Title: Impact of Meal Timing on Glycemic Profiles in Adolescents with Type 2 Diabetes

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1. SIGNIFICANCE

1.1. Increased pediatric obesity has been accompanied by a rising incidence of T2D in adolescents, specifically among Latino and Black youth.[72–74] Because the risk of complications in adults increases with both the duration of diabetes and the lack of glycemic control, it is imperative to achieve and sustain metabolic control in adolescents.[22,23] The Restoring Insulin Secretion Consortium showed that compared to adults, adolescents with T2D have higher levels of insulin resistance and rapid, progressive β-cell failure despite early treatment with pharmacotherapies.[22,75,76] Diet alone can improve glycemic control in adults with T2D, but little is known about the impact of dietary interventions in the early stages of T2D in adolescents. [95–103] The American Diabetes Association recommends that high-intensity dietary interventions be utilized to achieve a 500–750 kcal/day energy deficit and maintain >5% weight loss in adults living with T2D.[104,105] In adolescents with T2D, standard treatment is centered on pharmacotherapies, including insulin and Metformin, with the goal of improving glycemic control and preventing glycemic excursions, however minimal weight loss is achieved with these methods.[105,106] There is a paucity of research evaluating the effectiveness of dietary interventions to reduce body fat mass, improve β-cell responsiveness, and prevent insulin dependence in this age group.[79,85,89,107,108] Conventional pediatric obesity treatment comprehensively addresses nutritional, physical activity, and behavioral topics with the goal of achieving clinically meaningful weight loss. Adherence to comprehensive lifestyle interventions is challenging for adolescents, in part because these approaches require frequent monitoring and engaging in multiple behavioral targets continuously. Therefore, there is a growing interest in simplifying intervention recommendations to decrease reliance on numeracy (Kilo calories and macronutrients), goal-setting and complex skillsets. One simpler approach is based on timing of eating.[6–8,13,15,26–37]

1.2. Time-based interventions, such as time-limited eating (TLE), have become a promising dietary strategy for weight loss, glucose and lipid metabolism improvements, and overall well-being in adults.[1,6,8–10,113–132] It has been shown in rodent and human studies that misalignment between endogenous circadian clock rhythms and rhythms of meal timing and sleep/wake induces weight gain and metabolic disruptions.[9,109–112] TLE is a dietary approach that involves shortening the eating window to a pre-specified number of hours per day and fasting for the remaining hours of the day without necessarily altering diet quality and quantity.[113] TLE has also been shown to improve fasting glucose and postprandial glucose levels, mean daily glucose, and insulin resistance, as well as blood triglyceride, and total cholesterol in adults with obesity and T2D. [10,114–116] The results of TLE in adults appear to depend on when eating occur.[10,52,117] Previous evidence has shown glucose tolerance, skeletal muscle fatty acid oxidation, and diet-induced thermogenesis are higher in the morning than in the evening in adults with T2D. Consumption of an evening meal induces higher postprandial glucose concentrations and insulin resistance compared with the same meal consumed in the morning. [118–121] Many adult trials have thus promoted TLE early in the day because it has been hypothesized to synchronize the central and peripheral circadian clocks involved in energy expenditure and fat oxidation and minimizes glycemic excursions and endogenous glucose production.[10,52,117]

1.3. No trial to date has studied the effects of TLE on glycemic control and body composition in adolescents with T2D. Because of its simplicity, TLE may represent a more feasible approach for adolescents than other caloric restriction regimens because it does not require extensive nutritional knowledge and control of food quantity and quality.[5,85,86] However, an early eating window may conflict with many adolescents' shifting chronotype, or preference to stay awake later and sleep later.[122–127] This shifting chronotype, coupled with increasing sex steroids and growth hormone levels overnight, has been shown to cause increased insulin resistance in the early morning for this age group, contrary to what is seen in adults.[128–131] This age-related changing metabolic state may provide an argument for an afternoon/evening eating window for TLE implementation in this age group. Our preliminary data, collected in 50 adolescents with obesity without diabetes, and 15 adolescents with T2D, shows the feasibility, acceptability, and safety of implementing 8-hour TLE in this age group and confirms that when allowed to self-select their eating window, the majority chose an afternoon/evening period.[14,15] Thus, to further investigate the effect of TLE on cardiometabolic outcomes in adolescents with T2D, we aim to determine if late TLE minimizes glycemic excursions, delays β-cell deterioration, and reduces body fat mass compared to a prolonged eating period.

2. INNOVATION: The proposed study is theoretically and clinically innovative for the following reasons:
2.1. This study is the first trial evaluating the effect of TLE in adolescents with T2D on glycemic variability and β-cell function in a real-life setting. TLE is an easy-to-use dietary approach for adolescents with T2D that

does not require additional resources. This study will collect preliminary efficacy data on how TLE effects glucose control, β-cell function, and body composition. In addition, in this study participants will be prescribed an afternoon/evening eating window to align with social preference and eating habits. Thus, this data will add to the growing literature exploring how the efficacy of TLE is impacted by the timing of the eating window.

2.2. Shift in standard of care. There is a lack of time-based recommendations in current nutrition standards for adolescents with T2D. Results from this study could potentially change the way adolescents with T2D are treated in the future by incorporating meal-timing behaviors as part of their medical regimen.

2.3. New insights on progression to β-cell dysfunction. β-cell dysfunction at time of diagnosis may be reversible; yet there is a paucity of research evaluating if TLE can delay β-cell loss of function and disease progression in adolescents with T2D**.** By utilizing C-peptide, insulin, and glucose measures over time after the MMTT, coupled with data collected from CGM, this study has the potential to show how time-based dietary interventions effect insulin secretion and function in adolescents with T2D and delay β-cell deterioration.

3. APPROACH

3.1. Preliminary, Feasiblity, and Process Measure Data:

3.1.1. 8-hour TLE + CGM is feasible, acceptable, and safe in adolescents with obesity.[14,15]

We conducted a 12-week pilot study to examine the feasibility of 8-hour TLE combined with continuous glucose monitoring in adolescents with obesity, without diabetes compared to a prolonged eating window. Fifty adolescents with BMI ≥95th percentile received standard nutritional counseling, wore a CGM daily, and were randomized to: (1) Prolonged eating window: 12 h eating/12 h fasting + blinded CGM; (2) TLE (8 h eating/16 h fasting, 5 days per week) + blinded CGM; (3) TLE + real-time CGM feedback. Forty-five participants completed the study (16.4 ± 1.3 years, 64% female, 49% Hispanic, 75% public insurance, 70% annual household income <$50,000). Ninety percent of adolescents in the TLE groups selected to start their eating window between 10 AM and 12 PM (11AM-8PM, 81%). To monitor the dosage of the intervention received, all participants recorded their eating windows daily and reviewed those logs with study staff weekly. Self-reported eating periods were compared weekly to the CGM data to monitor for large glycemic excursions during a reported fasting period which might suggest a meal was consumed. These excursion periods were then reviewed with the participant by the study team to reinforce adherence. Overall, there was high adherence to the prescribed eating windows (TLE 5.2 d/wk [SD 1.1]; control 6.1 d/wk [SD 1.4]) and daily CGM wear (5.9 d/wk [SD 4.8]) across all participants with no difference noted between groups. Most of the adolescents (90%) assigned to TLE reported that limiting their eating window was feasible without negative impact on daily functioning or adverse events. Based on adolescents' responses to the Satisfaction Survey and exit interviews, TLE was viewed favorably. Post-intervention, 26% of the TLE + blinded CGM group lost >5% of their baseline weight vs. 31% in the TLE + real time CGM and 13% in the control group (no between group difference in mean percent weight loss p = 0.5, **Figure 1**). Consistent with intention-to-treat analysis, across the study period, there was a significant decrease in excess percent of the 95th percentile (%BMI$_{p95}$) across all three groups (Control (n=15): −3.27±3.34, TLE + blinded CGM (n=19): −3.76±5.76, and TLE + real time CGM (n=16): −4.85±5.08, with no significant difference between groups (p=0.7; **Figure 2**). Across all secondary outcomes there were no between group difference in terms of energy intake, quality of life, physical activity, or eating behaviors. Thus, data from this study indicate that we can reliably recruit and retain adolescents with obesity, without diabetes, to participate in a TLE intervention and that decreasing their eating window is acceptable to them. In addition, our findings indicate that we can consistently monitor the dosage of the intervention received through a combination

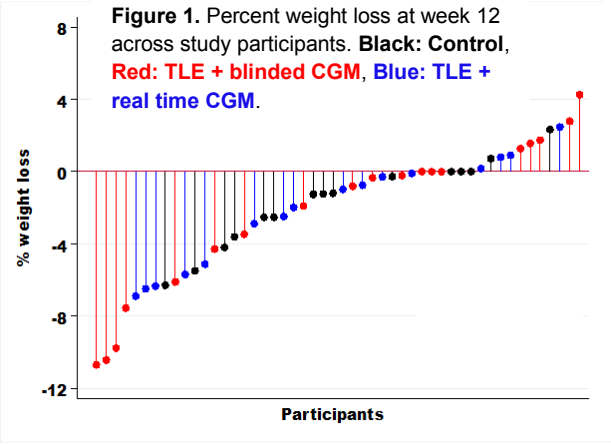

Figure 1. Percent weight loss at week 12 across study participants. **Black: Control**, **Red: TLE + blinded CGM**, **Blue: TLE + real time CGM**.

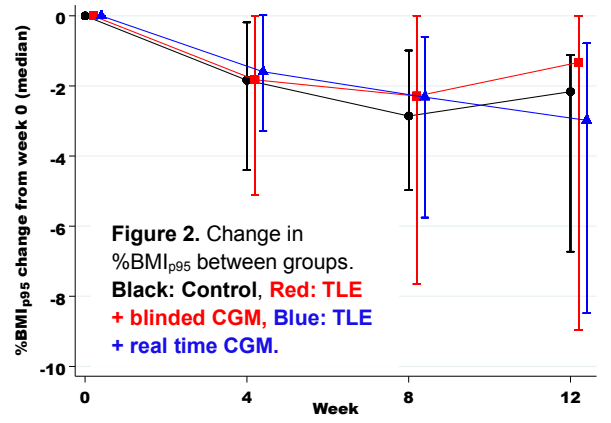

Figure 2. Change in %BMI$_{p95}$ between groups. **Black: Control**, **Red: TLE + blinded CGM**, **Blue: TLE + real time CGM.**

of daily logs, dietary intake, and evaluation of glycemic excursions on CGM. These preliminary data provide a strong premise for the study design of our proposed trial in adolescents with T2D.

3.1.2. 8-hour TLE + CGM is feasible, acceptable, and safe in adolescents with T2D.

We have been conducting a 12-week feasibility study (funded by the Pediatric Endocrine Society Clinical Scholar Award) to substantiate the feasibility, acceptability, and safety of TLE in adolescents with T2D. To date, fifteen adolescents with T2D (mean age 16.35 $\pm$1.26 years 70% female, 79% Latinx, 75% public insurance), diagnosed within the last 6 months, with a hemoglobin A1c $\leq$ 9%, and on Metformin monotherapy have been recruited and randomized to one of two meal-timing schedules for 12 weeks: (1) Control: $\geq$12-hour eating period or (2) TLE. All participated record their eating window daily and submit it to the study staff via REDcap survey. Since open enrollment September 2021, 41 participants have been screened, 23 met eligibility criteria, and of those 15 were enrolled, which achieved a recruitment rate of 65% for those who were contacted about the study. No participants have withdrawn from the study to date. To monitor the dosage of the intervention received, participants recorded their eating windows daily and reviewed those logs with study staff weekly. Overall, there has been high adherence to the prescribed eating windows (TLE 6.4 d/wk [SD 1.1]; control 6.6 d/wk [SD 1.4]) and daily CGM wear (6.4 d/wk [SD 4.8]) across all participants with no difference noted between groups. All eight participants assigned to TLE reported that limiting their eating window and wearing a CGM was feasible without negative impact on daily functioning or adverse events. To monitor safety, weekly CGM data was reviewed for episodes of hypoglycemia (defined as glucose level $\leq$70 mg/dL). For all participants to date, there have been no episodes of hypoglycemia captured on CGM. Thus, data from this study indicate that we can reliably recruit and retain adolescents with T2D to participate in a TLE intervention, monitor treatment adherence closely, and that decreasing their eating window is acceptable to them. Our findings indicate that TLE is a feasible and safe intervention for adolescents with T2D. These preliminary data provide a strong premise for the feasibility of our proposed trial.

3.2. Overview of Proposed Study Design:

The aim of this study will be to compare cardiometabolic effects of TLE (8-h eating period/16-h of daily fasting) versus a prolonged eating period (12+h eating period) in a randomized pilot study with careful control of continuous adherence to prescribed eating window. The implementation steps of the proposed study are as follows (**See Table 3**): **(1)** The staff will introduce the study to all eligible participants either in person or virtually and consent interested families for the study; **(2)** All participants and their families will complete baseline study surveys in REDcap; **(3)** All participants will be trained to wear a blinded CGM using manufacturer educational materials under the supervision of research staff. Participants will be asked to change the CGM sensor every 14 days for the duration of the study. During each study visit, the CGM reader will be connected to the site database to create an individual participant report. All equipment required for the duration of the study will be distributed to the participants at consent. Participants will receive enough sensors to wear the CGM daily for the entire study period. **(4)** All participants and their families will receive standard nutritional counseling and be randomized to one of two meal-timing schedules to be followed for 12 weeks: (1) Control or (2) TLE. During the eating window, participants will not be required to count calories or monitor their food intake. Participants will choose and pay for their own food during the intervention. All participants will record their eating window daily and submit it to the study staff via REDcap. All participants will receive standard recommendations for physical activity, screen, and sleep time as per the American Academy of Pediatrics age-appropriate recommendations at the first visit[132]; **(5)** The study staff will conduct study assessments with participants at week 0, 4, and 12; **(6)** The study staff will perform weekly phone encounters with the participants to assess barriers to adherence including diabetes specific components (Metformin side-effects, adjustment to diagnosis, etc.) and eating practices (responding to hunger cues, managing fasting periods in social situations, etc.). If a barrier is identified the study staff will create a solution plan to promote adherence and retention. The study staff will record any medication changes or health issues that have occurred in the last 7 days. The PI will review CGM downloads collected at each study visit to ensure no diabetes treatment escalation is required. Per clinical protocol at CHLA for adolescents with T2D on Metformin monotherapy, adolescents will check blood glucose with a glucometer twice weekly and be instructed to notify the clinical diabetes team for any blood glucose levels out of target range; **(7)** To further inform future trials and scalability we will continuously collect recruitment, consent, and retention rates, and barriers to engagement; **(8)** Adverse events (See Human Subject Protection Plan for full details) will be monitored. If at any time, the study staff notices any unhealthy compensatory behaviors the PI will be notified, and a treatment plan will be created to ensure that the participant receive the appropriate screening, work-up, and diagnosis from their

primary care provider and are withdrawn from the study if appropriate. **(9)** The PI and research team will meet bi-weekly to monitor all study procedures and oversee data management and analysis.

