OMIT: STATISTICAL ANALYSIS PLAN

Study Name: Calories or Time Restriction to Alter Biomarkers of Aging and Diabetes (OMIT)

Trial registration number(s): NCT05769335, H-2022-199

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CONTENTS

ABBREVIATIONS

AUC	Area under the curve
AUSDRISK	The Australian type 2 diabetes risk assessment tool
BMI	Body mass index
CGM	Continuous glucose monitoring
CR	Calorie restriction (30%)
dCR	Delayed calorie restriction (30% calorie restriction, 12pm – 8pm)
eCR	Early calorie restriction (30% calorie restriction, 8am – 4pm)
HbA1c	Glycated haemoglobin
iAUC	Incremental area under the curve
PP	Post-prandial
SAP	Statistical analysis plan
T2DM	Type II diabetes mellitus

PREFACE

This statistical analysis plan (SAP) describes the planned analyses and reporting for the OMIT study to compare early calorie restriction (eCR) or delayed calorie restriction (dCR) versus calorie restriction (CR) without time limits in men and women with overweight and obesity and elevated fasting blood glucose. The purpose of this SAP is to outline the considerations and the pre-specified analyses for the OMIT study.

The project is funded by the NHMRC Ideas grant #2012569 awarded to Prof Leonie Heilbronn.

This study has been approved by the University of Adelaide Human Research Ethics Committee (HREC 2022-199).

Study Rationale & Objectives

Background/Rationale

Caloric restriction (CR) is widely recognised for its ability to reverse or alleviate the metabolic health consequences of obesity, and even extends lifespan in mouse models. Time-restricted eating (TRE), whereby food intake is typically limited to 8 h eating window during the day may be a novel, alternative dietary strategy to improve cardiometabolic health individuals with obesity. Recent studies in mice suggest that CR+TRE was able to extend the health benefits of CR alone, with the maximal effect noted when the meal timing period was initiated at the onset of the active phase. The ideal meal timing to initiate TRE is under-researched in humans. The proposed randomised clinical trial will be the first to determine whether CR+TRE that is initiated early in the day (early CR) or delayed CR is able to extend the health benefits of CR alone in humans.

Primary Objective

- To establish whether early or delayed time-restricted eating plus calorie restriction, improve markers of type 2 diabetes, compared with calorie restriction alone.

Secondary Objective

- To explore the effect of time-restricted eating on insulin and gut peptide AUCs, 24-h glycaemia by CGM, and cardiometabolic health biomarkers.

Study Outcomes

Primary efficacy outcomes

- The difference in percentage change from baseline in the mean 2-hour post-meal glucose AUC levels after eight weeks of (i) time restricted (early) versus non-time restricted dieting and (ii) time restricted (delayed) versus non-time restricted dieting, in men and women with obesity.

Secondary efficacy outcomes at 8 weeks

- Changes in…
    - PP insulin AUC
    - fasting insulin,
    - fasting glucose, and
    - HbA1c.

Exploratory mechanistic outcomes: at 8 weeks

- Change in…
    - PP glucose and insulin AUCs for each meal
    - 24-h glucose by CGM (mean and iAUC),
    - nocturnal glucose by CGM (mean)
    - insulin sensitivity calculated by the Matsuda index
    - gut peptides (AUCs and iAUC),
    - insulin secretion by C-peptide,
    - HOMA-IR
    - 24-h profiles of glycaemia by CGM (i.e. time-above/below/in range, MAGE, MODD)

Exploratory outcomes

- Listed in the Appendix, see tables A4 & A5.

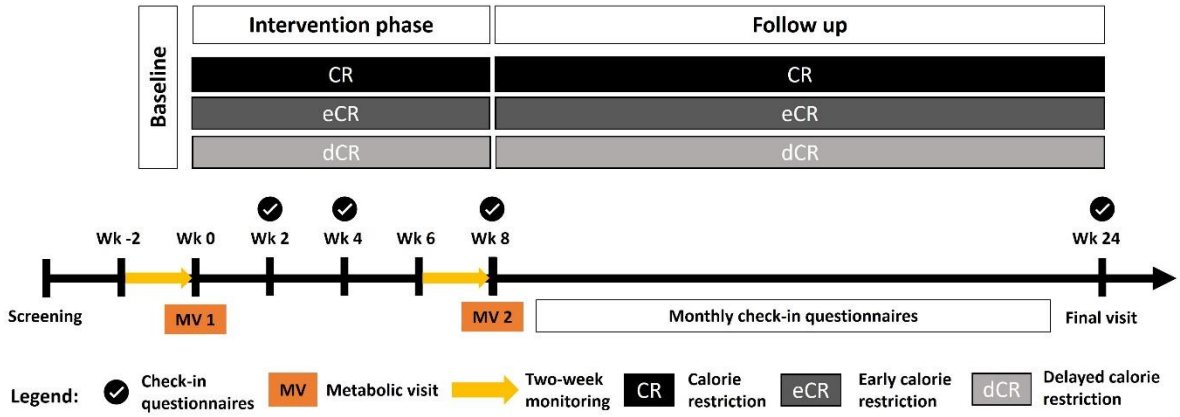
Compliance outcomes

- Self-reported adherence over the eight weeks
- Adherence to eating window assessed by smartphone application and diet diaries.
- Protocol deviations arising from inappropriate inclusion (ie contradicting inclusions/exclusion criteria) will be listed.

