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METABOLISM

ABSTRACT & COMMENTARY

From Childhood to Adolescence: Metabolic Disturbance Risk Factors

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SYNOPSIS: An innovative statistical model examining the development of metabolic disturbances in a large sample of youths finds that having media in a bedroom (associated with higher risk) and belonging to a sports club (associated with lower risk) are among the modifiable risk factors in this population.

SOURCE: Börnhorst C, Russo P, Veidebaum T, et al. The role of lifestyle and non-modifiable risk factors in the development of metabolic disturbances from childhood to adolescence. *Int J Obes (Lond)* 2020;44:2236-2245.

Metabolic syndrome (MetS), first described in adults in 2001 by the National Cholesterol Education Program, implies the presence of at least three of the following factors: central obesity, hyperglycemia, hypertriglyceridemia, low levels of high-density lipoprotein (HDL) and hypertension.[1] In recognition that MetS in adults may have roots developed in early life, medical research has turned to examining the early years of development to better understand this relationship.

However, with at least 40 different definitions of MetS in children, not only is there poor consensus on how to diagnose it, but also how to prevent or address MetS in this population.[2,3]

Citing the concern that MetS in children leads to a higher likelihood of MetS, type 2 diabetes mellitus (T2DM), and cardiovascular disease in later life, and noting studies that indicate that the risk is mitigated by remission of metabolic disturbances, Börnhorst et al set out to investigate risk factors for MetS in children during the transition to adolescence.[3] The group used data from a large multicenter population-based study spanning eight European countries: Identification and Prevention of Dietary- and Lifestyle-Induced Health Effects in

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Summary Points

- This study evaluated the effect of multiple modifiable and nonmodifiable risk factors and a measure of C-reactive protein (CRP) on the development of metabolic disturbance during puberty and beyond.
- Data from a large-scale European longitudinal study of 7,105 children (initially between ages 2 to 9 years) were examined three times over seven years.
- An innovative statistical technique (latent transitional analysis) estimated the probability of metabolic disturbance based on abdominal circumference, dyslipidemia, blood glucose, and hypertension in the study group.
- An increased risk for metabolic disturbance was associated with multiple factors, including having at least one type of media in the bedroom, entering puberty early, higher CRP, higher maternal body mass index, and familial hypertension, while a decreased risk was associated with membership in a sports club and having a higher "well-being" score.

Children and Infants (IDEFICS). This longitudinal study examined diet- and lifestyle-related conditions in children and families. IDEFICS began with children from ages 2 to 9 years in 2007 and includes periodic reassessment of parent and child interviews, physical exams, and blood draws.[4]

Börnhorst et al examined data from participants at three points over seven years — initially in 2007/2008, then again in 2009/2010, and finally in 2013/2014. Although more than 16,000 children participated in IDEFICS between 2007 and 2014, 7,105 members of this population, all of whom participated at each time point, were eligible for inclusion in this study. Metabolic outcomes included measurements of abdominal girth, diastolic and systolic blood pressure, lipid panel measurements, and blood glucose values.

Börnhorst et al identified multiple factors to measure, including C-reactive protein (CRP), an acute phase inflammatory protein, and modifiable and nonmodifiable items. Lifestyle or modifiable factors included a psychosocial wellbeing score, frequency of consumption of fresh fruits and vegetables, frequency of consumption of processed food, belonging to a sports club as a measure of physical activity, and having a media device in the bedroom as a measure of sedentary behavior. Nonmodifiable risk factors included educational level of parents, familial history of hypertension and T2DM, maternal body mass index (BMI), and age of puberty.

Latent transition analysis, an innovative statistical approach, enabled the team to generate an odds ratio (OR) and evaluate age-dependent associations between multiple risk factors and five metabolic health statuses:

- Metabolically healthy
- Abdominal obesity
- Dyslipidemia
- Hypertension
- A combination of more than one of the above

RESULTS

Notably, the percentage of children qualifying for inclusion in the "metabolically healthy" category was greater than 50% at all time points, while less than 7% of the children fell into either the dyslipidemia or hypertension category at any one point. In contrast, the prevalence of abdominal obesity rose from 15.2% at baseline to 17.5% at the end of the study, and the percentage of children in the combined metabolic disturbance group rose from 5.6% at baseline to 10.6% by the end of the study.

