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# Role of resistant starch on diabetes risk factors in people with prediabetes: Design, conduct, and baseline results of the STARCH trial

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ABSTRACT

Dietary resistant starch (RS) might alter gastrointestinal tract function in a manner that improves human health, particularly among adults at risk for diabetes. Here, we report the design and baseline results (with emphasis on race differences) from the STARCH trial, the first comprehensive metabolic phenotyping of people with prediabetes enrolled in a randomized clinical trial testing the effect of RS on risk factors for diabetes. Overweight/obese participants (BMI ≥ 27 kg/m$^2$ and weight ≤ 143 kg), age 35–75 y, with confirmed prediabetes were eligible. Participants were randomized to consume 45 g/day of RS (RS = amylose) or amylopectin (Control) for 12 weeks. The study was designed to evaluate the effect of RS on insulin sensitivity and secretion, ectopic fat, and inflammatory markers. Secondary outcomes included energy expenditure, substrate oxidation, appetite, food intake, colonic microbial composition, fecal and plasma levels of short-chain fatty acids, fecal RS excretion, and gut permeability. Out of 280 individuals screened, 68 were randomized, 65 started the intervention, and 63 were analyzed at baseline (mean age 55 y, BMI 35.6 kg/m$^2$); 2 were excluded from baseline analyses due to abnormal insulin and diabetes. Sex and race comparisons at baseline were reported. African-Americans had higher baseline acute insulin response to glucose (AIRg measured by frequently sampled intravenous glucose tolerance test) compared to Caucasians, despite having less visceral adipose tissue mass and intrahepatic lipid; all other glycemic variables were similar between races. Sleep energy expenditure was ~90–100 kcal/day lower in African-Americans after adjusting for insulin sensitivity and secretion. This manuscript provides an overview of the strategy used to enroll people with prediabetes into the STARCH trial and describes methodologies used in the assessment of risk factors for diabetes.

Clinicaltrials.gov identifier: STARCH (NCT01708694). The present study reference can be found here: https://clinicaltrials.gov/ct2/show/NCT01708694.

Submission Category: "Study Design, Statistical Design, Study Protocols".

## 1. Introduction

Prediabetes is characterized by insulin resistance and impaired glucose tolerance and is a significant predictor for developing type 2 diabetes. Proposed mechanisms for the development of prediabetes include the ectopic accretion of lipid in tissues such as liver, skeletal muscle, and pancreas [1]. Lifestyle interventions to treat prediabetes and stop/delay its progression to frank diabetes are necessary to prevent a deleterious disease that is often difficult to manage once developed.

High-amylose Type 2 resistant starch (RS) is a dietary ingredient that has garnered interest for its ability to slow digestion and improve metabolic health markers in rodents and humans. In rodents, a fermentable carbohydrate such as RS has been shown to reduce abdominal

*Abbreviations:* AIRg, Acute insulin response to glucose; AUC, Area under the curve; BMD, Bone mineral density; BMI, Body mass index; DI, Disposition index; DXA, Dual-energy X-ray absorptiometry; EMCL, Extramyocellular lipid; FFM, Fat-free mass; FM, Fat mass; FSIGTT, Frequently sampled intravenous glucose tolerance test; HbA1c, Hemoglobin A1c; HDL, High-density lipoprotein cholesterol; IHL, Intrahepatic lipid; IMCL, Intramyocellular lipid; RFPM, Remote food photography method; RQ, Respiratory quotient; RS, Resistant starch; SI, Insulin sensitivity index; Sg, Glucose effectiveness; SleepEE, Sleep energy expenditure; TAT, Total adipose tissue; TC, Total cholesterol; VAS, Visual analog scale; VAT, Visceral adipose tissue; $^1$H-MRS, Proton magnetic resonance spectroscopy

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fat [2–4] and cholesterol [5], as well as increase gut bacteria [2] and improve insulin sensitivity [4,6]. The mechanism for the observed reduction in abdominal fat may be due to an increase in energy expenditure and fat oxidation [7]. In humans, RS fermentation can enrich gut microbiota species such as *Bifidobacterium*, *Ruminococcus bromii*, and *Eubacterium rectale* [8]; improve cardiometabolic endpoints such as insulin sensitivity, body fat storage, and cholesterol levels [9–14]; and may suppress appetite [15–17].

To our knowledge, few studies have investigated the impact of dietary RS supplementation on metabolic risk factors in humans. Moreover, few studies have metabolically phenotyped adults with prediabetes given the challenges associated with recruiting this population [18–19]. Detailing successful recruitment strategies and retention methods in studies of individuals with prediabetes is critical to improve future recruitment and retention of similar populations. The clinical trial entitled *Role of Resistant Starch on Diabetes Risk Factors (STARCH)* was designed to examine the effects of daily RS supplementation in adults with prediabetes on metabolic outcomes—including insulin sensitivity and secretion, ectopic fat, energy expenditure and substrate oxidation, inflammation, food intake, and gut microbiota. While the effect of daily RS supplementation on metabolic health in adults with prediabetes will be assessed in future analyses, the primary goals of the present manuscript were to: 1) to describe the recruitment and screening process of adults with prediabetes for the STARCH trial; 2) to outline the study methods and procedures; and 3) to provide a comprehensive metabolic phenotype of adults with prediabetes (pre-intervention) in cross-sectional baseline analyses of sex and race.