STUDY DETAILS

Study Design: OMIT is a three-arm parallel, single-blinded, single-centre randomised controlled clinical trial.

Figure 1: Schedule of assessments



Study Population

Inclusion criteria

Study participants will be aged 35 to 75 years and overweight (BMI: >25.1 but < 45kg/m2) with elevated waist circumference, score 12 or greater on the AUSDRISK questionnaire and have elevated fasting blood glucose (≥5.6 mmol/L).

Elevated risk for waist circumference	Male(cm)	Female (cm)
Caucasian/African	>94	>80
Asian	>88	>74
South Asian, Aboriginal/Torres Strait Islander	>79	>70

Exclusion criteria

A personal history/diagnosis (self-reported) of:

- diabetes (type 1 or 2)
- major psychiatric disorders (schizophrenia, major depressive disorder, bipolar disorder, eating disorders)
- gastrointestinal disorders/disease (including malabsorption)
- haematological disorders (i.e. thalassemia, iron-deficiency anaemia)
- insomnia
- obstructive sleep apnea
- night eating syndrome
- currently receiving, or have received treatment/diagnosis of cancer in the past 3 years (excluding non-melanoma skin cancer)
- significant liver or kidney diseases that require ongoing medical care
- previous or planned gastro-intestinal surgery (including bariatric surgery)
- Congestive heart failure (NYHA stage 2 or above)
- Previous myocardial infarction or significant cardiac event ≤ 6 months prior to screening
- Previous cerebrovascular event ≤ 12 months prior to screening
- Any autoimmune disease (i.e. rheumatoid arthritis)
- Coeliac disease/gluten allergy
- Nut allergy
- other conditions deemed unstable by the study physician.

Currently taking the following medications:

- used, or known, to lower blood glucose, or antidiabetic medications, including, but not limited to: SGLT2 inhibitors, metformin, sulfonylureas, glucagon-like peptide-1 analogues [i.e. exenatide], thiazolidinediones or DPP-IV inhibitors [i.e. 'gliptins'])
- affecting weight, appetite or gut motility, including, but not limited to: (domperidone, cisapride, orlistat, phentermine, topiramate).
- Diuretics (i.e. thiazides) or combination blood pressure medications containing a

diuretic
- Beta-blockers
- Glucocorticoids
- Anti-epileptic medications (i.e. pregabalin and gabapentin)
- Tricyclic antidepressants
- Some serotonin and norepinephrine reuptake inhibitors (i.e. vortioxetine, mirtazapine and venlafaxine)
- Regular use of benzodiazepines or other sleep aids, including melatonin
- Antipsychotic medications
- Opioid medications unless combined with paracetamol in a single formulation and used occasionally on a PRN basis

Participants who are taking stable doses (i.e. > 3 mo.) of androgenic medications (i.e. testosterone), blood pressure medications (not listed above), lipid medications, thyroid medication, SSRI's or SNRIs (with the exception of those mentioned above) or benign prostatic hyperplasia will not be excluded.

Additional exclusion criteria include:

- AUSDRISK score of < 12
- Fasting blood glucose levels < 5.6
- Score ≥ 30 on Kessler Psychological Distress scale
- do not eat for 12 hours per day on an average of 5 or more days per week
- have extreme or restricted patterns of eating (i.e. following an intermittent fasting diet) or already engage in CR or TR
- night shift-workers (>3 shifts per month)
- pregnant, planning a pregnancy or currently breastfeeding
- those who have lost or gained >5% of body weight in the last 6 months
- donated blood in past 3 months
- current smokers of cigarettes/marijuana/e-cigarettes/vaporisers
- anyone unable to comprehend the study protocol or provide informed consent (i.e. due to English language or cognitive difficulties)
- do not own, or are not comfortable using, a smartphone and applications

Individuals with dietary restrictions or practices, including vegans and those with gluten or nut allergies will be excluded. Less restrictive dietary practices including vegetarians and those with lactose intolerance or specific dietary dislikes will be accommodated.

Pre-planned Sample size

An expected group difference is 0.46 mmol/L at 2-hrs after a glucose tolerance test (1). Our past data, DIRECT study (2) showed a mean glucose concentration of 7 mmol/L at two hours post meal. We note that 0.46/7.0 is a 6.5% reduction. T4DM powered for a 0.6 mmol/L between group difference, which is approximatively 6% change from baseline in a population including individuals with diabetes (3). We thereby assumed the MCID to be a 6% reduction from baseline in mean post meal AUC and use log (AUC) to estimate of the percentage difference between groups (4).

Using data from the DIRECT study (2), the SD of the log (meal test AUC) is expected to be 0.152 and pre-post AUC correlations were 0.87 at breakfast and 0.92 at dinner.

With N=114 (38 per group, randomized 1:1:1), a within-group SD of 0.152, pre-post correlation of at least 0.85 and a drop-out rate less than 10%, there is >80% to detect a difference of 0.06 in log-transformed AUC in a baseline adjusted ANCOVA (alpha = 0.027 two-sided) (5).