Of the modifiable and nonmodifiable risk factors examined, no significant association with any metabolic disturbance in the study population was found with breastfeeding, familial diabetes, fruit/vegetable consumption, or processed food consumption. Tables 1, 2, and 3 display the results for most of the other risk factors, controlled for multivariables. Note that age-related changes were found for two categories — entering puberty (age-related decrease in risk) and having

media in the bedroom leading to an age related increase in risk. (*See Tables 1 and 3 for details.*) The OR for selected risk factors, as well as the respective confidence intervals (CI), are displayed in each table.

■ COMMENTARY

This longitudinal, observational study shows a statistical association between nonmodifiable and modifiable risk factors and the development of metabolic disturbances in children over a seven-year period. Additionally, the authors noted an association between higher CRP levels and metabolic disturbances in this same population. The clinical relevance of this study hinges on understanding the connection between metabolic disturbance in children and teens, and the morbidity associated with MetS in adulthood. Not only have previous studies pointed out

Table 1. Nonmodifiable Risk Factors (Controlled for Multivariables)

	Abdominal Obesity	Dyslipidemia	Hypertension	Combined Metabolic Disturbance
Lower parental educational level	OR 1.14 (95% CI, 1-1.29)*	OR 1.01 (95% CI, 0.91-1.12)	OR 1.12 (95% CI, 0.99-1.26)	OR 1.25 (95% CI, 1.05-1.49)*
Lower age entering puberty	OR 2.43 (95% CI, 1.60-3.69)* (Decreasing by a factor of 0.25 yearly from ages 8 to 13 years)	OR 1.62 (95% CI, 1.09-2.42)* (Decreasing by a factor of 0.14 yearly from ages 8 to 13 years)	OR 1.05 (95% CI, 0.76-1.73)	OR 2.46 (95% CI, 1.53-3.96)* (Decreasing by a factor of 0.29 yearly from ages 8 to 13 years)
Higher maternal body mass index	OR 1.29 (95% CI, 1.25-1.34)*	OR 1.09 (95% CI, 1.07-1.11)*	OR 1.10 (95% CI, 1.07-1.12)*	OR 1.47 (95% CI, 1.39-1.55)*
Familial dyslipidemia	OR 0.96 (95% CI, 0.63-1.46)	OR 1.24 (95% CI, 1.01-1.52)*	OR 0.98 (95% CI, 0.77-1.26)	OR 1.08 (95% CI, 0.57-2.03)
Familial hypertension	OR 2.13 (95% CI, 1.45-3.12)*	OR 1.26 (95% CI, 1.05-1.52)*	OR 2.08 (95% CI, 1.67-2.60)*	OR 3.33 (95% CI, 1.87-5.91)*

OR: odds ratio; CI: confidence interval
*Statistically significant results

Table 2. C-Reactive Protein

	Abdominal Obesity	Dyslipidemia	Hypertension	Combined Metabolic Disturbance
One standard deviation increase	OR 1.40 (95% CI, 1.31-1.49)*	OR 1.16 (95% CI, 1.10-1.22)*	OR 1.18 (95% CI, 1.12-1.24)*	OR 1.59 (95% CI, 1.49-1.70)

OR: odds ratio; CI: confidence interval
*Statistically significant results

Table 3. Modifiable Risk Factors

	Abdominal Obesity	Dyslipidemia	Hypertension	Combined Metabolic Disturbance
Number of media (> 0) in the bedroom	OR 1.09 (95% CI, 1.00-1.19)	OR 0.98 (95% CI, 0.90-1.08)	OR 1.05 (95% CI, 0.96-1.16)	OR 1.30 (95% CI, 1.18-1.43)* (Increases by a factor of 0.18 per year from ages 8 to 30 years)
No membership in sports clubs	OR 1.08 (95% CI, 0.99-1.17)	OR 1.16 (95% CI, 1.07-1.26)*	OR 1.08 (95% CI, 0.99-1.18)	OR 1.30 (95% CI, 1.18-1.43)*
Well-being score	OR 0.90 (95% CI, 0.82-0.98)*	OR 1.01 (95% CI, 0.92-1.10)	OR 0.91 (95% CI, 0.92-1.00)	OR 0.91 (95% CI, 0.82-1.02)

OR: odds ratio; CI: confidence interval
*Statistically significant results

the likelihood of persistence of metabolic disturbances over time, but it also bears repeating that several studies have confirmed the mitigation of this risk with correction of the metabolic disturbance.[2,4] It follows that identifying and then addressing risk factors for metabolic disturbance at a young age can have profound health implications.