3.3. Participants: We will recruit 100 adolescents (age 14-21 years at enrollment, all gender expressions), with T2D. Inclusion criteria are: **(1)** age 14-21 years; **(2)** Tanner stage III and above; **(3)** diagnosis of T2D based on the ADA diagnostic guidelines[104]; **(4)** hemoglobin A1c ≤ 9% on Metformin monotherapy (At CHLA, based on the ADA and International Society for Adolescent and Pediatric Diabetes recommendations[104,105,133], we currently recommend Metformin monotherapy for any patients with HbA1c ≤9% at onset and therefore will use this cut off for the study); **(5)** participant must be willing and able to adhere to the assessments, visit schedules, and eating/fasting periods; and **(6)** baseline eating window greater than 10 hours. To limit confounding factors, individuals will be considered ineligible to participate if they meet any of the following exclusion criteria: **(1)** diagnosis of Prader-Willi Syndrome, brain tumor or hypothalamic obesity; **(2)** serious intellectual disability; **(3)** previous diagnosis or subthreshold symptoms of an eating disorder (anorexia nervosa, bulimia nervosa, binge-eating disorder); **(4)** parent/guardian-reported physical, mental of other inability to participate in the assessments; **(5)** previous bariatric surgery; **(6)** current use of an anti-obesity or other diabetes medication (e.g., phentermine, topiramate, orlistat, glucagon-like-peptide-1 agonist, naltrexone, buproprion, SGLT-2 Inhibitor, or insulin); or **(7)** current participation in other interventional weight loss studies. A random block stratified randomization scheme will be used. Participants will be randomized 1:1 via stratified, blocked randomization to ensure the groups are balanced in terms of number of participants and distribution of potential confounding variables including sex and age.

Table 3: Study Procedures and Measures

Weeks	0	4	12
Consent Completed	x		
Medical history	x		
Demographic Data	x		
CGM Education and equipment	x		
CGM (sensor change every 14 d, 12 w wear time)	x	x	x
Randomized	x		
Primary Outcomes			
Glycemic Control			
Percent Time in Range	x	x	x
Hemoglobin A1c	x		x
Mixed Meal Tolerance Test			
Insulinogenic Index	x		x
Body Composition			
DEXA Scan: Total body fat (Kg)	x		x
MRI-PDFF: Total liver fat fraction	x		x
Secondary Outcomes			
Nutrient Data System Recall: 24-hour dietary recall	x		x
International Physical Activity Questionnaire	x	x	x
Pittsburg Sleep Quality Index and Chronotype Questionnaire	x	x	x
Monitoring for Adverse Events			
Dutch Eating Behavior Questionnaire	x	x	x
Binge Eating Disorder Screen	x	x	x

3.4. Feasibility of recruiting economically, racially, and ethnically diverse participants. The CHLA endocrinology clinic has seen 160 patients with new onset T2D (≥ 14 to ≤ 21 years old) in the past year. Of those, 60 patients had an HbA1c ≤ 9.0% and would have been eligible for the study. We will also recruit from affiliate hospitals and pediatric clinics in the area. The demographics of our patient population are mean age 16.9 years, 60% female, mean age of diagnosis 13.2 ± 2.3 years. Sixty-five percent of our patients self-identify as Latino, compared to 47.5% of the population in Los Angeles.[134] At CHLA, we have a long history of conducting investigator-initiated studies in youth with T2D, including large consortium studies such as the Treatment of Diabetes in Adolescents and Youth (TODAY) trial[25], SEARCH for diabetes in youth[18,71] and Prevent Diabetes Consortium (PDC).[135] At CHLA, the recruitment rate in this population is between 50-60% with a retention rate of 60-80%. Based on the recruitment history from our feasibility trials, we anticipate a consent rate of 50-60%, retention rate of 75-80%, and recruitment of 35 adolescents per year to reach our target recruitment of 100 adolescents by year 3.

3.5. Retention strategies. To foster treatment adherence, participants will receive weekly calls from the study staff for the duration of the trial. Counseling will be conducted by trained research staff. The sessions will serve three purposes: (1) foster adherence, retention, and accountability; (2) troubleshoot intervention barriers; and (3) monitor safety endpoints. To support participants, the staff will use behavioral techniques, such as stimulus control, goal setting, behavioral contracting, and motivational interviewing. In order to reduce participant burden, if at all possible study procedures will be scheduled to coincide with participants' scheduled clinical visits.

3.6. Intervention Arms:

Components Common to All Study Arms. All participants will receive two hours of standard nutrition counseling recommended for adolescents living with T2D. No specific caloric restriction will be recommended. All participants will maintain their usual lifestyle, including physical activity and sleep patterns. Physical activity and sleep recommendations consistent with the American Academy of Pediatrics guidelines for adolescents will be encouraged but not formally prescribed.

Time Limited Eating. The TLE intervention arm will involve instructing participants to consume their usual kind and amount of food and beverages (all calories) within a pre-specified 8-hour period, fasting for the remaining 16-hours. They will be free to divide their food and beverage intake into as many meals or snacks as desired during the 8-hour period. We conducted a cross sectional analysis of a cohort of 100 adolescents with obesity and found that most total calories, carbohydrates, and added sugars were consumed between 11 AM and 8 PM.[136] In addition, in our feasibility trials, most adolescents selected an afternoon/evening eating window for both week days and weekend days, consistent with their shifting sleep/wake cycle and timing of social engagements.[14] Therefore, to align with the normal developmental eating patterns seen in adolescents, we will assign an afternoon/evening TLE approach (consumption of all calories between 12:00 and 20:00 [plus or minus 1 hour] seven days per week). Participants will be allowed to consume non-caloric beverages (water, tea, coffee) during the fasting period. No energy restriction will be required.

Control. Participants assigned to the control arm will be instructed to consume food over a 12-hour or more eating window. They will be free to divide their food and beverage intake into as many meals or snacks as desired during the 12-hour period. No energy restriction will be required.

Adherence Monitoring and Intervention Fidelity: To ensure differentiation between the intervention arms all participants will be asked to record the time they start, and finish eating each day and provide their eating logs to the study staff weekly. Each week, study staff will determine the daily eating window for each participant by reviewing the time interval between the first and last caloric intake of the day. These self-reported time windows will be verified by examining the pattern of glucose excursions using the 24-h CGM data. If a participant adheres to meal timing protocol $\leq$ 4 days/week, a follow-up call or videoconference will be scheduled to address challenges, give participants additional encouragement, support, and create a specific plan to promote adherence.

Continuous Glucose Monitor. All participants will be trained to wear a blinded continuous glucose monitor sensor using manufacturer educational materials under the supervision of research staff. Participants will be asked to wear the CGM for the duration of the study. During each study visit, the CGM reader will be connected to the site database to create an individual participant report. Participants will be provided enough sensors to replace the sensor every 14 days. The participants and guardians will be educated on how to use the CGM and receive 1:1 coaching on how to change the sensor, which will be completed either independently or under study team guidance. At each weekly phone meeting, study staff will monitor any challenges related to CGM wear, including participant discomfort, skin adherence, and other issues.

3.7. Measurements: The study team will conduct all assessments at week 0, 4, and 12. All data will be collected and stored in REDCap.

Aim 1: Test the effect of TLE on glucose control and β-cell function in youth with T2D.
Quantifying glycemic control (%TIR): Using a CGM, we will capture glucose readings every 5 minutes and obtain the weekly %TIR (defined as glucose levels from 70 mg/dL to 180 mg/dL[104]) over the course of the study. Vigersky et al. demonstrated that a 10% change in the %TIR is equivalent to a 0.8% change in HbA1c.[137]
Hemoglobin A1c: HbA1c will be measured from whole blood collected at the CHLA laboratory at week 0 and 12. HbA1c will be measured using a DCA 2000 (Bayer Corporation, Elkhart, IN).
Quantifying change in β-cell function: **Change in Insulinogenic index (IGI) after MMTT:** The MMTT provides a simultaneous estimate of insulin secretion and sensitivity.[137–142] To improve participant burden and decrease project cost, the modified MMTT will be utilized. Previous adult TLE trials have utilized the IGI as a surrogate marker of β-cell function in TLE trials.[10] Therefore, we will evaluate the effect of TLE on changes in IGI measured after MMTT. The MMTT will be performed at weeks 0 and 12. Participants will be instructed to not take their Metformin for 48 hours prior to their MMTT. Following baseline sampling (0 min), one 8-fluid-ounce Boost nutrition supplement drink (Nestlé Health Science) will be consumed. C-peptide, glucose, and insulin

concentrations will be measured in duplicate from plasma samples using YSI 2900 analyzer (YSI Life Sciences, Yellow Springs, OH, USA). Insulin and C-peptide concentrations will be measured using plasma with a commercially available ELIZA (Alpco Ltd, Windham, NH, USA), in duplicate. Total area under the cure (AUC) will be calculated for venous glucose, insulin, and c-peptide concentrations using the trapezoid methods using GraphPad Prism (Version .01, GraphPad Software Inc, San Diego, CA, USA).

Statistical Consideration (For Full Plan See Statistical Analysis Section): The sample size estimates, and analytical plans were developed under the guidance of Dr. Ramon Durazo-Arvizu. Descriptive statistics, including graphical depictions, will be utilized to assess the degree of symmetry/normality of continuous outcomes and identification of outliers. The statistical approach will be implemented with and without transformations in addition to generalized linear mixed models, when appropriate. All regression models will be adjusted for baseline levels, as this adjustment increases power.[143,144] A false discovery rate (FDR=10%)[145] approach will be applied to assess the effect of multiple testing. Statistical analyses will be performed using STATA 17.0 (STATA Corp, College Station, TX). Statistical analyses will be crafted under three different mechanisms, namely missing completely at random, missing at random, and other missing data patterns to account for missing data.[146–149] Our first approach to statistical analysis with missing data will follow common practice, such as last value carried forward, and multiple imputations.[150–153] Last value carried forward and multiple imputation will be carried out to generate complete data prior to analyzing data under the intention-to-treat (ITT) principle. A per-protocol analysis will also be performed and compared to results obtained under ITT. [154] Intervention adherence for all participants will be continuously monitoring and accounted for in the analysis process. To account for partial compliance, we will also complete an as treated approach to compare intervention arms by the actual intervention dosage they received. For participants with partial compliance, the treatment effect will be estimated by regressing the degree of compliance on the outcome in a logistic regression model. Participants will be compliers if they have complied with at least 80% of the intervention according to protocol.[155–159] No studies in the literature specifically addressed all our aims. Nevertheless, we were able to extract reasonable effect size information from several intervention-based studies, including some TLE studies conducted in adults.[10,47,49,50,160] The primary outcomes for Aim 1 are the difference between TLE and control in: a) average %TIR overtime, b) HbA1c at week 12 compared to baseline, and c) average IGI after MMTT at week 12 compared to baseline.

a) Percent Time in Range (%TIR): A two-step analysis plan will be executed starting with: 1) A change variable (%TIR at week 12 minus %TIR at week 0) will be generated for each study participant and average values adjusted for baseline %TIR and confounders compared via multivariable linear regression; 2) The previous analysis techniques do not take full advantage of the repeated measures in each individual. A multivariable linear mixed effect model with random intercept (LME) will be fit to compare the two treatment arms. Extracting from adult data, and data from youth with type 1 diabetes, a change in %TIR of greater than 5% is considered clinically significant, this correlates with an estimated change in HbA1c of -0.4%. Because we targeted improvements in %TIR, a one-sided at a 5% significance level to detect a benefit of TLE compared to control was used for each comparison, with a conservative within-subject correlation of 0.6. The required sample size to detect a pre-specified effect size (Cohen's d) of 0.34 with 80% power using an LME models (adjusting for baseline %TIR) with three %TIR determinations at weeks 0, 4, and 12 results in 40 subjects per group (80 total).[161] A 20% attrition rate was observed in our preliminary data thus the attrition-adjusted total sample size is 100 (80/0.8) participants. Furthermore, data extracted from adult studies suggests that the standard deviation of %TIR is between 16 and 25%.[137] Thus, a 0.34 effect size and a standard deviation of about 20% (midpoint between 16 and 25) amounts to a difference in %TIR of about 6.8% (0.34*20% = 6.8%).

b) Change in HbA1c: As above a two-step approach will be implemented. First, a two-sample, one sided, 5%-significance t-test to test the mean difference in HbA1c from baseline to week 12 between TLE and control. Second, a multivariable regression model will be fit. Calculations are based on the latter model. Carter et al. examined the impact of intermittent energy restriction compared to continuous energy restriction in adults with T2D and found that there was a between group difference of -0.2% with an SD of 0.1%.[14] On the other hand, Toledo-Corral, et. al. estimates the mean and standard deviation of HbA1c among children aged 8-17 years of about 5.75% and 0.2%, respectively.[162] An application of a one-sided, two-sample, 5%-significance t-test with 50 participants per intervention group (40 prior to attrition adjustment) will detect an effect size (mean HbA1c change) of -0.12% with 85% power, assuming a correlation between week 0 and week 12 HbA1c determinations of about 0.6.

c) Insulinogenic Index after MMTT: To evaluate the difference in β-cell function between TLE and control we will measure the difference in IGI change following MMTT at week 12 compared to baseline utilizing a two-

sample, one-sided, 5%-significance t-test. A multivariable linear regression model will be fit to the data to compare mean IGI change adjusting potential confounders, including baseline IGI values. A recent pilot study of TLE in an adult cohort without diabetes, showed TLE increased the IGI by 14 ± 7 U/mg compared to control at week 6 compared to baseline.[10] A total sample size of 100 participants (80 before adjusting for attrition) will thus detect a difference in IGI change of 4.2 with 85% power using the 5%-significance, one-sided, two-sample t-test. Additional power is gained by adjusting for baseline IGI and unbalanced participant characteristics.

Aim 2: Test the effect of TLE on obesity and liver fat in recently diagnosed youth with T2D.
Quantification of body composition: **Total Body Fat**: Using a Hologic QDR 5400 densitometer (Hologic, Inc., Bedford, MA) DEXA scan, we will measure the change in TBF at week 12 compared to baseline between TLE and control. **Liver Fat Fraction**: Change in liver fat will be measured by magnetic resonance imaging proton density fat fraction (MRI-PDFF). Participants will undergo MRI screening examinations at baseline and week 12 using an advanced magnitude-based spoiled-gradient-echo MRI-PDFF estimation technique previously validated to measure hepatic steatosis in children.[163–167] Key MRI-PDFF scanning parameters will be: 3T MRI scanner (GE 3T 750, and Siemens 3T TrioTim), 2D axial spoiled-gradient-echo breath hold acquisitions, TR > 100 ms, six TE values evenly spaced from 1.15 to 6.9 ms, flip angle 10 degrees, number frequency-encoding steps between 140 and 192, number phase-encoding steps between 128 and 140, no filters, no saturation, slice thickness 6 to 10 mm (contiguous), and rectangular field-of-view to accommodate body habitus. [163]

Statistical Consideration: We will utilize multivariate linear regression model to adjust for potentially unbalanced variables across group, in particular baseline values. A recent systematic review of the impact of TLE on cardiometabolic outcomes, showed that in adults TLE has variable effect on total body fat mass with some studies showing a decrease of up to 4 kg compared to control and others showing no change in TBF and liver fat fraction compared to control.[168–170] A previous study estimated the mean and standard deviation of Liver Fat Fraction among youth with obesity (ages 12-18 yrs.), is about 8%± 8%, respectively. A between-group mean change difference in liver fat fraction as large as 3.25 will be detected with 81% power.