Sample size adaption

None

Randomization details

Stratified random length blocked randomisation by sex (male or female) and fasting plasma glucose (≤6.0 vs >6.0 mmol/L)

STATISTICAL CONSIDERATIONS

Estimand Considerations

<table>
<tr><td colspan="2">Study objective
- To establish whether early or delayed time-restricted eating plus calorie restriction (eCR, dCR), improve markers of type 2 diabetes, compared with calorie restriction (CR) alone</td></tr>
<tr><td colspan="2">Estimand
- The difference in percentage change from baseline in the mean 2-hour post-meal glucose AUC levels after eight weeks of time restricted versus non-time restricted dieting, in obese men and women</td></tr>
<tr><td colspan="2">Treatment
- eCR (30% calorie restriction, 8am – 4pm);
- dCR (30% calorie restriction, 12pm – 8pm);
- CR (30% calorie restriction, 8am-8pm); Control group</td></tr>
<tr><td>ESTIMAND</td><td>ANALYSIS</td></tr>
<tr><td>Target population
- Men and women with obesity and elevated fasting blood glucose</td><td>Analysis set
- All randomized
- Initiated diet</td></tr>
<tr><td>Variable
- Glucose AUC over 3 meals (breakfast, lunch, dinner).</td><td>Outcome measure
- Blood glucose AUC
- Measured at 0,30,60,120 post-meal
- Averaged over three meals</td></tr>
<tr><td>Handling of inter-current events
1. Death (while on treatment strategy, or ‘‘while alive’’)
2. Discontinuation: other reason (while on treatment strategy)
3. Discontinuation: dislike of diet (treatment policy strategy)
4. Lost-to-follow-up no reason provided (treatment policy strategy)</td><td>Handling of missing data
1. Death believed not to be relevant for this study, included for completeness.
2. All individuals discontinuing early will (i) be invited to attend the week 6 assessment for fasting bloods and body weight only, (ii) asked whether the reason for discontinuation is due to allocated diet.
3. Missing-at-random will be assumed for individuals who do not specify whether discontinuation was due to diet, or when the reason was not due to the diet.
4. For individuals who discontinued due to the diet a missing-not-at-random assumption will be made, assuming zero adherence after discontinuation, and conditional on adherence missing-at-random assumed to impute week 8 outcomes.</td></tr>
</table>

	5. Imputation is by treatment group with individuals imputed in the groups they were allocated to.
Population level summary measure - Mean between group differences in baseline adjusted log-transformed (within-individual) mean post-meal glucose AUC, of the time-restricted groups verses the control (non time-restricted) group.	**Analysis approach** - Group differences of log transformed mean post-prandial AUC will be estimated using a single linear regression with a treatment (three levels) and baseline log transformed mean post-prandial glucose AUC and stratification factors (sex and fasting plasma glucose).

Hypothesis testing framework: All analyses are to test for superiority of eCR and dCR over CR.

Analyses: No interim analyses are planned. The analysis of the primary outcome will be conducted after the final subject has completed their 8 week assessment and the blood samples assessed for glucose concentrations.

Error Control: There are two primary comparisons, eCR vs CR and dCR vs CR with a common control and thereby use a Dunnett multi-test adjustment that controls the familywise error rate at 0.05 (two-sided) when each pairwise test uses an alpha of 0.027 (two-sided).

There are four secondary efficacy outcomes that will be tested to support a confirmatory finding: (i) PP insulin AUC, (ii) fasting insulin, (iii) fasting glucose, and (iv) HbA1c. An ordered testing procedure with per comparison (eCR vs CR and dCR vs CR) will be applied testing these four secondary outcomes in the order listed here, testing each subsequent outcome only if the previous outcome (and primary outcome) rejected the null. This procedure is applied separately for each comparison: eCR vs CR and dCR vs CR. The same pairwise alpha level, 0.027 (two sided), as the primary outcome will be applied to ensure that the familywise error rate is controlled at 0.05 (two-sided).

Standard multiplicity unadjusted 95% confidence intervals will be reported for all comparisons.

Covariate adjustment: All comparisons of treatment effect will include adjustment for…

1. The outcome variable's baseline assessment if appropriate,
2. Stratification factors (sex and baseline fasting plasma glucose as a continuous variable)

Sensitivity Analyses: A best-worst case sensitivity analysis will be performed for the analysis of the primary outcome and secondary efficacy outcomes.

- For all individuals missing the week 8 assessment in the CR (control) group the outcome will be imputed assuming missing-at-random. In other words, as if each individual's mean adherence was continued, or the cohort's mean adherence if no adherence data is available for an individual.
- For individuals in missing the week 8 assessment in the eCR and dCR groups their outcome, a missing-not-at-random assumption will be applied by assuming zero adherence and outcomes imputed thereafter, i.e., assuming missing-at-random conditional on zero subsequent adherence.
- These assumptions will be made irrespective of the stated reason for diet discontinuation.

A secondary, complete-case sensitivity analysis will be performed for the analysis of the primary outcome and secondary efficacy outcomes in this analysis individuals with both baseline and week 8 assessments will only be included for each analysis.