## 2. Study design & methods

### 2.1. Study design

The STARCH trial was designed as a randomized, double-blind, placebo-controlled, parallel-arm trial conducted at Pennington Biomedical Research Center (PBRC). Participants were recruited, screened, and randomized with a 1:1 allocation to 45 g/day of resistant starch (RS = amylose) or amylopectin (Control) for 12 weeks. Both the RS and placebo were consumed in yogurt packets that were provided to the participants. Multi-stage screening (3 clinic visits) was implemented to identify eligible participants with confirmed prediabetes. Week 0 (baseline, pre-intervention) and Week 12 (end of intervention) study visits involved 2.5 days of inpatient testing conducted within a one-week period and included: (1) dual-energy X-ray absorptiometry (DXA) to measure body composition; (2) proton magnetic resonance spectroscopy ($^1$H-MRS) to measure lipid in the liver and skeletal muscle; (3) 12-h overnight respiratory chamber to assess energy metabolism including energy expenditure and macronutrient oxidation; (4) frequently sampled intravenous glucose tolerance test (FSIGTT) to assess insulin sensitivity and insulin secretion; (5) standardized meal test to assess glucose, insulin, and incretins; (6) Visual Analog Scales (VAS) to measure appetite; (7) food intake tests and remote food photography to measure food intake; (8) gut permeability testing (sugar absorption); (9) fecal collection to measure gut microbiota, short-chain fatty acids, and RS; (10) blood markers of endotoxemia, inflammation, and hormones; and (11) breath hydrogen and methane analyses to assess microbial fermentation. The study was approved by the PBRC Institutional Review Board, and participants provided written informed consent before participating. All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### 2.2. Study population and eligibility criteria

Males and females of all races and ethnicities between 35 and 75 years of age, with a body mass index (BMI) ≥ 27 kg/m$^2$ and weight ≤ 143 kg, were eligible to participate. Confirmed prediabetes as assessed by either impaired fasting glucose or elevated HbA1c was required. Prior to enrollment, participants underwent detailed screening assessments, completed diet and physical activity records for a 7-day period, and were encouraged to maintain the same level of exercise and body weight throughout the study. Eligibility criteria are detailed in Table 1.

**Table 1**
Eligibility criteria for the STARCH trial.

| |
|---|
| **Inclusion criteria** |
| Are 35–75 years of age |
| Have a body mass index ≥ 27 kg/m$^2$, and weight ≤ 143 kg |
| Have pre-diabetes, as confirmed by having *either*: (1) impaired fasting glucose (IFG), i.e. fasting glucose of 100–125 mg/dL, or (2) elevated HbA1c level between 5.7 and 6.4%. |
| Are willing to maintain the same level of exercise throughout the trial |
| **Exclusion criteria** |
| *Medical criteria* |
| History or clinical manifestation of a significant medical condition |
| Blood pressure > 150/100 mm Hg (at screening) |
| Have metal objects in the body (e.g., pacemaker, metal pins, bullet) |
| Have clinically significant GI malabsorption, chronic diarrhea, or use antibiotics within 1 month of study |
| Abnormal laboratory markers (e.g., elevated potassium, low hemoglobin or hematocrit) |
| *Psychiatric and behavioral criteria* |
| Clinical depression or other psychological conditions |
| Chronically consume alcohol (> 4 servings per day) or actively smoke cigarettes (> 1/4 pack per day) |
| *Medication criteria* |
| Chronic use of medications (e.g., diuretics, steroids, and adrenergic-stimulating agents) |
| Short-term (less than a month) treatment with any other medications |
| Use contraceptives, oral/parenteral glucocorticoids, or meds influencing glucose or insulin within 1 month of study |
| Use of proton pump inhibitors |
| *Other criteria* |
| Breastfeeding or pregnant women, or women intending to become pregnant. |
| Pre-menopausal women lacking a regular menstrual cycle |
| Are required to perform any kind of heavy physical activity |

### 2.3. Sample size determination

The primary intent of the present analysis was to provide a comprehensive metabolic phenotype of adults with prediabetes (pre-intervention); therefore, we provide here only overall baseline descriptive characteristics of those participants who started the intervention, as well as sex and race comparisons. No power analysis was done for these baseline descriptive comparisons. In future analyses of primary outcomes from the STARCH trial, the following sample size determination criteria were applied: the primary outcome of the STARCH trial was the change in insulin sensitivity (SI). Assuming a maximum 15% loss due to attrition, a minimum of 94 participants were targeted for enrollment and randomization. Power calculations revealed that 40 completers per group provides 85% and 95% power (two-tailed, $\alpha = 0.05$) to detect 15% and 18% improvements, respectively, in insulin sensitivity relative to the control group, assuming a within-group standard deviation of 22% [20]. Unfortunately, because of slow recruitment rates, the study was prematurely ended. Specifically, 59 participants (29 RS, 30 Control) of the total 65 participants who started the intervention actually completed the trial. These numbers provided 80% statistical power to detect a 16.3% improvement in insulin sensitivity, which is equivalent to an effect size of $d = 0.74$.

### 2.4. Recruitment and screening strategies

Participants were recruited by the PBRC recruitment core via media advertising (e.g. radio, online, and television ads), health promotion