Aim 3: Test the effect of TLE on sleep, physical activity, and dietary intake.
Secondary Outcomes: Twenty-four-hour dietary recalls will be conducted for all participants pre- and post-intervention via the Nutrient Data System Recall (NDSR) 24 Hour Dietary Recall[171]. One weekday and one weekend day will be collected for all participants. Physical activity will be measured with the International Physical Activity Questionnaire (IPAQ).[172–177] The IPAQ has been developed to estimate physical activity across different countries and socio-cultural environments and will be collected at 5 time points. Adult trials of TLE have reported sleep improvement upon shortening daily eating windows and so to analyze sleep we will collect the Munich Chronotype Questionnaire for children and adolescents (MTCQ)[178,179] and Pittsburg Sleep Quality Index (PSI)[180–182] at five time points. The MCTQ is a self-rated scale used to estimate an individual's circadian preference by a single phase-reference point, the mid-sleep point on free days. The PSI evaluates seven components of sleep architecture, sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction.

Statistical Consideration: All outcome variables (sleep, physical activity, and dietary intake) will be treated as continuous. The ladder of transformations approach[150,151] will be implemented to improve symmetry and/or approximate normality of their distribution. The study was not powered to assess mediation or moderation of each secondary outcome; however, we will estimate direct and indirect effects of the interaction between the outcomes. Given the estimated sample size, and desired statistical power, the minimal effect size (Cohen's d) is estimated, under the assumption of 0.6 correlation of each of the outcome variables between baseline (week 0) and follow-up (week 12). A 5%-significance, one-sided, two-sample t-test with the operating characteristics described above will detect an effect size as large as 0.5 (mean difference in standard deviation units). As an alternative to hypothesis testing, we will determine 95% confidence intervals in response to the interventions.[183–186] Confidence intervals not only allow for a better interpretation of effect estimates and their variability but could also be used to discriminate between group differences. Although results from this study will be evaluated using traditional techniques, such as p-values, we will rely on interpretation via confidence intervals. As a result, parameter estimates (e.g., mean difference, change and trends) will be used to aid scientific reasoning.[183]

PROTECTION OF HUMAN SUBJECTS

1) RISKS TO HUMAN SUBJECTS:

a) Human Subject Involvement, Characteristics and Design: This study is a prospective, two-parallel-arm, randomized pilot trial comparing Time Limited Eating (TLE) to a standard 12+hour eating window (Control). We will enroll 100 economically, ethnically, and racially diverse adolescents of all gender expressions, diagnosed with type 2 diabetes (T2D), aged 13-21 years, with a BMI $\geq 95^{th}$ percentile from Children's Hospital Los Angeles (CHLA, Los Angeles, CA). Randomization to the two groups (1:1 allocation) will be blocked and stratified by age and sex. Participant allocation will be concealed from the study staff until after all randomization has occurred.

i) Inclusion Criteria: Participants must meet all of the following criteria to be enrolled in the trial:

(1) Age 13-21 years
(2) Tanner stage III and above
(3) Diagnosis of T2D based on the American Diabetes Association diagnostic guidelines
(4) Hemoglobin A1c $\leq$ 9% and on monotherapy with Metformin monotherapy (This criterion is based on the ADA and International Society for Pediatric and Adolescents Obesity recommendations for treatment of T2D in adolescents who receive insulin for HbA1c $\geq$9%. At CHLA we currently recommend Metformin Monotherapy for any patients with HbA1c $\leq$9% at onset and therefore will use this cut off for the study).
(5) Participant and/or parent/guardian or family member must have a personal smartphone that is compatible with a continuous glucose monitor (CGM)
(6) Willing and able to adhere to the assessments, visit schedules, and eating/fasting windows

ii) Exclusion Criteria: Participants will not be eligible to participate if they meet any of the following criteria:

(1) Previous diagnosis of Prader Willi Syndrome, brain tumor or hypothalamic obesity
(2) Serious developmental or intellectual disability
(3) Previous diagnosis of an eating disorder (anorexia nervosa, bulimia nervosa, binge-eating disorder
(4) Parent/guardian-reported physical, mental of other inability to participate in the assessments (e.g., inability to wear CGM, inability to be in the imaging modality without sedation)
(5) Previous or planned bariatric surgery
(6) Current planned use of an anti-obesity or T2D medication (e.g. phentermine, topiramate, orlistat, glucagon like peptide-1 agonist, naltrexone, bupropion, SGLT-2 Inhibitor, etc.) or insulin
(7) Current participation in other interventional weight loss studies.
(8) Currently eats for less than 10 hours a day.

iii) Inclusion of Women: We will enroll adolescents of all gender expressions, diagnosed with T2D. We expect approximately 60% of the study participants will be female.

iv) Inclusion of Minorities: The study site will make it possible to recruit an ethnically and racially diverse sample, with CHLA serving Latinx and Black adolescents. The anticipated racial and ethnic composition of the study reflects the T2D population at CHLA.

v) Inclusion of Children: Children constitute the target population for this study as we aim to evaluate the impact of TLE on adolescents with T2D. In our experience, children younger than 13 years of age and older than 21 years would require different intervention/counseling strategies. Therefore, we can develop a more consistent "age-neutral" approach if we limit the age range to 13-21 years. In addition, based on our ongoing experience, this age range incorporates the general window of late pubertal development and we will limit recruitment to participants who are Tanner stage 3 or greater to exclude the potential confounding effects of early pubertal transition. Puberty will be determined by Tanner staging during examination by a physician and included as a co-variate. The IRB has strict regulations for the approach to and documenting of assent by minors and consent by their parents/guardians. Documentation of assent/consent is done via IRB-approved study-specific forms.

2) Study Procedures, Materials, and Potential Risks:

a) Study Clinical Sites: The study will be conducted at CHLA. The Clinical Trial Office (CTO) at CHLA will be the primary regulatory unit for the study, with oversight for human protection from the CHLA Institutional Review Board (IRB). The CHLA IRB will be the IRB of record. Data protection will be ensured by storing on an IS-approved university database on encrypted servers. All participants will be issued a study ID with data entered in de-identified manner. All databases will be password-protected with access

only to the study team. All paper/documentation/research charts will be maintained in locked locations accessible only to the study team.

b) **Sources of Material.** Data sources include questionnaires, blood samples, and anthropometric data. Privately identifiable information will therefore be collected. All data will be kept confidential and used only for research purposes.

c) **Questionnaires, and Medical Chart Abstractions.** Participants will be asked to complete standard/validated questionnaires data using web-based (Research Electronic Data Capture, REDCap) or paper-based forms. Demographic variables include age, race, ethnicity, marital status, education, and income level. The baseline questionnaire will also ascertain data on a variety of potential risk factors, including family history, medical history, supplement use, medication use, and lifestyle factors. We will measure weight and height. Clinical variables will be extracted from medical records, i.e., date of diagnosis and treatment (start date and dose). NIH PROMIS short forms, validated in pediatric populations, will be used to assess symptoms of anxiety, and depression. For lifestyle behaviors, we focus on four activities of interest: (1) physical activity; (2) sleep; (3) dietary intake; and (4) attitudes towards food and eating because intermittent fasting could positively or negatively affect these areas. Diet intake will be assessed using 24-hour recalls, while attitudes around food and eating will be assessed using the Dutch Eating Behavior Questionnaire (DEBQ) and the Binge Eating Disorder Screener (BED-S). Questionnaires will be used to measure sleep and physical activity. The Pittsburgh Sleep Quality Index (PSQI) and Munich ChronoType Questionnaire (MCQ) will be used to assess subjective sleep quality and disturbance. Assessments will be conducted at baseline, weeks 4, 8, and 12.

d) **Blood Collection**: We will collect, process, and store blood according to standard protocols for the hemoglobin A1c, C-peptide, insulin, Insulin-Like Growth Factor (IGF-1), and glucose levels. Blood will be collected at onboarding and week 12 and stored at -70°C.

e) **Intervention Compensation:** Each youth participant, regardless of the group they are assigned to, will receive compensation in the form of gift cards. Each youth participant will receive $50 at each study visit they attend (5 visits in total, for a total of $250 per participant). Parents/guardians/family members will also receive a $20 gift card for each study visit they attend for a total of $100 for participation in the study to account for time and effort required to support their participant. Parking validation will be provided. All families who do not have a car will be offered free ride-sharing transportation via UBER to- and from study visits upon request.

f) **Potential Risks/Adverse Events Monitoring and Procedures Used to Minimize the Risks**: Participants will be queried about adverse events at each phone call and study visit and will additionally be instructed to report adverse events as they occur. Participants will be provided with (A) a phone number and email address to report non-urgent adverse events to the research coordinator; and (B) a phone number to directly reach the study physician, in case of serious adverse events. In addition, all participants will be provided with our diabetes hotline number. This hotline is covered 24 hours per day by rotating certified diabetes educators during the day and on-call endocrinologist at night. The study physicians will immediately refer participants to the appropriate medical care (e.g., urgent care or non-urgent care) should any pressing concerns arise during the study period. In case of emergency, participants will be instructed to call 911 before calling the study physician. Should a participant require urgent or emergency care, the study physician will follow up with the participant's healthcare provider to determine whether it is safe for the participant to continue in the trial.

g) Adverse events will be subsequently documented and reported as described above. The severity of the event is graded as follows:

- **i)** Mild (Grade 1): the event causes discomfort without disruption of normal daily activities.
- **ii)** Moderate (Grade 2): the event causes discomfort that affects normal daily activities.
- **iii)** Severe (Grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- **iv)** Life-threatening (Grade 4): the patient is at risk of death at the time of the event.
- **v)** Fatal (Grade 5): the event causes death.

h) **Risks Related to Time Limited Eating (TLE):** Adverse events are unlikely as a result of participation in this study. The PI, co-investigators, and study team will monitor participants for mild symptoms associated with TLE, such as thirst, headaches, and gastrointestinal issues, as well as the potential risk for significant weight loss or malnutrition. All participants are on Metformin and will complete a standard Metformin titration plan in which they will be instructed to increase the dose by 500 mg per week to a goal dose of 1000 mg twice daily. This titration plan will prevent gastrointestinal side effects. Participants

will be instructed to take the medication with the first and last meal of the day during their eating window. At a minimum, the study staff will talk with study participants weekly to monitor for adverse events. To reduce the risks of increased thirst, headaches, and gastrointestinal issues, participants will be encouraged to stay hydrated by drinking water. Significant weight loss is defined as a 2% reduction in body weight in a week, a 5% change in one month or a 7.5% change within three months. Weight change will be closely monitored at every study visit to avoid triggering any hazardous medical conditions. In the event that a participant loses too much weight or loses weight too rapidly, the PI will counsel the participant and design a nutrition plan to increase daily caloric intake as needed.

i) **Attitudes and practices around food and eating**: None is anticipated. We will continuously monitor for unforeseen or unanticipated events and risks. If a participant report unhealthy compensatory eating behavior (i.e., binge eating, excessive restraint, purging, etc.) during the weekly phone calls or research visits, we will refer them to their primary provider to have an official psychological evaluation. If we suspect that the adolescent is purging or placing themselves in immediate medical danger, we will contact their parent or guardian and create a safety plan and instruct them to go the local emergency room for evaluation. In addition, the PI will contact the primary care provider to ensure appropriate referrals for psychiatric support are obtained. Adolescents who experience psychiatric emergencies will be withdrawn from the study. Dr. Salvy is a clinical behavioral psychologist and will provide oversight, monitoring and guidance to the PI regarding the monitoring of any adverse events related to behavior changes that may occur during the study period.

j) **Progression of diabetes requiring escalation of care**: The current International Society for Pediatric and Adolescents Diabetes (ISPAD) clinical practice guidelines for the management of T2D in adolescents recommend monotherapy with Metformin if the hemoglobin A1c (HbA1c) is $\leq$ 9% and to escalate treatment should the HbA1c trends $\geq$ 10%. To monitor glycemic control during the 12-week study period, all participants will wear a CGM. The study team will review the data weekly for each participant. If the data reveal average blood glucose levels $\geq$ 240 mg/dL, consistent with an HbA1c level $\geq$10%, then the participant will be instructed to contact his/her primary endocrinologist to determine if insulin initiation is required. Participants who experience progression of their diabetes and require insulin initiation will be allowed to remain in the study.

k) **Risk associated with DEXA**: The participants will be exposed to a small amount of radiation during their DEXA scan (radiation dose of 0.001 mSv), which is equivalent to 3 hours of natural background radiation and less than a coast-to coast round trip airline flight, which is about 0.03 mSv and poses minimal risk to the youth.

l) **Risk associated with MRI**: MRI images are obtained without using any ionizing radiation; thus, participants will not be exposed to the harmful effects of radiation. There are very few known health concerns from temporary exposure to the MRI environment; however, the MR environment does involve strong, static magnetic fields that carry specific safety concerns including: may attract magnetic objects which could damage the scanner or injure the participants if those objects become projectile, loud knocking noises which may harm hearing if adequate ear protection is not used, enclosed space which could induce anxiety or feelings of claustrophobia, and peripheral muscle or nerve stimulation and overheating of the body.

m) **Risk associated with CGM use:** There are risks for developing pain, bleeding, or burning at the insertion site of the CGM. In rare cases, there is a risk an infection may develop. There are risks of skin irritation to the adhesive tape. We have a process to address skin irritation, which involves evaluation by the PI with recommendations for topical treatments as needed, which may include over-the-counter hydrocortisone ointment or barrier creams.

n) **Risks Related to Blood Draws**: A small minority of participants will likely experience transient discomfort, pain, bleeding, and/or bruising from the needle insertion and/or IV. This poses minimal risk. Infection is also possible in rare cases. This risk will be minimized by having trained nursing and phlebotomy staff use sterile techniques to draw blood.

o) **Psychological Risks**: Though none of the questionnaires contain items that are particularly sensitive, personal, or potentially upsetting, it is possible that a participant may become upset thinking about some of the questions or topics in this study. Trained research coordinators will be conducting the assessments to address any potential incidents. All participants will be informed that they are free to refuse to answer any questions or questionnaires. They will also be informed that they can withdraw from the study at any time without penalty.

p) **Social Risks**: Some participants in the TLE group may spend less time engaged with family and friends while eating and may feel socially disconnected. Social functioning will be monitored as part of the weekly phone calls. Social risks will be minimized by requiring that participants adhere to TLE an average of 6 days per week (minimum of 5 days per week, 7 days prescribed). Dr. Salvy will also be available to counsel participants and help problem-solve social conflicts around meal-timing.