As additional analysis will explore the treatment effects within subjects who were adherent to the protocol using data collected with the MyCircadianClock app plus the dietary checklists. This analysis will be reported in a secondary mechanistic publication of this study.

STATISTICAL METHODS

Primary Outcome

The primary analysis of the primary outcome is a covariate adjusted linear regression of the differences in PP glucose log AUC at 8 weeks from baseline. Covariates included will be treatment (three groups), baseline glucose log AUC, sex and fasting plasma blood glucose (as a continuous linear variable). Visual inspection of the residual distribution will be used to determine if assumptions of normality and the absence of a variance-mean association appear to be violated. If assumptions appear violated a generalized linear models will be considered with differing link functions will be considered and presented as sensitivity analyses. Given the limited sample size, no subgroup analyses are planned.

This analysis will be performed in all randomized individuals with individuals using multiple imputation using chained equations within treatment groups and combined using Rubin's rules. The variables used in the multiple imputation are age and sex; baseline and week 8 assessments of weight, PP glucose and insulin AUC (per meal), fasting glucose, fasting insulin and HbA1c; and the self-reported adherence over the 8 weeks and reason for discontinuation (related/unrelated to diet) if applicable. All concentrations will be imputed on the log scale, with the 3-meal mean of PP glucose and insulin AUC being calculated on the original scale after a back-transformation. Compliance will be imputed as per the intercurrent event strategies and the average compliance calculated over each period. Imputation will use multiple chained equations (*mice* R package), details of which are attached separately (file: *OMIT – Imputation code 2024-12-18.r*).

Secondary Efficacy Outcomes

The four secondary efficacy outcomes used in the multiple imputation of the primary outcome will be assessed using the same methodology as for the primary outcome, i.e. covariate adjusted linear regressions with multiple imputation for missing data.

Exploratory Outcomes

Exploratory outcomes will also be analysed using baseline and stratification factor adjusted linear regressions. The weight and PP glucose and insulin meal specific analyses will be performed in the imputed data sets. All other outcomes will be analysed using complete case data sets.

Safety Outcomes

Summaries, for all adverse events and for those events believed to be related to the intervention, will be reported. In both cases, if an individual has experienced the adverse event on multiple occasions, only the event with the maximum grade will be reported.

When there are at least four individuals who experience a particular adverse event, a Fisher exact test will be conducted comparing the rates of occurrence (irrespective of grade) between the two intervention groups. No adjustments for multiple testing will be performed.

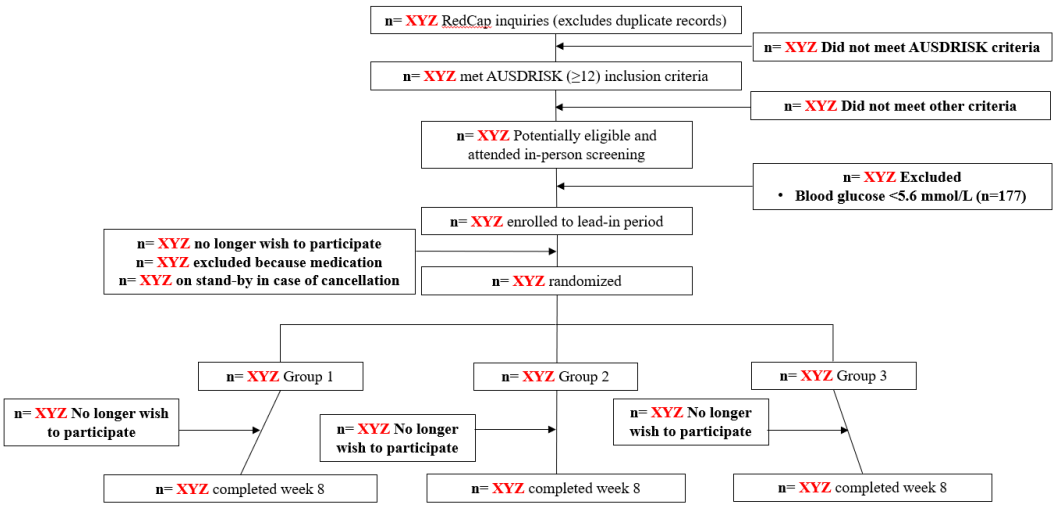
STUDY SUMMARY TABLES

Descriptive Statistics: A CONSORT flow chart will present all individuals screened through to randomization and week 8 assessment will be presented (Figure 2). The number of individuals who discontinue their allocated intervention and/or withdraw from the study, the week and reason for discontinuation will be reported.

Descriptive summary statistics will be reported for baseline characteristics of all individuals who were randomized. In addition to baseline glycemia indices we will report on age, sex, menopausal status, AUSDRISK, body composition, markers of CVD risk, sleep, activity and appetite measures. For continuous variables means, standard deviations, medians and ranges will be reported, and for discrete variables frequency and percentages will be reported. No demographic summary statistics were collected for the screened cohort.

Results tables presenting the analyses of the primary, secondary and exploratory outcomes are presented in Appendix A.

Figure 2: CONSORT flow chart of OMIT study.



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Appendix A: Results Tables.

