Restoring Insulin Secretion (RISE)

Data Release Documentation

Adult Surgery (BetaFat) Study

Prepared by the RISE Coordinating Center, in conjunction with BetaFat study Investigators

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1. Introduction

1.1 General

The Restoring Insulin Secretion (RISE) Study was 3 parallel randomized clinical trials designed to investigate whether early intervention in patients with prediabetes or early type 2 diabetes could restore β-cell function, and whether improved β-cell function is maintained following a 3-month medication washout period. The three studies comprising RISE are:

1) RISE Adult Medication Study, which recruited adult participants at 1) The University of Washington/VA Medical Center in Seattle, WA, 2) Indiana University in Indianapolis, IN and 3) University of Chicago/Jesse Brown VA in Chicago, IL.
2) RISE Pediatric Medication Study, which recruited pediatric participants at 1) University of Colorado, Denver, in Denver CO, 2) University of Pittsburgh in Pittsburgh, PA, 3) Yale University in New Haven CT, and 4) Indiana University in Indianapolis, IN.
3) RISE Surgery Study (the BetaFat) Study, which recruited adult participants at Kaiser Permanente in Los Angeles, CA.

This data release is relevant to the RISE BetaFat Study only.

Detailed information about RISE including RISE protocols, manuals, references, publication list, and links to abstracts and manuscripts is available at http://risestudy.org. This report describes the complete public release of the RISE BetaFat Study dataset. A brief description of the trial is given below; further details can be found in Reference 1.

1.2 Participants

Adults aged 22-65 years were eligible for the RISE Adult BetaFat Study if they had a fasting plasma glucose >90 mg/dl plus a 2-hour oral glucose tolerance test (OGTT) glucose ≥140 mg/dl, along with HbA1c ≤7.0% and BMI 30-40 kg/m^2. For participants with diabetes, known duration < 1 year, and no history of use of antidiabetic medications except during pregnancy. Detailed eligibility and exclusion criteria can be found in Reference 1.

1.3 Visits

Randomization into the RISE BetaFat Study began in June 2013 and continued for three years through June 2016. Participants were seen for follow-up visits for 24 months. Specifically, every two months after randomization during the first year and every three months during the second year. All visits included adverse event assessment. Comprehensive 2-day baseline (BAS), Month 12 (M12) and Month 24 (M24) assessments included physical measurements, medical history updates, medication adherence and dispensing, a 3-hour 75g oral glucose tolerance test (OGTT) and a 2-step hyperglycemic clamp. Month 6 (M06) and Month 18 (M18) visits included fasting/biomarkers, and HbA1c. Visits at all other months were brief and included limited physical measurements, medication adherence and dispensing, and adverse event assessment.

1.4 Treatment Arms

At randomization, participants were randomly assigned with 1:1 ratio to one of two treatment groups:

1. metformin for 24 months
2. adjustable gastric band surgery

Participants randomized to metformin were given their medications and instructions at the end of the second baseline visit, to begin treatment the following day and medication refills were given at each follow-up visit up to M24. Titration details can found in Reference 1. Participants assigned to gastric

banding were scheduled for pre-operative screening with the goal of having them undergo the operation within one month.

1.5 Primary Measurements

The primary RISE BetaFat Study aim was to assess ß-cell preservation or restoration through mitigation of the metabolic effects of obesity. Specifically, we compared weight loss induced by gastric banding to the standard pharmacological approach, metformin, for effects on β-cell function in pre- and mild T2D. By comparing changes in β-cell function between treatment groups, we aimed to compare the most used medical monotherapy to a surgical approach for long-term effects on β-cell health.

RISE used a two-step hyperglycemic clamp to directly quantify first phase (first ten minutes after priming glucose bolus) and steady state (at plasma glucose ~200 mg/dl; ~11.1 mmol/l) ß-cell responses to intravenous glucose, and the maximal arginine-stimulated ß-cell response during hyperglycemia (>450 mg/dl; >25.0 mmol/l). A 3-hour OGTT was used to evaluate ß-cell responses in the context of an enterally delivered stimulus. Laboratory outcome measures were measured in a central laboratory.