q) **Risks Related to Biohazards**: All staff will follow the Code of Federal Regulations on the handling of biospecimens (29 CFR Part 1910-1030) and hazardous chemicals (29 CFR Part 1910-1450). Human biospecimens (serum blood collected to measure: HbA1c, C-Peptide, Insulin, and Glucose) will be collected by doctors, nurses, or other trained personnel, and the collected samples will be processed and analyzed by trained technicians. All blood samples and reagents will be handled in approved areas using established guidelines set by Children's Hospital Los Angeles Occupational Health and Safety Offices. The collected blood specimens will be documented and stored in monitored and locked facilities. Blood, chemicals, and any materials that encounter biospecimens will be disposed of in designated biohazard waste receptacles, following federal and local biohazard regulations. All staff members who will encounter blood samples and chemical reagents are trained to safely handle these biospecimens and are retrained annually.

r) **Risks Related to Privacy and Confidentiality**: To protect privacy, each study participant will be assigned a unique identification (ID) number. Data forms, participant information, and biological specimens will be coded using these ID numbers. Personal, identifiable information will not appear on these materials; instead, the key linking the participant's identity to their unique identification number will be stored separately in a secure location. Records that identify study participants will be kept confidential as required by law, and every effort will be made to maintain the confidentiality of participants' study records. Except when required by law or if necessary, to protect their rights or welfare, study participants will not be identified by name or any other identifying characteristics in records disclosed outside of the investigational team. To manage study data, we will use REDCap, a secure web application that meets both HIPAA and 21 CFR Part 11 requirements. REDCap leaves a pristine audit trail by documenting all changes to data, and data access is strictly controlled with password authentication and user controls. Data from the medical chart and clinical outcomes and adverse events will be electronically uploaded to the database, and all questionnaires will be coded into and administered through REDCap. Such electronically stored data will be protected through stringent security measures assured by Children's Hospital Los Angeles technical departments and through the use of coded ID numbers and electronic security systems required by HIPAA. Paper documents will be scanned and saved on each site's secure network and also stored in locked cabinets in locked offices. Biological specimens will be stored and analyzed in locked areas with restricted access. Access to participants' data and biological specimens will be limited only to the study's investigators, clinical support staff for this study, the overseers of clinical facilities, and the study sponsor—all on a need-to-know basis. The study team has significant experience with the operation of clinical trials and safeguarding confidentiality

s) **Trauma, Bullying, and Domestic Violence Risks**: None anticipated. We will continuously monitor unforeseen or unanticipated events and risks. If trauma and/or domestic violence is suspected, either through completion of the questionnaires or through participants' report or staff observation, we will implement the following procedures: (1) we will make participants aware of resources available to them in their communities, such as shelters; (2) we will work with participants to develop a safety plan for addressing violence and seeking shelter; and (3) we will ascertain risk to the child(ren) in the household. If we suspect that the child(ren) has/have been abused or witnessed domestic violence, we will report the incident to child protective services. Participants who are victims of domestic violence will be allowed to remain in the study if they wish to do so.

t) **Suicidal Behavior Risks**: None anticipated. We will continuously monitor for unforeseen or unanticipated events and risks. We follow the Substance Abuse and Mental Health Services Administration SAFE-T: Suicide Assessment Five-Step Evaluation and Triage approach to determine risk and the appropriate clinical response. The five steps are Identify Risk Factors, Identify Protective Factors, Conduct Suicide Inquiry, Determine Risk Level/Intervention, and Document (which includes intervention and follow-up). As per practice guidelines, we will estimate suicide risk as low, moderate, or high. All potentially suicidal participants will be given an emergency plan with numbers to call (e.g., local hospital emergency rooms, suicide hotlines, staff, and study physicians). Each plan will be individually tailored to the needs and resources of the participants. Family members will be incorporated into the plan.

Adolescents who experience psychiatric emergencies such as suicidal behavior will be withdrawn from the study.

u) Alternative Treatments: Participants will be informed that the alternative option is not to enroll in the trial and their decision whether to enroll will not affect the quality or extent of medical care that they receive.

v) Handling Incidental Findings: If any clinically abnormal result or illness is uncovered, or if participants exhibit signs of depression or mental illness, the affected participant will be notified and referred to his/her physician or an appropriate health professional for treatment. Participants will be offered copies of any tests or incidental findings.

w) Stopping Rules: The Data Safety Monitoring Board (DSMB) will stop the trial if there is sufficient evidence of harm from TLE, as determined by adverse event reporting and/or safety monitoring of malnutrition diagnoses, or in the unlikely event that it appears the study cannot be conducted successfully. If there are statistically significant cases of negative compensatory eating behaviors or negative mental health with a difference in rates between groups is $\geq$30%, then the trial will be stopped. These endpoints will be assessed on a quarterly basis by the independent safety monitors and Drs. Vidmar and Salvy, to monitor intervention fidelity. However, these possibilities are considered unlikely, given the low adverse event rate, evidence of benefits in our pilot studies.

3) ADEQUACY OF PROTECTION AGAINST RISK

a) Informed Consent: Participants will be recruited from Children's Hospital Los Angeles (Los Angeles, CA). The typical approach will be through direct involvement with the treating physician. In their clinics, they will introduce the study to their patients and connect interested participants with the study staff. Research staff will carefully review the full consent form with the participant and parent or guardian in person or via phone, answering the participant's questions about the study. Participants will be allowed to electronically sign consent forms online using DocuSign, REDCap, or printed forms in-person. Alternativley, research staff will review medical records of potential participants in order to identify participants who may be eligible. CHLA has natural language processing algorithms that allows for rapid searches of electronic medical records to identify patients with specified criteria for recruitment into studies. Research staff will first discuss potential participants with the PI and treating physician before making contact. After the initial recruitment process, a follow-up phone call will be made by a trained recruiter within one week to answer questions and solicit participation. Consent can be withdrawn from at any time. Potential participants will have the following carefully explained: (1) the investigational nature of the research; (2) the objectives of the research; (3) the procedures involved in the research; (4) any and all risks and discomforts due to participation; and (5) alternative options to participation that are currently available. Clarification questions will then be elicited from the potential participants and their parents/guardians. Only after the above will an IRB-approved document recording informed consent be signed as per institutional guidelines with a copy to be given to the participant and the original stored with the research record in a secure location.

b) Protection Against Risk:

i) Safety Reviews: The PI (Vidmar) and Primary Mentors (Goran, Raymond), and Advisory Committee (Salvy, Espinoza and Durazo-Arvizu) will review this protocol on a continuing basis for participant safety. The IRB will review this protocol on an annual basis for subject safety, and we will include results of the review in the annual progress reports submitted to NIH. The annual reports will include a list of adverse events and will address: (1) whether adverse event rates are consistent with pre-study assumptions; (2) reasons for dropouts from the study; (3) whether all participants met entry criteria; and (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study.

ii) Monitoring plan: Data monitoring will focus on *performance* (participant follow-up and retention, participant privacy and confidentiality, protocol adherence, and data quality) and *safety* (adverse events and required action/response). The PI and Mentoring team will be responsible for the regular monitoring of data and safety issues and will maintain the record of any reported adverse events and other concerns. The study data safety and monitoring plan will entail several components, overseen by the PI:

(1) All CHLA IRB policies and continuous reporting requirements will be followed in conducting the study. Any actions taken by the IRB as part of its continuing review will be immediately reported to the NIH.

(2) The PI will implement procedures to ensure that each participant provides informed consent and that all data remain confidential. This will also include a rigorous data management protocol to

optimize data entry, accuracy/checking, and retrieval. Data will be stored in password-protected files accessible only to the investigators and staff under their supervision. In the database, only an ID code number will identify subjects. A list linking names and other identifiers with their ID codes will be stored in a separate file with a separate password. All original paper surveys and case report forms will be stored in locked file cabinets. The PI will review all data collection forms for completeness and accuracy and for protocol compliance. In the case of a breach of confidentiality or other adverse event, the PI will report the event to the IRB and the appropriate NIH officials, and appropriate procedural changes will be implemented to prevent future breaches or adverse events.

(3) An internal committee comprised of the PI, Mentoring team, and consultants will meet quarterly to assess participant recruitment, accrual, and retention; data quality and timeliness; participant risk versus benefit; and the development of external conditions that could potentially affect the study.

(4) Data Safety Monitoring Board (DSMB): Although this is an early-phase clinical trial, the study will nevertheless enlist an external DSMC. A data monitoring plan has been filed with the DSMC and IRB at time of study submission for IRB consideration. The DSMC will meet every 6 months and as needed to review study progress. Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will also be monitored by the DSMC. The safety monitor will also be responsible for: a) Reviewing and approving the protocol and consent documents; b) Providing input on protecting the safety of participants; c) Approving the data and safety monitoring plan; d) Considering any major changes to the protocol, consent, and data and safety monitoring plans after enrollment has started; e) Reviewing all adverse event data; f) Providing an independent, objective review of participant safety and study progress, in conjunction with the quarterly reports; g) Considering new findings that may affect participant safety or the ethics of the study; h) Stopping the trial, if merited

- **(a)** DSMB Members:
  - **(i)** TBD: Pediatric endocrinologist (Potential candidates: Steven Mittelman, MD, PhD, Division Chief Pediatric Endocrinology, Mattel Children's Hospital, University of California at Los Angeles, Los Angeles, CA; Omar Ali, MD, Pediatric Endocrinologist, Valley Children's Hospital, Fresno, CA).
  - **(ii)** TBD: Occupational therapist or psychologist (Potential candidates, Beth Pyatak, OTD, Associate Professor, Chan School of Occupational Therapy, University of Southern California, Los Angeles, CA).
  - **(iii)** Brittany Belcher, PhD: Health Behaviors Researcher who conducts clinical research related to physical activity and sedentary behavior measurement, and their relationships with disease outcomes.

(5) All personnel who will interact with subjects will receive training on adverse event reporting. In response to any adverse event, forms will be completed promptly and returned to the study physicians for review and implementation of an appropriate action plan.

(6) Quarterly safety reports will begin with a brief statement of the purpose of the study and a summary of the study design, including an organizational chart of all study personnel, as well as the projected timetable and targeted numbers for participant recruitment, intervention, and assessment. The study progress will be summarized, including enrollment, status, and retention of each cohort. In addition, a cumulative summary of the demographic breakdown of the sample will be summarized. Interim analyses will then be summarized. We will provide a detailed summary of any SAEs that have occurred since the previous Safety Report, including the participant name, nature of the event, date reported, action taken, resolution or ongoing complication(s) from the serious event, and whether the serious event was likely or unlikely related to participation in the study. In addition, any major issues or problems encountered, and steps taken to correct or address them will be summarized. Finally, in the latter stages of the study when it becomes relevant, the Safety Reports will also include a study summary, including a summary of the main findings, and procedures for preparing a report of study findings. Interim analyses of change in weight will be conducted, and the results summarized in the Safety Report.

4) POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

a) Benefits to Individual:

i) Potential benefits of the proposed research to human participants and others: This study will help researchers and professionals understand how TLE impacts β-cell function and body composition in adolescents with T2D with the potential that the intervention will improve glycemic control and delay disease progression. Thus, the benefits of this project to the individual and society greatly outweigh the risks.

ii) Importance of the knowledge to be gained: Research participants may expect benefits from learning about their health. All participants will be offered copies of test results from procedures performed during the study. In the case of an abnormal test result of other incidental finding, participants will be instructed to visit their physician or other appropriate health care providers. Finally, participants may benefit from better understanding nutritional strategies. Overall, this clinical trial may inform future interventions for adolescents with T2D.

iii) Risk-to-benefit ratio: As the known risks to participants from the intervention (i.e., increased thirst, headaches, gastrointestinal issues) and procedures like blood draws (e.g., bruising, temporary pain) are minor, we believe that these benefits outweigh the risks, as the risks to participants are minimal and will be monitored by regularly assessing participant safety

5) CLINICAL TRIALS REGISTRATION: This trial is currently registered at clinicaltrials.gov with the identifier NCT04536480

References

1 Melkani GC, Panda S. Time-restricted feeding for prevention and treatment of cardiometabolic disorders. Journal of Physiology. 2017; **595**. doi:10.1113/JP273094.

2 Lobene AJ, Panda S, Mashek DG, Manoogian ENC, Hill Gallant KM, Chow LS. Time-Restricted Eating for 12 Weeks Does Not Adversely Alter Bone Turnover in Overweight Adults. *Nutrients* 2021; **13**. doi:10.3390/NU13041155.

3 Crose A, Alvear A, Singroy S, Wang Q, Manoogian E, Panda S *et al.* Time-restricted eating improves quality of life measures in overweight humans. *Nutrients* 2021; **13**. doi:10.3390/NU13051430.

4 Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, Panda S *et al.* Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring, Md)* 2019; **27**: 724–732.

5 Gabel K, Hoddy KK, Varady KA. Safety of 8-h time restricted feeding in adults with obesity. *Applied Physiology, Nutrition and Metabolism* 2019; **44**. doi:10.1139/apnm-2018-0389.

6 Gabel K, Cienfuegos S, Kalam F, Ezpeleta M, Varady KA. Time-Restricted Eating to Improve Cardiovascular Health. *Current Atherosclerosis Reports* 2021; **23**. doi:10.1007/S11883-021-00922-7.

7 Gabel K, Hoddy KK, Burgess HJ, Varady KA. Effect of 8-h time-restricted feeding on sleep quality and duration in adults with obesity. Applied Physiology, Nutrition and Metabolism. 2019; **44**. doi:10.1139/apnm-2019-0032.

8 Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Pavlou V, Lin S *et al.* The effect of 4-h versus 6-h time restricted feeding on sleep quality, duration, insomnia severity and obstructive sleep apnea in adults with obesity. *Nutrition and Health* 2021. doi:10.1177/02601060211002347.

9 Jamshed H, Beyl RA, Manna DLD, Yang ES, Ravussin E, Peterson CM. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients* 2019; **11**. doi:10.3390/nu11061234.

10 Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metabolism* 2018; **27**. doi:10.1016/j.cmet.2018.04.010.

11 Przulj D, Ladmore D, Smith KM, Phillips-Waller A, Hajek P. Time restricted eating as a weight loss intervention in adults with obesity. *PloS one* 2021; **16**. doi:10.1371/JOURNAL.PONE.0246186.

12 Phillips NE, Mareschal J, Schwab N, Manoogian ENC, Borloz S, Ostinelli G *et al.* The Effects of Time-Restricted Eating versus Standard Dietary Advice on Weight, Metabolic Health and the Consumption of Processed Food: A Pragmatic Randomised Controlled Trial in Community-Based Adults. *Nutrients* 2021; **13**. doi:10.3390/NU13031042.

13 Vidmar AP, Goran MI, Raymond JK. Time-Limited Eating in Pediatric Patients with Obesity: A Case Series. *Journal of food science and nutrition research* 2019; **2**: 236–244.

14 Vidmar AP, Naguib M, Raymond JK, Salvy SJ, Hegedus E, Wee CP *et al.* Time-Limited Eating and Continuous Glucose Monitoring in Adolescents with Obesity: A Pilot Study. *Nutrients* 2021; **13**. doi:10.3390/NU13113697.

15 Vidmar AP, Goran MI, Naguib M, Fink C, Wee CP, Hegedus E *et al.* Time limited eating in adolescents with obesity (time LEAd): Study protocol. *Contemporary Clinical Trials* 2020; **95**. doi:10.1016/j.cct.2020.106082.