It is interesting to evaluate how best to address the nonmodifiable risk factors in a clinical setting. These include parental educational level, maternal BMI, family history of hypertension or hyperlipidemia, and entering puberty at a young age. Primary care physicians may want to keep in mind that children with such risk factors have a higher risk of developing metabolic disturbances over time. Other studies have consistently confirmed that adverse childhood experiences (ACE) convey ongoing health risks to affected individuals.[5] Educating parents and children (as age-appropriate) about these connections is a reasonable first step toward addressing the risk.

The modifiable risk factors identified in this study include having media in the bedroom (as a reflection of sedentary behavior), not belonging to a sports club (as a reflection of physical activity), and having a lower wellness index.

One clear clinical message is that the risk of metabolic disturbance is associated with having media (more than zero) in the bedroom — and that this risk increases with age. This study did not specify the type(s) of media involved and did not compare quantity of media in the bedroom to the risk of having media available out of the bedroom. Both of these are interesting areas for further exploration. However, it still is relevant for primary care physicians to address the findings from this study. According to a 2019 Common Sense Media survey, about one in five U.S. children have a cell phone by 8 years of age, and more than half have a cell phone by 11 years of age.[6] Additionally, the pandemic has ushered in an era of more online connectivity and rising screen time among youth.[7] The risk of metabolic disturbances is one of a number of risks associated with unsupervised media use among children and can be used as a concrete starting point for a broader discussion about removing media from the bedroom for wellness.

Likewise, encouraging physical activity (or a sports club equivalent) for children at all ages has benefits beyond those examined in this study.

The wellness score was based on a self-completed questionnaire regarding psychosocial stressors, such as stability within the home — a lower score in this area was associated with a higher risk of abdominal obesity. Incorporating community and regional resources (such as therapists, social workers, etc.) into the provider toolbox may support family efforts to develop a healthier and more desired lifestyle. Connection with such providers also may assist in addressing emotional disturbances stemming from ACEs and potentially build resilience.[5]

It is unclear if the association with higher CRP levels is a manifestation of metabolic disturbance or a contributor to etiology. Future studies in this area will be helpful in broadening our understanding of the role of CRP in metabolic disturbances.

The strength of Börnhorst et al's work lies in several key areas: the large number of participants and the longitudinal and detailed nature of the study, allowing comprehensive data collection from the participants starting at a young age. This may serve as a reminder of the importance of large-scale, long-term, multi-site studies (in this case spanning multiple countries) when attempting to understand factors involved in population health.

A relative weakness of the study is that the bulk of the lifestyle data was self-reported and that proxy measures were necessary to evaluate both sedentary behavior and physical activity. For example, it is unclear if not belonging to a sports club reflects lower socioeconomic status as well as lower levels of physical activity; if so, this could influence findings. Future studies may precisely measure extent and types of activity to further the understanding of the relationship between movement and metabolic disturbance.

However, the take-home message for clinicians from this study is clear. Although the development of metabolic disturbances in youth appears multifactorial, intervention on a lifestyle level has potential health benefits. Specifically, advising parents to limit media in children's bedrooms and encourage physical activity may have a significant effect in reducing metabolic disturbances in this age group. With studies suggestive of the likelihood of early metabolic patterns continuing into adulthood, these simple recommendations may help to potentiate lifelong metabolic health. ■

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ABSTRACT & COMMENTARY

Time-Restricted Eating, Weight Loss, and Metabolism

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SYNOPSIS: A randomized clinical trial comparing time-restricted eating with a 16-hour fasting interval to a structured three-meal-per-day control group resulted in equivalent weight loss in both groups and no reduction in metabolic markers in either group.

