TEMPORAL DIETARY AND PHYSICAL ACTIVITY PATTERNS ARE ASSOCIATED WITH OBESITY

by

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I would like to dedicate this project to my husband Raed for his support and encouragement and for always being a good listener. To my son Faris for helping me realize what's most important and for being such a wonderful boy. I want to thank my mom and dad who motivate me to strive for excellence. I will be forever grateful for each and every one of you.

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INTRODUCTION

Obesity is a major public health problem globally and in the United States (U.S.). Amongst adults in the U.S., prevalence estimates of obesity reached 42.4% in 2017-2018 [1]. Obesity is both a contributor and outcome of chronic disease development including type 2 diabetes and metabolic syndrome [2,3]. Underlying modifiable risk factors for these chronic conditions include lifestyle habits such as dietary intake and physical activity.

Much of nutrition research investigating the relationship of dietary intake to health outcomes has taken a reductionist approach with a focus on single nutrients and food groups; however, the complexity of the overall diet with all its constituents is being increasingly recognized. Dietary patterns examine the quantities, frequencies, and combinations of food and beverages consumed allowing a more comprehensive investigation of the diet-health relationship [4], yet, the concept and creation of patterns have not considered elements beyond nutrients and food, such as time of eating, which could be an important aspect of dietary patterns. Moreover, most physical activity research has focused on the effect of intensity or counts of activity on health [5–8], while studies investigating daily physical activity patterns have focused on distinct time periods i.e., type of day (weekday vs. weekend) or seasonality [9,10]. Nevertheless, connecting these patterns to health outcomes through the integration of time across an entire day has received little attention.

Studies that have incorporated time to the concept of dietary patterns focus on behaviors such as breakfast skipping and late meal consumption and show associations with health [11–14]. For instance, compared to early lunch eaters, late lunch eaters lost less weight and had reduced glucose tolerance [15,16]. In contrast, studies that have investigated timing of exercise focused on early vs. evening exercise [17–19]. For example, exercise performed in the morning vs. evening has been associated with a greater reduction in weight and odds of obesity [17,18]. Furthermore, several studies have investigated links between timing of exercise relative to a single meal or over a single day with health [20–24] and revealed a potential benefit to modulating time of these behaviors on postprandial metabolic response. Together, these studies establish the importance of timing of these behaviors in terms of links to health; however, studies are limited by a focus on single time spans or blocks of time in a day. Consideration of the patterns of dietary intake and activity throughout a day, or “temporal dietary and physical activity patterns”, are a novel concept

that may provide insight to the behavioral patterns related to health outcomes. Notably, one of the challenges in this work is utilizing methods that will characterize dietary and physical activity patterns as an exposure by integrating timing and other characteristics of these patterns in relation to health.

To our knowledge, there are no published reviews that have emphasized joint consideration of the time of eating and exercise, with a focus on the time of day of these events and association with health outcomes. Therefore, Chapter 1 focuses on summarizing current literature that has integrated both of these concepts by answering the question, how does the timing of exercise relative to eating throughout the day effect postprandial response in adults? Moreover, Chapters 2 and 3, include primary research in which a novel distance measure, based on dynamic time warping, is used to develop independent temporal dietary and physical activity patterns over a 24-hour period using data from the National Health and Nutrition Examination Survey and examine their association with short- and long-term health outcomes.

This thesis is divided into three chapters written in the form of research papers entitled:

1. Chapter 1: The Effect of Timing of Exercise and Eating on Postprandial Response in Adults: A Systematic Review.
2. Chapter 2: Temporal Dietary Patterns are Associated with Obesity.
3. Chapter 3: Temporal Physical Activity Patterns are Associated with Obesity.

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CHAPTER 1. THE EFFECT OF TIMING OF EXERCISE AND EATING ON POSPTRANDIAL RESPONSE IN ADULTS: A SYSTEMATIC REVIEW

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1.1 Abstract

Background: Type 2 diabetes is a major public health concern. Management of this condition has focused on behavior modification through diet and exercise interventions. A growing body of evidence has focused on temporality of dietary intake and exercise and potential effects on health. This review summarizes current literature that investigates the question "how does the timing of exercise relative to eating throughout the day effect postprandial response in adults?"

Methods: Databases PubMed, Scopus, Cochrane Library, CINAHL, and SPORTDiscus were searched between March–May 2019. Experimental studies conducted in healthy adults (≥ 18 y) and those with type 2 diabetes were included. Full texts were examined by at least two independent reviewers. Seventeen studies with a total of 332 participants met the inclusion criteria.

Results: The primary finding supports that exercise performed post-meal regardless of time of day had a beneficial impact on postprandial glycemia. There was insufficient evidence regarding

whether timing of exercise performed pre- vs. post-meal or vice versa in a day is related to improved postprandial glycemic response due to inherent differences between studies.

Conclusions: Future studies focusing on the investigation of timing and occurrence of meal intake and exercise throughout the day are needed to inform whether there is, and what is, an optimal time for these behaviors regarding long-term health outcomes.

1.2 Introduction

Type 2 diabetes (T2D) has increased globally and represents a major public health concern. An estimated 30.3 million people of all ages, 9.4% of the U.S. population, had diabetes in 2015 [1]. Underlying modifiable risk factors for T2D include behavioral and lifestyle habits such as dietary intake and physical activity patterns [2,3].

There is an abundance of research focused on the management of T2D, with most of the effort focusing on evaluating the effect of increased physical activity in combination with dietary interventions [2,4,5]. Specifically, increased exercise has been shown to aid in weight loss and maintenance [6], and improve insulin sensitivity [7] and glycemic control [8]; while a dietary pattern characterized by a high intake of fruits, vegetables, and whole grains and lower intake of processed products, meat, and sugar has been linked to a reduced risk of T2D [3].

A growing body of evidence has focused on temporality, or timing, and health behaviors to better understand whether or how time and behaviors like eating and exercising interact to influence health. For instance, the association between breakfast-skipping and eating later in the day, and adverse metabolic alterations [9,10] and increased risk of T2D, are prominent in this literature [11–14]. Fewer studies addressed timing of exercise with regard to weight and metabolic control, but preliminary data point to a possible association with health [15,16].

A considerable number of studies have examined the association between timing of exercise relative to a single meal or over a single day with health [17–21]. Joint consideration of the timing of these two behaviors is critical in the context of their potential synergistic relationship with long-term health. To our knowledge, there are no published reviews that focused on this investigation with emphasis on the time of day of these events. Therefore, the aim of this review is to summarize current literature that investigates the question; how does the timing of exercise relative to eating throughout the day effect postprandial response in adults?

1.3 Materials and Methods

1.3.1 Literature Search Strategy

A health sciences librarian (B.M.) performed literature searches during March 2019 through May 2019 in the following databases: MEDLINE (via PubMed), SPORTDiscus, Scopus, Cochrane Library Database of Systematic Reviews, and CINAHL. A final search was executed in November 2019 to capture new publications. Searches designed for each database included controlled vocabulary terms (Medical Subject Headings), when applicable, and keywords (see Table S1 in the Supplementary material). No filters were used during the search process. The literature was searched using combinations of terms including "meal timing" or "eating time" or "time of eating" or "eating patterns" or "eating behavior" or "ingestive behavior" or "exercise time" or "pre-prandial exercise" or "postprandial exercise", and "obesity" and "overweight" and "Type 2 diabetes" (Figures 1.1 and 1.2). PRISMA recommendations were followed and the study protocol was registered with Prospero (ID: CRD42019135459).

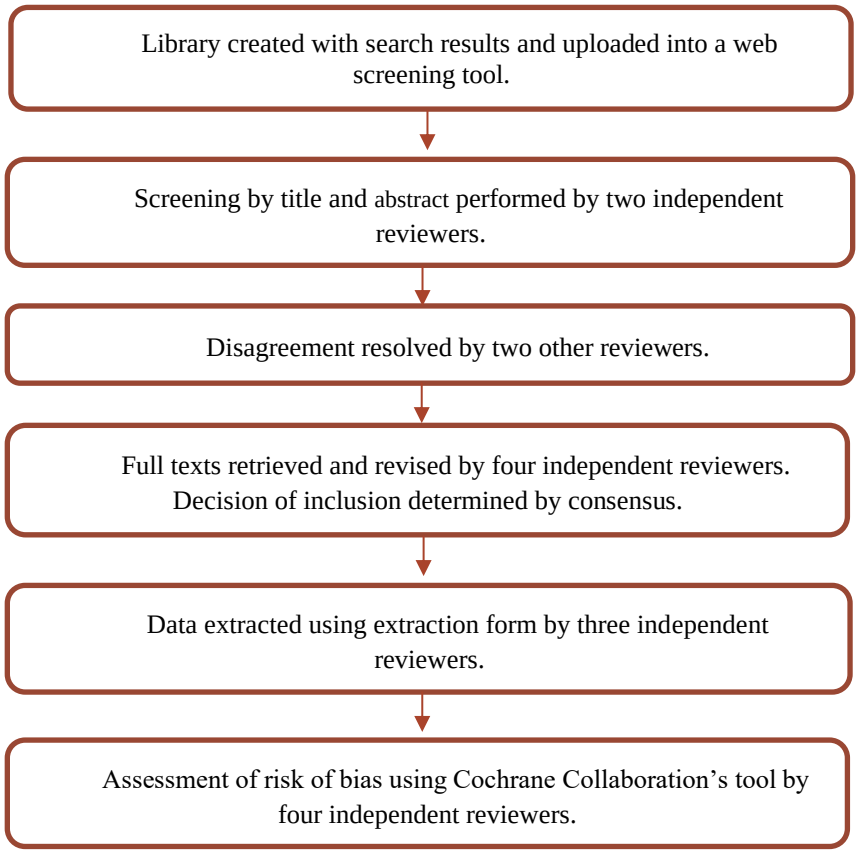

Figure 1.1. Flow chart representing the review process.

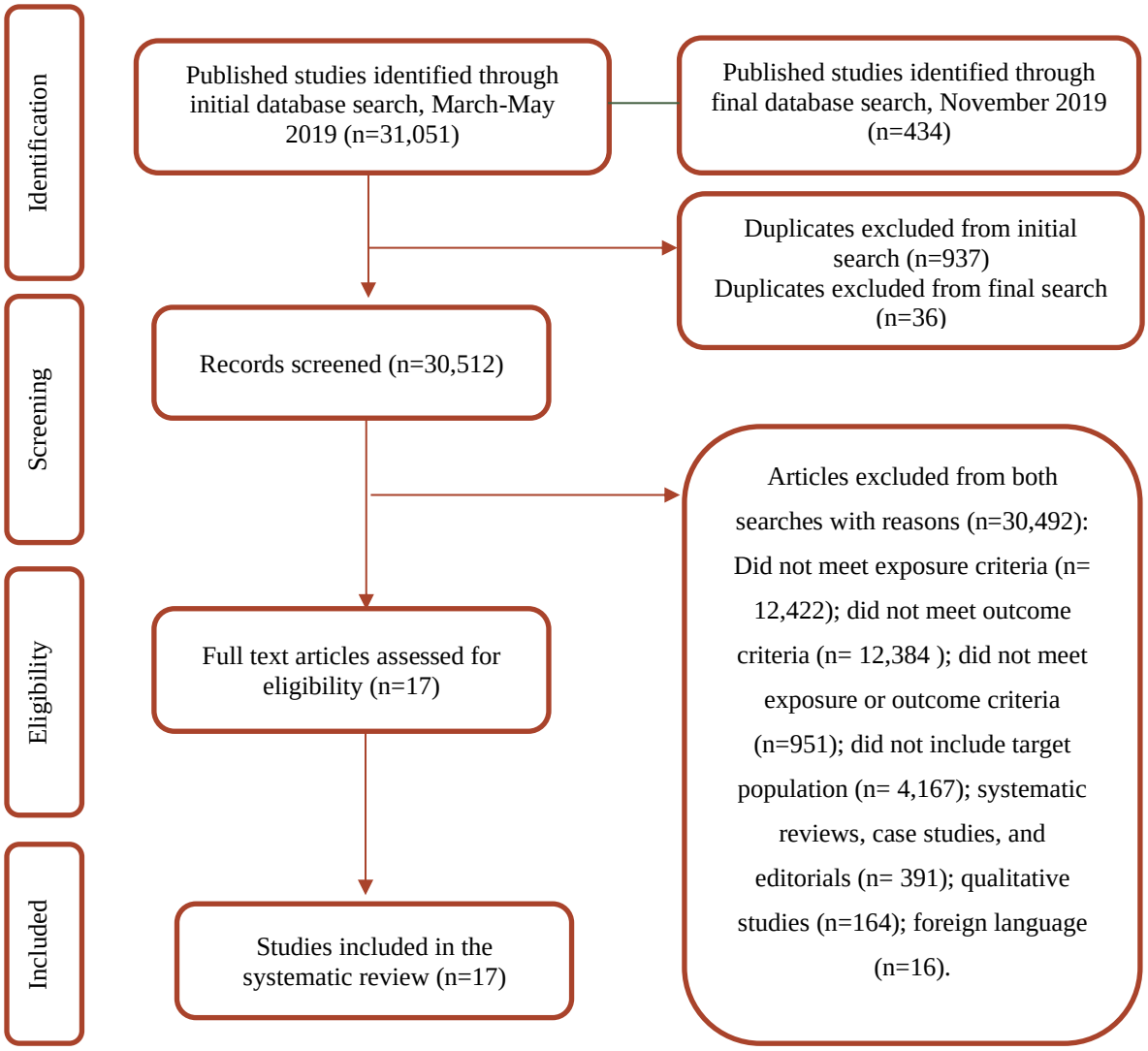

Figure 1.2. Flow chart representing selection of studies in the systematic review.

1.3.2 Types of Studies and Eligibility Criteria

Both experimental and observational studies were eligible for inclusion to be more inclusive of current evidence pertaining to the research question. Criteria specified healthy adults (≥ 18 years old) or individuals with overweight/obesity and/or T2D. Studies investigating the interaction of eating and exercising behaviors in the morning (i.e., exercise pre- or post-breakfast), evening (i.e., exercise pre- or post-dinner), or across an entire day (i.e., exercise pre- or-post several meals throughout the day) were eligible for inclusion. Studies involving children, women who were pregnant or lactating, or individuals with type 1 diabetes, gestational diabetes, or other chronic diseases were excluded from this review.

1.3.3 Study Selection

Two reviewers independently screened articles retrieved from the search strategy by title and abstract simultaneously (M.A., A.F.) to determine inclusion. Articles with disagreement were allocated to two additional independent reviewers (H.A.E.-M., E.A.R.). Full texts were obtained for articles meeting inclusion criteria and were reviewed by four independent reviewers. Final study selection was determined by consensus. This systematic review included experimental trials reporting comparisons of different exercise timing interventions relative to meal consumption (e.g., exercise performed pre- or post-meal), which reported on postprandial (PP) glycemia.

1.3.4 Data Collection and Extraction

For studies meeting the inclusion criteria, three reviewers (M.A., A.F., E.H.) independently extracted data using an established data extraction form. The following information was extracted from the included studies; (i) study characteristics: Citation, publication year, setting, and purpose/objectives; (ii) inclusion and exclusion criteria; (iii) study design; (iv) sample characteristics: Sample location, size, demographic information, health status, and baseline anthropometric and metabolic variables; (v) description of the intervention; (vi) key results pertaining to the outcomes of interest; (vii) conclusions reported by the authors; (viii) funding sources and conflict of interest statement.

1.3.5 Study Quality and Assessment of Risk of Bias in Included Studies

The validity of each study was independently assessed by two reviewers (M.A., A.F.) using the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials (RCTs) [22]. Reviewers were not blinded to study authors or journal. The process involved critical assessment of several domains including selection bias (random sequence allocation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases. Studies were further assessed by two additional reviewers (H.A.E.-M., E.A.R.), uncertainties were discussed, and consensus was reached in all cases.

1.3.6 Data Synthesis and Analysis

A narrative synthesis of the findings was conducted and structured around timing of exercise intervention relative to meal consumption throughout the day.

1.4 Results

1.4.1 Characteristics of Studies Included in the Review

Seventeen studies met the inclusion criteria for this systematic review (Table 1.1). These studies included adults with T2D [17,18,20,21,23–29], as well as healthy [30–33] individuals and those with overweight/obesity and no reported comorbidities [19,34]. In terms of the interventions, included studies examined the effect of exercise performed relative to a meal on PP metabolic response. Fifteen studies included moderate-intensity aerobic exercise, three examined high-intensity training [17,18,21], and only one consisted of resistance exercise [26]. Furthermore, ten studies investigated exercise relative to breakfast/morning meal [17,19–21,25,28,31–34], four included dinner/evening meal [23,26,27,29], and three examined exercise performed at several time points throughout the day [18,24,30]. In this review, the results were organized by time of day of performing exercise relative to meal consumption to maintain a focus on the timing and order of these activities.