16 Mayer-Davis EJ, Kahkoska AR, Jefferies C, Dabelea D, Balde N, Gong CX *et al.* ISPAD Clinical Practice Consensus Guidelines 2018: Definition, epidemiology, and classification of diabetes in children and adolescents. *Pediatric Diabetes* 2018; **19**: 7–19.

17 Lascar N, Brown J, Pattison H, Barnett AH, Bailey CJ, Bellary S. Type 2 diabetes in adolescents and young adults. *The lancet Diabetes & endocrinology* 2018; **6**: 69–80.

18 Jensen ET, Dabelea D. Type 2 Diabetes in Youth: New Lessons from the SEARCH Study. *Current diabetes reports* 2018; **18**. doi:10.1007/S11892-018-0997-1.

19 Lynch JL, Barrientos-Pérez M, Hafez M, Jalaludin MY, Kovarenko M, Rao PV *et al.* Country-Specific Prevalence and Incidence of Youth-Onset Type 2 Diabetes: A Narrative Literature Review. *Annals of nutrition & metabolism* 2020; **76**: 289–296.

20 Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J *et al.* Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA - Journal of the American Medical Association* 2014; **311**: 1778–1786.

21 Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, Pihoker C *et al.* Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. *JAMA* 2021; **326**: 717–727.

22 Arslanian SA, el Ghormli L, Kim JY, Tjaden AH, Barengolts E, Caprio S *et al.* OGTT Glucose Response Curves, Insulin Sensitivity, and β-Cell Function in RISE: Comparison Between Youth and Adults at Randomization and in Response to Interventions to Preserve β-Cell Function. *Diabetes care* 2021; **44**: 817–825.

23 Edelstein SL. Effects of treatment of impaired glucose tolerance or recently diagnosed type 2 diabetes with metformin alone or in combination with insulin glargine on β-cell function: Comparison of responses in youth and adults: The RISE consortium. *Diabetes* 2019; **68**: 1670–1680.
24 Tryggestad JB, Willi SM. Complications and comorbidities of T2DM in adolescents: Findings from the TODAY clinical trial. Journal of Diabetes and its Complications. 2015; **29**. doi:10.1016/j.jdiacomp.2014.10.009.
25 Gidding SS, Bacha F, Bjornstad P, Levitt Katz LE, Levitsky LL, Lynch J *et al.* Cardiac Biomarkers in Youth with Type 2 Diabetes Mellitus: Results from the TODAY Study. *Journal of Pediatrics* 2018; **192**. doi:10.1016/j.jpeds.2017.09.012.
26 Copeland KC, Zeitler P, Geffner M, Guandalini C, Higgins J, Hirst K *et al.* Characteristics of adolescents and youth with recent-onset type 2 diabetes: The TODAY cohort at baseline. *Journal of Clinical Endocrinology and Metabolism* 2011; **96**. doi:10.1210/jc.2010-1642.
27 Weinstock RS, Drews KL, Caprio S, Leibel NI, McKay SV, Zeitler PS. Metabolic syndrome is common and persistent in youth-onset type 2 diabetes: Results from the TODAY clinical trial. *Obesity* 2015; **23**. doi:10.1002/oby.21120.
28 Arslanian S, el ghormli L, Kim JY, Bacha F, Chan C, Ismail HM *et al.* The shape of the glucose response curve during an oral glucose tolerance test: Forerunner of heightened glycemic failure rates and accelerated decline in B-cell function in today. *Diabetes Care* 2019; **42**. doi:10.2337/dc18-1122.
29 Narasimhan S, Weinstock RS. Youth-onset type 2 diabetes mellitus: Lessons learned from the TODAY study. Mayo Clinic Proceedings. 2014; **89**. doi:10.1016/j.mayocp.2014.01.009.
30 Arslanian S, el Ghormli L, Bacha F, Caprio S, Goland R, Haymond MW *et al.* Adiponectin, insulin sensitivity, β-cell function, and racial/ethnic disparity in treatment failure rates in TODAY. *Diabetes Care* 2017; **40**: 85–93.
31 Arslanian S, el Ghormli L, Bacha F, Caprio S, Goland R, Haymond MW *et al.* Adiponectin, insulin sensitivity, β-cell function, and racial/ethnic disparity in treatment failure rates in TODAY. *Diabetes Care* 2017; **40**. doi:10.2337/dc16-0455.
32 Shah R, Mckay S v., Levitt Katz LE, el Ghormli L, Anderson BJ, Casey TL *et al.* Adherence to multiple medications in the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) cohort: Effect of additional medications on adherence to primary diabetes medication. *Journal of Pediatric Endocrinology and Metabolism* 2020; **33**. doi:10.1515/jpem-2019-0315.
33 Berkowitz RI, Marcus MD, Anderson BJ, Delahanty L, Grover N, Kriska A *et al.* Adherence to a lifestyle program for youth with type 2 diabetes and its association with treatment outcome in the TODAY clinical trial. *Pediatric Diabetes* 2018; **19**. doi:10.1111/pedi.12555.
34 Marcus MD, Wilfley DE, el ghormli L, Zeitler P, Linder B, Hirst K *et al.* Weight change in the management of youth-onset type 2 diabetes: the TODAY clinical trial experience. *Pediatric Obesity* 2017; **12**. doi:10.1111/ijpo.12148.
35 Gow ML, Garnett SP, Baur LA, Lister NB. The effectiveness of different diet strategies to reduce type 2 diabetes risk in youth. Nutrients. 2016; **8**. doi:10.3390/nu8080486.
36 Garnett SP, Gow M, Ho M, Baur LA, Noakes M, Woodhead HJ *et al.* Improved insulin sensitivity and body composition, irrespective of macronutrient intake, after a 12 month intervention in adolescents with pre-diabetes; RESIST a randomised control trial. *BMC Pediatrics* 2014; **14**. doi:10.1186/s12887-014-0289-0.
37 Garnett SP, Gow M, Ho M, Baur LA, Noakes M, Woodhead HJ *et al.* Optimal macronutrient content of the diet for adolescents with prediabetes; RESIST a randomised control trial. *Journal of Clinical Endocrinology and Metabolism* 2013; **98**: 2116–2125.
38 Gandica R, Zeitler P. Update on Youth-Onset Type 2 Diabetes: Lessons Learned from the Treatment Options for Type 2 Diabetes in Adolescents and Youth Clinical Trial. Advances in Pediatrics. 2016; **63**. doi:10.1016/j.yapd.2016.04.013.
39 Zeitler P. Progress in understanding youth-onset type 2 diabetes in the United States: recent lessons from clinical trials. World Journal of Pediatrics. 2019; **15**. doi:10.1007/s12519-019-00247-1.
40 Parr EB, Devlin BL, Lim KHC, Moresi LNZ, Geils C, Brennan L *et al.* Time-Restricted Eating as a Nutrition Strategy for Individuals with Type 2 Diabetes: A Feasibility Study. *Nutrients* 2020; **12**: 1–22.
41 Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, Liu YE *et al.* Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity: The TREAT Randomized Clinical Trial. *JAMA internal medicine* 2020; **180**: 1491–1499.
42 AT H, P R, ENC M, JG F, GA W, S P *et al.* Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity (Silver Spring, Md)* 2019; **27**: 724–732.
43 Manoogian ENC, Panda S. Circadian rhythms, time-restricted feeding, and healthy aging. Ageing Research Reviews. 2017; **39**. doi:10.1016/j.arr.2016.12.006.

44 Page AJ, Christie S, Symonds E, Li H. Circadian regulation of appetite and time restricted feeding: Food intake and time restricted feeding. Physiology and Behavior. 2020; **220**. doi:10.1016/j.physbeh.2020.112873.

45 Longo VD, Panda S. Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan. Cell Metabolism. 2016; **23**. doi:10.1016/j.cmet.2016.06.001.

46 Ismail S, Manaf R, Mahmud A. Comparison of time-restricted feeding and islamic fasting: A scoping review. *Eastern Mediterranean Health Journal* 2019; **25**. doi:10.26719/emhj.19.011.

47 Currenti W, Buscemi S, Cincione RI, Cernigliaro A, Godos J, Grosso G *et al.* Time-restricted feeding and metabolic outcomes in a cohort of Italian adults. *Nutrients* 2021; **13**. doi:10.3390/nu13051651.

48 Schilperoort M, van den Berg R, Dollé MET, van Oostrom CTM, Wagner K, Tambyrajah LL *et al.* Time-restricted feeding improves adaptation to chronically alternating light-dark cycles. *Scientific Reports* 2019; **9**. doi:10.1038/s41598-019-44398-7.

49 Tinsley GM, Moore ML, Graybeal AJ, Paoli A, Kim Y, Gonzales JU *et al.* Time-restricted feeding plus resistance training in active females: A randomized trial. *American Journal of Clinical Nutrition* 2019; **110**. doi:10.1093/ajcn/nqz126.

50 Lustig E, Shubrook JH, Pfotenhauer KM. Time-restricted feeding and potential for type 2 diabetes mellitus: A narrative review. *Journal of the American Osteopathic Association* 2020; **120**. doi:10.7556/jaoa.2020.101.

51 Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metabolism* 2014; **20**. doi:10.1016/j.cmet.2014.11.001.

52 Regmi P, Chaudhary R, Page AJ, Hutchison AT, Vincent AD, Liu B *et al.* Early or delayed time-restricted feeding prevents metabolic impact of obesity in mice. *Journal of Endocrinology* 2021; **248**. doi:10.1530/JOE-20-0404.

53 Tinsley GM, Forsse JS, Butler NK, Paoli A, Bane AA, la Bounty PM *et al.* Time-restricted feeding in young men performing resistance training: A randomized controlled trial†. *European Journal of Sport Science* 2017; **17**. doi:10.1080/17461391.2016.1223173.

54 She Y, Sun J, Hou P, Fang P, Zhang Z. Time-restricted feeding attenuates gluconeogenic activity through inhibition of PGC-1α expression and activity. *Physiology and Behavior* 2021; **231**. doi:10.1016/j.physbeh.2021.113313.

55 Rynders CA, Thomas EA, Zaman A, Pan Z, Catenacci VA, Melanson EL. Effectiveness of intermittent fasting and time-restricted feeding compared to continuous energy restriction for weight loss. Nutrients. 2019; **11**. doi:10.3390/nu11102442.

56 Chung H, Chou W, Sears DD, Patterson RE, Webster NJG, Ellies LG. Time-restricted feeding improves insulin resistance and hepatic steatosis in a mouse model of postmenopausal obesity. *Metabolism: Clinical and Experimental* 2016; **65**. doi:10.1016/j.metabol.2016.09.006.

57 Schroder JD, Falqueto H, Mânica A, Zanini D, de Oliveira T, de Sá CA *et al.* Effects of time-restricted feeding in weight loss, metabolic syndrome and cardiovascular risk in obese women. *Journal of Translational Medicine* 2021; **19**. doi:10.1186/s12967-020-02687-0.

58 Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, Panda S *et al.* Time-Restricted Feeding Improves Glucose Tolerance in Men at Risk for Type 2 Diabetes: A Randomized Crossover Trial. *Obesity* 2019; **27**. doi:10.1002/oby.22449.

59 Li C, Xing C, Zhang J, Zhao H, Shi W, He B. Eight-hour time-restricted feeding improves endocrine and metabolic profiles in women with anovulatory polycystic ovary syndrome. *Journal of Translational Medicine* 2021; **19**. doi:10.1186/s12967-021-02817-2.

60 Jones R, Pabla P, Mallinson J, Nixon A, Taylor T, Bennett A *et al.* Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men. *American Journal of Clinical Nutrition* 2020; **112**. doi:10.1093/ajcn/nqaa192.

61 Chen L, Fatima S, Haq IU, Chen A, Majeed F, Feng Q *et al.* Effect of time-restricted feeding on metabolic risk and circadian rhythm associated with gut microbiome in healthy males. *British Journal of Nutrition* 2020; **123**. doi:10.1017/S0007114519003428.

62 Chow LS, Manoogian ENC, Alvear A, Fleischer JG, Thor H, Dietsche K *et al.* Time-Restricted Eating Effects on Body Composition and Metabolic Measures in Humans who are Overweight: A Feasibility Study. *Obesity (Silver Spring, Md)* 2020; **28**: 860–869.

63 Moro T, Tinsley G, Bianco A, Marcolin G, Pacelli QF, Battaglia G *et al.* Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *Journal of translational medicine* 2016; **14**. doi:10.1186/S12967-016-1044-0.

64 Gabel K, Hoddy KK, Haggerty N, Song J, Kroeger CM, Trepanowski JF *et al.* Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutrition and healthy aging* 2018; **4**: 345–353.
65 de Goede P, Foppen E, Ritsema WIGR, Korpel NL, Yi CX, Kalsbeek A. Time-Restricted Feeding Improves Glucose Tolerance in Rats, but Only When in Line With the Circadian Timing System. *Frontiers in Endocrinology* 2019; **10**. doi:10.3389/fendo.2019.00554.
66 Charlot A, Hutt F, Sabatier E, Zoll J. Beneficial effects of early time-restricted feeding on metabolic diseases: Importance of aligning food habits with the circadian clock. Nutrients. 2021; **13**. doi:10.3390/nu13051405.
67 Pureza IR de OM, Macena M de L, da Silva Junior AE, Praxedes DRS, Vasconcelos LGL, Bueno NB. Effect of early time-restricted feeding on the metabolic profile of adults with excess weight: A systematic review with meta-analysis. *Clinical Nutrition* 2021; **40**. doi:10.1016/j.clnu.2020.10.031.
68 Lynch S, Johnston JD, Robertson MD. Early versus late time-restricted feeding in adults at increased risk of developing type 2 diabetes: Is there an optimal time to eat for metabolic health? *Nutrition Bulletin* 2021; **46**. doi:10.1111/nbu.12479.
69 Saydah SH, Imperatore G, Henkin L, D'agostino R, Divers J, Mayer-Davis EJ *et al.* Trends and characteristics of self-reported case presentation of diabetes diagnosis among youth from 2002 to 2010: Findings from the SEARCH for diabetes in youth study. Diabetes Care. 2015; **38**: e84–e85.
70 Imperatore G, Boyle JP, Thompson TJ, Case D, Dabelea D, Hamman RF *et al.* Projections of type 1 and type 2 diabetes burden in the U.S. population aged <20 years through 2050: Dynamic modeling of incidence, mortality, and population growth. *Diabetes Care* 2012; **35**: 2515–2520.
71 Hamman RF, Bell RA, Dabelea D, D'Agostino RB, Dolan L, Imperatore G *et al.* The SEARCH for diabetes in youth study: Rationale, findings, and future directions. Diabetes Care. 2014; **37**: 3336–3344.
72 Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clinic Proceedings. 2017; **92**. doi:10.1016/j.mayocp.2016.09.017.
73 August GP, Caprio S, Fennoy I, Freemark M, Kaufman FR, Lustig RH *et al.* Prevention and treatment of pediatric obesity: An Endocrine Society clinical practice guideline based on expert opinion. *Journal of Clinical Endocrinology and Metabolism* 2008; **93**. doi:10.1210/jc.2007-2458.
74 Lobstein T, Baur L, Uauy R. Obesity in children and young people: A crisis in public health. Obesity Reviews, Supplement. 2004; **5**. doi:10.1111/j.1467-789x.2004.00133.x.
75 Edelstein SL. Effects of treatment of impaired glucose tolerance or recently diagnosed type 2 diabetes with metformin alone or in combination with insulin glargine on β-cell function: Comparison of responses in youth and adults: The RISE consortium. *Diabetes* 2019; **68**: 1670–1680.
76 Buse JB, D'Alessio DA, Riddle MC. Can we RISE to the challenge of youth-onset type 2 diabetes? Diabetes Care. 2018; **41**: 1560–1562.
77 Songer TJ, Haymond MW, Glazner JE, Klingensmith GJ, Laffel LM, Zhang P *et al.* Healthcare and associated costs related to type 2 diabetes in youth and adolescence: the TODAY clinical trial experience. *Pediatric Diabetes* 2019; **20**. doi:10.1111/pedi.12869.
78 Huang YS, Zheng Q, Yang H, Fu X, Zhang X, Xia C *et al.* Efficacy of Intermittent or Continuous Very Low-Energy Diets in Overweight and Obese Individuals with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analyses. Journal of Diabetes Research. 2020; **2020**. doi:10.1155/2020/4851671.
79 Kelly J, Karlsen M, Steinke G. Type 2 Diabetes Remission and Lifestyle Medicine: A Position Statement From the American College of Lifestyle Medicine. *American journal of lifestyle medicine* 2020; **14**: 406–419.
80 Skytte MJ, Samkani A, Petersen AD, Thomsen MN, Astrup A, Chabanova E *et al.* A carbohydrate-reduced high-protein diet improves HbA1c and liver fat content in weight stable participants with type 2 diabetes: a randomised controlled trial. *Diabetologia* 2019; **62**: 2066–2078.
81 Carter P, Achana F, Troughton J, Gray LJ, Khunti K, Davies MJ. A Mediterranean diet improves HbA1c but not fasting blood glucose compared to alternative dietary strategies: A network meta-analysis. *Journal of Human Nutrition and Dietetics* 2014; **27**: 280–297.
82 Sbraccia P, D'Adamo M, Guglielmi V. Is type 2 diabetes an adiposity-based metabolic disease? From the origin of insulin resistance to the concept of dysfunctional adipose tissue. *Eating and weight disorders : EWD* 2021. doi:10.1007/s40519-021-01109-4.
83 Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert GA *et al.* Comparison of low- and high-carbohydrate diets for type 2 diabetes management: A randomized trial. *American Journal of Clinical Nutrition* 2015; **102**: 780–790.