Hyperglycemic Clamp: A two-step hyperglycemic clamp was performed as described in Reference 1. Participants fasting for 10-hours overnight prior to the visit. Using variable rate 20% dextrose infusions, glucose was clamped using a computerized algorithm combined with bedside blood glucose monitoring every 5-10 minutes. For the first step, a targeted, steady-state plasma glucose concentration of 11.1 mmol/L was achieved and maintained through 120 minutes. Blood samples were drawn through an indwelling intravenous catheter in a warmed hand prior to starting the clamp and at 100, 110 and 120 minutes (steady-state) after commencing the dextrose infusion. Thereafter, the infusion rate was increased to achieve the second step target, which was a plasma glucose >450 mg/dL (>25 mmol/L). After this target glucose had been attained for a minimum of 30 minutes after commencing the second step, a bolus of L-arginine (5 grams) was administered over one minute. Blood samples for subsequent assays were drawn at -5, -1, 2, 3, 4 and 5 minutes relative to the arginine injection.

Oral Glucose Tolerance Test: Following a 10-hour overnight fast, a 3-hour, 75-gram OGTT was performed. Blood samples were obtained -10, -5, 10, 20, 30, 60, 90, 120, 150 and 180 minutes relative to glucose ingestion.

1.6 Primary Outcomes

Hyperglycemic clamp measurements were made at baseline (BAS), after 12 months on-treatment (M12) and after 24 months on-treatment (M24).

Insulin Sensitivity: Insulin sensitivity (M/I) was quantified as the mean of the glucose infusion rate (M) at 100, 110 and 120 minutes of the hyperglycemic clamp corrected for urinary glucose loss, divided by the mean steady-state plasma insulin concentration at these same time points (I). This measure was expressed per kg body weight.

C-peptide and Insulin Responses: From the hyperglycemic clamp, the following measures were calculated.

- Fasting concentrations were the average of the two samples drawn prior to glucose administration.
- Acute (first-phase) C-peptide (ACPRg) and insulin (AIRg) responses to glucose were calculated as the mean incremental response above fasting from samples drawn at 2, 4, 6, 8 and 10 minutes following intravenous dextrose administration.
- Steady-state C-peptide, insulin and glucagon concentrations were calculated as the mean of the respective measurements at 100, 110 and 120 minutes.
- Acute C-peptide (ACPRmax) and insulin (AIRmax) responses to arginine at maximal glycemic potentiation (>450 mg/dl; >25.0 mmol/l) were calculated as the mean concentrations in samples drawn 2, 3, 4 and 5 minutes after arginine injection minus the average concentration of the samples drawn 1 and 5 minutes prior to arginine.

RISE included two co-primary outcome measures derived from the hyperglycemic clamp: 1) the clamp-derived glucose-stimulated steady state C-peptide secretion (SS C-peptide) and maximal C-peptide

response to arginine during hyperglycemia (ACPRmax), along with a major secondary outcome of acute (first-phase) C-peptide (ACPRg). Primary and secondary outcome analyses were adjusted for the prevailing insulin sensitivity.

2. Release Information

2.1 General Information

- No participant identifying information is included.
- A randomly generated RISE_REPOSITORY_ID uniquely identifies each participant.
- Clinic and all other location identifiers have been removed.
- No dates are included; visit dates are provided as days from randomization.
- Only randomized participants who provided consent to distribute their data to the repository are included. Out of the 88 original RISE BetaFat Study participants, the 77 participants who consented are included in this release dataset.
- In accordance with HIPAA regulations and to protect the identification of participants, the data has been de-identified to ensure that no participant is identifiable. For example, data was sorted into small, clearly identifiable groups and collapsed if the sample size was small.
- Only research data is included in the released dataset, including data for screening and post-randomization clinic visits, and laboratory data. Non-research data, including tracking forms, are not included. Detailed serious adverse event data were collected but are also not included in the data release to protect participant confidentiality.
- Missing data was caused by a variety of reasons: the visit was not completed in its entirety; the variable or blood sample was not collected or measured; the variable was completed incorrectly; the visit was missed, etc.

2.2 Data Location

Data are released from the RISE Coordinating Center at the George Washington University Biostatistics Center and the BetaFat clinical site at the University of Southern California/Kaiser Permanente, to the Data Repository at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health.

2.3 De-identified Data

The RISE BetaFat Study dataset was de-identified in the following manner.

- All personal identifiers were removed, including participant ID and other personal identifiers, clinical center, and all dates.
- Variables that might identify a particular individual were collapsed into wider groupings.
    - Age at baseline was collapsed into 22-49, 50-59, 60+ year old age groups.
    - Race/ethnicity was coded as non-Hispanic White and all other race/ethnicity groups combined.
- Text string data that include participant or staff names, initials and dates have that PID removed.

2.4 Structure of the Datasets

2.4.1 Data Files

- The files are included as SAS datasets. The contents of variables in each dataset is provided.
- One record exists in each file for each participant for each visit at which that particular data was collected. Variable RISE_REPOSITORY _ID is used to identify a particular participant and variable VISIT to identify which visit was completed.