SOURCE: Lowe DA, Wu N, Rohdin-Bibby L, 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 Intern Med* 2020;180:1-9.

Obesity prevalence in U.S. adults is at an alarming age-adjusted 42.4%.[1] Given the fact that even modest weight loss appears to have a beneficial effect on insulin resistance and cardiovascular risk, identifying effective, simple, and acceptable ways for patients to achieve this goal is desirable. Intermittent fasting has been widely promoted in popular media as a means to lose excess body weight "without dieting." A specific type of intermittent fasting known as time-restricted eating (TRE) refers to eating within a specific time period and fasting outside this time period. Although TRE's benefits have been demonstrated in animal models, particularly obese mice, the literature regarding the benefits or effects on human populations is limited in quantity and quality.[2]

In this randomized controlled trial by Lowe et al, TRE was compared to consistent meal timing (CMT). Participants of the TRE group were asked to restrict eating for a 16-hour period and eat ad libitum during an eight-hour window (noon to 8 p.m.). The CMT group consumed three structured meals per day and was permitted to have snacks between meals. The TRE group was permitted only noncaloric drinks outside of the eating window. Neither of the groups were given a daily caloric restriction. The primary outcome assessed was weight loss for all participants. Secondary outcomes assessed for the in-person cohort included changes in weight, fat mass, lean mass, fasting insulin, fasting glucose, insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c) levels, lipids (triglycerides, total cholesterol, low-density lipoproteins [LDL], and high-density lipoproteins [HDL]), estimated energy intake, total energy expenditure, and resting energy expenditure from an in-person cohort. Participants were recruited from across the United States between August 2018 and June 2019, and data collection was completed October 2019. The total length of the study was 12 weeks.

Out of 1,975 potential candidates, 141 met inclusion criteria and were randomized to CMT or TRE intervention groups. Exclusion criteria were extensive and are listed in Table 1. Data were collected from 116 participants aged 18 to 64 years with a body mass index (BMI) range of 27 kg/m^2 to 43 kg/m^2. However, only 105 participants completed the study. Of the 11 participants who did not complete the study, eight were lost to follow-up and three discontinued the intervention. An in-person cohort of 50 participants who lived within a 60-mile radius of the University of California, San Francisco (UCSF) was randomized and enrolled for metabolic testing, with a total of 46 participants completing the four in-person visits. Data were collected via a mobile application (app) created for the study, and patients were given a Bluetooth scale that connected to the study app. Participants of the TRE group received daily reminders of their eating window through the app. All participants were instructed to use the scale daily in the morning prior to eating or drinking and prior to structured physical activity.

Looking at the weight change in the total cohort, there was a significant decrease in weight in the TRE group (P = 0.01) and a decrease in weight in the CMT group that was not statistically significant. Weight change between groups also was not statistically significant. Percentage decrease in weight from baseline was statistically significant in both the TRE group (-1.17%; 95% confidence interval [CI], -1.89% to -0.45%; P = 0.002) and the CMT group (-0.75; 95% CI, -1.47% to -0.04%;

Summary Points

- A time-restricted eating (TRE) group, which ate ad libitum from noon to 8 p.m. and fasted until noon the following day, was compared to a consistent meal timing control group, which ate three structured meals per day. The goal was to assess differences in weight changes and cardiometabolic markers.
- There was a significant decrease in weight in the TRE group ($P = 0.01$) and a decrease in weight in the CMT group that was not statistically significant.
- There was no significant difference in percentage weight loss between the experimental and control groups. Likewise, there was no significant decrease in metabolic markers in either group.
- There was a significant difference between the groups in appendicular lean mass loss in the TRE group.