Table 1.1. Summary of studies included in the systematic review.

Citation	Study Length	*n* (M: F)	Age (Years) Mean ± SD	Disease Condition	Intervention/ Comparison	Treatment Effects (↑, ↓, ↔)	Assessment Duration	Glycemic Response	
								PP Plasma Glucose	**Glucose AUC**
Exercise relative to breakfast/morning meal consumption									
Erickson et al. [20]	2 days	8 (5:3)	60 ± 10.7	Obesity/T2D	Control day (no exercise) vs. exercise post-breakfast	↓ glucose	2 h	Exercise post-breakfast: Significantly lower PG peak and decreasing glucose over time	Significant difference in average on 2 h iAUC
Huang et al. [17]	4 days	26 (12:14)	53.8 ± 8.6	OW/T2D	No exercise (control) vs. exercise post-breakfast (EX30) vs. exercise 60 min post-breakfast (EX60) vs. exercise 90 min post-breakfast (EX90)	↓ PPG	NA	Compared to control, declines in PG immediately post-exercise were larger in EX30, EX60, and EX90; capillary glucose decreased significantly after exercise in EX30, EX60, and EX90	Not reported
Nelson et al. [33]	2 days	7 (4:3)	33.3 ± 2	Healthy	Control (no exercise) vs. post-breakfast exercise	↓ glycemia	0, 30, 75, 95, 135, 180 min.	Post-breakfast exercise: Significant ↓ in glycemia	Not reported
Oberlin et al. [25]	4 days	9 (4:5)	60.1 ± 1	Obesity/T2D	Control (no exercise) vs. pre-breakfast exercise	↓ 24 h average blood glucose	24 h avg glucose, 4 h glucose AUC, 2 h PPG	Pre-breakfast exercise significantly lowered avg. PG concentration during first 24 h period compared to control (5.98 vs. 6.62 mmol/L)	Main effect of exercise to lower PPG-AUC across all 6 meals compared to control

Table 1.1 continued

Poirier et al. [28]	2 days	10 (10:0)	54 ± 5	Sedentary/T2D	Exercise pre-meal vs. post-breakfast exercise	↓ plasma glucose (post-meal exercise)	2 h	Mean decrease in PG concentration was 4.8 ± 1.9 mmol/L (60 ± 14% of baseline) vs. 1.0 ± 0.8 mmol/L (91 ± 6% of baseline) in post-meal vs. pre-meal exercise, respectively. Significantly lower PG level in post-meal vs. pre-meal condition (7.6 vs. 10.0 mmol/L)	Not reported
Terada et al. [21]	5 days	10 (8:2)	60 ± 6	Obesity/T2D	Control (no exercise) vs. pre-breakfast HIIE vs. post-breakfast HIIE vs. pre-breakfast MICE vs. post-breakfast MICE	↓ PPG	24 h mean interstitial glucose concentration, 1 h mean PPG	Compared to post-meal exercise, pre-meal condition significantly attenuated PP glycemic increments	Comparing all exercise conditions to control, pre-meal HIIE significantly lowered total post-meal iAUC
Farah et al. [19]	3 days	10 (10:0)	28.1 ± 10.7	OW	Control (no exercise) vs. pre-breakfast vs. post-breakfast exercise	↔ PPG	7 h PPG	No difference in glycemic response between conditions	Not reported
Lunde et al. [34]	3 days	11 (0:11)	44 ± NA	Obesity/diabetes prone	Control (no exercise) vs. post-breakfast 20 min. walk vs. post-breakfast 40 min walk	↓ PPG	2 h PPG	PPG and PG peak value significantly decreased with increasing duration of slow post-breakfast walking	2 h glucose iAUC decreased with increasing duration of slow post-meal walking

Table 1.1 continued

Høstmark et al. [32]	2 days	39 (0:39)	Trained young: 22.5 ± 0.5 Trained middle-age: 49.2 ± 1.3 Sedentary young: 24.1 ± 0.7 Sedentary middle-age: 59.2 ± 1.7	Sedentary and trained	Control vs. exercise post-breakfast	↓ peak glucose value ↓ blood glucose	NA	Exercise post-breakfast: Peak PG was lower than control	Not reported
Nygaard et al. [31]	3 days	13 (0:13)	Not listed	Healthy	Control (no exercise) vs. post-breakfast 15 min. walk vs. post-breakfast 40 min walk	↓ blood glucose	15, 22.5, 30, 37.5, 45, 55, 65, 75, 90, 105, 120 min	Compared to control, peak PG value was 0.8 mmol/L lower (significant) in post-breakfast 40 min walk condition	Significant main effect of walking time on 2 h iAUC; participants with the largest 2 h PG iAUC on the control day demonstrated the greatest reduction in PPG response when walking 40 min post-breakfast
Exercise relative to dinner/ evening meal consumption									
Colberg et al. [27]	3 days	12 (6:6)	61.47 ± 2.7	Obesity/T2D	Control day (no exercise) vs. exercise pre-dinner vs. exercise post-dinner	↓ plasma glucose	4 h	Exercise post-dinner: Significantly lower PG levels at the end of exercise compared to at the same time point when participants had exercised pre-dinner	Total glucose AUC over 4 h was not significantly different among trials

Table 1.1 continued

Heden et al. [26]	3 days	13 (5:8)	48.5 ± 11.9	Obesity/T2D	No resistance exercise (control) vs. pre-dinner resistance exercise vs. post-dinner resistance exercise	↓ glucose iAUC (exercise pre-meal)	NA	Not reported	Significant reduction in glucose iAUC by ~18% and 30% in pre- and post-dinner exercise, respectively
Li et al. [23]	2 days	29 (22:7)	51 ± 11.2	T2D	Control (no exercise) vs. post-dinner exercise	↓ PP hyperglycemia	2 h PPG	Post-dinner exercise vs. control: Significant lowering in 2 h PPG spike (1.9 ± 1.3 vs. 2.7 ± 1.4 mmol/L), 2 h PP peak glucose (9.3 ± 1.6 vs. 10.3 ± 2.3 mmol/L), and 2 h PP mean glucose levels (8.2 ± 1.3 vs. 8.9 ± 2.0 mmol/L)	Post-dinner exercise: Glucose tAUC 1 h after exercise was significantly lower than control (493.9 ± 84.0 vs. 559.3 ± 130.5 mmol/L × 60 min)
Rees et al. [29]	1 week	73 (33:40)	63.5 ± 9.1	Obesity/T2D	Control (no exercise) vs. pre-dinner walking	↓ blood glucose	24 h glucose, 2 h PPG	Exercise had no effect on PPG or 24 h glucose variability; significant reduction in PG concentration during walking in exercise condition vs. control (−1.56 mmol/L)	Not reported

Table 1.1 continued

Divided bouts vs. conventional continuous exercise performed pre- or post-meals consumed throughout the day									
Francois et al. [18]	3 days	9 (7:2)	48 ± 6	Obesity/insulin resistant T2D	Control (continuous exercise pre-dinner) vs. exercise snacking pre-mean meals (ES) vs. composite exercise snacking pre- main meals (CES)	↓ mean PPG (post- dinner and breakfast)	3 h PPG and mean PPG, 24 h glucose concentration	ES significantly attenuated mean 3 h PPG concentrations following breakfast (0.4 ± 1.0 mmol/L) and 24 h mean PG concentrations by 0.7± 0.6 mmol/L relative to baseline	Not reported
Manohar et al. [30]	3 days	12 (5:7)	37.7 ± 13.7	Healthy	Control (no exercise) vs. post-meal exercise	↓ PPG excursions	NA	Baseline CGM PG concentration lower with post-meal exercise vs. control (5.61 mmol/L vs. 5.58 mmol/L); peak CGM PG concentration lower with post-meal exercise vs. control (8.25 mmol/L and 11.99 mmol/L)	Post-meal exercise: iAUC was estimated to be significantly lower than control (4.5 mmol/L/270 min vs. 9.6 mmol/L/270 min), respectively
Reynolds et al. [24]	2 weeks	41 (26:15)	60 ± 9.9	Obesity/T2D	30 min walk at any time of day vs. 10 min walk post 3 main meals	↓ PPG	3 h	Significantly lower 3 h mean PG levels following evening meal with post-meal walking compared to conventional condition (−0.50 mmol/L)	Glucose iAUC was 12% lower in the post-meal compared to conventional condition

Abbreviations: M (male); F (female); Avg (average); PP (postprandial); PG (plasma glucose); PPG (postprandial glucose); AUC (area under the curve); tAUC (total AUC); iAUC (incremental AUC); HIIE (high intensity interval exercise); MICE (moderate intensity continuous exercise); OW (overweight); CGM (continuous glucose monitoring); ↑ (increase); ↓ (decrease); ↔ (no change).

1.4.2 Risk of Bias Assessment

Most of the assessed studies provided insufficient information regarding randomization procedures (Table 1.2), whereas a few were non-randomized trials [20,32,34]. All of the studies were considered to be at low risk of bias for selective reporting because studies pre-specified their primary and secondary outcomes of interest. All of the studies reported the number of participants who completed the study but did not provide the total number of participants who initially enrolled. Additionally, blinding of participants and personnel was not feasible due to the nature of the interventions, thus this domain was deemed to be of low risk of bias; however, blinding of outcomes assessment was determined as unclear due to insufficient information for all included studies except Reynolds et al. [24] which was considered low risk due to blinding of their statistician to primary analysis. Incomplete outcome data were judged to be of low risk of bias in 11 of the included studies; the rest of the studies [19,21,25–27,32] were considered unclear due to insufficient reporting of attrition.

Table 1.2. Risk of bias assessment of included studies.

Author [ref]	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding		Incomplete Outcome Data	Other Bias
				Participant /personnel	Outcomes assessment		
Colberg et al. [27]	U	L	L	L	U	U	L
Erickson et al. [20]	H	L	L	L	U	L	L
Farah et al. [19]	L	L	L	L	U	U	L
Francois et al. [18]	U	L	L	L	U	L	L
Heden et al. [26]	U	L	L	L	U	U	L
Høstmark et al. [32]	H	L	L	L	U	U	L
Huang et al. [17]	U	L	L	L	U	L	L
Li et al. [23]	U	L	L	L	U	L	L
Lunde et al. [34]	H	L	L	L	U	L	L
Manohar et al. [30]	U	L	L	L	U	L	M
Nelson et al. [33]	U	L	L	L	U	L	M
Nygaard et al. [31]	U	L	L	L	U	L	L
Oberlin et al. [25]	U	L	L	L	U	U	L
Poirier et al. [28]	U	L	L	L	U	L	L
Rees et al. [29]	L	L	L	L	U	L	L
Reynolds et al. [24]	L	L	L	L	L	L	L
Terada et al. [21]	L	L	L	L	U	U	L

Abbreviations: H (high risk of bias); M (moderate risk of bias); L (low risk of bias); U (unclear risk of bias).

1.4.3 Exercise Relative to Breakfast/Morning Meal Consumption

Studies that investigated the effect of time of exercise performance relative to a breakfast/morning meal on glycemic response were designed to examine PP glycemic response after acute intake of a standardized meal. These interventions included participants with T2D [17,20,21,25,28] and/or overweight/obese [19,34] as well as healthy individuals [31–33].

Studies in participants with T2D included an exercise intervention performed pre- [25] and post-meal [17,20], and pre- or post-breakfast [21,28]. Evidence regarding the glucose-lowering effect of exercise performed pre-meal was limited. Only one study by Oberlin et al. assessed the effect of pre-breakfast exercise on PP glycemic response to subsequent meals using continuous glucose monitors, for a two-day period under two conditions; no exercise (control), or 60 min of moderate-intensity exercise. The findings revealed that blood glucose concentration was significantly lower in the exercise condition compared to no exercise in the first 24 h period ($p < 0.038$). Additionally, compared to the control, exercise was associated with lower PP glucose area under the curve (AUC) across all meals on both days ($p = 0.015$). When comparing glycemic response to both conditions after each meal, lower PP glucose AUC was observed only after lunch (1:00 p.m.) on day 1 ($p = 0.04$) [25]. Thus, it remains unclear whether exercise performed pre-meal in the morning compared with no exercise is more advantageous for lowering PP glycemia in individuals with T2D.

Findings regarding the effect of morning post-meal exercise on glycemic response in participants with T2D were more consistent. Erickson et al. assessed whether post-meal exercise provided an additional glucose lowering effect, beyond medication alone, in patients using add-on hypoglycemic agents [20]. Participants were involved in two experimental conditions in a crossover design in which they were provided with a standardized meal and either exercised or remained sedentary afterward. Glucose peak (drug only: 13.8 ± 3.7 mmol/L, drug/exercise: 9.9 ± 2.7 mmol/L) and glucose AUC (drug only: 500 ± 136 mmol/L, drug/exercise: 357 ± 89 mmol/L) were significantly lower during the time of the exercise bout ($p = 0.02$ and $p = 0.03$, respectively); moreover, compared to the control, average 2 h incremental AUC (iAUC) during the breakfast PP period was significantly lower on the exercise day ($p = 0.047$). A finding that supported this evidence while evaluating the effect of varying duration of high intensity exercise revealed that exercise for 30 min post-meal significantly reduced blood glucose concentration to a greater extent compared to 60 and 90 min of post-meal exercise or no exercise [17]. Therefore, compared with

no exercise, post-meal exercise performed in the morning is more effective at attenuating PP glycemic response in participants with T2D.

Two studies investigated the effect of pre- and post-meal exercise performed in the morning on PP response among individuals with T2D and reported inconsistent findings [21,28]. Poirier et al. compared changes in blood glucose levels in response to 1 h of moderate-intensity exercise performed pre-breakfast or 2 h after consumption of a standardized breakfast meal [28]. Compared to baseline, blood glucose concentration was significantly lower in both conditions ($p = 0.003$ and $p < 0.001$, respectively); however, the reduction in the post-meal condition was sustained during the recovery period while it returned to pre-exercise levels in the pre-breakfast exercise condition. Conversely, Terada et al. compared pre- vs. post-breakfast walking (60-min of continuous moderate intensity exercise or intervals of 1 min high/3 min lower intensity) to a no exercise control condition [21]. Compared to post-meal exercise, pre-meal exercise was more effective at reducing PP glycemic increments ($p < 0.05$). Moreover, high-intensity interval exercise lowered mean nocturnal and fasting glucose to a larger extent compared to moderate-intensity continuous exercise (both $p < 0.05$). When comparing all exercise conditions to control, pre-meal high-intensity exercise performed in the morning lowered mean amplitude of glycemic excursion and total post-meal iAUC ($p < 0.05$). Hence, it is unknown whether morning pre- vs. post-meal exercise is more effective at lowering PP glycemia in participants with T2D.

Two studies conducted in individuals with obesity (diabetes prone) and those with overweight assessed glycemic response to moderate-intensity exercise performed post-breakfast [34] and pre- or post-breakfast [19], respectively. Lunde et al. showed that compared to a no exercise condition, post-meal walking attenuated the glycemic response to a carbohydrate-rich meal with improved outcomes with longer walking duration (40 min vs. 20 min). Contrary to these reports, Farah et al. assigned participants to three experimental conditions including no exercise (control) and exercise pre- or post-breakfast. There was no significant difference in glucose response over an 8.5 h observation period between conditions; however, compared to the control, both pre- and post-meal exercise lowered insulin response (by 19% and 24% in pre-meal and post-meal, respectively, both $p < 0.01$), while only pre-breakfast exercise was associated with lower PP triglyceride ($p = 0.025$). Among those with overweight and obesity, morning exercise was shown to be effective at improving PP metabolic response with no clear benefit based on timing of exercise relative to meal consumption.

Studies among healthy participants included an exercise intervention performed post-breakfast [31–33]. One intervention assessed the effect of post-breakfast walking on glycemic response (Three conditions: No exercise, 15 or 40 min walking) [31]. Findings revealed that post-meal exercise performed in the morning attenuated the glycemic response to a carbohydrate-rich meal and this effect was enhanced with prolonged walking duration. Similarly, another study revealed lower peak blood glucose value in the exercise condition compared to no exercise irrespective of age and training condition [32]. Nelson et al. further confirmed these findings in a randomized controlled trial that characterized the metabolic response to moderate-intensity exercise performed post-meal in healthy individuals [33]. Participants were provided with a standardized breakfast after which they either rested for 3 h or exercised for 45 min. Compared to no exercise, PP glycemic response was significantly lower in the exercise condition between 45–75 min ($p < 0.05$). Amongst healthy participants, compared with no exercise, post-meal exercise performed in the morning is more effective at attenuating PP glycemic response.