- This dataset includes data collected at all visits, including baseline, and follow-up visits through M24. Section 3 describes in detail the data included.

3. Serious Adverse Events

As noted, detailed serious adverse events were collected but are not included in the data release to protect participant confidentiality. A complete listing of RISE BetaFat Study SAEs is below, some were related to study intervention and expected (hospitalization for band removal). SAEs were reviewed by the Data Safety and Monitoring Board (DSMB) and no concerns were raised.

RISE Adult Medication Study
All Serious Adverse Events by Treatment Group

Metformin	Gastric Band
• Motor vehicle accident w/ right calcenous fracture	• Hospitalizations for surgery to treat breast cancer • Hospitalizations for band removal • Cholelithiasis/ Cholecystitis requiring surgery • Hospitalized for elective gastric sleeve surgery

4. File Descriptions

4.1 Data Structure

4.1.1 Variable Names in Database

- All datasets are HIPAA de-identified as described above.
- Coding and formats for all variables can be found on the original data dictionary except where described below.
- Some lab values were clinic-use only and not available for release. Personal identifying information has been removed.

4.2 Variables Common to All Datasets

Several variables are used to identify a specific participant, visit and time on all datasets. These include:

- RISE_REPOSITORY_ID: This is a randomly generated ID used to link a participant to all other records, and is unique to each participant.
- VISIT: This identifies the visit number. VISIT is coded as follows:
  - BAS: Baseline (randomization) visit.
  - M02, M04, M06, M08, M10, M12, M15, M18, M21, M24: Regularly scheduled post-randomization visits.
- DAYSRAND: The number of days a particular visit occurred on (0), or after (positive values)

randomization.

4.3 Baseline Key Data

- A baseline data file which includes one record for each participant with randomized treatment assignment, baseline age group, sex, and race-ethnicity.
- RISEBetaFat_BASEDATA includes one record for each participant in the released database. Age and race/ethnicity were collapsed to protect identities. This file includes the following variables:

Variable	Type	Coding	Details
RISE_REPOSITORY_ID	Character	9-characters beginning with "RISE"	RISE ID for NIDDK release datasets. Randomly assigned.
AGEGROUP	Character	20-49 50-59 60+	Age group (years) at randomization collapsed into three groups.
TREATMENT	Character	LapBand METFORMIN	Randomized treatment assignment.
RACE	Numeric	1 = Non-Hispanic White 2 = All other	Self-reported race/ethnicity
SEX	Numeric	1 = Male 2 = Female	

4.4 Laboratory Data

Laboratory data are included in this release are as follows:

- Hyperglycemic clamp data: One record for each participant for each visit where the hyperglycemic clamp was completed. This includes both the raw glucose, C-peptide and insulin data, along with the key computed variables.
- Oral glucose tolerance test data: One record for each participant for each visit where the OGTT was completed. This includes both the raw glucose, C-peptide and insulin data, along with the key computed variables.
- Other laboratory data: One record for each participant for each visit where additional laboratory measurements were completed.

4.4.1 RISEADULT_CLAMPDATA: Centrally-Measured Laboratory Data: Hyperglycemic Clamp

Dataset RISEAdult_CLAMPData includes the laboratory results from the hyperglycemic clamp procedure. Variable names and labels also include the blood draw times. A hyperglycemic clamp was completed at the baseline (BAS), Month 12 (M12) and Month 24 (M24) visit.

Notes:

- -10 and -5 are fasting values taken 10 and 5 minutes prior to initial glucose bolus.
- Minutes 2, 4, 6, 8, 10 were collected following the initial glucose bolus and infusion. These were used to compute the first phase response above fasting (ACPRg, AIRg).
- Minutes 100, 110 and 120 were used to compute steady state values.
- Minutes 155 and 159 were used to compute hyperglycemic state >450 mg/dl; these are samples drawn at least 15 minutes after reaching hyperglycemia, at 1 and 5 minutes prior to arginine injection.
- Minutes 162, 163, 164 and 165 were used to compute maximal glycemic potentiation, e.g., these are samples drawn 2, 3, 4 and 5 minutes after arginine injection (ACPRmax, AIRmax).
- The major variables computed from this data are included.

- Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable name	Brief description	Details
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	BAS, M12, M24
GLUC# GLUC_#	Glucose (mg/dL)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
CPEP# CPEP_#	C-peptide (ng/ml)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
INS# INS_#	Insulin (uU/ml)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
GLUCAGON# GLUCAGON_#	Glucagon (pM/L)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
ACPRg	Acute (first-phase) C-peptide response to glucose (ACPRg) (ng/dL)	Mean incremental C-peptide response above baseline (average of -10 and -5 min) from samples drawn at 2, 4, 6, 8, and 10 min after intravenous dextrose administration
ACPRmax	Acute C-peptide response to arginine at maximal glycemic potentiation (>450 mg/dL) (ACPRmax) (ng/dL)	Mean incremental C-peptide above concentrations achieved with hyperglycemia prior to the arginine bolus (i.e. mean concentration in samples drawn 2, 3, 4, and 5 min after arginine injection minus the mean concentration of the samples drawn 1 and 5 min prior to arginine)
M_I	M/I * 1000 (mg/kg/min/pg/L)	Mean glucose infusion rate (M) at 100, 110, and 120 min of the clamp divided by the corresponding mean steady-state plasma insulin concentration (I), adjusted for urine glucose lost
GIR	Glucose infusion rate (M) (mg/min)	D20 Glucose infusion Rate
INSULIN_STEADY	Steady-state insulin (I) (uU/ml)	Mean insulin at 100, 110, and 120 min

CPEPTIDE_STEADY	C-Peptide at steady state (ng/dL)	Mean c-peptide at 100, 110, and 120 min
AIRg	AIRg (Insulin)	Mean incremental insulin response above baseline (average of -10 and -5 min) from samples drawn at 2, 4, 6, 8, and 10 min after intravenous dextrose administration
AIRmax	AIRmax incremental mean (Insulin)	Mean incremental insulin above concentrations achieved with hyperglycemia prior to the arginine bolus (i.e. mean concentration in samples drawn 2, 3, 4, and 5 min after arginine injection minus the mean concentration of the samples drawn 1 and 5 min prior to arginine)

4.4.2 RISEADULT_OGTTDATA: Centrally-Measured Laboratory Data: 3-Hour Oral Glucose Tolerance Test

Dataset RISEAdult_OGTTData includes the laboratory results from the 3-hour, 75g oral glucose tolerance test. Variable names and labels also include the blood draw times. The 3-hour oral glucose tolerance test was completed at the baseline (BAS), Month 12 (M12), and Month 24 (M24) visits.

Notes:

- -10 and -5 are fasting values taken 10 and 5 minutes prior to glucose ingestion.
- Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable	Brief description	Details
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	BAS, M12, M24
GLUC# GLUC_#	Glucose (mg/dL)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
CPEP# CPEP_#	C-peptide (ng/ml)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
INS# INS_#	Insulin (uU/ml)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
GLUCAGON# GLUCAGON_#	Glucagon (pM/L)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.

4.4.3 RISEADULT_OTHERLABDATA: All Other Centrally-Measured Laboratory Results

Dataset RISEAdult_OtherLabData includes all other laboratory results measured at the Central Biochemistry Laboratory. Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable name	Brief description	Details
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	All visits possible.
HBA1C	HbA1c (%)	BAS, M6, M12, M18, M24
CHOL	Total cholesterol (mg/dL)	BAS, M12, M24
TRIG	Triglycerides (mg/dL)	BAS, M12, M24
HDL	HDL (mg/dL)	BAS, M12, M24
LDL	LDL (mg/dL)	BAS, M12, M24
VLDL	VLDL (mg/dL)	BAS, M12, M24

4.5 Other Created Datasets

4.5.1 RISEBetaFat_VitalSignDATA: Vital Sign at baseline and follow-up

RISEBetaFat_VitalSignDATA includes vital signs collected at baseline and each follow-up visit. This dataset includes visit month number, DAYSRAND, systolic (SBP) and diastolic (DBP) blood pressure, weight in kg, and height in cm measured at the baseline visit. This file includes the following variables:

Variable	Type	Coding	Details
RISE_REPOSITORY_ID	Character	9-characters beginning with “RISE”	RISE ID for NIDDK release datasets. Randomly assigned.
VISIT	Character	BAS M02 M04 M06 M08 M10 M12 M15 M18 M21 M24	Visit Month Vital Sign Taken
DAYSRAND	Numeric	Range 0 - 967	The number of days a particular visit occurred after randomization
SBP	Numeric	Range 85.7-162	Systolic Blood Pressure (mmHg)

DBP	Numeric	Range 55-115.5	Diastolic Blood Pressure (mmHg)
WEIGHT	Numeric	Range 59.5 – 130.2	Weight (kg)
HEIGHT	Numeric	Range 153.6 - 184	Height (cm) measured at baseline

5. References:

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