P = -0.04), with no significant differences in results between these groups (-0.41%; 95% CI, -1.43% to 0.60%; P = 0.43). Tables 2 and 3 summarize additional results. In the in-person cohort, there were no statistically significant within-group or between-group differences in metabolic measurements (fasting glucose, fasting insulin, HOMA-IR, HbA1c, triglycerides, total cholesterol, LDL, or HDL levels). A significant decrease in appendicular lean mass was reported in the TRE group ($P < 0.001$) and between groups ($P = 0.009$), but not in the CMT group. There also was a significant decrease in appendicular lean mass index in the TRE group ($P < 0.001$) and between groups ($P = 0.005$), but not in the CMT group. Various other body composition measurements (fat mass, lean mass, waist and hip circumference, etc.) were assessed with no significant difference found between the groups. Finally, no adverse effects of either intervention were reported in this study.

Table 1. Exclusion Criteria

Criterion	Number of Participants Excluded
Older than age 64 years	5
Body mass index (BMI) less than 27	348
BMI greater than 43	72
Did not regularly consume breakfast	566
Unwilling or unable to skip breakfast	761
Current or past cancer diagnosis	21
Breastfeeding, pregnant, or planning pregnancy within six months	21
Current diagnosis of type 1 or type 2 diabetes mellitus	177
Taking glucose-lowering medication	133
Taking weight-loss medication	116
History of weight-loss surgery	66
Weight fluctuation > 15% in past five years	467
History of anorexia or bulimia	39
Frequent travel across time zones	99
Work unusual hours	182
Unable to fast for prolonged periods	168

■ COMMENTARY

Although the simplicity of TRE eating may make it easy to implement, the authors in this study showed that there was no statistically significant difference in weight changes or cardiometabolic markers for those who fast for an extended period during the day (TRE) compared to those eating three consistent meals per day (CMT group). The strengths of this study include its randomized control design, the recruitment of participants from across the United States, and inclusion of an in-person cohort to assess metabolic marker measurements. This study was conducted for a period of three months, and there was a large percentage of participants who were able to be analyzed at the end of the study period.

However, there are some limitations to this study. Although the primary objective of the study was to assess the effects of TRE on weight loss and various metabolic markers, only one eating/fasting regimen (eight hours/16 hours) was assessed. The reasoning offered by the authors for the chosen TRE interval was to mimic skipping breakfast for the participants, making it easier to adopt. Thus, results from this study may not be generalizable to all TRE regimens.

In a similar study by Chow et al, for example, TRE was compared to an ad libitum diet, and participants randomized to the TRE group were allowed to self-select an eight-hour eating window.[3] In this study, the earliest end of the eating period chosen was 5 p.m. Although this was a small study population of 20 participants and was unable to address the contribution of TRE timing to the weight loss and metabolic improvements observed in study participants, it is reasonable to question whether alternative eating windows might affect results. Comparison of TRE to a single CMT structure of three meals daily also is a limitation of this study. Considering additional CMT eating schedules, such as six smaller evenly distributed meals daily, would be a valuable enhancement.

Table 2. Total Cohort Weight Changes Between Groups

	Preintervention	Postintervention	Change (*P* value)
Mean weight in kg (95% confidence interval)			
Consistent meal timing group	99.2 (95.1 to 103.3)	98.5 (94.3 to 102.7)	-0.68 (-1.41 to 0.05) ($P = 0.07$)
Time-restricted eating group	99.2 (95.1 to 103.2)	98.2 (94.1 to 102.4)	-0.94 (-1.68 to -0.20) ($P = 0.01$)
Difference between groups	N/A	N/A	-0.26 (-1.30 to 0.78) ($P = 0.63$)