In summary, studies reporting the effect of exercise performed relative to a morning meal on glycemic response were mostly drawn from randomized crossover trials that either examined PP response to a breakfast/morning meal or monitored response to successive meals. Consistently, results showed that exercise performed in the morning post-meal had an advantageous effect on PP glycemia in participants with T2D, overweight/obese, and healthy subjects. However, results were limited in regards to the effect of pre-meal exercise performed in the morning on glycemia in participants with T2D. Additionally, three studies, conducted in individuals with T2D [21,28] and those who were overweight [19], directly assessed the effect of exercise performed pre- vs. post-breakfast on glycemia and resulted in inconclusive findings.

1.4.4 Exercise Relative to Dinner/Evening Meal Consumption

Evidence regarding the effect of exercise performed relative to a dinner/evening meal on glycemic response has resulted from randomized crossover trials in participants with T2D [23,26,27,29]. Li et al. evaluated the effect of post-dinner exercise on glycemic response using continuous glucose monitors [23]. Participants consumed a standardized diet and were randomized to two experimental conditions including a no exercise group (control) or a 20 min post-dinner exercise group. Significant declines in 2 h PP glucose spike ($p = 0.04$), peak glucose ($p = 0.02$), and mean glucose ($p = 0.04$) levels were reported under the exercise condition compared to the

control. Moreover, compared to the control, 12 h standard deviation of blood glucose and the coefficient of variation of glucose were both significantly lower in the exercise condition (both $p < 0.009$), while mean amplitude of glycemic excursion was not significantly different. Supporting this evidence, two other studies examined the effect of resistance [26] or aerobic [27] exercise performed pre- or post-dinner on cardiovascular disease risk factors [26] and glycemic control [27] with a similar methodological approach. Participants were randomized to three experimental conditions including no exercise (control), pre-, or post-dinner exercise and were provided with standardized meals on experimental days. Researchers reported similar findings of improved markers of cardiometabolic control (significant lower triglyceride and improved insulin clearance) [26] and lower blood glucose values [27] with both exercise types performed post-dinner. Interestingly, a study by Rees et al. investigating the effect of walking pre-dinner on 24 h glycemic outcomes revealed no difference in most of the examined glycemic variables including 24 h glucose, fasting glucose, PP glucose, and glucose variability in an exercise condition compared to the control condition [29]. In summary, evidence regarding the effect of exercise relative to consumption of a dinner/evening meal on glycemic response was drawn from studies conducted in participants with T2D. Findings revealed that exercise in the evening has an advantageous effect on PP glycemic response with a potential superior effect in post-dinner exercise compared to pre-dinner exercise.

1.4.5 Divided Exercise Bouts vs. Conventional Continuous Sessions Performed Pre- or Post-Meals Consumed Throughout the Day

Studies that investigated the effect of continuous vs. divided exercise bouts performed pre- or post-meal throughout the day on glycemic response were conducted in participants with T2D [18,24] and healthy individuals [30]. Reynolds et al. randomized participants to two experimental conditions, each lasting for 2 weeks, and included walking for 30 min at any time of day (conventional) or walking for 10 min post main meals [24]. PP glucose iAUC was 12% lower in the post-meal compared to conventional condition; additionally, 3 h mean blood glucose was significantly reduced after the evening meal in the post-meal vs. conventional condition ($p = 0.034$). Nevertheless, it is important to note a significant difference in overall physical activity (counts/minute) between the two exercise conditions ($p = 0.006$) explained by reduced sedentary time and increased walking duration in the post-meal condition. A study that supported this

evidence of reduced PP glucose concentration with brief bouts of exercise compared to a single bout also added that this effect persisted for the subsequent 24 h with pre-meal exercise [18]. Supporting these results in healthy participants, Manohar et al. quantified the effect of low-intensity exercise on glycemic variability in individuals consuming a standardized diet for three days at fixed times [30]. Participants walked for 5–6 h each day and were assessed using a physical activity monitor; in random order, one meal per day was followed by inactivity, and the other two meals were followed by walking. The PP glucose iAUC was significantly lower in meals followed by walking compared to meals followed with inactivity (p = 0.022). In summary, these studies showed that exercise has a beneficial effect on glycemic response in healthy participants and those with T2D. Furthermore, brief bouts of exercise pre- or post-meals performed throughout the day could be more beneficial compared to one continuous exercise bout in participants with T2D.

1.5 Discussion

This review sought to investigate current literature focused on the temporality of health behaviors to better understand whether, or how, time and activities of eating and exercising interact to influence health. Most research that integrated these concepts included randomized crossover trials conducted in participants with T2D. Studies mainly examined the effect of exercise performed relative to a morning or evening meal on PP glycemic response, given the importance of this component in T2D management [20]. Seventeen crossover studies with a total of 332 participants were included in this review. The primary findings were: (1) Exercise performed post-meal regardless of time of day had a beneficial impact on PP glycemia including lower plasma glucose concentration and glucose AUC; and, (2) there was insufficient evidence regarding whether the timing of exercise performed (e.g., pre- vs. post-meal) throughout the day is related to improved PP glycemic response.

Exercise performed in the morning post-meal in participants with T2D, healthy, and obese individuals was consistently linked to acute attenuation in PP glycemia compared to sedentary controls (2–3 h after ingestion of a meal) [17,20,31–34]. These findings align with observations by Haxhi et al. in individuals with T2D and healthy participants [35]. The blunting effect of PP exercise on peak blood glucose level has been well established [28,32,36]. These results may be explained by an elevation in endogenous insulin stimulated by food intake [27] as well as muscular contraction which co-act to enhance skeletal muscle glucose uptake independent of insulin [37].

Only three studies assessed the effect of exercise performed post-meal in the evening [23] or post several meals throughout the day [24,30] and reported an advantageous effect on glycemic response.

Fewer studies examined the association between pre-meal exercise performed in the morning [25] and the evening [29] and metabolic response in participants with T2D. One study was conducted in the morning and revealed a decrease in mean 24 h glucose concentration in exercise conditions compared to control, although, the improvement from exercise was observed in the second meal (~4.5 h post-exercise) but not in the first meal (~30 min post-exercise) [25]. Additionally, Rees et al. investigated the effect of walking pre-meal in the evening and reported no difference in most examined glycemic outcomes in the exercise condition compared to no exercise [29]. A possible explanation for this finding is related to the timing of exercise which was performed 3–5 h post-lunch and 20 min pre-dinner. The limited evidence from studies examining pre-meal exercise and glycemic response may be further elucidated by future randomized controlled trials focused on this examination.

Relating to this investigation, five studies compared the effect of pre- vs. post-meal exercise performed in the morning [19,21,28] or evening [26,27] on glycemic response. Studies that examined the effect of exercise performed pre- or post-meal in the morning resulted in inconclusive findings. One crossover trial including healthy participants [19] and another involving high-intensity interval training [21] reported a larger attenuation in PP glycemia with exercise performed pre- compared to post-breakfast. Conversely, a study including participants with T2D revealed significantly lower blood glucose levels when moderate-intensity exercise was completed 2 h post- rather than pre-breakfast [28]. The discrepancy in these findings could be related to differences in the type of exercise and health status of the study population (healthy vs. T2D). Moreover, studies differed in frequency and duration of blood sampling, specifically, post-exercise glucose concentration was measured at 30–60 min, 15 min, or continuous intervals (using continuous glucose monitor) up to 7, 1.5, or 24 h in [19,21,28], respectively. Differences also existed in timing of the exercise bout relative to meal consumption; exercise was performed in the fasted state and at 30, 60, or 120 min post-meal in the morning in [19,21,28], respectively. On the other hand, two crossover trials examined the effect of exercise performed in the evening pre- or post-meal in participants with T2D and resulted in more consistent findings. Colberg et al. reported lower blood glucose levels with the completion of 20 min of walking, starting 15–20 min post-

dinner, compared to pre-dinner or no walking [27]. Contrastingly, both pre- and post-dinner resistance exercise similarly improved blood glucose AUC subsequent to dinner irrespective of timing in Heden et al.; however, lower PP triglyceride was reported with post-dinner exercise suggesting a potential superior benefit on metabolic response [26]. The inherent differences in study design including time of day of exercise and eating (morning vs. evening), type of exercise (aerobic vs. resistance), and intensity and modality (moderate continuous vs. high intensity interval training) preclude conclusions regarding optimal exercise–meal timing throughout the day for management of glycemic response. In addition, the above findings resulted from short-term studies that typically included 10–13 participants observed in a controlled setting with standardized meals provided; therefore, further longer-term studies preferably simulating "real life" settings are needed to demonstrate whether modulating time of exercise relative to meals translates into an overall improvement in glycemic control.

Of note, there was insufficient evidence in the reviewed studies regarding whether and how the time of day of eating and exercising interact to impact health outcomes. Only three studies investigated the effect of exercise performed pre- or post- several meals consumed during the day on PP response [18,24,30]; however, their main goal was to examine whether continuous vs. divided bouts of exercise could differentially effect PP glycemia. Additionally, although current findings indicate that post-meal exercise regardless of time of day has an advantageous impact on PP response, available evidence is limited by a focus on blocks of time during the day, specifically the morning period. Future studies that emphasize time of day of these behaviors, i.e., including both exercise and eating conditions in the morning and evening or across an entire day, are warranted to inform whether time of day of these behaviors is indeed related to clinically meaningful effects on health.

Most of the studies included in this review involved mild- or moderate-intensity exercise and showed an advantageous effect on PP glycemic response. Moderate-intensity exercise is the most commonly recommended strategy for individuals with impaired glucose tolerance or T2D [38]. Self-paced exercise for 20 min in the evening resulted in lower plasma glucose levels compared to a no exercise condition in one study [27]. However, high-intensity interval training has gained recent attention as a time-efficient strategy for metabolic disease management [17,39]. Compared to no exercise, a single bout of high-intensity interval training performed in the morning was associated with reduced same-day PP glucose AUC [21]. Additionally, performing brief bouts of

exercise (six 1 min uphill walking intervals at 90% HRmax) before main meals throughout the day was more effective at reducing PP hyperglycemia when compared with a single bout of pre-dinner moderate-intensity walking (30 min, ~60% HRmax) [18]. Limited evidence exists examining the effect of high-intensity interval training on PP glycemic response; thus, this training modality is under-represented in this review; nevertheless, available findings suggest that engaging in any physical activity mode and intensity throughout the day lowers PP glycemic response in individuals with T2D.

One major strength of this review included the selection of recently published studies investigating the interaction between eating and exercising behaviors while emphasizing the sequence of these behaviors throughout the day and their potential effect on health. Additionally, most of the studies included both male and female participants with approximately 50% of the study sample being female. However, collectively, the studies were not representative of a certain population nor group, which limits generalizability. Major limitations pertain to the crossover nature of the interventions, with lack of a control group in a few studies [18,24,28]. Moreover, three of the included trials were non-randomized [20,32,34] and most others were unclear in terms of their randomization procedures. Additionally, included studies varied with regards to time of day of eating and exercise, duration of assessment, type of exercise, and timing between exercise and meals, and were short-term in nature; nonetheless, findings were similar in showing an advantageous effect of post-meal exercise in lowering PP hyperglycemia regardless of time of day and pointing to a potential benefit of modulating exercise timing relative to meal consumption for optimizing metabolic control. Of note, most of the included studies examined the effect of exercise performed relative to a morning meal on health status indicators, while there was inadequate evidence emphasizing the time of day of both eating and exercising, and their potential associations with health. Considering that the distribution of eating and exercising throughout the day has a repetitious pattern, timing of these activities, in isolation and relative to each other, throughout the day could have an important link to health. Future studies focusing on the investigation of timing and occurrence of these behaviors across an entire day are needed to inform whether the development of time-specific recommendations is relevant to improved long-term health outcomes including T2D.

1.6 Conclusions

In conclusion, the findings of this systematic review show a beneficial effect of post-meal exercise on improved PP glycemic response regardless of time of day in healthy individuals and participants with overweight/obesity and/or T2D. However, findings were less clear regarding optimal exercise–meal timing for enhanced glycemic response due to inherent differences between studies. Moreover, studies pertaining to this investigation have mostly resulted from randomized crossover trials with the provision of standardized meals; thus, more studies simulating "real life" settings are needed to elucidate how timing of eating and exercising throughout the day interact to influence long-term health outcomes.

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CHAPTER 2. TEMPORAL DIETARY PATTERNS ARE ASSOCIATED WITH OBESITY

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2.1 Abstract

Background: The integration of time with dietary patterns throughout a day, or temporal dietary patterns, have been linked with dietary quality but relationship to health outcomes are unknown.

Objective: Determine the association between temporal dietary patterns and health status indicators and disease outcomes.

Methods: The first-day 24-hour dietary recall from 1,627 non-pregnant U.S. adult participants 20-65 years of the National Health and Nutrition Examination Survey 2003-2006 was used to determine timing and amount of energy intake and sequence of eating occasions. Modified dynamic time warping and kernel k-means algorithm clustered participants into four groups representing distinct temporal dietary patterns. Multivariate regression models determined associations between temporal dietary patterns and health outcomes, controlling for potential confounders, and adjusting for multiple comparisons and the complex survey design ($p<0.05/6$).

Results: A cluster representing a temporal dietary pattern with evenly spaced, energy-balanced eating occasions from 6:00 a.m. to 11:00 p.m. with peaks reaching 1,200 kcal at 6:00 a.m. to 10:00 a.m., 12:00 p.m. to 3:00 p.m., and 6:00 p.m. to10:00 p.m., had statistically significant and clinically

meaningful lower body mass index (p<0.0001), waist circumference (p<0.0001) and 75% lower odds of obesity compared to three other clusters representing patterns with higher peaks of energy: 1,000-2,400 kcal between 3:00 p.m. to 6:00 p.m. (OR: 5.3; 95% CI: 2.8, 10.1), 800-1,600 kcal between 11:00 a.m. to 3:00 p.m. (OR: 4.4; 95% CI: 2.5, 7.9), and 2400 kcal between 6:00 p.m. to 11:00 p.m. (OR: 6.7; 95% CI: 3.9, 11.6).

Conclusions: Individuals with a temporal dietary pattern characterized by evenly spaced, energy-balanced eating occasions had lower body mass index, waist circumference, and odds of obesity compared to the other three patterns with much higher energy intake peaks at different times throughout the day, providing evidence that incorporating time with other aspects of a dietary pattern may be important to health outcomes.

Keywords: temporal, timing, dietary, patterns, body mass index, waist circumference, obesity.

2.2 Introduction

Obesity has increased globally and represents a major public health concern. The prevalence of obesity among U.S. adults was 42.4% in 2017-2018 [1]. Obesity is both an outcome and a contributor to chronic disease development including type 2 diabetes and the metabolic syndrome [2,3]. Behavioral and lifestyle habits like dietary intake are underlying modifiable risk factors for obesity and chronic disease [4,5]. Traditional investigation of the diet-health relationship has focused on singular behaviors (e.g., breakfast skipping) or aspects of dietary intake (e.g., individual nutrients) in relationship to health outcomes; however, numerous aspects of behavior and dietary components could interact to influence health [4]. Dietary patterns refer to a way of conceptualizing several dietary exposures including the quantities, proportions, frequencies, and combinations of different foods and beverages in diets, as a multi-faceted construct [4,6]. This multidimensional approach allows for a more inclusive examination of the diet-health relationship that might reveal stronger associations between indicators of health and the role of diet compared with single nutrients or food group approaches [6,7].

Temporality, or timing, of eating and the influence on health is a recent area of interest [8–12]. Most of the accumulated evidence has evaluated timing of dietary intake in a classification-based way, for example, characterizing participants as early energy consumers or later energy

consumers based on the timing of the majority of their energy intake throughout the day followed by regression to determine links with health outcomes [13–16]. Similar classification-based designation of breakfast skippers compared with those who eat breakfast suggests that breakfast skipping is associated with higher body mass index (BMI) and impaired glucose metabolism manifesting as higher fasting plasma glucose and hemoglobin A1c levels in adults [17,18]. Moreover, studies that examined the association of late-night eating with health reported a higher risk of obesity, metabolic syndrome, and inflammation in late-night eaters compared to early eaters [13,19–21]. Collectively, these studies demonstrate that time of eating could be associated with health. However, the studies are limited by the focus on eating occasions at a single timespan or part of the day with disregard to eating occasions at other times of the day. Yet, the amount of energy or nutrient consumed at a certain time may affect the amount consumed at following eating occasions or be related to total energy intake throughout the day [23]. Thus, understanding whether and how patterns of intake over a 24-hour day, including the timing, amount of energy, and sequence of eating occasions, are linked with health outcomes will advance knowledge of the importance of these multiple factors to health. Insight into whether and to what extent the integration of time, amount, and sequence of eating determines health outcomes may also advance opportunities for early detection of behavioral patterns that predispose to obesity and chronic disease.