84 Tay J, Thompson CH, Luscombe-Marsh ND, Wycherley TP, Noakes M, Buckley JD *et al.* Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial. *Diabetes, Obesity and Metabolism* 2018; **20**: 858–871.
85 Gow ML, Pham-Short A, Jebeile H, Varley BJ, Craig ME. Current Perspectives on the Role of Very-Low-Energy Diets in the Treatment of Obesity and Type 2 Diabetes in Youth. *Diabetes, metabolic syndrome and obesity : targets and therapy* 2021; **14**: 215–225.
86 Gow ML, Baur LA, Johnson NA, Cowell CT, Garnett SP. Reversal of type 2 diabetes in youth who adhere to a very-low-energy diet: a pilot study. *Diabetologia* 2017; **60**: 406–415.
87 Furmli S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *BMJ Case Reports* 2018; **2018**. doi:10.1136/bcr-2017-221854.
88 Huang YS, Zheng Q, Yang H, Fu X, Zhang X, Xia C *et al.* Efficacy of Intermittent or Continuous Very Low-Energy Diets in Overweight and Obese Individuals with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analyses. Journal of Diabetes Research. 2020; **2020**. doi:10.1155/2020/4851671.
89 Salsberry P, Tanda R, Anderson SE, Kamboj MK. Pediatric type 2 diabetes: Prevention and treatment through a life course health development framework. In: *Handbook of Life Course Health Development*. Springer International Publishing, 2017, pp 197–236.
90 Roden M, Shulman GI. The integrative biology of type 2 diabetes. Nature. 2019; **576**: 51–60.
91 Zheng C, Sui B, Zhang X, Hu J, Chen J, Liu J *et al.* Apoptotic vesicles restore liver macrophage homeostasis to counteract type 2 diabetes. *Journal of extracellular vesicles* 2021; **10**: e12109.
92 Toyoshima Y, Gavrilova O, Yakar S, Jou W, Pack S, Asghar Z *et al.* Leptin improves insulin resistance and hyperglycemia in a mouse model of type 2 diabetes. *Endocrinology* 2005; **146**: 4024–4035.
93 Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. Journal of Clinical Investigation. 2016; **126**: 12–22.
94 Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocrine Reviews. 2002; **23**: 201–229.
95 Gruss SM, Nhim K, Gregg E, Bell M, Luman E, Albright A. Public Health Approaches to Type 2 Diabetes Prevention: the US National Diabetes Prevention Program and Beyond. Current Diabetes Reports. 2019; **19**. doi:10.1007/s11892-019-1200-z.
96 Baucom KJW, Pershing ML, Dwenger KM, Karasawa M, Cohan JN, Ozanne EM. Barriers and Facilitators to Enrollment and Retention in the National Diabetes Prevention Program: Perspectives of Women and Clinicians Within a Health System. *Women's health reports (New Rochelle, NY)* 2021; **2**: 133–141.
97 Vojta D, Koehler TB, Longjohn M, Lever JA, Caputo NF. A coordinated national model for diabetes prevention: Linking health systems to an evidence-based community program. *American Journal of Preventive Medicine* 2013; **44**. doi:10.1016/j.amepre.2012.12.018.
98 Subramanian K, Midha I, Chellapilla V. Overcoming the Challenges in Implementing Type 2 Diabetes Mellitus Prevention Programs Can Decrease the Burden on Healthcare Costs in the United States. *Journal of Diabetes Research* 2017; **2017**. doi:10.1155/2017/2615681.
99 Ackermann RT. From programs to policy and back again: The push and pull of realizing type 2 diabetes prevention on a national scale. Diabetes Care. 2017; **40**: 1298–1301.
100 Mensa-Wilmot Y, Bowen SA, Rutledge S, Morgan JM, Bonner T, Farris K *et al.* Early results of states' efforts to support, scale, and sustain the national diabetes prevention program. *Preventing Chronic Disease* 2017; **14**. doi:10.5888/pcd14.170478.
101 Ely EK, Gruss SM, Luman ET, Gregg EW, Ali MK, Nhim K *et al.* A national effort to prevent type 2 diabetes: Participant-level evaluation of CDC's national diabetes prevention program. *Diabetes Care* 2017; **40**: 1331–1341.
102 Baucom KJW, Pershing ML, Dwenger KM, Karasawa M, Cohan JN, Ozanne EM. Barriers and Facilitators to Enrollment and Retention in the National Diabetes Prevention Program: Perspectives of Women and Clinicians Within a Health System. *Women's health reports (New Rochelle, NY)* 2021; **2**: 133–141.
103 Li R, Qu S, Zhang P, Chattopadhyay S, Gregg EW, Albright A *et al.* Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: A systematic review for the community preventive services task force. Annals of Internal Medicine. 2015; **163**: 452–460.
104 Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G *et al.* Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the european association for the study of diabetes (EASD). Diabetes Care. 2018; **41**: 2669–2701.

105 Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C *et al.* 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2020; **63**: 221–228.
106 Copeland KC, Silverstein J, Moore KR, Prazar GE, Raymer T, Shiffman RN *et al.* Management of newly diagnosed type 2 diabetes mellitus (T2DM) in children and adolescents. *Pediatrics* 2013; **131**: 364–382.
107 Cardel MI, Atkinson MA, Taveras EM, Holm JC, Kelly AS. Obesity Treatment among Adolescents: A Review of Current Evidence and Future Directions. JAMA Pediatrics. 2020; **174**: 609–617.
108 Templeman I, Gonzalez JT, Thompson D, Betts JA. The role of intermittent fasting and meal timing in weight management and metabolic health. *Proceedings of the Nutrition Society* 2020; **79**. doi:10.1017/S0029665119000636.
109 Domaszewski P, Konieczny M, Pakosz P, Baczkowicz D, Sadowska-Krępa E. Effect of a six-week intermittent fasting intervention program on the composition of the human body in women over 60 years of age. *International Journal of Environmental Research and Public Health* 2020; **17**. doi:10.3390/ijerph17114138.
110 Chaix A, Zarrinpar A. The effects of time-restricted feeding on lipid metabolism and adiposity. *Adipocyte* 2015; **4**. doi:10.1080/21623945.2015.1025184.
111 Gill S, Le HD, Melkani GC, Panda S. Time-restricted feeding attenuates age-related cardiac decline in Drosophila. *Science* 2015; **347**. doi:10.1126/science.1256682.
112 Hou T, Wang C, Joshi S, O'Hara BF, Gong MC, Guo Z. Active Time-Restricted Feeding Improved Sleep-Wake Cycle in db/db Mice. *Frontiers in Neuroscience* 2019; **13**. doi:10.3389/fnins.2019.00969.
113 Ho SY, Wu YC, Chen YH, Yang SK. The effects of feeding time and time-restricted feeding on the fattening traits of White Roman geese. *Animal* 2014; **8**. doi:10.1017/S1751731113002383.
114 Sundaram S, Yan L. Time-restricted feeding reduces adiposity in mice fed a high-fat diet. *Nutrition Research* 2016; **36**. doi:10.1016/j.nutres.2016.02.005.
115 Pan X, Taylor MJ, Cohen E, Hanna N, Mota S. Circadian clock, time-restricted feeding and reproduction. International Journal of Molecular Sciences. 2020; **21**. doi:10.3390/ijms21030831.
116 Hosono T, Ono M, Daikoku T, Mieda M, Nomura S, Kagami K *et al.* Time-Restricted Feeding Regulates Circadian Rhythm of Murine Uterine Clock. *Current Developments in Nutrition* 2021; **5**. doi:10.1093/cdn/nzab064.
117 Vollmers C, Gill S, DiTacchio L, Pulivarthy SR, Le HD, Panda S. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *Proceedings of the National Academy of Sciences of the United States of America* 2009; **106**. doi:10.1073/pnas.0909591106.
118 Chaix A, Lin T, Le HD, Chang MW, Panda S. Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. *Cell Metabolism* 2019; **29**. doi:10.1016/j.cmet.2018.08.004.
119 Fanti M, Mishra A, Longo VD, Brandhorst S. Time-Restricted Eating, Intermittent Fasting, and Fasting-Mimicking Diets in Weight Loss. *Current Obesity Reports* 2021; **10**: 70–80.
120 Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. *Metabolism: clinical and experimental* 2018; **84**: 11–27.
121 Mason IC, Qian J, Adler GK, Scheer FAJL. Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes. *Diabetologia* 2020; **63**: 462–472.
122 Heilbronn LK, Civitarese AE, Bogacka I, Smith SR, Hulver M, Ravussin E. Glucose tolerance and skeletal muscle gene expression in response to alternate day fasting. *Obesity Research* 2005; **13**: 574–581.
123 https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170088.pdf. .
124 Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM *et al.* Recommended amount of sleep for pediatric populations: A consensus statement of the American Academy of Sleep Medicine. *Journal of Clinical Sleep Medicine* 2016; **12**: 785–786.
125 Doyle-Delgado K, Chamberlain JJ, Shubrook JH, Skolnik N, Trujillo J. Pharmacologic Approaches to Glycemic Treatment of Type 2 Diabetes: Synopsis of the 2020 American Diabetes Association's Standards of Medical Care in Diabetes Clinical Guideline. *Annals of internal medicine* 2020; **173**: 813–821.
126 Couper JJ, Haller MJ, Greenbaum CJ, Ziegler AG, Wherrett DK, Knip M *et al.* ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. *Pediatric Diabetes* 2018; **19**: 20–27.
127 Chang N, Yeh MY, Raymond JK, Geffner ME, Ryoo JH, Chao LC. Glycemic control in youth-onset type 2 diabetes correlates with weight loss. *Pediatric Diabetes* 2020; **21**: 1116–1125.
128 Cengiz E, Cheng P, Ruedy KJ, Kollman C, Tamborlane W v., Klingensmith GJ *et al.* Clinical outcomes in youth beyond the first year of type 1 diabetes: Results of the Pediatric Diabetes Consortium (PDC) type 1 diabetes new onset (NeOn) study. *Pediatric diabetes* 2017; **18**: 566–573.
129 Vidmar AP, Jones RB, Wee CP, Berger PK, Plows JF, Claudia Rios RD *et al.* Timing of food consumption in Hispanic adolescents with obesity. *Pediatric Obesity* 2021; **16**. doi:10.1111/ijpo.12764.