Table 3. In-Person Cohort Measurements

	Preintervention	Postintervention	Change (*P* value)
Mean weight in kg (95% confidence interval)			
Consistent meal timing group	93.0 (87.4 to 98.5)	92.4 (86.9 to 97.9)	-0.57 (-1.40 to 0.26) ($P = 0.18$)
Time-restricted eating group	92.6 (87.0 to 98.1)	90.9 (85.3 to 96.4)	-1.70 (-2.56 to -0.83) ($P < 0.001$)
Difference between groups	N/A	N/A	-1.13 (-2.33 to 0.07) ($P = 0.07$)
Appendicular lean mass in kg (95% confidence interval)			
Consistent meal timing group	25.8 (23.6 to 28.0)	25.6 (23.4 to 27.8)	-0.17 (-0.41 to 0.07) ($P = 0.16$)
Time-restricted eating group	26.1 (24.0 to 28.3)	25.5 (23.3 to 27.7)	-0.64 (-0.89 to -0.39) ($P < 0.001$)
Difference between groups	N/A	N/A	-0.47 (-0.82 to -0.12) ($P = 0.009$)
Appendicular lean mass index kg/m² (95% confidence interval)			
Consistent meal timing group	8.62 (8.10 to 9.14)	8.56 (8.04 to 9.08)	-0.058 (-0.136 to 0.02) ($P = 0.14$)
Time-restricted eating group	8.80 (8.28 to 9.32)	8.58 (8.06 to 9.10)	-0.22 (-0.301 to -0.139) ($P < 0.001$)
Difference between groups	N/A	N/A	-0.162 (-0.274 to -0.05) ($P = 0.005$)

Although sleep activity was recorded for participants in this study, the circadian system was not considered in the intervention design. In previous animal models, it has been hypothesized that the circadian system's role in regulating glucose, lipid, and energy metabolism throughout the day requires an appropriate alignment of feeding interval to result in improvement in these outcomes.[4-6]

Indeed, in prior TRE trials in humans, results do appear to depend on the timing of the chosen eating window.[6] Prior studies in humans show eating a larger breakfast and a smaller dinner improves glycemic control, weight loss, lipid levels, and reduces hunger.[4] In human studies, the association between BMI and the timing of food intake strengthens substantially when considering food intake in relation to the internal circadian time, best aligned with sleep/wake cycles as opposed to time of day.[6]

The in-person cohort was derived from a select population near the UCSF campus. This population most likely is exposed to similar environmental, social, and economic factors, which may contribute to dietary choices.[7] It is possible that, with a larger and more varied selection for the in-person cohort, results may have differed.

A significant decrease in appendicular lean mass and lean mass index was observed in the TRE group, an observation that adds to findings from the current literature that have resulted in recommendations for protein supplementation for individuals using TRE for weight management.[3]

Ultimately, additional high-quality studies in human subjects are required to determine if this method of eating, or any of its variations, can be safely advised to patients to help with weight loss, especially those with weight- and diet-related health risks. The true test of a successful weight loss diet is long-term weight loss maintenance, and most studies to date have been conducted over a short period of time, often less than six months.[2-6] Because of the limited effect on weight reduction over a short period of time, no effect on cardiometabolic markers, and potentially significant reduction in measures of lean body mass, intermittent fasting currently cannot be recommended to patients as an alternative to calorie reduction and regular exercise for weight control.

Longer-term studies of intermittent fasting regimens that account for circadian rhythms, employ food diaries to assess dietary quality, and track lean body mass changes are required to determine if sustained and meaningful weight loss or metabolic improvements can result from time-restricted eating. ■

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CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

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CME QUESTIONS

1. Based on a study that followed more than 7,000 children over seven years, which statement is true regarding children, adolescents, and metabolic disturbances?

a. In this double-blind, randomized controlled trial, the authors found that having media in the bedroom was associated with higher abdominal obesity and combined metabolic disturbance (with this association attenuating over time), and also that eating a diet high in processed foods was not associated with any clear metabolic disturbances.
b. In this long-term observational study, the authors found that having media in the bedroom was associated with combined metabolic disturbance (with risk increasing over time), and that not belonging to a sports club was associated with a similar risk (stable over time).*
c. In this double-blind, randomized controlled trial, the authors found that eating a diet with less red meat and more fruits and vegetables was associated with significantly less metabolic disturbances in all categories by age 13 years.
d. In this long-term observational study, the authors found that most children were metabolically healthy throughout the study, making it difficult to generalize results based on statistical inferences.

2. Time-restricted fasting is a type of intermittent fasting best defined as:

a. alternating periods of fasting and eating every 24-hour cycle.
b. consistent fasting and eating periods within a 24-hour cycle.*
c. consistent fasting and eating periods within a 48-hour cycle.
d. cessation of the eating period by a set evening time.

[IN FUTURE ISSUES]

Sedentary Behavior and Cancer Mortality

Dairy and Bone Loss

Exercise and Screen Time During COVID