Table A1: Primary outcome and confirmatory secondary outcomes with ordered testing procedure per comparison. Analyses from the prespecified multiply imputed analysis.

	A: Est [95% CI]	B: Est [95% CI]	C: Est [95% CI]	AvC: Est [95% CI]	AvC p-value	BvC: Est [95% CI]	BvC p-value
PP glucose AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
PP insulin AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	*	NA [NA; NA]	*
Fasting insulin	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	*	NA [NA; NA]	*
Fasting glucose	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	*	NA [NA; NA]	*
HbA1c	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	*	NA [NA; NA]	*

Table A2: Best-worst case sensitivity analysis of the primary analysis.

	A: Est [95% CI]	B: Est [95% CI]	C: Est [95% CI]	AvC: Est [95% CI]	BvC: Est [95% CI]
PP glucose AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
PP insulin AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
Fasting insulin	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
Fasting glucose	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
HbA1c	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]

Table A3: Complete case sensitivity analysis of the primary analysis.

	A: Est [95% CI]	B: Est [95% CI]	C: Est [95% CI]	AvC: Est [95% CI]	BvC: Est [95% CI]
PP glucose AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
PP insulin AUC	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
Fasting insulin	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
Fasting glucose	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]
HbA1c	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]

Table A4: Exploratory outcome analyses for outcomes used in the multiple imputation of the primary outcome, ie using the imputed data.

	A: Est [95% CI]	B: Est [95% CI]	C: Est [95% CI]	AvC: Est [95% CI]	AvC p-value	BvC: Est [95% CI]	BvC p-value
Glucose.auc.break	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Glucose.auc.lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Glucose.auc.dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Insulin.auc.break	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Insulin.auc.lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Insulin.auc.dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Weight	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA

Table A5: Exploratory outcome analyses for outcomes not used in the multiple imputation of the primary outcome, ie complete case analyses.

	A: Est [95% CI]	B: Est [95% CI]	C: Est [95% CI]	AvC: Est [95% CI]	AvC p-value	BvC: Est [95% CI]	BvC p-value
Mean Glucose CGM	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
iAUC glucose CGM	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Nocturnal glucose CGM	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
CGM time below range	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
CGM time in range	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
CGM time above range	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
MAGE	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
MODD	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Insulin secretion rate	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Insulin sensitivity index	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
HOMA-IR	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fasting C-peptide	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fasting Triglycerides	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fasting free fatty acids	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Trigs AUC of 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Trigs AUC of breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Trigs AUC of lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Trigs AUC of dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
FFA AUC of 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
FFA AUC of breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA

FFA AUC of lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
FFA AUC of dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Systolic BP	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Diastolic BP	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Total cholesterol	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
HDL	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
LDL	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
C-reactive protein	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
BMI	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Sleep duration	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Arousals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
AHI	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Light sleep	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Deep sleep	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
REM sleep	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Sleep latency	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Sitting time	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Standing time	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Stepping time	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Mean daily steps	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Adherence	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Eating window	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
95% Eating window	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Protein	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Carbohydrate	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fat	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Sat fat	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fibre	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Alcohol	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Hunger AUC 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Hunger AUC breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Hunger AUC lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Hunger AUC dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fullness AUC 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fullness AUC breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fullness AUC lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA

Fullness AUC dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Desire AUC 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Desire AUC breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Desire AUC lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Desire AUC dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Consumption AUC 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Consumption AUC breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Consumption AUC lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Consumption AUC dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fasting ghrelin	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Ghrelin AUC of 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Ghrelin AUC of breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Ghrelin AUC of lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Ghrelin AUC of dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
Fasting GLP1	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
GLP1 AUC of 3 meals	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
GLP1 AUC of breakfast	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
GLP1 AUC of lunch	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA
GLP1 AUC of dinner	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA [NA; NA]	NA	NA [NA; NA]	NA

Appendix B: SAP checklist.

Section	Index	Page	Description
1: Administration	1a	1	Title matches the protocol with SAP as forerunner or subtitle
	1b	1	Trial registration number
	2	1	SAP version number with dates
	3	1	Reference to version of protocol being used
	4a	1	SAP revision history
	4b	NA	Justification for each revision
	4c	NA	Timing of SAP revisions in relation to interim analyses
	5	1	Names, affiliations and roles of SAP contributors
	6a	1	Person writing SAP
	6b	1	Senior statistician responsibility
	6c	1	Chief investigator/Clinical lead
2: Introduction	7	5	Synopsis of trial background and rationale
	8	5	Description of specific objectives or hypothesis
3: Study Methods	9	7	Brief description of trial design
	10	10	Randomisation details
	11	10	Sample size calcs
	12	12	Superiority/equiv/non-inferiority
	13a	12	Info regarding interim analyses
	13b	NA	Adjustment to significance
	13c	NA	Stopping rules
	14	12	Timing of final analysis
	15	6	Time points at which outcomes are measured
4: Statistical principals	16	12	Level of statistical significance
	17	12	Rationale for multiplicity adjustments and T1 error control
	18	12	Confidence intervals to be reported.
	19a	6	Definition of adherence
	19b	6	Description of how adherence will be presented
	19c	6, 8, 9	Definition of protocol deviations