Data-driven methods including cluster and factor analyses and investigator-driven methods including index-based analysis [25,26] have previously been used to determine dietary patterns and association with health outcomes; time was uniquely integrated with dietary patterns in Eicher-Miller et al. [22]. Temporal dietary patterns (TDPs) were created by integrating the time, amount of energy, and sequence of eating occasions through a 24-hour day using a novel distance measure based on dynamic time warping technique combined with cluster analysis and was determined to be associated with dietary quality among U.S. adults 20-65 years [22]. Considering the elevated disease risk associated with poor dietary quality, these findings support hypotheses that TDPs may also be linked with health outcomes; yet, this relationship has not been examined. Thus, the aim of this study was to investigate whether TDPs, determined using dynamic time warping and kernel k-means clustering approach, are associated with selected health status indicators and disease outcomes in adult men and women in the U.S. The hypothesis builds on evidence by Eicher-Miller et al. [22] showing that a TDP characterized by moderate and proportionally equivalent energy

consumed during evenly spaced eating occasions was associated with improved dietary quality; therefore the hypothesis of this study is that this same TDP would emerge and associate with improved health status indicators and lower risk of chronic disease compared to other TDP not exhibiting these characteristics.

2.3 Methods

2.3.1 Participants and Data Collection

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey of the noninstitutionalized, civilian, U.S. population that uses a complex, stratified, multistage probability cluster sampling method [27]. The National Center for Health Statistics (NCHS), a program of the U.S. Centers for Disease Control and Prevention, administers NHANES. The NCHS Research Ethics Review Board approval and documented consent is obtained from all participants [28]. NHANES survey protocol includes an in-person household interview followed by a health examination in a mobile examination center. During the in-person household interview, sociodemographic data including age, sex, race/ ethnicity, and income to poverty ratio (PIR) were collected using an in-depth questionnaire [27]. The health examination included the collection of a 24-hour dietary recall, anthropometric measurements, and laboratory tests.

2.3.2 Analytic sample

Four years of NHANES data 2003-2006 were combined for this analysis. The analytic sample included non-pregnant U.S. adults aged 20-65 years with reliable 24-hour recall dietary data, and complete anthropometric and health status indicator data (n=1,627). Pregnant women, children, adolescents, and adults older than retirement age were excluded because their daily patterns may include variations characteristic to the life stages they represent.

2.3.3 Anthropometric Assessment and Laboratory Tests

Selected health status indicators were chosen for their previous links with dietary components [29–33]. Weight was assessed using a digital scale and was measured to the nearest 0.1 kilogram [34]. Height and WC were measured with a stadiometer and tape measure,

respectively to the nearest 0.1 centimeter [34]. BMI was calculated as weight in kilograms divided by height in meters squared [35]. Results were based on a single body measurement at examination.

A phlebotomist obtained blood samples from participants according to a standardized protocol [36,37]. Fasting plasma glucose and triglycerides were assessed after participants fasted at least 8 hours and not more than 24 hours. Fasting plasma glucose was measured using a hexokinase method with a Roche/Hitachi 911 (cycle 03-04) or a Roche Cobas Mira (cycle 2005-2006) [38,39]. Triglycerides were measured enzymatically [40,41]. Hemoglobin A1c, total cholesterol, and HDL-C were based on samples taken regardless of fasting state. Hemoglobin A1c was measured with high performance liquid chromatography using Primus CLC 330 and Primus CLC 385 (Primus Corporation, Kansas City, MO) in the 2003-2004 cycle and using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA) in the 2005-2006 cycle [42,43]. Total cholesterol was measured enzymatically. An instrument change occurred in NHANES 2005-2006 for total cholesterol, but the method and laboratory location were the same as in the 2003-2004 survey [44,45]. HDL-C was analyzed using a direct immunoassay method from 2003-2006 [45,46]. There was a change in equipment to measure HDL-C from 2005-2006, however the laboratory method and location were the same as in 2003-2004 [45,46]. Blood pressure was measured using a mercury sphygmomanometer, with systolic and diastolic blood pressures determined based on up to 4 measures [47]; if more than 1 measurement was obtained, the first was not considered, and the remaining measurements were averaged; otherwise, the first measurement was used.

2.3.4 Dietary Data Assessment

The first reliable 24-hour dietary recall collected using the U.S. Department of Agriculture (USDA) Automated Multiple-Pass Method [48] was used to determine energy intake, time of intake, and sequence of eating occasions throughout a day [49]. A reliable dietary recall indicates that a participant has a food record that specifies each individual food consumed, the quantity in grams and nutrient amounts per food component. The USDA Food and Nutrient Database for Dietary Studies (FNDDS) for 2003-2004 data (USDA FNDDS, version 2.0, Beltsville, MD) and 2005-2006 data (USDA FNDDS, version 3.0, Beltsville, MD) were used to convert reported dietary intake information into gram amounts and to determine their energy values.

2.3.5 Assessment of Energy Misreporting

Energy misreporting was examined as research shows that misreporting could bias the relationship between TDPs and adiposity [13,50]. Energy misreporting was assessed as the ratio of reported total energy intake to estimated energy requirement (EER) [51]. EER was calculated using the Dietary Reference Intake equations for adults based on sex, weight, height, and physical activity level [52]. Using accelerometry data from one valid weekday revealed that participants in this sample spent most of their time (minutes/day) in sedentary behavior. Calculation of physical activity level was attempted using methods by Gerrior et al. [53], however, the method resulted in very high estimates of activity levels and thus tended to overestimate energy expenditure. Therefore, a low active physical activity level (≥1.4 to<1.6) was used which conforms with national objectively measured physical activity data showing that most adults spend their time in sedentary behavior or light activity [54,55].

2.3.6 Temporal Dietary Patterns

A detailed description of the methodology used to determine the temporal dietary patterns has been previously described [56], with one minor change in this study in which patterns were developed based on absolute energy intake rather than fractional energy intake data computed over a 24-hour period. Briefly, one 24-hour dietary recall was used to develop time series of length 24, with each entry representing absolute amount of energy during an hourly time interval. The absolute energy and hourly time stamps of non-zero intake occasions were extracted from the time series to form the compact representation as defined in [56,57]. Based on our previous work to pattern dietary intake, several distance measures were investigated including the constrained DTW with Sakoe-Chiba band (CDTW) and the modified DTW (MDTW) [58]. Both CDTW and MDTW belong to the elastic distance family and find the optimal matching path among intake occasions in two time series [58]. The matching is "optimal" in the sense that the summed difference between matched intake occasion is minimized. The Sakoe-Chiba band in CDTW and the weight parameter β in MDTW are controlling parameters to avoid pathological matchings (e.g. matching intake activities in the morning to intake activities in the evening). While the Sakoe-Chiba band rigorously limits the maximum time difference between matched intake occasions, the weight parameter β controls the matching through a time difference penalty term: larger β indicates more

penalty on matching intake occasions that are different in time. Bands ranging between 60-720 minutes (60-minute increments) and β ranging from 0-10 (2 increments) were explored in this paper, and parameter values outside of these ranges were omitted as they did not bring significant changes in the clustering results. Further, the distance measures were coupled with kernel k-means algorithm [59] to partition the time series into several clusters such that intake occasions are more similar within the same cluster and more dissimilar among different clusters. Cluster number k=4 was selected to divide the population into clusters representing similar TDPs to maintain consistency with previous development of temporal patterning [22,56,58]. MDTW β=10 was selected out of each distance measure pairing of CDTW bandwidth=420 and MDTW β=10 with k-means clustering, based on inferential analyses with health outcomes prioritized as: 1) most significant differences between the six pairwise comparisons among all health outcomes, 2) highest model R_2 values, and 3) largest difference between highest and lowest mean of health status indicators.

2.3.7 Statistical Analysis

The Rao Scott F adjusted chi-square statistic determined significant differences among clusters by selected characteristics: survey year (2003-2004 and 2005-2006), sex (male or female), race/ethnicity (Mexican American and other Hispanic, Non-Hispanic white, Non-Hispanic black, and other-race including multi-race), age groups (20-34, 35-49, and 50-65 years), poverty-income ratio (PIR), and BMI classified as underweight (<18.5 kg/m_2), normal weight (18.5-24.9 kg/m_2), overweight (25.0-29.9 kg/m_2), and obese (>30.0 kg/m_2) [35]. PIR, calculated as reported household income divided by the federal poverty guideline for household income, was divided into six categories: 0-0.99, 1-1.99, 2-2.99, 3-3.99, 4-4.99, and 5 or more. Ratios below 1 indicate a PIR below the officially defined poverty threshold [60].

Disease categories included obesity, diabetes, and metabolic syndrome. Diabetes definition was based on elevated fasting plasma glucose (≥126 mg/dL), hemoglobin A1c (≥6.5%), or self-report of: "yes" in response to the question "have you ever been told by a doctor you have diabetes?", or to the use of glucose-lowering medications [61]. The National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome was applied to classify this condition based on the presence of three or more of the following risk factors: 1) WC (>102 cm for men, >88 cm for women); 2) triglycerides (>150 mg/dl) or taking antihyperlipidemic

medications; 3) HDL-C (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (>130/>85 mmHg) or taking antihypertensive medications; and 5) impaired fasting glucose (>110 mg/dl) or taking glucose-lowering medications [62].

Analysis of variance determined differences in mean health status indicators by TDPs. Multivariate models determined associations between four TDPs and health outcomes accounting for potential confounders including survey year, sex, race/ethnicity, age group, BMI, PIR, and energy misreporting (EI: EER). The EI:EER ratio was used as a continuous covariate in the analyses based on methods by Murakami and Livingstone, as this technique has been shown to result in similar findings when compared to excluding implausible reporters while avoiding selection bias [51,63]. Appropriate survey weights were constructed for the 2003-2006 survey years as directed by the NCHS [64]. Sampling weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006. Adjustment for the complex survey design including clustering and stratification was completed following NCHS guidelines [65]. Comparisons between groups were considered statistically significant when $p<0.05/6$ (Tukey-Kramer type adjustment for multiple comparisons). Analyses were completed using SAS Survey procedures and inferential analysis version 9.4.

2.3.8 Visualization

The visualization illustrates the distribution of non-zero energy intake occasions in each cluster using heat maps (Figure 2.1). Each eating occasion in the heat map is marked by its time stamp (x-axis) and absolute amount of energy intake (y-axis). Time axis ranged from 0=12:00 a.m. to 24=12:00 a.m. the next day with absolute energy intake (y-axis) ranging from 0 kcal to 4,000 kcal at a particular time. The proportion of individuals reporting intake occasions (certain absolute energy intake and time stamp) is indicated through shading and ranged from 0=0% to 0.15=15% of each cluster. Darker shading signifies that a greater proportion of that particular cluster reported that specific energy intake at that specific time. Figure 2.1 exhibits four distinct TDPs of energy intake. Figure 2.2 adds color to differentiate the 4 clusters.

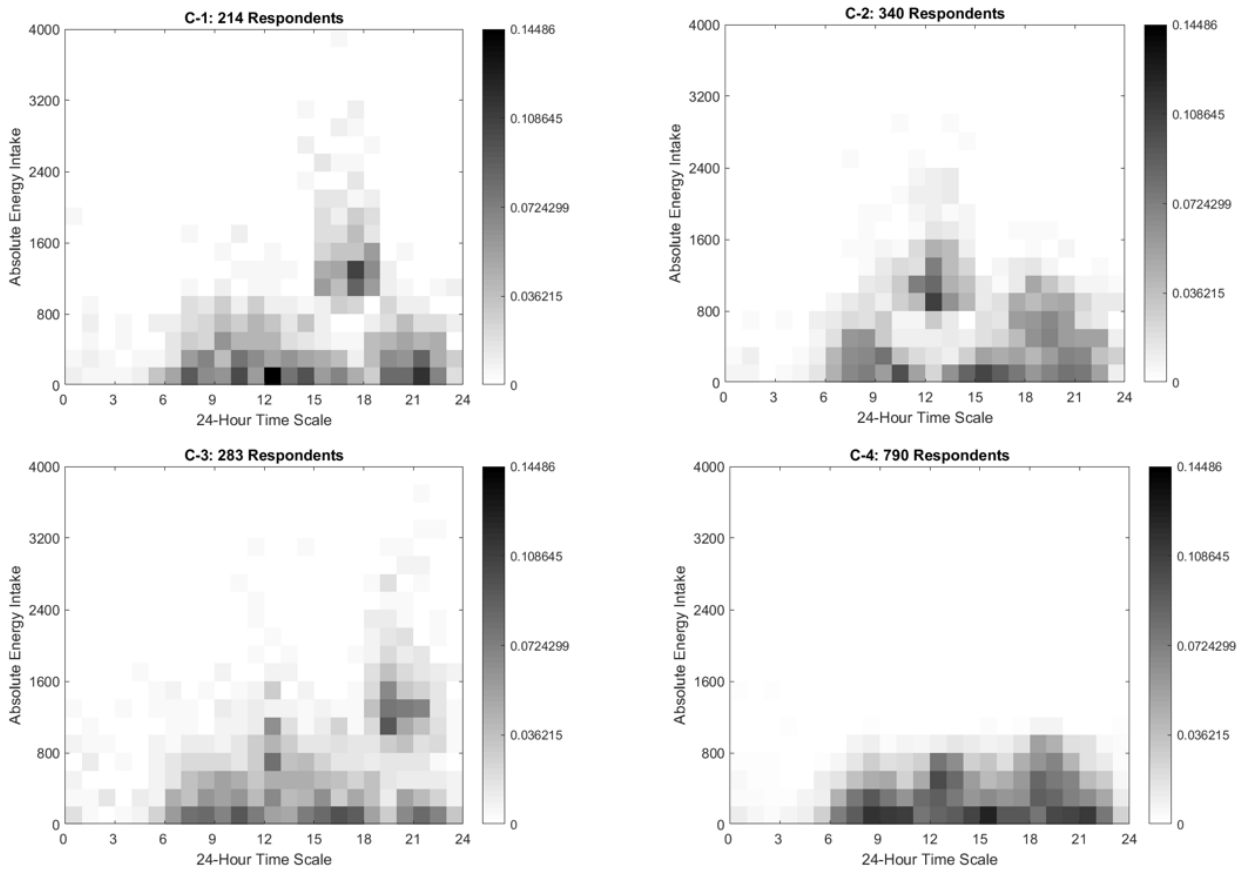

Figure 2.1. Heat maps for MDTW clusters which depict the absolute amount of energy intake (y-axis) for U.S. adults 20-65 years as drawn from NHANES 2003-2006 over a 24-hour day from time 0=12:00 a.m. to time 24= 12:00 a.m. the next day (x-axis).

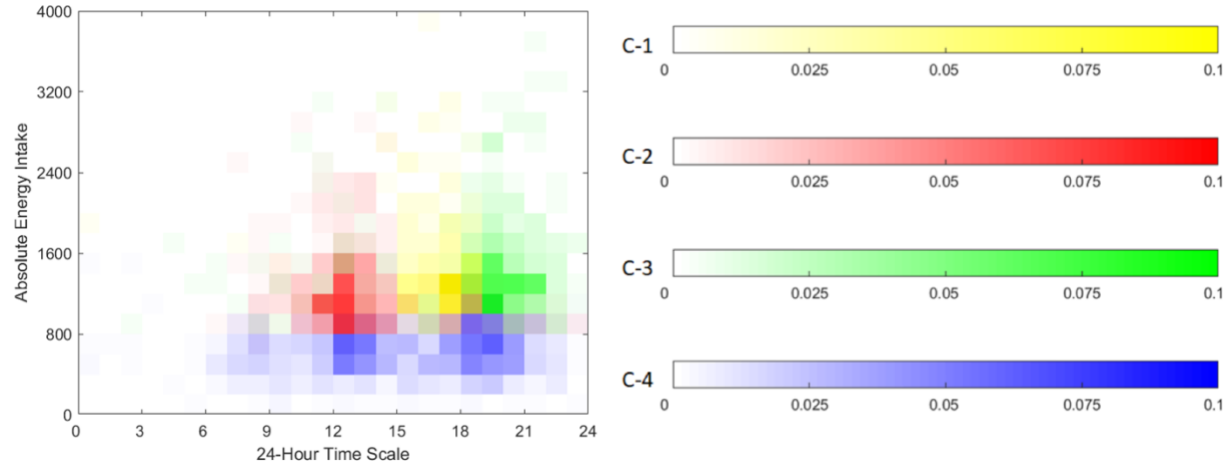

Figure 2.2. Heat maps for MDTW clusters which depict the distribution of the largest eating occasion within each cluster for U.S. adults 20-65 years as drawn from NHANES 2003-2006.