130 Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes Technology and Therapeutics* 2019; **21**: 81–85.
131 Saisho Y. Postprandial C-peptide to glucose ratio as a marker of β cell function: Implication for the management of type 2 diabetes. International Journal of Molecular Sciences. 2016; **17**. doi:10.3390/ijms17050744.
132 Peter R, Dunseath G, Luzio SD, Chudleigh R, Roy Choudhury S, Owens DR. Daytime variability of postprandial glucose tolerance and pancreatic B-cell function using 12-h profiles in persons with type 2 diabetes. *Diabetic Medicine* 2010; **27**: 266–273.
133 Mixed-meal tolerance test to assess residual beta-cell secretion: Beyond the area-under-curve of plasma C-peptide concentration - PubMed. https://pubmed.ncbi.nlm.nih.gov/30652426/ (accessed 20 Jun2021).
134 Ciresi A, Cicciò F, Radellini S, Giordano C. Utility of C-peptide for a reliable estimate of insulin secretion in children with growth hormone deficiency. *Growth Hormone and IGF Research* 2016; **29**: 71–77.
135 Ruan Y, Willemsen RH, Wilinska ME, Tauschmann M, Dunger DB, Hovorka R. Mixed-meal tolerance test to assess residual beta-cell secretion: Beyond the area-under-curve of plasma C-peptide concentration. *Pediatric Diabetes* 2019; **20**: 282–285.
136 Hobbs BP, Sargent DJ, Carlin BP. Commensurate priors for incorporating historical information in clinical trials using general and generalized linear models. *Bayesian Analysis* 2012; **7**: 639–674.
137 Prieto-Merino D, Pocock SJ. The science of risk models. *European Journal of Preventive Cardiology* 2012; **19**: 7–13.
138 Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. Journal of Clinical Epidemiology. 2014; **67**: 850–857.
139 Hogan JW, Roy J, Korkontzelou C. Tutorial in biostatistics. Handling drop-out in longitudinal studies. Statistics in Medicine. 2004; **23**: 1455–1497.
140 Touloumi G, Pocock SJ, Babiker AG, Darbyshire JH. Impact of missing data due to selective dropouts in cohort studies and clinical trials. *Epidemiology* 2002; **13**: 347–355.
141 Touloumi G, Babiker AG, Kenward MG, Pocock SJ, Darbyshire JH. A comparison of two methods for the estimation of precision with incomplete longitudinal data, jointly modelled with a time-to-event outcome. *Statistics in Medicine* 2003; **22**: 3161–3175.
142 Touloumi G, Babiker AG, Pocock SJ, Darbyshire JH. Impact of missing data due to drop-outs on estimators for rates of change in longitudinal studies: A simulation study. *Statistics in Medicine* 2001; **20**: 3715–3728.
143 Cook T, Zea R. Missing data and sensitivity analysis for binary data with implications for sample size and power of randomized clinical trials. *Statistics in Medicine* 2020; **39**: 192–204.
144 Mehran R, Baber U, Dangas G. Guidelines for patient-reported outcomes in clinical trial protocols. JAMA - Journal of the American Medical Association. 2018; **319**: 450–451.
145 Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. *JAMA - Journal of the American Medical Association* 2018; **319**: 483–494.
146 Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: A gentle introduction to imputation of missing values. *Journal of Clinical Epidemiology* 2006; **59**: 1087–1091.
147 Little R, Kang S. Intention-to-treat analysis with treatment discontinuation and missing data in clinical trials. *Statistics in Medicine* 2015; **34**: 2381–2390.
148 Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, Liu YE *et al.* Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: The TREAT randomized clinical trial. *JAMA Internal Medicine* 2020. doi:10.1001/jamainternmed.2020.4153.
149 Frison L, Pocock SJ. Repeated measures in clinical trials: Analysis using mean summary statistics and its implications for design. *Statistics in Medicine* 1992; **11**: 1685–1704.
150 Toledo-Corral CM, Vargas LG, Goran MI, Weigensberg MJ. Hemoglobin A1c above threshold level is associated with decreased β-cell function in overweight latino youth. *Journal of Pediatrics* 2012; **160**: 751–756.
151 di Martino M, Pacifico L, Bezzi M, di Miscio R, Sacconi B, Chiesa C *et al.* Comparison of magnetic resonance spectroscopy, proton density fat fraction and histological analysis in the quantification of liver steatosis in children and adolescents. *World Journal of Gastroenterology* 2016; **22**: 8812–8819.
152 Vu KN, Gilbert G, Chalut M, Chagnon M, Chartrand G, Tang A. MRI-determined liver proton density fat fraction, with MRS validation: Comparison of regions of interest sampling methods in patients with type 2 diabetes. *Journal of Magnetic Resonance Imaging* 2016; **43**: 1090–1099.
153 Hong CW, Mamidipalli A, Hooker JC, Hamilton G, Wolfson T, Chen DH *et al.* MRI proton density fat fraction is robust across the biologically plausible range of triglyceride spectra in adults with nonalcoholic steatohepatitis. *Journal of Magnetic Resonance Imaging* 2018; **47**: 995–1002.

154 Hong CW, Wolfson T, Sy EZ, Schlein AN, Hooker JC, Fazeli Dehkordy S *et al.* Optimization of region-of-interest sampling strategies for hepatic MRI proton density fat fraction quantification. *Journal of Magnetic Resonance Imaging* 2018; **47**: 988–994.
155 Park CC, Hooker C, Hooker JC, Bass E, Haufe W, Schlein A *et al.* Assessment of a high-SNR chemical-shift-encoded MRI with complex reconstruction for proton density fat fraction (PDFF) estimation overall and in the low-fat range. *Journal of Magnetic Resonance Imaging* 2019; **49**: 229–238.
156 Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, Pavlou V *et al.* Effects of 4- and 6-h Time-Restricted Feeding on Weight and Cardiometabolic Health: A Randomized Controlled Trial in Adults with Obesity. *Cell Metabolism* 2020; **32**. doi:10.1016/j.cmet.2020.06.018.
157 Gabel K, Hoddy KK, Haggerty N, Song J, Kroeger CM, Trepanowski JF *et al.* Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. *Nutrition and Healthy Aging* 2018; **4**. doi:10.3233/NHA-170036.
158 Rothschild J, Hoddy KK, Jambazian P, Varady KA. Time-restricted feeding and risk of metabolic disease: A review of human and animal studies. *Nutrition Reviews* 2014; **72**. doi:10.1111/nure.12104.
159 Harnack L, Stevens M, van Heel N, Schakel S, Dwyer JT, Himes J. A computer-based approach for assessing dietary supplement use in conjunction with dietary recalls. *Journal of Food Composition and Analysis* 2008; **21**. doi:10.1016/j.jfca.2007.05.004.
160 Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE *et al.* International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise* 2003; **35**: 1381–1395.
161 Helou K, el Helou N, Mahfouz M, Mahfouz Y, Salameh P, Harmouche-Karaki M. Validity and reliability of an adapted Arabic version of the long international physical activity questionnaire. *BMC Public Health* 2017; **18**. doi:10.1186/s12889-017-4599-7.
162 Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ) [2]. Medicine and Science in Sports and Exercise. 2004; **36**: 556.
163 Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE *et al.* International physical activity questionnaire: 12-Country reliability and validity. *Medicine and Science in Sports and Exercise* 2003; **35**: 1381–1395.
164 Joseph KL, Dagfinrud H, Christie A, Hagen KB, Tveter AT. Criterion validity of The International Physical Activity Questionnaire-Short Form (IPAQ-SF) for use in clinical practice in patients with osteoarthritis. *BMC Musculoskeletal Disorders* 2021; **22**. doi:10.1186/s12891-021-04069-z.
165 Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. International Journal of Behavioral Nutrition and Physical Activity. 2011; **8**. doi:10.1186/1479-5868-8-115.
166 Santisteban JA, Brown TG, Gruber R. Association between the Munich Chronotype Questionnaire and Wrist Actigraphy. *Sleep Disorders* 2018; **2018**: 1–7.
167 Ghotbi N, Pilz LK, Winnebeck EC, Vetter C, Zerbini G, Lenssen D *et al.* The μMCTQ: An Ultra-Short Version of the Munich ChronoType Questionnaire. *Journal of Biological Rhythms* 2020; **35**: 98–110.
168 Fontes F, Gonçalves M, Maia S, Pereira S, Severo M, Lunet N. Reliability and validity of the Pittsburgh Sleep Quality Index in breast cancer patients. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2017; **25**: 3059–3066.
169 Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry research* 1989; **28**: 193–213.
170 Mollayeva T, Thurairajah P, Burton K, Mollayeva S, Shapiro CM, Colantonio A. The Pittsburgh sleep quality index as a screening tool for sleep dysfunction in clinical and non-clinical samples: A systematic review and meta-analysis. *Sleep medicine reviews* 2016; **25**: 52–73.
171 Pandis N. Confidence intervals rather than P values. American Journal of Orthodontics and Dentofacial Orthopedics. 2013; **143**: 293–294.
172 Gardner MJ, Altman DG. Confidence intervals rather than P values: Estimation rather than hypothesis testing. *British Medical Journal (Clinical research ed)* 1986; **292**: 746–750.
173 Simon R. Confidence intervals for reporting results of clinical trials. *Annals of Internal Medicine* 1986; **105**: 429–435.
174 Rothman KJ. Significance questing. Annals of Internal Medicine. 1986; **105**: 445–447.
175 Dhaliwal R, Shepherd JA, el Ghormli L, Copeland KC, Geffner ME, Higgins J *et al.* Changes in visceral and subcutaneous fat in youth with type 2 diabetes in the TODAY study. *Diabetes Care* 2019; **42**. doi:10.2337/dc18-1935.

176 Walders-Abramson N, Anderson B, Larkin ME, Chang N, Venditti E, Bzdick S *et al.* Benefits and barriers to participating in longitudinal research of youth-onset type 2 diabetes: Results from the TODAY retention survey. *Clinical Trials* 2016; **13**. doi:10.1177/1740774515613949.
177 Vidmar AP, Naguib M, Raymond JK, Salvy SJ, Hegedus E, Wee CP *et al.* Time-Limited Eating and Continuous Glucose Monitoring in Adolescents with Obesity: A Pilot Study. *Nutrients* 2021; **13**. doi:10.3390/NU13113697.
178 Vidmar AP, Goran MI, Naguib M, Fink C, Wee CP, Hegedus E *et al.* Time limited eating in adolescents with obesity (time LEAd): Study protocol. *Contemporary Clinical Trials* 2020; **95**. doi:10.1016/j.cct.2020.106082.
179 Vidmar AP, Salvy SJ, Pretlow R, Mittelman SD, Wee CP, Fink C *et al.* An addiction-based mobile health weight loss intervention: protocol of a randomized controlled trial. *Contemporary Clinical Trials* 2019; **78**: 11–19.
180 Naguib MN, Raymond JK, Vidmar AP. New onset diabetes with diabetic ketoacidosis in a child with multisystem inflammatory syndrome due to COVID-19. *Journal of Pediatric Endocrinology and Metabolism* 2021; **34**: 147–150.
181 Vidmar AP, Wee CP, Salvy SJ. Food addiction, executive function and mood in adolescents with obesity seeking treatment. *Appetite* 2021; **159**. doi:10.1016/j.appet.2020.105049.
182 Vidmar AP, Salvy SJ, Pretlow R, Mittelman SD, Wee CP, Fink C *et al.* An addiction-based mobile health weight loss intervention: protocol of a randomized controlled trial. *Contemporary Clinical Trials* 2019; **78**. doi:10.1016/j.cct.2019.01.008.
183 Lopez KE, Salvy S-J, Fink C, Werner J, Wee CP, Hegedus E *et al.* Executive Functioning, Depressive Symptoms, and Intervention Engagement in a Sample of Adolescents Enrolled in a Weight Management Program. *Childhood Obesity* 2021; **17**: 281–290.
184 Hegedus E, Salvy SJ, Wee CP, Naguib M, Raymond JK, Fox DS *et al.* Use of continuous glucose monitoring in obesity research: A scoping review. *Obesity research & clinical practice* 2021; **15**: 431–438.

CHILDREN'S HOSPITAL LOS ANGELES
INFORMED CONSENT/PARENTAL PERMISSION/ASSENT TO PARTICIPATE IN A RESEARCH STUDY

Subject's Name:	_____	**Birth Date:**	_____
CHLA MRN#	_____		

A person who takes part in a research study is called a research subject or research participant. If you are reading this consent form as a parent/legal guardian, "you" also refers to "your child" (the research participant) and/or the research participant, as applicable.

KEY INFORMATION
You are being asked to participate in a research study. This section describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide the details of the research.

What should I know about this research?
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't want to take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you.
- If you don't understand, ask the research team questions.
- Ask all the questions you want before you decide.

How long will I be in this research?
Participation will last up to 16 weeks.

Why is this research being done?
This research is being done to find the effectiveness of a diet plan (Time Limited Eating or TLE) on glycemic control, β-cell function, body fat and body mass index (BMI) in adolescents with Type 2 Diabetes (T2D).

What happens to me if I agree to take part in this research?
Study procedures for this research are:
- You will be randomized into 1 of 2 groups.
    - Group 1: Non-TLE (Non Time Limited Eating) - 12-hour or more eating window without mealtime restrictions
    - Group 2: TLE (Time Limited Eating) – 8-hour eating window 7 days per week
- You will attend 5 visits at CHLA and have follow-up phone calls.
- You will be trained and wear a continuous glucose monitor every day for 12 weeks.
- You will have weight and height measured, research blood draws and Mixed Meal Tolerance Testing. Research imaging which will include a DEXA and MRI scan will be done.
- You will be asked to completing surveys.

Could being in the research hurt me?
The most important risks or discomforts that you may expect from taking part in the research are:

- Feeling uncomfortable answering some of the questions.
- Mild discomfort (pain), bruising and swelling where the needle is placed in your arm, and dizziness or fainting from blood draws.
- Small radiation exposure from scans.
- Headache or dizziness after not eating for prolonged periods if you're in the time limited eating group.
- Mild discomfort (pain), bruising or irritation at the insertion site from wearing a continuous glucose monitor.

Please see the POSSIBLE RISKS AND DISCOMFORTS section below for a complete list of expected risks.

Will being in this research benefit me?

The most important benefits that you may expect from taking part in this research are:

- Learning new skills for healthy eating and weight management.
- Improving glycemic control.
- Delaying disease progression.

What other choices do I have besides taking part in this research?

Instead of being in this study, your choices may include:

- Get routine care or treatment for your condition.
- Join another clinical research study.

INTRODUCTION

You are invited to join a research study led by Dr. Alaina Vidmar, MD from the Endocrinology Department at Children's Hospital Los Angeles (CHLA). The study is paid for by the Pediatric Endocrine Society.

You are invited to join this study because you have Type-2 Diabetes. Participation in this study is voluntary. Please read the information below and ask questions about anything you do not understand before deciding whether or not to be in the study.

PURPOSE OF THE STUDY

This research is being done to find the effectiveness of a diet plan (Time Limited Eating or TLE) on glycemic control, β-cell function, body fat and body mass index (BMI) in adolescents with Type 2 Diabetes (T2D).

NUMBER OF PARTICIPANTS

Up to 100 adolescents and 100 family members will be invited to join the study at CHLA.

LENGTH OF PARTICIPATION

Participation in this research will last 16 weeks with up to 5 in-person study visits at CHLA.

PROCEDURES

If you volunteer to be in this study, we will ask you to do the following things:

You will be randomized into 1 of 2 groups below. A computer program will randomly (like flipping a coin) assign you to one of the following groups after 1 week of wearing a continuous glucose monitor (CGM):

Group 1: Non-TLE (Non Time Limited Eating) - 12-hour or more eating window without mealtime restrictions

Group 2: TLE (Time Limited Eating) – 8-hour eating window 7 days per week

During the research study you will be asked to do the following things (each of these items is specific for the research study and not considered standard of care for your condition):

- **Follow the dietary guidelines provided to you by the study team:**
  - **TLE (Group 2 only):** only eat during an 8-hour window i.e. 11 AM – 7 PM 7 days per week.
- **Continuous glucose monitor (both groups):** You will wear a continuous glucose monitor called the Dexcom G6 Mobile CGM system every day to monitor your blood sugar level. The study team will create a Dexcom research account on your behalf using a research email. The study team will review your blood sugar levels with you over the phone each week. We will provide you with the device to use for 12 weeks. You will be trained on the use of this device. The Dexcom app will be downloaded to your or family member's personal smart phone. If you, your parent, legal guardian family member does not own a Dexcom compatible smart phone, you will use the Dexcom receiver. Please see appendix B for information about this device.
- **Phone Follow Up (both groups):** A member of the research team will call you once a week to discuss any barriers you may be experiencing. These conversations will be audio-recorded for educational purposes and should last approximately 15-30 minutes. A code name of your choice will be used during these conversations.
- **Follow-up plan (both groups):** At the end of the intervention, your participation in this study will be complete.