	19d	6	Description of which deviations will be summarized
	20	11	Definition of analysis populations
5: Trial population	21	15	Reporting of screening data to describe representativeness of trial sample
	22	8,9	Summary of eligibility criteria
	23	15	Information to be included in CONSORT flow chart
	24a	15	Level of withdrawal, from intervention and/or follow-up
	24b	15	Timing of withdrawals
	24c	15	Reasons and details how withdrawals will be presented.
	25a	15	List of baseline characteristics to be summarized
	25b	15	Details of how baseline characteristics will be summarized
6: Analysis	26	6	List of primary and secondary outcomes
	26a	12	Outcome timings and order of importance
	26b	10, 11	Specific measurement and units
	26c	14	Calculation or transformation used to derive the outcome
	27a	14	Analysis method to estimate treatment effects
	27b	12	Covariates adjusted for
	27c	14	Methods to check assumptions
	27d	14	Details of alternative methods if distributional assumptions do not hold
	27e	13	Planned sensitivity analyses
	27f	14	Planned subgroup analyses and definitions of subgroups
	28	11, 12	Assumptions methods for dealing with missing data.

OMIT STUDY – CODE FOR IMPUTATION (R) 18-12-2024

```
####################

## Data construction

####################



{

  ## Imputation data set

  imp.data



  ## Reformat adherence so that 0 = worst adherence.

  imp.data$adher.w2 <- 5 - as.numeric(imp.data$adher.w2)
```

```
imp.data$adher.w4 <- 5 - as.numeric(imp.data$adher.w4)

imp.data$adher.w8 <- 5 - as.numeric(imp.data$adher.w8)



## Calculate mean adherence

imp.data$adherence <- (as.numeric(imp.data$adher.w2) + as.numeric(imp.data$adher.w4) + 2*as.numeric(imp.data$adher.w8))/4



## Assume control is group 'C'

imp.data$treat <- relevel(imp.data$treat, ref='C')



## Construct log data to present analyses as percentage change.

for (var. in var.list[var.list %in% data.list$log.list]) {
```

```
  for (visit. in c('w0', 'w8')) {

    imp.data[,paste(var., visit., sep='.')] <- log(imp.data[,paste(var., visit., sep='.')])

  }; rm(visit.)

}; rm(var.)



## Variable lists

w0.list <- names(imp.data)[grepl('w0', names(imp.data))]

sum(!w0.list %in% names(imp.data)) # 0

w0.list <- w0.list[order(colSums(is.na(imp.data[,w0.list])))]; w0.list



w8.list <- names(imp.data)[grepl('w8', names(imp.data)) & !grepl('adher', names(imp.data))]
```

```
sum(!w8.list %in% names(imp.data)) # 0

w8.list <- w8.list[order(colSums(is.na(imp.data[,w8.list])))]; w8.list



calculated.list <- c("adherence", "glucose.auc.w0", "insulin.auc.w0", "glucose.auc.w8", "insulin.auc.w8")

w0.list <- w0.list[!w0.list %in% calculated.list]

w8.list <- w8.list[!w8.list %in% calculated.list]



adher.list <- c('drop.out', 'week.drop', 'adher.w2', 'adher.w4', 'adher.w8')

sum(!adher.list %in% names(imp.data)) # 0



aux.list <- c("id", "treat", 'sex');
```

```
sum(!aux.list %in% names(imp.data)) # 0



table(table(c(w0.list, w8.list, aux.list, adher.list, calculated.list))) # all 1s

sum(!names(imp.data) %in% c(w0.list, w8.list, aux.list, adher.list, calculated.list)) # 0



## List of meal data for formula construction

meal.list <- c(

  "glucose.auc.break.w0", "glucose.auc.lunch.w0", "glucose.auc.dinner.w0"

  , "insulin.auc.break.w0", "insulin.auc.lunch.w0", "insulin.auc.dinner.w0"

  , "glucose.auc.break.w8", "glucose.auc.lunch.w8", "glucose.auc.dinner.w8"

  , "insulin.auc.break.w8", "insulin.auc.lunch.w8", "insulin.auc.dinner.w8"
```

```
  )

  sum(!meal.list %in% names(imp.data)) # 0

}



##################

## Multiple Imputation

##################



## MI

set.seed(1234)

M. <- 100; N.iter <- 100
```

```
options(warn=0)

time. <- Sys.time()

for (MNAR.type in 0:1) {



 ## Code assumes control group = 'C'



 library(mice)

 # Set up data assumptions dropout

 {

  temp.data <- imp.data[, c(w0.list, w8.list, calculated.list, aux.list, adher.list)]

  colSums(is.na(temp.data))
```

```
## MAR: impute unknown drop out reason.

if (MNAR.type == 0) {

  temp.data$drop.out[temp.data$drop.out == 'Unknown'] <- NA

  sum(length(unique(temp.data$drop.out)) != 3) # 0

}

## MNAR: Do not impute unknown drop.out, set at best-worst case: A & B due to diet vs C not diet

if (MNAR.type == 1) {

  temp.data$drop.out[temp.data$treat == 'C' & temp.data$drop.out == 'Unknown'] <- 'Not diet'