2.4 Results

Characteristics of participants in the four clusters representing TDPs are shown in Table 2.1. The number of participants was similar between Clusters 1, 2 and 3, though Cluster 4, characterized by evenly spaced energy-balanced eating occasions, included the highest number of participants, approximately 2 times the total number in the other clusters. Significant differences were present among clusters by sex (p<0.0001), age (p=0.001), and BMI (p=0.03), but not by survey year, race/ethnicity, or household PIR. Compared to the other 3 clusters, Cluster 4 had a proportionally greater representation of females vs. males (64.7% vs. 35.3%). Cluster 4 included a higher proportion of ages 50-65 years (44.6%) compared to the other age groups, specifically 20-34 years (23.5%) and 35-49 years (31.9%). In respect to BMI, normal weight was more heavily represented in Cluster 4 (30.8%) compared to the other clusters (22.9%-28.3%); whereas obese category was prominent in Clusters 2 and 3 (38.5% and 39.2%, respectively) compared to Clusters 1 and 4 (34.6% and 33.2%, respectively).

Table 2.1. Characteristics of clusters representing temporal dietary patterns of U.S. adults aged 20-65 years as drawn from the NHANES, 2003-2006 (n=1,627).

Characteristic	**Total (*n*)**	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	***P*-value[a]**
			n (%)[b]			
Total	1,627	214 (13.2)	340 (20.9)	283 (17.4)	790 (48.5)	
Survey year						
2003-2004	804	116 (54.2)	170 (50.0)	134 (47.3)	384 (48.6)	
2005-2006	823	98 (45.8)	170 (50.0)	149 (52.7)	406 (51.4)	0.66
Sex						
Male	839	134 (62.6)	216 (63.5)	210 (74.2)	279 (35.3)	
Female	788	80 (37.4)	124 (36.5)	73 (25.8)	511 (64.7)	<0.0001
Race/ Ethnicity						
Mexican American	350	56 (26.2)	84 (24.7)	47 (16.6)	163 (20.6)	
Other Hispanic	46	4 (1.9)	10 (2.9)	3 (1.1)	29 (3.7)	
Non-Hispanic White	826	112 (52.3)	168 (49.4)	157 (55.5)	389 (49.2)	
Non-Hispanic Black	331	33 (15.4)	61 (17.9)	66 (23.3)	171 (21.6)	
Other	74	9 (4.2)	17 (5.0)	10 (3.5)	38 (4.8)	0.35
Age group (year)						
20-34	458	72 (33.6)	99 (29.1)	101 (35.7)	186 (23.5)	
35-49	548	67 (31.3)	130 (38.2)	99 (35.0)	252 (31.9)	
50-65	621	75 (35.0)	111 (32.6)	83 (29.3)	352 (44.6)	0.001
PIR[c]						
0-0.99	219	28 (13.1)	43 (12.6)	40 (14.1)	108 (13.7)	
1.00-2.99	352	51 (23.8)	76 (22.4)	60 (21.2)	165 (20.9)	
2.00-2.99	221	27 (12.6)	41 (12.1)	36 (12.7)	117 (14.8)	
3.00-3.99	254	34 (15.9)	59 (17.4)	44 (15.5)	117 (14.8)	
4.00-4.99	152	21 (9.8)	32 (9.4)	23 (8.1)	76 (9.6)	
>5.00	370	46 (21.5)	80 (23.5)	69 (1.6)	175 (22.2)	0.98
BMI[d]						
Underweight	20	3 (1.4)	3 (0.9)	4 (1.4)	10 (1.3)	
Normal weight	466	49 (22.9)	94 (27.6)	80 (28.3)	243 (30.8)	
Overweight	562	88 (41.1)	112 (32.9)	88 (31.1)	274 (34.7)	
Obese	579	74 (34.6)	131 (38.5)	111 (39.2)	263 (33.2)	0.03

[a]Rao Scott F adjusted χ^2 P-value is a goodness-of-fit, one-sided test; statistical significance is indicated when P<0.05. Analyses were adjusted for clustering and stratification. Sample weights were constructed and applied to the analysis as directed by NCHS. Weight were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 03-06.

[b]Total numbers do not always add up to sample size due to missing values.

[c]PIR: poverty-income ratio.

[d]BMI: body mass index; categories were defined per the World Health Organization [35].

2.4.1 Characteristics of Temporal Dietary Patterns

Compared to the other 3 clusters, the absolute amount of energy intake in Cluster 4 was moderate, reaching up to 1,200 kcal for each of three main eating occasions throughout the day from 6:00 a.m. to 11:00 p.m. with a greater proportion (~10%) of the cluster engaging in eating occasions from 6:00 a.m. to 10:00 a.m., 12:00 p.m. to 3:00 p.m., and 6:00 p.m. to 10:00 p.m. In contrast, the other 3 clusters revealed patterns with one distinct peak in absolute amount of energy intake. For instance, participants in Cluster 1 consumed less mean absolute energy (reaching up to 1,200 kcal) at earlier hours of the day between 7:00 a.m. to 1:00 p.m., compared to a peak in intake between 3:00 p.m. to 6:00 p.m. with a higher proportion of the cluster (~12%) consuming between 1,000- 2,400 kcal. Energy intake tended to be lower towards later hours of the day 7:00 p.m. to 11:00 p.m. reaching up to 1,000 kcal. Participants in Cluster 2 had a lower average energy intake between 6:00 a.m. to 10:00 a.m. reaching up to 1,000 kcal compared with a peak reaching up to 2,400 kcal from 11:00 a.m. to 3:00 p.m. (a higher proportion of the cluster ~10% consumed energy ranging between 800-1,600 kcal), followed by intake reaching up to 1,400 kcal between 5:00 p.m. to 10:00 p.m. Finally, Cluster 3 exhibited a spread-out pattern in regards to amount of energy consumed with mean energy intake reaching up to 1,400 kcal between 7:00 a.m. to 1:00 p.m. and a much higher intake occasion with energy ranging between 1,000-2,600 kcal towards later hours of the day between 6:00 p.m. to 11:00 p.m. (a higher proportion of the cluster ~8-10% consumed energy between 1,000-1,600 kcal). Figure 2.2 represents the distribution of the largest eating occasion for each cluster and confirms patterns observed in Figure 2.1 in which Clusters 1, 2 and 3 exhibited distinct peaks in energy intake at different times of the day, whereas Cluster 4 displayed energy-balanced eating occasions with no distinct peaks.

2.4.2 Association of Temporal Dietary Patterns with Adiposity and Chronic Disease

Significant differences in mean BMI were present between Clusters 3 and 4 in the unadjusted model ($p<0.05/6$, simple linear regression model results not shown). Significant differences in mean WC and odds of obesity relative to normal weight status were present between Clusters 1 and 4, 2 and 4, and 3 and 4 in the unadjusted model ($p<0.05/6$, simple linear regression model results not shown). Cluster 3 had the highest mean BMI (29.2±0.4 kg/m$_2$) and WC (100.2±1.0 cm), whereas Cluster 4 had the lowest mean BMI (28.4±0.2 kg/m$_2$) and WC (96.1±0.5

cm) compared to the other clusters. Analysis to examine the dependence of BMI, WC, and odds of obesity relative to normal weight status on cluster in the adjusted models indicated significant differences between Clusters 1 and 4, 2 and 4, and 3 and 4 (all $p<0.0001$), while there were no significant differences in all other cluster comparisons $p>0.05/6$ (Tables 2.2, 2.3, and 2.4). The significantly different mean BMI and WC and odds of obesity were greatest between Clusters 3 and 4 (BMI: β=4.8±0.4 kg/m2, WC: β=12.7±1.2 cm, obesity OR: 6.7; 95% CI: 3.9, 11.6), similar to the results of the unadjusted model (BMI: β=1.1±0.3 kg/m2, WC: β=5.9±0.9 cm, obesity OR: 1.7; 95% CI: 1.2, 2.4; data not shown).

Table 2.2. Mean body mass index (kg/m2) and covariate-adjusted regression model results for clusters representing temporal dietary patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006a.

Mean Body Mass Index (kg/m2)								
			βd±(SE)e	95% CI	βd±(SE)e	95% CI	βd ±(SE)e	95% CI
			Compared with:					
Adjusted models[b]	*n* (%)	Mean (SEM)[c]	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	214 (13.2)	29.1±0.4	0.2±0.5	-1.3,1.6	-0.9±0.6	-2.4,0.7	4.0±0.6	2.3, 5.6*
Cluster 2	340 (20.9)	29.1±0.3			-1.0±0.5	-2.4,0.4	3.8±0.6	2.2, 5.3*
Cluster 3	283 (17.4)	29.2±0.4					4.8±0.4	3.7, 6.0*
Cluster 4	790 (48.6)	28.4±0.2						

[a]Simple regression model results are not shown but differences in the mean BMI were present among clusters 3 and 4 at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, PIR, and energy misreporting (EI:EER).
[c]SEM: standard error of the mean.
[d]ß represents the difference between mean BMI of cluster and reference cluster. Differences in mean BMI are different than those between raw means because they represent differences in least square means.
[e]SE: standard error.
*P-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Table 2.3. Mean waist circumference (cm) and covariate-adjusted regression model results for clusters representing temporal dietary patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006[a].

		Mean WC (cm)						
			β_d±(SE)[e]	95% CI	β_d±(SE)[e]	95% CI	β_d ±(SE)[e]	95% CI
			Compared with:					
Adjusted models[b]	*n* (%)	Mean (SEM)[c]	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	214 (13.2)	99.4±1.1	0.4±1.5	-3.5,4.4	-2.5±1.4	-6.4,1.4	10.2±1.5	6.2,14.3*
Cluster 2	340 (20.9)	99.5±0.8			-2.9±1.4	-6.7,0.9	9.8±1.4	6.1,13.5*
Cluster 3	283 (17.4)	100.2±1.0					12.7±1.2	9.5,15.8*
Cluster 4	790 (48.6)	96.1±0.5						

[a]Simple regression model results are not shown but differences among clusters in mean WC were similar to those in the adjusted model at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, PIR, and energy misreporting (EI:EER).
[c]SEM: standard error of the mean.
[d]ß represents the difference between mean WC of cluster and reference cluster. Differences in mean WC are different than those between raw means because they represent differences in least square means.
[e]SE: standard error.
*P-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Table 2.4. Odds ratio of obesity relative to normal weight and covariate-adjusted regression model results for clusters representing temporal dietary patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006[a].

		Obesity[d] Odds Ratio					
		OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
		Compared with:					
Adjusted models[b]	*n* (%)	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	214 (13.2)	1.2	0.7, 2.2	0.8	0.4, 1.5	5.3	2.8, 10.1*
Cluster 2	340 (20.9)			0.7	0.4, 1.2	4.4	2.5, 7.9*
Cluster 3	283 (17.4)					6.7	3.9, 11.6*
Cluster 4	790 (48.6)						

[a]Simple regression model results are not shown but differences among clusters in odds ratio of obesity were similar to those in the adjusted model at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, PIR, and energy misreporting (EI:EER).
[c]OR represents odds ratio of obesity of cluster and reference cluster.
[d]Obesity defined as BMI $\geq 30 kg/m^2$ [35].
*P-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Regarding the other health status indicators and outcomes investigated, there were three significant differences in mean HDL-C between Clusters 1 and 3, 2 and 4, and 3 and 4 ($p<0.05/6$) in the unadjusted model, however, these differences were not observed in the adjusted model except between Clusters 1 and 2 (data not shown). Moreover, there were no significant differences amongst clusters in any of the other health status indicators and diseases outcomes including type 2 diabetes and metabolic syndrome in both unadjusted and adjusted models (data not shown).

2.5 Discussion

TDPs generated from one 24-hour recall are associated with BMI, WC, and obesity but not with any of the other health status indicators or disease outcomes investigated. To our knowledge, this is the first study to assess the association of TDP based on timing, amount, and sequence of eating occasions throughout a 24-hour period with health outcomes in an adult U.S. population, while adjusting for potential confounders. Of note, the mean differences in BMI and WC associated with TDP were both statistically significant and clinically meaningful, implicating their relevance in disease management and clinical application [66–68]. Thus, observed mean

differences in these health status indicators may suggest that TDP could be an important health exposure that requires further exploration. A few studies have assessed the temporal patterning of energy intake in adults throughout the day [22,69]. Using latent class analysis approach, Leech et al., found a "conventional" pattern defined by evenly spaced meals and snacks consumed at conventional times in Australia, similar to Cluster 4 found in this study, to be associated with lower odds of overweight or obesity and central overweight or obesity in women compared to another pattern characterized by a higher eating frequency [69]. Moreover, findings from the current study support previous work which revealed that a TDP characterized by three evenly spaced, energy-balanced eating occasions throughout the day was linked with improved dietary quality [22,24].

The findings of significant lower mean BMI and WC, and odds of obesity relative to normal weight status in Cluster 4 compared to all other clusters indicates that a pattern with evenly spaced energy-balanced eating occasions consumed throughout a day may be more advantageous in relationship to health compared to patterns with one distinct peak in absolute amount of energy intake throughout the day. Regular intervals of energy intake throughout the day has a positive impact on risk factors for diabetes mellitus and heart disease [10]. In fact, irregular patterns of total energy intake i.e., with intake limited to one portion of the day or continuously through the day, seem to be less advantageous for the maintenance of body weight and optimum cardiometabolic health compared to a more intentional eating strategy which entails eating at planned intervals to distribute total energy intake during day [10]. Further, Cluster 4 includes a higher proportion of the age groups 35-49 years and 50-65 years compared to 20-34 years which is consistent with evidence indicating that by age group, likelihood of eating three times a day is lowest during adolescence and young adulthood and progressively increases with age [4]. Interestingly, Cluster 4 also included the highest number of participants (48.6%) which is consistent with evidence that shows that the majority of the U.S. population consumes three main meals/ day in addition to at least one snack [4]; however, among the U.S. population, around one fourth (24%) of daily energy is consumed at lunch and 24% through snacks, while most of daily energy is consumed at dinner (~35%) which is contradictory to a pattern of energy-balanced eating occasions [4].

Furthermore, Cluster 3 characterized with the highest absolute energy intake towards later hours of the day (6:00 p.m. to 11:00 p.m.) had the highest mean BMI and WC, and odds of obesity relative to normal weight status compared to Cluster 4. On the other hand, compared to Cluster 4, Cluster 2 with the highest energy intake at earlier hours of the day (11:00 a.m. to 3:00 p.m.) had

the lowest mean BMI and WC, and odds of obesity relative to normal weight status. Models controlled for total energy intake; thus, these findings may indicate that observed differences in the magnitude of outcomes examined could be explained by temporal differences in these patterns. Evidence from epidemiologic studies suggests a positive association between evening meal consumption and obesity. For example, in a study of 1,245 middle-aged adults, consuming greater energy intake at dinner (≥48%) compared with <33% or 33-48%, was associated with a 2.33-fold greater odds of developing obesity [70]. Another study reported significant decreases in BMI among those who consumed breakfast or lunch as the largest meal relative to those who ate their largest meal at dinner [71]. Findings from this analysis also revealed a greater magnitude of difference in mean BMI and WC, and odds of obesity in a pattern with later meal intake; yet, instead of assessing the timing of a single meal or energy intake across stratified timespans, this study examined TDPs based on a novel data-driven approach which integrates the timing, amount, and sequence of eating occasions throughout the day

The finding of no significant differences in health outcomes among Clusters 1, 2, and 3 was unexpected. These clusters were similar in terms of number of main eating occasions, however they differed in the timing of the highest energy intake occasion: Cluster 1 (3:00 p.m.-6:00 p.m.), Cluster 2 (11:00 a.m.-3:00 p.m.) and Cluster 3 (6:00 p.m. to 11:00 p.m.). Notably, the effect of evening meal intake on measures of adiposity remains inconclusive [72]; specifically, some observational studies showed that evening meal intake is associated with increased weight, BMI, and/or odds of overweight [13,73,74], whereas others found no association [75–77] which may help explain why there were no significant differences in examined health status indicators and disease outcomes amongst those clusters. Additionally, it is possible that the lack of observed differences could be due to other factors including sleep timing and exercise which could interact with daily dietary patterns.

Interestingly, TDPs were associated with long-term markers of health including BMI and WC, whereas no significant associations were found between patterns and other examined health indicators including serum biomarkers especially fasting plasma glucose and triglycerides which may more closely reflect dietary intake reported in the collected 24-hour recalls. Using latent class analysis, Leech et al. reported a “later lunch” temporal eating pattern characterized by a later lunch eating occasion (between 1:00 p.m.-2:00 p.m.) to be associated with systolic and diastolic blood pressures compared to a “conventional” pattern in women; however, no such associations were

found between TDPs and systolic or diastolic blood pressures in the current study. These results may be an artifact of laboratory procedures or may be explained by large intra- and inter-individual variability in serum biomarkers and blood pressure compared to BMI and WC. Otherwise, findings may indicate that TDPs more strongly associate with long-term or chronic health outcomes; however, more research is needed that examines links between TDPs and these outcomes to further elucidate these findings.

