 2006;17(10):2937-2944.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412-419.
10. Chiang CH, Lai JS, Hung SH, Lee LT, Sheu JC, Huang KC. Serum adiponectin levels are associated with hepatitis B viral load in overweight to obese hepatitis B virus carriers. *Obesity (Silver Spring).* 2013;21(2):291-296.
11. Chiang CH, Lai JS, Sheu JC, Yen LL, Liu CJ, Huang KC. The risky body mass index ranges for significant hepatitis B viral load: A campus-based study. *Obes Res Clin Pract.* 2012;6(1):e31-e38.
12. Simental-Mendia LE, Rodriguez-Moran M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metabolic syndrome and related disorders.* 2008;6(4):299-304.
13. Hills AP, Mokhtar N, Byrne NM. Assessment of physical activity and energy expenditure: an overview of objective measures. *Front Nutr.* 2014;1:5.
14. Chien CP, Cheng TA. Depression in Taiwan: epidemiological survey utilizing CES-D. *Seishin Shinkeigaku Zasshi.* 1985;87(5):335-338.
15. Tsai PS, Wang SY, Wang MY, et al. Psychometric evaluation of the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life Res.* 2005;14(8):1943-1952.