In addition to the above, the following research procedures will be done to all subjects in both groups through the end of the study:

- **Weight and height checks:** At every visit, we will weigh you and measure your height. This will be done in a private area.
- **Surveys:** You will complete several surveys at every visit. These surveys collect information such as your eating behaviors, how well you cope with stress, and satisfaction with the intervention. Each survey will take approximately 5-10 minutes to complete. You also have the option of completing the surveys virtually via WebEx or over the phone.
- **Dietary Recall:** You will complete a dietary recall of all the food and beverages you consumed over 2 days (48 hours) prior to the day of the visit. This will take approximately 45 minutes to complete and will occur at Visit 2 and 5. The dietary recalls will take place at your in-person visits or virtually via WebEx or over the phone. **Daily Eating Log:** You will complete eating logs every day. These logs will collect the time you started eating and the time you stopped eating each day for 16 weeks. A member of the research team will record your logs once a week.
- **Medical record review:** If you are a patient at CHLA, as part of your regular care, you may have blood work done every year to evaluate for your health. We will review your medical record and collect the results of your blood work if they occurred in the last 8 weeks from the consent date.
- **Research blood draws (fasting blood tests are considered standard of care at baseline for anyone entering into a weight management program):** Approximately 9 mL (2 teaspoon) of blood will be collected by sticking a needle in a vein of your arm for each blood draw. You will have to fast (not eat anything for at least 6 hours) before each blood draw. Blood draws will occur at visit 1 and 5.
- **Research images (during Onboarding [visit 1] and at day 84 [Visit 5]):**
  - DEXA scan: this will take a picture of your entire body and will take 30 minutes to obtain the image.
  - MRI scan: this will take a picture of your entire body and will take 30 minutes to obtain the image.
- **Mixed Meal Tolerance Testing (during Onboarding [visit 1] and day 84 [Visit 5]):** In preparation for the test, you will eat a high carbohydrate diet for the three days leading up to the test and fast the morning of the test. During the test, you will drink a liquid meal. You will have an IV placed in your arm and have a

small blood sample drawn at 0, 60, 90, and 120 minutes after consuming the liquid meal. Approximately 9 mL (2 teaspoons) of blood will be collected from the IV for mixed meal tolerance testing at each visit.

FOR YOUR PARENT/GUARDIAN OR OTHER FAMILY MEMBER

Your participation is optional if your child is over the age of 18 years.

- **Surveys**: Your family member will be asked to complete several surveys. These surveys will collect information such as age, job, health insurance, and ethnicity. Each survey will take about 5-10 minutes to complete. Your parent/legal guardian or family member will spend approximately 1 hour completing surveys. They will have the option to complete at in person visits or virtually via WebEx or over the phone.
- **Weight and Height**: Your family members' height and weight will be measured.

Your family member will need to travel to CHLA with you for your in-person study visits and/or to complete in person study procedures.

RESULTS OF TESTS PERFORMED FOR THE STUDY

The results of the following research tests and research information will be shared with you and your doctor upon request:

- **Lab Testing**: hemoglobin A1c, glucose level, liver function tests (AST&ALT), insulin, lipid panel, c-reactive protein (CRP), c-peptide, Insulin-Like Growth Factor (IGF-1) and mixed meal tolerance tests.
- **Research image studies** – DEXA scans and MRI scans
- Weight trends over the study period

Any abnormal lab test results from this study will be sent to your doctor as they may be important to your safety.

POSSIBLE RISKS AND DISCOMFORTS

Surveys: You may feel uncomfortable answering some of the questions. You can choose to skip or stop answering questions at any time. Surveys that will be completed by you and your family member ask about anxiety and depression. If you report extreme anxiety, binge eating disorder, or depression, we will refer you to a healthcare provider for immediate evaluation and a referral for mental health services if appropriate. This may result in additional costs to you if you require additional procedures, tests and/or treatments as determined by your healthcare providers.

Research blood draws: Having blood taken may cause pain, swelling, bruising, redness, and/or minor bleeding at the site of the needle stick. In rare cases, an infection or small blood clot may happen.

Imaging:

Risk associated with DEXA: You will be exposed to a small amount of radiation during your DEXA scan (radiation dose of 0.001 mSv) which is equivalent to 3 hours of natural background radiation and less than a coast-to-coast round trip airline flight which is about 0.03 mSv and poses minimal risk.

Risks associated with MRI: There are no known risks of physical harm associated with MRI. However, MRI machines produce loud banging noises, which cause some people to become stressed or upset. You may also feel uncomfortable inside the magnet if you do not like to be inside small places or have difficulty lying still. The MRI magnet is always on and attracts certain metal objects. Any metal objects on or inside of your body may heat up, move, and/or not function properly within the scanning room. Metal objects in the room can fly through the air toward the magnet and hit those nearby. There are many safety measures in place to reduce these risks. The staff will screen all persons and materials entering the scanning room for metal. When the study begins, the door to the room will be closed to minimize the risk of someone accidentally bringing a metal object into the scanner room.

Unexpected (incidental) Findings: It is possible that unexpected findings may be discovered from the research DEXA or MRI which you may find upsetting. You will be notified by the principal investigator if any unexpected findings are discovered. The principal investigator will advise you as to the nature of the findings and provide recommendations regarding appropriate follow-up with your physician. These findings may result in the need for you to have additional procedures, testing, and/or treatments as determined by your physician. This may result in additional costs to you and/or your health insurance.

Time Limited Eating: There are risks and discomforts associated with calorie restricted diet, such as hunger, anxiety, drowsiness, dizziness, headache, muscle aches, fatigue, low blood pressure and, in rare cases, fainting. These diet interventions may also cause abnormal heart rhythms, short-term nutrient deficiency, and a weakened immune response.

Continuous Glucose Monitor: While wearing the Continuous Glucose Monitor, you are at risk for developing pain, bleeding, or burning at the insertion site. In rare cases, an infection may develop.

Psychological risks: It is possible that you may become upset thinking about some of the questions or topics in this study.

Bullying or violence: If we suspect that you are a victim of bullying or violence at home or in your neighborhood, either through completion of the questionnaires, we will implement the following procedures: 1) we will make you are aware of resources available in your community; 2) we will work with you to develop a safety plan for addressing bullying or violence; 3) we will ascertain the risk to you. If we suspect that you have been abused or witnessed domestic violence, we will make a report to child protective services. Children/adolescents who are victims of bullying or domestic violence will not be dropped from the study, unless they ask to drop out.

Suicidal Behavior: If we suspect that you are suicidal, we will follow the Substance Abuse and Mental Health Services Administration SAFE-T: Suicide Assessment Five-Step Evaluation and Triage approach to determining risk and clinical response. The five steps are Identify Risk Factors, Identify Protective Factors, Conduct Suicide Inquiry, Determine Risk Level/Intervention, and Document (which includes intervention and follow-up). Adolescents who experience psychiatric emergencies such as suicidal behavior will not be dropped from the study, unless they request to terminate their participation.

Binge Eating Behavior: If we suspect that you are developing any binge eating behaviors either assessed in the screening questionnaires or reported by you to a research staff during a weekly phone meeting, we will implement the following procedure: (1) we will make you aware of resources available in your community, (2) we will encourage you to contact your primary care physician for an evaluation and determination is psychiatric referral is warranted, (3) we will ascertain risk to you and (4) the PI will contact your primary care provider to ensure you receive the appropriate evaluation and referrals for treatment. If we suspect that you are purging or placing yourself in immediate medical danger, we will contact your parent or guardian and instruct you to go the local emergency room for evaluation.

Mixed Meal Tolerance Test: You may experience discomfort with the IV placement or blood draw which should resolved with rest and laying down. You may experience dizziness, nausea, lightheadedness during the test.

Privacy Risks (for both youth and the parent/legal guardian/family member subjects): As this study involves the use of your identifiable, personal information, there is a chance that a loss of confidentiality may occur.

The researchers have procedures in place to lessen the possibility of this happening (see the CONFIDENTIALITY section below for details).

There may be additional risks to participation in this research that we do not know about and therefore cannot describe.

POSSIBLE BENEFITS TO SUBJECTS
You may benefit from participating in this study by

- learning new skills for healthy eating and weight management.
- improving glycemic control.
- delaying disease progression.

Your parent/legal guardian/family member will not have direct benefits from participating in this study.

POSSIBLE BENEFITS TO SOCIETY
Your participation in this study may allow us to learn more about how adolescents can lose weight and develop healthier eating habits in the future by limiting the time during the day in which they eat. Hopefully this information will help in the treatment of future patients with obesity and Type-2 Diabetes.

YOUR OPTIONS IF YOU CHOOSE NOT TO BE IN THIS STUDY
The alternative to being in this research is to get the standard of care. The standard of care is to receive care at a multi-disciplinary weight management clinic which includes meeting with several doctors to develop a weight loss program and techniques to help you lose weight and maintain your weight loss. You can also choose not to participate in this study.

COSTS TO YOU FOR BEING IN THIS STUDY
Participants and their families are not responsible for any of the costs involved in this study. The CGM will be provided to you at no cost while you take part in the study. Neither you nor your insurance company will be billed for your participation in this research. However, participants will continue to be responsible for their phone and service plans.

Parking validation will be provided on an as needed basis, upon request. All families who do not have a car will be offered ride share options (UBER or Lyft) for travel to and from CHLA for the study visits.

RESEARCH INJURY
If you think you have been hurt by taking part in this study, tell the doctor in charge of this research study as soon as possible. The research doctor's name and phone number are provided in this consent form. CHLA will offer you the care needed to treat injuries directly resulting from taking part in this research. This care will be billed to you or your insurance company. You will be responsible for deductible and co-payments, or any costs not paid by your insurer.

CONFIDENTIALITY
The telephone sessions will be audio-recorded; therefore, the audio-recordings are considered "directly identifiable" since they will contain your voice. The audio-recordings will be kept in a secure location and only the research team will have access to them. These recordings will be listened to by people on the research team.

If audio recordings of you will be used for educational purposes, your identity will be protected or disguised. The recordings will be listened to at 1.5 times speed to disguise the voices. You have the right to review the tapes if you desire.

The data collected as part of this study will be "coded." Coded means that the data collected for this study will be assigned a unique code or Study ID. Your research data will not include your name or any other identifying information about you. The code that could be linked back to your identifying information will be kept separate from your research data and specimens. Only the members of the study team will be able to see the link or the information that can identify you.

People on the research team and your doctors and nurses will know that you are in this research study. All results will be kept confidential.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you. Your private information, data and medical records will be shared with individuals and organizations that oversee this research, including:

- Government agencies, such as the Food and Drug Administration (FDA), and the Department of Health and Human Services.
- Pediatric Endocrine Society
- The CHLA Institutional Review Board (IRB) that reviewed this research, and authorized representatives of CHLA.

Because this study involves medical procedures, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about any medications and/or procedures you are receiving in the study and treat you appropriately.

We will take steps to keep your personal information private, but we cannot guarantee complete secrecy. All identifiable information about you will be replaced with a unique code or study ID. A list linking the code and your identifiable information will be kept separate from the research data. All research data and records will be stored electronically on a secure network with encryption and password protection to help prevent unauthorized access to your personal information.

We will not release information about you to others not listed above, unless required or permitted by law. For instance:

- if we learn of child or elder abuse, harm to self or others, or
- if you have certain infectious diseases; or
- you are injured and need emergency care.

The results of the research may be presented or published. We will keep your name and other identifying information confidential.

FUTURE RESEARCH USE OF DATA AND/OR SPECIMENS

The data and specimens collected as part of this study will not be used for future research, even if all identifiers are removed.

STUDY WITHDRAWAL

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researchers might also decide to stop the study at any time.

If you decide to stop being in the study, or are removed from the study, or the study is stopped, the data/specimens collected before you leave will be used but no more data will be collected.

QUESTIONS ABOUT THE STUDY
If you have questions, concerns, or complaints about the study, or think this research has hurt you or made you sick, talk to the CHLA research team:

Daytime, Monday through Friday, 8:00 A.M. through 4:30 P.M. you may call the CHLA Principal Investigator, Dr. Alaina Vidmar at 323-361-3385.

Evenings, nights, weekends or holidays you may call the hospital number, (323) 660-2450 and ask for the Endocrinology Service doctor on-call.

ClinicalTrials.gov is a Web site that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This research is being overseen by the CHLA Institutional Review Board ("IRB"). An IRB is a group of people who perform ethical review of research studies. You may talk to them at (323) 361-2265, or hspp@chla.usc.edu if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

FINANCIAL INTEREST OF THE INVESTIGATOR
If your doctor is an investigator for this study, he/she is interested in both your healthcare and the conduct of this research. You are not under any obligation to participate in a research study conducted by your doctor.

RIGHTS OF RESEARCH SUBJECTS
You can agree to take part in this study and stop your participation in the study anytime. You should not sign this form if you have any questions that have not been answered or if you are unclear about any information in this form.

Your participation in the study is entirely voluntary. If you choose not to take part in the study or decide to stop your participation in this study at any time, there will be no penalty or loss of benefits to which you are otherwise entitled. If you wish to leave the study after agreeing to participate, you should let the Principal Investigator know. You are not under any obligation to participate in a research study conducted by your doctor.

You will be told about any new information found during the course of the study that may affect your health, welfare, or choice to stay in the research. If this happens, you might be asked to sign a new consent form.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from CHLA.
- If you decide not to take part, you can still receive medical care from CHLA.
- You will be given a copy of this signed and dated consent form and the "Experimental Subject's Bill of Rights" to keep.
- You will be asked to sign a separate CHLA HIPAA Research Authorization form authorizing the access, use, creation, and/or disclosure of your health information.

SIGNATURE OF RESEARCH SUBJECT
(*For adults who are capable of providing consent; children ages 14 to 17 years old who are capable of providing assent*)

Your signature below indicates:

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You consent/assent to your participation in this research study; and
- You will be given a signed copy of this form.

_____
Print Name of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF RESEARCH SUBJECT (PARENT/LEGAL GUARDIAN/FAMILY MEMBER)

Your signature(s) below indicates:

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your participation in this research study; and
- You will be given a signed copy of this form.

_____
Print Name(s) of Subject

_____ _____
Signature of Subject Date

SIGNATURE OF PARENT(S)/LEGAL GUARDIAN(S)
(*For all subjects under the age of 18*)

Your signature(s) below indicates:

- You have read this document and understand its meaning;
- You have had a chance to ask questions and have had these questions answered to your satisfaction;
- You agree to your child's participation in this research study; and
- You will be given a signed copy of this form.

_____ _____

Print Name(s) of Parent(s)/Legal Guardian(s)

_____ _____

Signature of Parent/Legal Guardian Date

_____ _____

Signature of Parent/Legal Guardian Date

SIGNATURE OF INDIVIDUAL OBTAINING CONSENT

I have explained the research to the subject and/or the subject's parent(s)/legal guardian(s) and have answered all of their questions. I believe that they understand all of the information described in this document and freely give consent/permission/assent to participate.

_____

Print Name of Individual Obtaining Consent

_____ _____

Signature of Individual Obtaining Consent Date

SIGNATURE OF WITNESS (if applicable)

Your signature below indicates:

- You were present for the entire consent conference.
- The information in the consent document and any other written information was accurately explained to the subject and/or the subject's parent(s)
- The subject and/or the subject's parent(s)/legal guardian(s) had an opportunity to ask questions and those questions were answered; and
- The subject and/or the subject's parent(s)/legal guardian(s) voluntarily signed the consent/permission/assent form in your presence.

_____

Print Name of Witness

_____ _____

Signature of Witness Date