Sociodemographic characteristics such as those included in this study (Table 2.1) have been shown to be associated with diet-related differences in health outcomes. Limited studies have examined how energy distribution or timing of energy intake throughout the day may differ between population groups and results suggest potential differences by sociodemographic factors including sex and age [78]. For instance, females have been reported to be generally more regulated in their eating patterns compared to males [79]. Striegel-Moore et al. found that males are more likely than females to engage in night eating [80], which is consistent with the higher proportion of males in Cluster 3 with the latest meal intake occasion (6:00 p.m.-11:00 p.m.) compared to Cluster 4 characterized by evenly spaced energy-balanced eating occasions. Moreover, Cluster 4 also included the highest proportion of the age group 50-65 years compared to all other clusters; a regular meal pattern has been more commonly observed in older adults compared to young adults, where the latter group has been described as having a more "de-synchronized" eating pattern [78,79]. Further, taken in the context of relative differences in BMI among the clusters, the TDP associated with the lowest BMI, WC and odds of obesity (Cluster 4), was more significantly represented by characteristics: female and age group 50-65 years; whereas the TDP associated with the highest BMI, WC, and odds of obesity (Cluster 3) comprised a higher proportion of males compared to females and ages 20-34 years compared to the other 2 age groups. Of note, multivariate regression models adjusted for sociodemographic characteristics, therefore observed differences in health status indicators and outcomes may be explained by differences amongst temporal patterns; however, variables in Table 2.1 show that certain participant characteristics more prevalently represented certain patterns.

Daily dietary patterns that may be associated with behavioral factors that were outside of the scope of this study include exercise and sleep timing across the day and over time. As such, insight into how these behavioral components interact within a day and overall as part of a lifestyle pattern may unfold stronger associations with health outcomes compared to when they are considered

separately. Understanding how these behaviors interact on an individual basis could also inform more targeted advice and strategies that promote healthy eating and protect against chronic disease. Such data has become more available recently through the use of technology-assisted assessment tools including those targeting dietary and activity patterns and could be potentially integrated to determine whether or how timing of these behaviors interact to influence health. Moreover, the use of nutrition epidemiology analysis along with data-driven methods to integrate time to these behavioral patterns holds promise to explore how these temporal patterns through the day and over time effect health outcomes and with further development, this evidence may provide insight to inform population-level dietary and physical activity guideline recommendations.

The strengths of the current analyses include the use of a data-driven approach that integrates amount and time of eating and sequence of eating occasions throughout an entire day for the development of TDPs. Additionally, our approach avoids between-subject variation that participants may have in regard to eating occasion definitions. Limitations of this study include the cross-sectional nature which provides a snapshot of the participants' dietary intake and the small sample size representing ~8% of the original sample of participants included in survey years 2003-2006; therefore, study results should be interpreted with caution. Of note, sample size attrition is mostly attributable to the selected age range 20-65 years and the inclusion of health status indicators examined in a fasting subsample of participants (both criteria resulted in loss of ~84% of the original sample). Cluster descriptions describe the group and do not represent individuals. Moreover, patterns were developed based on one day of self-reported 24-hour dietary recalls; however, the inclusion of a second recall would have further limited our sample size; also, since information regarding the distribution of timing of dietary patterns over multiple days is unknown, exploration of the time, amount, and sequence of dietary intake over multiple days represents a research gap for future study. Furthermore, in this sample, around 60% of recalls were collected on a weekday; since dietary patterns could differ significantly between weekdays and weekends, it remains unclear whether different patterns could appear if the analysis was focused on weekends, thus future studies should consider investigation of dietary patterns over weekend days.

2.6 Conclusions

This paper demonstrates that TDPs are associated with differences in BMI, WC, and obesity. Individuals with a TDP characterized by evenly spaced, energy-balanced eating occasions exhibited improved health status indicators and lower odds of disease compared to the other three patterns characterized by distinct peaks in energy intake at different times throughout the day. The incorporation of time to the concept of dietary patterns including amount and sequence of eating occasions may be important to determine links with health and could provide insight into the detection of behavioral patterns that predispose obesity and chronic disease to inform dietary guidelines recommendations.

Author contributions

H.A.E.-M, E.D., S.G., A.B., E.A.R., E.H., M.A., J.G., and L.L. designed research; M.A., J.G., and L.L. analyzed data; M.A. wrote paper. H.A.E.-M, E.A.R., E.H., A.B., S.G., J.G., and E.D., reviewed and edited paper. All authors have read and agree to the published version of the manuscript.

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Conflict of Interest:

The authors declare no conflict of interest.

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CHAPTER 3. TEMPORAL PHYSICAL ACTIVITY PATTERNS ARE ASSOCIATED WITH OBESITY

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3.1 Abstract

Background: Few attempts have been made to incorporate multiple aspects of physical activity, including timing and volume, to classify patterns that link to health outcomes. Temporal physical activity patterns integrating time and activity counts were created to determine their association with health status indicators: body mass index, waist circumference, fasting plasma glucose, hemoglobin A1c, triglycerides, high-density lipoprotein cholesterol, total cholesterol, blood pressure, and chronic diseases of obesity, diabetes, and metabolic syndrome.

Methods: Physical activity accelerometry data collected from the National Health and Nutrition Examination Survey 2003-2006 was used to pattern absolute physical activity counts and time of activity from 1,627 non-pregnant adults with one random valid weekday. Modified dynamic time warping and kernel k-means clustering grouped participants to 4 clusters representing temporal physical activity patterns. Multivariate regression models controlling for potential confounders and adjusting for multiple comparisons ($p<0.05/6$) determined associations between clusters and health outcomes.

Results: Participants in Cluster 2, represented by a temporal physical activity pattern with the highest absolute activity counts reaching >2,000 counts/minute between 9:00 a.m.-11:00 a.m. and tapering off through the day, had lower body mass index ($p<0.0001$), waist circumference

(p<0.0001), and 70% lower odds of obesity compared with participants in Cluster 1 with the lowest absolute physical activity counts of approximately 0 to 600 counts/minute from 6:00 a.m. to 11:00 p.m. (95% CI: 0.1, 0.5). Cluster 3, characterized by a temporal physical activity pattern with high absolute activity counts reaching a maximum of 1,600 to 2,000 counts/minute between 6:00 p.m.-9:00 p.m., was also associated with lower body mass index (p=0.0003) and waist circumference (p=0.001), and 60% lower odds of obesity compared to Cluster 1 (95% CI: 0.2, 0.6).

Conclusions: Temporal physical activity patterns with higher activity counts ranging between 1,600 ->2,000 counts/minute early (9:00 a.m.-11:00 a.m.) or later (6:00 p.m.-9:00 p.m.) in a day had significantly lower body mass index, waist circumference, and obesity odds compared with Cluster 1 with the lowest physical activity counts of approximately 0 to 600 counts/minute from 6:00 a.m. to 11:00 p.m. Temporal physical activity patterns created by integrating time with physical activity counts throughout a day meaningfully link to health outcomes.

Keywords (3-10 words): temporal, timing, physical activity, patterns, body mass index, waist circumference, obesity.

3.2 Introduction

Obesity is a global health problem with about 13% of the world's adult population considered obese in 2016 [1]. Prevalence estimates of obesity in the United States (U.S.), increased between 2003-2004 and 2013-2014, reaching 42.4% among adults in 2017-2018 [2]. Obesity is both an outcome and a contributor to chronic disease development including type 2 diabetes and metabolic syndrome [3,4]. Low physical activity (PA) behavior is a potentially modifiable risk factor for obesity [5]. Though trends in meeting the U.S. PA Guidelines have improved between 2008-2018 based on self-reports [5,6], percentages of U.S. adults meeting both aerobic and muscle strengthening guidelines remain low at around 20.6% [7].

Engaging more of the population in PA is a public health priority given that the beneficial effects of PA are well documented. Specifically, increased exercise has been shown to aid in weight loss and maintenance [8], and lower waist circumference (WC) [9], blood pressure [10], and postprandial triglycerides [11]. Moreover, most previous PA research has focused on the association between intensity (i.e., moderate to vigorous) or counts of PA and health outcomes [11–14]. Beyond these two aspects of activity, the timing of activity may also be relevant to health.

A few studies have showed a potential benefit to modulating time of activity in relationship with health outcomes [15–18]. For instance one study reported higher odds of obesity in women who were less active in the morning hours compared to the evening [15], while another randomized clinical trial revealed significant lowering of body mass index (BMI) after 6 weeks of aerobic exercise was performed in the morning vs. evening in a group of women with overweight [16]. A limitation of these studies is a focus on vague unspecified parts of the day i.e., morning vs. evening without considering the specific timing of these activities or activity counts at other time points through the day. Consideration of the patterns of activity throughout a day, or "temporal PA patterns", are a novel concept that may provide insight to the behavioral patterns related to health outcomes. One of the challenges in this work however is utilizing methods that will characterize PA patterns as an exposure by integrating timing and other characteristics of PA in relation to health outcomes.

A novel distance measure based on dynamic time warping (DTW) is used herein to identify similarities in the time and counts of activity over a 24-hour period and reduce the data using cluster analysis. Groups exhibiting similar activity throughout the day, or temporal PA patterns, are expected to display similar health status indicator values and chronic disease outcomes that are distinct from other temporally defined groups. Thus, the hypothesis for this study was that differences in health status indicators and disease outcomes exist between U.S. adult (aged 20-65y) participant clusters demonstrating similar 24-hour temporal PA patterns as generated from accelerometry data of the 2003-2006 National Health and Nutrition Examination Survey (NHANES).

3.3 Methods

3.3.1 Participants and Data Collection

NHANES is a program of studies designed to assess the health and nutritional status of adults and children in the United States [19]. Participants were recruited using a complex, stratified, multistage probability sampling design in order to represent the civilian non-institutionalized U.S. population [19]. Participant characteristics including age, sex, race/ethnicity, and income to poverty ratio (PIR) were collected using an in-depth questionnaire during the in-person household interview. Survey participants were interviewed in their homes and subsequently examined in the

Mobile Examination Center. The health examination included the collection of anthropometric measurements, laboratory tests, and recruitment for the PA assessment component. Consent was required for all participants [20]. The NHANES protocols and content were approved by the NCHS Research Ethics Review Board [20].

3.3.2 Analytic Sample

The NHANES data are released in 2-year cycles; because PA accelerometry data was collected and publicly released for survey years 2003-2004 and 2005-2006, these 4 years of data were combined for this analysis. Previous studies show no significant differences in the PA levels in these 2 cycles [21]. Data used for this analysis included non-pregnant U.S. adults ages 20-65y with one random weekday of valid accelerometer data and complete anthropometric and laboratory data (n=1,627). Pregnant women, children, adolescents, and adults older than retirement age were excluded because their daily activity patterns may include variation characteristic to the life stages they represent [5].

3.3.3 Anthropometric assessment and Laboratory Tests

Selected health status indicators and disease outcomes were chosen for their previous associations with PA [10,11,22,23]. Weight was measured using a digital scale to the nearest 0.1 kilogram [24]. Standing height and WC were measured with a stadiometer and tape measure, respectively to the nearest 0.1 centimeter [24]. BMI was calculated as weight in kilograms divided by height in meters squared. Results were based on a single body measurement at examination.

A phlebotomist obtained a blood sample from participants according to a standardized protocol [25,26]. Fasting plasma glucose and triglycerides were assessed after participants fasted at least 8 hours and not more than 24 hours. Fasting plasma glucose was measured using a hexokinase method with a Roche/Hitachi 911 (cycle 2003-2004) or a Roche Cobas Mira (cycle 2005-2006) [27,28]. Triglycerides were measured enzymatically [29,30]. Hemoglobin A1c, total cholesterol, and high-density lipoprotein cholesterol (HDL-C) were based on samples taken regardless of fasting state. Hemoglobin A1c was measured with high performance liquid chromatography using Primus CLC 330 and Primus CLC 385 in the 2003-2004 cycle and using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer in the 2005-2006 cycle [31,32]. Total cholesterol

was measured enzymatically. An instrument change occurred in NHANES 2005-2006 for total cholesterol, but the method and laboratory location were similar to 2003-2004 cycle [33,34]. HDL-C was analyzed using a direct HDL-C immunoassay method from 2003-2006 and similarly, a change in equipment to measure HDL-C was made for 2005-2006, yet the laboratory method and location were similar to 2003-2004 [33,35]. Blood pressure was measured using a mercury sphygmomanometer, with systolic and diastolic blood pressures determined based on up to 4 measures [36]; if more than 1 measure was obtained, the first measure was not considered, and the remaining measures were averaged, otherwise, the first measure was used.

3.3.4 Physical Activity Assessment

The ActiGraph model 7164 accelerometer was used to collect objective information on participants' PA. One-minute time intervals (epochs) were used to assign a count value which is a relative measure of changes in momentum that occurred during these intervals and which then could be converted to an estimate of PA intensity [37]. Monitors began recording activity information (for 7 consecutive days) at 12:01 a.m. the day after the health examination [38]. Ten hours of wear time was considered a valid day which was calculated by subtracting non-wear time (i.e., periods of $\geq$60 consecutive minutes of zero activity counts allowing for intervals of 1-2 consecutive minutes of relatively low activity counts i.e., 1-100 counts) from the total daily observation time (24 hours) [39].

3.3.5 Temporal Physical Activity Patterns

One random weekday of valid accelerometer data was chosen for this analysis as PA patterns on weekdays are shown to be different from weekend day [40]. Data from this day was used to develop time series of length 24, with each entry representing absolute PA counts during an hourly time interval. From each person's valid days, one day was randomly selected so that each valid day had an equal chance of being chosen. The activity counts and hourly time stamps of non-zero counts were extracted from the time series to form the compact representation as defined in [41,42]. Several distance measures for comparing time series were investigated including the constrained DTW with Sakoe-Chiba band (CDTW) and the modified DTW (MDTW) based on our previous work to pattern dietary intake [43]. Both CDTW and MDTW belong to the

elastic distance family and find the optimal matching path among counts of activity in two time series [43]. The matching is "optimal" in the sense that the summed difference between matched counts is minimized. The Sakoe-Chiba band in CDTW and the weight parameter β in MDTW are controlling parameters to avoid pathological matchings (e.g. matching activities in the morning to activities in the evening). While the Sakoe-Chiba band rigorously limits the maximum time difference between matched entries, the weight parameter β controls the matching through a time difference penalty term: larger β indicates more penalty on matching entries that are different in time. Bands ranging between 60-720 minutes (60-minute increments) and β ranging from 0-10 (2 increments) were explored in this paper, and parameter values outside of these ranges were omitted as they did not bring significant changes in the clustering results. Further, the distance measures were coupled with kernel k-means algorithm [44] to partition the time series into several clusters such that activity occasions are more similar in the same cluster and more dissimilar among different clusters. Cluster number k=4 was selected to divide the population into clusters representing similar temporal PA patterns to maintain consistency with previous development of temporal patterning [42,43,45]. MDTW β=10 was selected out of each distance measure pairing of CDTW bandwidth=360 and MDTW β=10 with k-means clustering, based on inferential analyses with health outcomes prioritized as: 1) most significant differences between the six pairwise comparisons among all health outcomes, 2) highest model R_2 values, and 3) largest difference between highest and lowest mean of health status indicators.

3.3.6 Statistical Analysis

The Rao Scott F adjusted chi-square statistic was used to determine significant differences among clusters by selected characteristics: survey year (2003-2004 and 2005-2006), sex (male or female), race/ethnicity (Mexican American and other Hispanic, Non-Hispanic white, Non-Hispanic black, and other-race including multi-race), age groups (20-34, 35-49, and 50-65y), PIR, and BMI categorized as underweight (<18.5 kg/m_2), normal weight (18.5-24.9 kg/m_2), overweight (25.0-29.9 kg/m_2), and obese (>30.0 kg/m_2) [46]. PIR, calculated as reported household income divided by the federal poverty guideline for household income, was divided into six categories: 0-0.99, 1-1.99, 2-2.99, 3-3.99, 4-4.99, and 5 or more. Ratios <1 indicate a PIR below the officially defined poverty level [47].

Disease categories included obesity, diabetes, and metabolic syndrome. Diabetes classification was based on fasting plasma glucose (≥126 mg/dl), hemoglobin A1c (≥ 6.5%) or self-report of: "yes" in response to the question "have you ever been told by a doctor you have diabetes?" or to the use of glucose-lowering medications [48]. The National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome was applied to classify this condition based on the presence of three or more of the following risk factors: 1) WC (>102 cm for men, >88 cm for women); 2) triglycerides (>150 mg/dl) or taking antihyperlipidemic medications; 3) HDL-C (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (>130/>85 mmHg) or taking antihypertensive medications; and 5) impaired fasting glucose (>110 mg/dl) or taking glucose-lowering medications [49].