  temp.data$drop.out[temp.data$treat %in% c('A', 'B') & temp.data$drop.out == 'Unknown'] <- 'Diet'

  sum(length(unique(temp.data$drop.out)) != 3) # 0
```

```
}

temp.data$drop.out <- temp.data$drop.out[drop=T]

if (nlevels(temp.data$drop.out) != 2) cat('Error wrong number of drop options.\n')



## Set individuals who did not discontinue to 'Not diet' drop out at week 8 (ie so data is not imputed)

cond. <- rowSums(!is.na(temp.data[,w8.list[w8.list != 'fasting.glucose.w8']])) > 0

temp.data$drop.out[is.na(temp.data$drop.out) & cond.] <- 'Not diet'

temp.data$week.drop[is.na(temp.data$week.drop) & cond.] <- 8; rm(cond.)



## Set adherence to "Strongly Disagree" (ie 0) when due to diet and after drop-out week

for (id. in temp.data$id[temp.data$drop.out == 'Diet' & !is.na(temp.data$drop.out)]) {
```

```
  week. <- temp.data$week.drop[temp.data$id == id.]

  if (week. < 2) temp.data$adher.w2[temp.data$id == id.] <- 0

  if (week. < 4) temp.data$adher.w4[temp.data$id == id.] <- 0

  if (week. < 8) temp.data$adher.w8[temp.data$id == id.] <- 0

  rm(week.)

 }; rm(id.)



 ## Calculate mean adherence over the eight weeks.

 temp.data$adherence <- ((temp.data$adher.w2) + (temp.data$adher.w4) + 2*(temp.data$adher.w8))/4

}
```

```
# Set up imputation functions

{

 fm.list <- NULL

 for (var. in w0.list) { # [!sub('.w0', '', w0.list) %in% data.list$log.list]

  if (!var. %in% meal.list) {

   fm. <- paste(var., "~ sex + ", paste(c(w0.list[!w0.list %in% c(var., meal.list)], "glucose.auc.w0", "insulin.auc.w0"), collapse=' + '))

   fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)

  } else {

   fm. <- paste(var., "~ sex + ", paste(c(w0.list[!w0.list %in% (var.)]), collapse=' + '))

   fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)

  }
```

```
}; rm(var.)

for (var. in w8.list) {

  # var. <- w8.list[1]

  if (!var. %in% meal.list) {

    fm. <- paste(var., "~ (", paste(c(

      sub('w8', 'w0', var.)

      , c('sex', 'adherence', "fasting.glucose.w0", "glucose.auc.w0", "insulin.auc.w0")

      , w8.list[!w8.list %in% c(var., meal.list)]

      , c("glucose.auc.w8", "insulin.auc.w8")

    ), collapse=' + '), ')')

    fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)
```

```
  } else {

    fm. <- paste(var., "~ (", paste(c(

      sub('w8', 'w0', var.)

      , c('sex', 'adherence', 'fasting.glucose.w0')

      , w8.list[!w8.list %in% c(var.)]

      ), collapse=' + '), ')')

      fm.list <- c(fm.list, as.formula(fm.)); rm(fm.)

  }

}; rm(var.)

fm.list <- as.list(fm.list)

names(fm.list) <- c(w0.list, w8.list)
```

```
  ## Drop out & adherence

  fm.list$drop.out <- as.formula('drop.out ~ 1')

  fm.list$adher.w2 <- as.formula('adher.w2 ~ 0 + I(as.numeric(drop.out != "Diet")*as.numeric(week.drop >= 2))')

  fm.list$adher.w4 <- as.formula('adher.w4 ~ 0 + I(as.numeric(drop.out != "Diet")*as.numeric(week.drop >= 4)*as.numeric(adher.w2))')

  fm.list$adher.w8 <- as.formula('adher.w8 ~ 0 + I(as.numeric(drop.out != "Diet")*as.numeric(adher.w2)) + I(as.numeric(drop.out !=
"Diet")*as.numeric(adher.w4))')



 }



 library(mice)
```

```
# Set up imputation methods

var.list <- c(w0.list, adher.list, w8.list, calculated.list)

{

  mice.fit <- mice(

    data=temp.data

    , m=1, maxit=0

    , blocks=var.list

    , visitSequent=var.list

    , formulas=fm.list

  )

  mice.fit$loggedEvents
```

```
method. <- mice.fit$method



## Construct calculated methods

{

  method.[names(method.) == 'glucose.auc.w0'] <- gsub(

    '\n', '',

    "~ I(

      log((

        exp(glucose.auc.break.w0)

        + exp(glucose.auc.lunch.w0)

        + exp(glucose.auc.dinner.w0)
```

```
    )/3)
  )"
)
method.[names(method.) == 'insulin.auc.w0'] <- gsub(
  '\n', '',
  "~ I(
    log((
      exp(insulin.auc.break.w0)
      + exp(insulin.auc.lunch.w0)
      + exp(insulin.auc.dinner.w0)
    )/3)
```

```
  )"
)
method.[names(method.) == 'glucose.auc.w8'] <- gsub(
  '\n', '',
  "~ I(
    log((
      exp(glucose.auc.break.w8)
      + exp(glucose.auc.lunch.w8)
      + exp(glucose.auc.dinner.w8)
    )/3)
  )"
```

```
)

method.[names(method.) == 'insulin.auc.w8'] <- gsub(

  '\n', '',

  "~ I(

    log((

      exp(insulin.auc.break.w8)

      + exp(insulin.auc.lunch.w8)

      + exp(insulin.auc.dinner.w8)

    )/3)

  )"

)
```

```
  method.[names(method.) == 'adherence'] <- gsub(
    '\n', '',
    "~ I(
      ((
        as.numeric(adher.w2)