Analysis of variance determined differences in mean health status indicators by temporal PA patterns. Multivariate regression models examined associations between temporal PA patterns and health outcomes accounting for potential confounders: survey year, sex, race/ethnicity, age group, PIR, and BMI. Appropriate survey weights were constructed for the 2003-2006 survey years as directed by the NCHS [50]. Sampling weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006. Adjustment for the complex survey design including clustering and stratification was completed following NCHS guidelines [44]. Comparisons between groups were considered statistically significant when $p<0.05/6$ (Tukey-Kramer type adjustment for multiple comparisons). Analyses were completed using SAS survey procedures and inferential analysis version 9.4.

3.3.7 Visualization

The visualization illustrates the distribution of non-zero PA counts in each cluster using heat maps (Figure 3.1). Each activity occasion in the heat map is marked by its time stamp (x-axis) and activity counts (y-axis). Time axis ranged from 0=12:00 a.m. to time 24=12:00 a.m. the next day with absolute daily PA counts (y-axis) ranging from 0 to > $1.2e_5$ counts per hour (cph) at a particular time (equivalent to 0-> 2,000 counts per minute (cpm)). The proportion of individuals that had the corresponding activity (certain activity count and time stamp) is indicated through shading and ranged from 0=0% to 0.12=12% of each cluster. Darker shading signifies that a greater proportion of that cluster reported activity at that specific time. Figure 3.1 exhibits four distinct

temporal PA patterns of activity occasions. Figure 3.2 adds color in order to differentiate the 4 clusters.

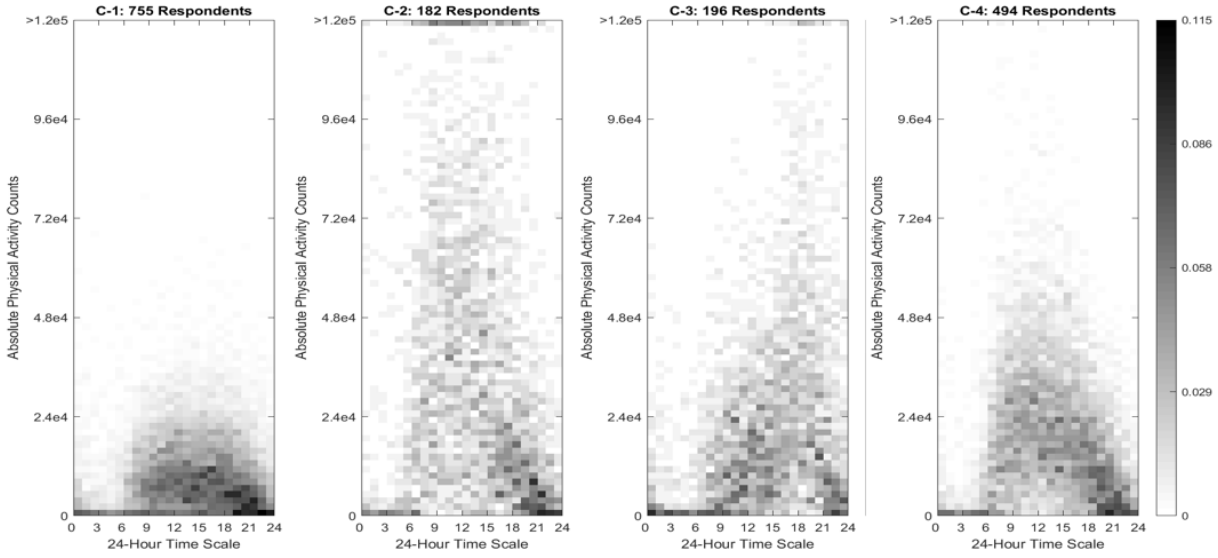

Figure 3.1. Heat maps for MDTW clusters which depict the absolute amount of activity counts (y-axis) for U.S. adults 20-65 years as drawn from NHANES 2003-2006 over a 24-hour day from time 0=12:00 a.m. to time 24= 12:00 a.m. the next day (x-axis).

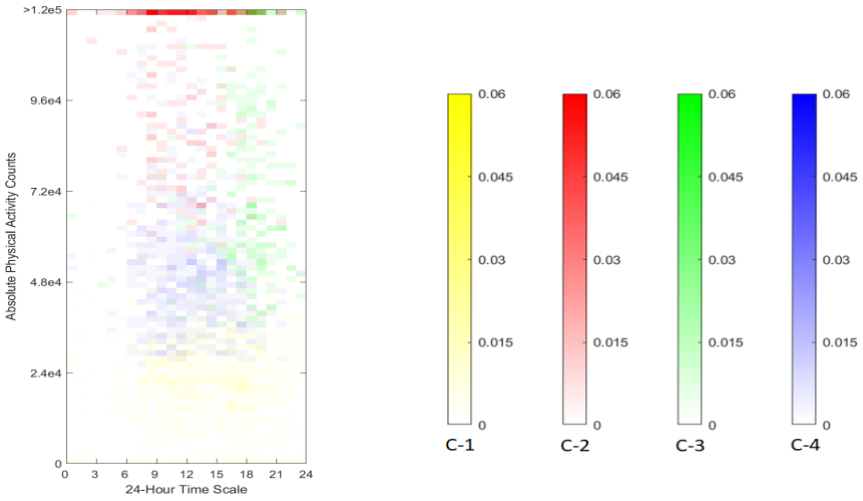

Figure 3.2. Heat maps for MDTW clusters which depict the distribution of the largest activity occasion within each cluster for U.S. adults 20-65 years as drawn from NHANES 2003-2006.

3.4 Results

Characteristics of participants in the four clusters representing temporal PA patterns are presented in Table 3.1. Clusters 2 and 3 included proportionately equivalent numbers of participants, 11.2% and 12.0%, respectively, whereas Cluster 1 had the largest proportion (46.4%) followed by Cluster 4 (30.4%). Significant differences were present among clusters by sex (p<0.0001), race/ethnicity (p=0.001), age (p=<0.0001), and BMI (p=<0.0001), but not by survey year or PIR. Females were more heavily represented in Clusters 1 and 4 characterized by lower PA counts (58.1% and 44.9%, respectively) compared to Cluster 2 and 3 characterized by higher PA counts (29.7% and 37.2%, respectively). Whereas, Clusters 1 and 4 included a lower proportion of males (41.9% and 55.1%, respectively) compared to Clusters 2 and 3 (70.3% and 62.8%, respectively). Additionally, the non-Hispanic white group featured more prominently in Clusters 3 and 4 (52.5% and 51.4%, respectively) compared with Clusters 1 and 2 (50.2% and 49.5%, respectively); whereas non-Hispanic blacks were more heavily represented in Clusters 1 and 3 (22.9% and 20.9%, respectively) compared to the other two clusters (17.0 % and 17.4%). Further, Cluster 1 with the lowest activity counts included a higher proportion of age group 50-65y compared to other age groups, whereas Clusters 2 and 3 with much higher PA counts, included a higher proportion of the age group 20-34y. Regarding BMI, normal weight was more highly represented in Clusters 2 and 3 (36.2% and 37.2%, respectively) compared to Clusters 1 and 4 (24.9% and 28.2%, respectively); while obese category was more heavily represented in Clusters 1 and 4 (41.9% and 36.2%, respectively) compared to Cluster 2 and 3 (19.8% and 24.5%, respectively).

Table 3.1. Characteristics of clusters representing temporal physical activity patterns of U.S. adults aged 20-65 years as drawn from the NHANES, 2003-2006 (n=1,627).

Characteristic	Total (*n*)	Cluster 1	Cluster 2	Cluster 3	Cluster 4	*P*-value[a]
			n (%)[b]			
Total	1,627	755 (46.4)	182 (11.2)	196 (12.0)	494 (30.4)	
Survey year						
2003-2004	804	368 (48.7)	89 (48.9)	117 (59.7)	230 (46.6)	
2005-2006	823	387 (51.3)	93 (51.1)	79 (40.3)	264 (53.4)	0.19
Sex						
Male	839	316 (41.9)	128 (70.3)	123 (62.8)	272 (55.1)	

Table 3.1 continued

Female	788	439 (58.1)	54 (29.7)	73 (37.2)	222 (44.9)	<0.0001
Race/Ethnicity						
Mexican American	350	141 (18.7)	51 (28.0)	38 (19.4)	120 (24.3)	
Other Hispanic	46	15 (2.0)	8 (4.4)	6 (3.1)	17 (3.4)	
Non-Hispanic white	826	379 (50.2)	90 (49.5)	103 (52.5)	254 (51.4)	
Non-Hispanic black	331	173 (22.9)	31 (17.0)	41 (20.9)	86 (17.4)	
Other	74	47 (6.2)	2 (1.1)	8 (4.1)	17 (3.4)	0.001
Age group (year)						
20-34	458	194 (25.7)	69 (37.9)	83 (42.3)	112 (22.7)	
35-49	548	226 (29.9)	71 (39.0)	65 (33.2)	186 (37.7)	
50-65	621	335 (44.4)	42 (23.1)	48 (24.5)	196 (39.6)	<0.0001
Household PIR[c]						
0-0.99	219	115 (15.2)	17 (9.3)	28 (14.3)	59 (11.9)	
1.00-2.99	352	163 (21.6)	48 (26.4)	36 (18.4)	105 (21.3)	
2.00-2.99	221	112 (14.8)	21 (11.5)	31 (15.8)	57 (11.5)	
3.00-3.99	254	99 (13.1)	35 (19.2)	34 (17.3)	86 (17.4)	
4.00-4.99	152	69 (9.1)	16 (8.8)	21 (10.7)	46 (9.3)	
>5.00	370	170 (22.5)	44 (24.2)	40 (20.4)	116 (23.5)	0.24
BMI[d]						
Underweight	20	13 (1.7)	2 (1.1)	2 (1.1)	3 (0.6)	
Normal weight	466	188 (24.9)	66 (36.2)	73 (37.2)	139 (28.2)	
Overweight	562	238 (31.5)	78 (42.9)	73 (37.2)	173 (35.0)	
Obese	579	316 (41.9)	36 (19.8)	48 (24.5)	179 (36.2)	<0.0001

[a]Rao Scott F adjusted χ_2 P-value is a goodness-of-fit, one-sided test; statistical significance is indicated when P<0.05. Analyses were adjusted for clustering and stratification. Sample weights were constructed and applied to the analysis as directed by NCHS. Weight were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 03-06.
[b]Total numbers do not always add up to sample size due to missing values.
[c]PIR: poverty-income ratio.
[d]BMI: body mass index; categories were defined per the World Health Organization [47].

3.4.1 Characteristics of Temporal Physical Activity Patterns

Table 3.2. Qualitative description of clusters representing temporal PA patterns of U.S. adults NHANES 2003-2006 (n=1,627).

	Cluster 1	**Cluster 2**	**Cluster 3**	**Cluster 4**
Characteristics				
Activity level compared to other clusters	Lowest activity	Highest activity	High activity	low activity
Range of activity counts (cpm)	0-600	0->2,000	0-2,000	0-1,000
Peak in activity	No peaks	Peak between 9:00 a.m.-11:00 a.m. (>2,000cpm)	Peak between 6:00 p.m.-9:00 p.m. (1,600-2,000)	Peak between 11:00 a.m.-2:00 p.m. (1,000cpm)
Overall temporal pattern	Low activity counts throughout the day with a sharp decline between 7:00 p.m-9:00 p.m. (0-200cpm)	Highest during early hours; tapers off between 4:00 p.m.-9:00 p.m. (0-400cpm)	Lowest between 9:00 a.m.-2:00 p.m. (0-400cpm); increases as day goes on	Low activity counts throughout the day; lowest between 6:00 p.m.-9:00 p.m. (0-200cpm)
Percentage of cluster engaging in high vs. low activity (within cluster)	Higher percentage of the cluster ~10-12% engaged in low activity (0-400cpm); lower percentage ~1-2% engaged in activity between 400-600cpm	Higher percentage of cluster ~3-8% engaged in activity between 0-1,200 cpm; lower percentage ~1-3% engaged in activity counts between 1,200->2,000cpm	Higher percentage of the cluster ~5-8% engaged in activity counts between 0-1,000cpm; lower percentage 1-3% engaged in activity counts between 1,200-2,000cpm	Higher percentage of the cluster ~8-10% engaged in activity between 0-800cpm; lower percentage of the cluster 1-2% engaged in activity counts ~1,000cpm

cph: counts per hour
cpm: counts per minute
$1.2e_4$ cph=200 cpm; $2.4e_4$ cph=400 cpm; $3.6e_4$ cph= 600 cpm; $4.8e_4$ cph=800 cpm; $6.0e_4$ cph= 1,000 cpm; $7.2e_4$ cph=1,200 cpm; $9.6e_4$ cph=1,600cpm, $>1.2e_5$ cph =2,000cpm

Compared to all other clusters, Cluster 1 demonstrated the lowest PA counts reaching $3.6e_4$ cph (600 cpm) for activity occasions throughout the day from 6:00 a.m.-11:00 p.m. with no distinct peaks (Figure 3.1 and Table 3.2). A more prominent decrease in activity was observed towards the end of the day between 7:00 p.m.-9:00 p.m. with a greater proportion of the cluster (9-12%) engaging in activity between 0-$1.2e_4$ cph (0-200 cpm). Contrarily, Cluster 2 revealed a pattern with the highest PA counts with a major peak between 9:00 a.m.-11:00 a.m. reaching $>1.2e_5$ cph (>2,000 cpm). The activity tended to taper off through the day with a higher proportion of the cluster (4-12%) engaging in lower activity counts ranging between 0-$2.4e_4$ cph (0-400 cpm) between 4:00 p.m.-9:00 p.m. Cluster 3 demonstrated low activity counts between 9:00 a.m.- 2:00

p.m., where a higher proportion of the cluster (5-12%) engaged in activity ranging between 0-2.4e4 cph (0-400 cpm), whereas the level of activity tended to increase towards later hours during the day reaching 9.6e4-1.2e5 cph (1,600-2,000 cpm) between 6:00 p.m.-9:00 p.m. The activity counts in Cluster 4 were low compared to Clusters 2 and 3 peaking at around 6.0e4 cph (1,000 cpm) between 11:00 a.m.-2:00 p.m., while a higher proportion of the cluster (9-12%) engaged in lower activity ranging between 0-1.2e4 cph (0-200 cpm) towards the end of the day 6:00 p.m.-9:00 p.m. Generally, in all of the clusters, the percentage of participants engaging in high activity counts tended to be lower compared to the percentage of participants engaging in low activity counts. Figure 3.2 confirms patterns revealed in Figure 3.1, most variation in patterns pertains to total activity counts and timing of activity peaks throughout the day.

3.4.2 Association of Temporal Physical Activity Patterns with Adiposity and Chronic Disease

Significant differences in mean BMI and WC were present among all clusters except for clusters 1 and 4 and 2 and 3 in the unadjusted model ($p<0.05/6$, simple linear regression model results not shown). Cluster 1 had the highest mean BMI (29.7±0.3 kg/m2) and WC (99.9±0.6 cm), whereas Cluster 2 had the lowest BMI (26.6±0.3 kg/m2) and WC (93.3±0.9 cm) compared to the other clusters. There were significant differences between all clusters (BMI: $p<0.0001$, WC: $p<0.0002$) except Clusters 1 and 4 as well as 2 and 3 ($p>0.05/6$) in the adjusted models (Tables 3.3 and 3.4). The significantly different mean BMI and WC were greatest between Clusters 1 and 2 (BMI: β=3.1±0.5 kg/m2, WC: β=8.2±1.3 cm), similar to the results of the unadjusted model (BMI: β=2.9±0.5 kg/m2, WC: β=6.5±1.4 cm; data not shown).

Table 3.3. Mean body mass index (kg/m2) and covariate-adjusted regression model results for clusters representing temporal physical activity patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006a.