        + as.numeric(adher.w4)
        + 2*as.numeric(adher.w8)
      )/4)
    )"
  )
}
```

```
}



for (treat. in c('A', 'B', 'C')) {

  mice.fit2 <- mice(

    data=temp.data[temp.data$treat == treat.,]

    , m=M., maxit=N.iter

    , blocks=var.list

    , visitSequent=var.list

    , formulas=fm.list

    , method=method.

    , print=F
```

```
  )

  mice.fit2$loggedEvents



  if (treat. == 'A') mice.fit.A <- mice.fit2

  if (treat. == "B") mice.fit.B <- mice.fit2

  if (treat. == "C") mice.fit.C <- mice.fit2



  rm(mice.fit2)

}; rm(treat.)

rm(mice.fit, method., fm.list, var.list)
```

```
  if (MNAR.type == 0) mice.full.fit0 <- rbind(rbind(mice.fit.A, mice.fit.B), mice.fit.C)

  if (MNAR.type == 1) mice.full.fit1 <- rbind(rbind(mice.fit.A, mice.fit.B), mice.fit.C)

  rm(mice.fit.A, mice.fit.B, mice.fit.C)

}; rm(MNAR.type)

rm(M., N.iter, temp.data, adher.list, aux.list, meal.list, calculated.list, w0.list, w8.list)



ls()



############################

## Analyses

############################
```

```
output <- NULL

for (MNAR.type in 0:1) {

 if (MNAR.type == 0) mice.full.fit <- mice.full.fit0

 if (MNAR.type == 1) mice.full.fit <- mice.full.fit1



 library(mice)

 var.list <- c(

  'glucose.auc', "glucose.auc.break", "glucose.auc.lunch", "glucose.auc.dinner", 'fasting.glucose'

  , 'insulin.auc', "insulin.auc.break", "insulin.auc.lunch", "insulin.auc.dinner", 'fasting.insulin'

  , 'weight', "hba1c"
```

```
)

for (var. in var.list) {

  for (visit. in c('.w8')) {

    output <- rbind(output, c(

      c('MI', 'MI-worst')[0:1 == MNAR.type]

      , 'diff - orig'

      , var.

      , toupper(substring(visit.,2,3))

      , summary(pool(with(

        data = mice.full.fit

        , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep=''))
```

```
)))$estimate[1]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$std.error[1]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$estimate[2]

,summary(pool(with(

  data = mice.full.fit
```

```
  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$std.error[2]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$estimate[3]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$std.error[3]

,summary(pool(with(
```

```
  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$estimate[1]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$std.error[1]

,summary(pool(with(

  data = mice.full.fit

  , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))

)))$estimate[2]
```

```
  ,summary(pool(with(
    data = mice.full.fit
    , expr = eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0)))', sep='')))
  )))$std.error[2]
))
## Include complete case analysis
if (MNAR.type == 1) {
  output <- rbind(output, c(
    c('CC')
    , 'diff - orig'
    , var.
```

```
        , toupper(substring(visit.,2,3))

        , summary(eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0, na.rm=T)),
data=imp.data)', sep=''))))$coef[1,1:2]

        , summary(eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0, na.rm=T)),
data=imp.data)', sep=''))))$coef[2,1:2]

        , summary(eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ 0 + treat + sex + I(', var., '.w0 - mean(', var., '.w0, na.rm=T)),
data=imp.data)', sep=''))))$coef[3,1:2]

        , summary(eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0, na.rm=T)),
data=imp.data)', sep=''))))$coef[2,1:2]

        , summary(eval(parse(text=paste('lm(I(', var., visit., ' - ', var., '.w0) ~ treat + sex + I(', var., '.w0 - mean(', var., '.w0, na.rm=T)),
data=imp.data)', sep=''))))$coef[3,1:2]

      ))

    }
```

```
    }; rm(visit.)

  }; rm(var., var.list)

  rm(mice.full.fit)

}; rm(MNAR.type)



output



output <- as.data.frame(output)

names(output) <- c('analysis', 'type', 'var', 'visit', 'est.C', 'se.C', 'est.A', 'se.A', 'est.B', 'se.B', 'est.BvC', 'se.BvC', 'est.BvC', 'se.BvC')

for (col. in 5:ncol(output)) output[,col.] <- as.numeric(output[,col.]); rm(col.)
```

```
## Multiply by 100 for percentage scale

cond. <- output[,var] %in% data.list$log.list

output[cond.,-(1:4)] <- 100*output[cond.,-(1:4)]




########################## END ############################

########################## END ############################

########################## END ############################

########################## END ############################
```