		Mean BMI (kg/m2)						
			βd±(SE)e	95% CI	βd±(SE)e	95% CI	βd±(SE)e	95% CI
			Compared with:					
Adjusted modelsb	*n (%)*	Mean (SEM)c	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	755 (46.4)	29.7 (0.3)	3.1±0.5	1.8, 4.5*	2.9±0.4	1.7, 4.0*	0.4±0.5	-0.9, 1.8
Cluster 2	182 (11.2)	26.6 (0.3)			-0.3±0.4	-1.5, 0.9	-2.7±0.5	-4.0, -1.4*
Cluster 3	196 (12.1)	27.1 (0.4)					-2.4±0.5	-3.8, -1.0*
Cluster 4	494 (30.4)	28.9 (0.3)						

aSimple regression model results are not shown but significant differences among clusters in mean BMI were similar to those in the adjusted model at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
bModels were adjusted for survey year, sex, age, race/ethnicity, and PIR.
cSEM: standard error of the mean.
dß represents difference between mean BMI of cluster and reference cluster. Differences in mean BMI are different than those between raw means because they represent differences in least square means.
eSE: standard error.
**P*-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Table 3.4. Mean waist circumference (cm) and covariate-adjusted regression model results for clusters representing temporal physical activity patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006[a].

		Mean WC (cm)						
			$\beta_d \pm (SE)_e$	95% CI	$\beta_d \pm (SE)_e$	95% CI	$\beta_d \pm (SE)_e$	95% CI
			Compared with:					
Adjusted models[b]	*n (%)*	Mean (SEM)[c]	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	755 (46.4)	99.9 (0.6)	8.2±1.3	4.7, 11.7*	7.5±1.2	4.2, 10.7*	1.6±1.3	-1.8, 5.0
Cluster 2	182 (11.2)	93.3 (0.9)			-0.7±1.1	-3.7, 2.3	-6.6±1.1	-9.5, -3.7*
Cluster 3	196 (12.1)	94.0 (1.0)					-5.9±1.4	-9.6, -2.1*
Cluster 4	494 (30.4)	98.3 (0.7)						

[a]Simple regression model results are not shown but significant differences among clusters in mean WC were similar to those in the adjusted model at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, and PIR.
[c]SEM: standard error of the mean.
[d]ß represents difference between mean WC of cluster and reference cluster. Differences in mean WC are different than those between raw means because they represent differences in least square means.
[e]SE: standard error.
*_P_-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Significant differences in the odds of obesity relative to normal weight status and metabolic syndrome were present between all clusters except Clusters 1 and 4 and 2 and 3 in the unadjusted model ($p<0.05/6$, simple linear regression model results not shown). In the adjusted models, there were significant differences between all clusters ($p=0.001$) except Clusters 1 and 4 as well as 2 and 3 for the obesity outcome relative to normal weight status, as well as significant differences between all clusters ($p=0.01$) except Clusters 1 and 3, 1 and 4, and 3 and 4 for odds of metabolic syndrome (Tables 3.5 and 3.6). The significantly different odds of obesity relative to normal and metabolic syndrome was greatest between Clusters 1 and 2 (obesity OR: 3.7; 95% CI: 2.0, 6.9, metabolic syndrome OR: 4.3; 95% CI: 1.6, 11.6), similar to the results of the unadjusted model (obesity OR: 2.9; 95% CI: 1.6, 5.3, metabolic syndrome OR: 6.3 95% CI: 2.3, 17.0; data not shown).

Table 3.5. Odds ratio of obesity relative to normal weight and covariate-adjusted regression model results for clusters representing temporal physical activity patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006[a].

		Obesity[d] Odds Ratio					
		OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
		Compared with:					
Adjusted models[b]	*n (%)*	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	755 (46.4)	3.7	2.0, 6.9*	3.0	1.7, 5.5*	1.2	0.7, 1.9
Cluster 2	182 (11.2)			0.8	0.4, 1.6	0.3	0.2, 0.5*
Cluster 3	196 (12.1)					0.4	0.2, 0.7*
Cluster 4	494 (30.4)						

[a]Simple regression model results are not shown but significant differences among clusters in odds ratio of obesity were similar to those in the adjusted model at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, and PIR.
[c]OR represents odds ratio of obesity relative to normal of cluster and reference cluster.
[d] Obesity was defined as BMI $\geq$ 30 kg/m^2 [46].
*P-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Table 3.6. Odds ratio of metabolic syndrome and covariate-adjusted regression model results for clusters representing temporal physical activity patterns of U.S. adults ages 20-65 years as drawn from the NHANES, 2003-2006[a].

		Metabolic Syndrome[d] Odds Ratio					
		OR[c]	95% CI	OR[c]	95% CI	OR[c]	95% CI
		Compared with:					
Adjusted models[b]	*n (%)*	Cluster 2		Cluster 3		Cluster 4	
Cluster 1	755 (46.4)	4.3	1.6, 11.6*	1.1	0.6, 2.0	1.3	0.8, 1.9
Cluster 2	182 (11.2)			0.3	0.1, 0.8*	0.3	0.1, 0.8*
Cluster 3	196 (12.1)					1.1	0.7, 2.0
Cluster 4	494 (30.4)						

[a]Simple regression model results are not shown but significant differences among clusters in odds ratio of metabolic syndrome were similar to those in the adjusted model (except between Clusters 1 and 3) at $p<0.05/6$ (Tukey Kramer adjustment for multiple comparisons).
[b]Models were adjusted for survey year, sex, age, race/ethnicity, PIR, and BMI.
[c]OR represents odds ratio of metabolic syndrome of cluster and reference cluster.
[d]Metabolic syndrome was defined using the National Cholesterol Education Program Adult Treatment Panel III based on the presence of ≥ 3 of the following risk factors: 1) WC (>102 cm for men, >88 cm for women); 2) triglycerides (>150 mg/dl) or taking antihyperlipidemic medications; 3) HDL-C (<40 mg/dl in men, <50 mg/dl in women); 4) hypertension (>130/>85 mmHg) or taking antihypertensive medications; and 5) impaired fasting glucose (>110 mg/dl) or taking glucose-lowering medications [49].
*P-values are two-sided; statistical significance is indicated when $p<0.05/6$; estimates were adjusted for clustering and stratification. Sample weights were appropriately constructed and applied to the analysis as directed by the NCHS. Weights were rescaled so that the sum of the weights matched the survey population at the midpoint of the 4 years covering 2003-2006.

Regarding the other health status indicators and outcomes examined, three significant differences in mean hemoglobin A1c, fasting plasma glucose and odds of diabetes were observed between Clusters 1 and 2, 1 and 3, as well as 2 and 4 ($p<0.05/6$) in the unadjusted models, however, these differences were not observed in the adjusted models (data not shown). Additionally, there was one significant difference in mean HDL-C between Clusters 2 and 4 in the unadjusted model, while there were two significant differences between Clusters 1 and 2 as well as 2 and 4 in the adjusted model (data not shown). Two significant differences existed in mean triglycerides among Clusters 1 and 2 and 2 and 4 in the unadjusted models and these differences remained in the adjusted models (data not shown). Finally, one significant difference in mean total cholesterol (Clusters 1 and 3) and diastolic blood pressure (Clusters 1 and 2) and two significant differences in mean systolic blood pressure (Clusters 1 and 2 and 1 and 3) were observed in the unadjusted model; but these differences were not observed in the adjusted model (data not shown).

3.5 Discussion

Temporal PA patterns generated from one valid random day of accelerometry data are associated with BMI, WC, obesity, and metabolic syndrome, but not with any of the other health status indicators examined. To our knowledge, previous studies have not attempted to derive temporal PA patterns through the integration of time and counts of activity throughout the day. An abundance of research investigates the relationship between PA and health outcomes; however, most studies have focused on categorizing participants based on intensity and frequency of activity and their links to health outcomes [51–53], while others examined daily PA patterns by focusing on distinct time periods when PA was reported such as type of day (weekday vs. weekend) [54], activity phenotypes including "weekend warrior" [40,55], and seasonality [56], without the additional contextual factors including the timing of activity throughout the day considered in the current study. It is noteworthy that mean differences in BMI and WC associated with temporal PA patterns were also clinically relevant implicating their potential application to clinical practice and treatment management [57–59]. Therefore, observed mean differences in health status indicators imply that temporal PA patterns could be an important health exposure that holds promise for early detection of lifestyle factors promoting health and disease in the population.

Cluster 1 was associated with higher BMI, WC, and odds ratio of obesity compared with Clusters 2 and 3, which demonstrates that an inactive pattern (with activity counts ranging between 0-600 cpm) throughout the day is linked with the most adverse health outcomes as evidenced by prior research [51,60,61]. The fact that this cluster included the highest number of participants (46.4%) is alarming but not surprising as previous literature has documented a high level of sedentary behavior (>50% of waking time) among U.S. adults [5,62,63]. Moreover, Cluster 1 predominantly includes ages 50-65y, which is consistent with evidence that shows that activity tends to decline with age [64].

Findings of lower mean BMI and WC and odds of obesity associated with Clusters 2 and 3 (maximum counts ranging between 1,600- >2,000 cpm performed earlier or later in a day, respectively) compared with Cluster 1 (maximum counts of 600 cpm through the day) and Cluster 4 (maximum counts reaching 1,000 cpm between 11:00 a.m. to 2:00 p.m.) support previous literature showing that higher activity counts are associated with lower BMI and WC [13,14,65], but add new information regarding the timing of these patterns. Limited evidence exists regarding the relevance of time of activity through the day in terms of links to health [15–18], so further

development of temporal PA patterns may allow further exploration of time as a potentially important factor. Moreover, the integration of time and counts of activity to clustering along with the findings of clinically meaningful differences in health outcomes, based on distinctive time and count features of activity patterns, indicates that applying a more complex patterning technique to characterize activity through the day, has the potential to unfold the complexity of behavior rather than solely describing PA patterns by sums or labels of maximum activity levels. The present study also contributes to evidence of how usual activity, as part of a lifestyle pattern, occurs throughout the day; for instance, around 3 hours involve increased activity counts as was observed in Clusters 2, 3, and 4 which may indicate planned exercise regimens or doing household work, whereas more prolonged periods of time are tied to lower activity counts, possibly indicating time while sleeping or time spent at classrooms or work. This is consistent with evidence that during weekdays, average hours per day spent in sports, exercise and recreation activities is lower than average hours spent per day on other leisure activities including watching television and socializing as well as time spent in primary activities such as sleeping, working, attending class, and eating and drinking [66].

Certain socio-demographic characteristics such as those included in this study (Table 3.1) have been shown to be associated with PA-related differences in health outcomes. Trends observed in two U.S. surveillance systems revealed that among racial/ethnic groups, non-Hispanic whites had the highest prevalence of being physically active and lowest prevalence of being inactive compared to non-Hispanic blacks [67]. Based on this, we would expect that Cluster 2, with the highest activity counts, would be more heavily represented by non-Hispanic whites compared to non-Hispanic blacks and vice versa for Cluster 1, with the lowest activity counts. However, in this study, Cluster 1 comprised the highest number of participants from all race/ethnicity groups, with the highest proportion of non-Hispanic whites. Further, taken in the context of relative differences in BMI among the clusters, the temporal PA pattern associated with the lowest BMI and WC (Cluster 2) was more significantly represented by characteristics: male, non-Hispanic white, and age group 35-49y, while the temporal PA pattern (Cluster 1) associated with the highest BMI and WC included a higher proportion of females, non-Hispanic white participants compared to non-Hispanic black and Mexican Americans, and age group 50-65y compared to the other two age groups.

In general, activity counts tended to be lower towards the end of the day (6:00 p.m.-10:00 p.m.) in all clusters except for Cluster 3. Cluster 3 is characterized by lower activity counts during earlier hours (9:00 a.m.-2:00 p.m.) with higher counts observed towards the end of the day between 6:00 p.m.-9:00 p.m. As this cluster was more heavily represented by ages 20-35y, perhaps these higher PA counts in the evening may reflect sports activities or going to a gym. On the other hand, Cluster 2 with higher activity during early hours (9:00 a.m.-11:0 a.m.) included a higher proportion of ages 35-49y, potentially indicating PA during work. Finally, Clusters 1 and 4 characterized by lower activity counts ranging between 200-1,000 cpm were more heavily represented by age group 50-65y which is consistent with findings that activity tends to decline with age [64].

Elements other than intensity and duration of activity such as time of activity can be an important aspect of PA patterns and may describe PA better within the context of lifestyle. Moreover, timing of activity occasions may also be tied to dietary intake and sleep-wake regimens. For instance, an individual with a "night owl" behavior pattern may have a greater evening preference and choose to exercise later in a day compared to one with an "early bird" behavior pattern with morning preference [68]. Therefore, insight into how these various factors interact within a day and within an overall routine over longer periods of time such as over a week, month, or year, may reveal stronger associations to health outcomes compared to when they are considered separately and thus allow for more targeted interventions based on overall lifestyle, work schedules, and family life. Further, the rapid accumulation of data on health behaviors through technology-assisted assessment tools including those targeting dietary and activity patterns will provide additional data for future investigation of whether and how the timing of these activities influences health. Integrating analyses of these datasets will add further knowledge of how these behavioral factors may contribute to metabolic dysfunction and chronic disease. Moreover, utilization of complex analytic tools including data-driven techniques and methods of epidemiology, to integrate time to behavioral patterns including activity and dietary intake, holds promise to understand how these temporal patterns through the day and over time influence long-term health outcomes.

Strengths of this research include the use of a comprehensive approach to classifying PA exposure that considers the complexity of activity over a 24-hour period rather than examining single activity occasions (i.e., in the morning or evening). To our knowledge, this is the first study to attempt integrating time in a 24-hour day to patterns of activity. In addition, the methodology used in the current study to create temporal PA patterns and compare groups by health status

indicators and disease outcomes performed similarly when compared with the traditional clustering methods based on reported activity occasion (such as by engaging in different activity levels vs. inactivity) [69,70], and the results reveal efficacy that might be enhanced by additional methodologic refinement in future studies. The limitations of the study should also be mentioned. One important limitation is the small sample size representing ~8% of original sample of participants included in survey years 2003-2006; therefore, study results should be interpreted with caution. Of note, sample size attrition is mostly attributable to the selected age range 20-65y and the inclusion of health status indicators examined in a fasting subsample of participants (both criteria resulted in loss of ~84% of the original sample). Additionally, one valid weekday was used to represent the activity occasions of the participants; though one random valid day has been shown to be sufficient for producing reliable population-level estimates of accelerometer-measured activity [71], patterns of activity could differ based on type of day and may potentially vary more on the weekends compared with the weekdays. Thus, further studies should consider investigation of activity patterns over weekend days. Moreover, accelerometers do not capture all types of activity including static activities (e.g., riding a stationary bike or water activities such as swimming) [38]; therefore, although this is an objective measure of PA, it still may not represent the true activity levels of the U.S. population [40].

3.6 Conclusion

Temporal PA patterns are associated with differences in BMI, WC, and chronic disease. Individuals with higher activity counts performed early (9:00 a.m.-11:00 a.m.) or later (6:00 p.m.-9:00 p.m.) in a day exhibited lower BMI, WC and odds of chronic disease compared to those with lower activity counts based on objectively measured PA data collected on one random weekday. The incorporation of time of day with counts and sequence of activity is possible to create temporal PA patterns that are related to health and could provide insight into early detection of behavioral patterns that predispose obesity and chronic disease.

Author contributions

H.A.E.-M, E.D., S.G., A.B., E.A.R., E.H., M.A., J.G., and L.L. designed research; M.A., J.G., and L.L. analyzed data; M.A. wrote paper. H.A.E.-M, E.A.R., and E.H., A.B., S.G., J.G., and E.D.,

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Conflict of Interest:

The authors declare no conflict of interest.

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CONCLUSION

Primary findings from the systematic review (Chapter 1) revealed a potential benefit to modulating exercise timing relative to meal consumption for optimizing postprandial glycemic response in adults. However, a gap still remains in understanding whether the time of day of both these behaviors may drive this association due to a limited number of studies that investigate the timing of exercise performed pre- vs. post-meal, at several time points throughout the day, and links to health.

Findings from Chapters 2 and 3 showed that the incorporation of time to the concepts of both dietary and physical activity patterns is possible and may be important to determine links with health. Specifically, findings showed that a temporal dietary pattern characterized by evenly spaced, energy-balanced eating occasions throughout the day was associated with improved outcomes including lower mean body mass index and waist circumference and odds of obesity compared to three other patterns characterized by distinct peaks in energy intake at different times throughout the day. This pattern is supported in the Dietary Guidelines for Americans based on evidence linking diet to chronic disease prevention. Moreover, a temporal physical activity pattern characterized by higher activity counts performed early or later in a day was associated with lower mean body mass index and waist circumference and odds of obesity compared to patterns with lower activity counts. These findings are consistent with evidence linking higher activity counts to improved health outcomes; and add new information regarding timing of these patterns and with further development may expand exploration of timing as a potentially important factor to physical activity patterns.

Collectively, results from Chapters 2 and 3 revealed an independent association of temporal dietary and physical activity patterns with body mass index, waist circumference, and obesity using a novel methodology. This evidence may serve as a platform to investigating the potential joint effects of both these behaviors and explore their interaction within a joint temporal lifestyle pattern, to better understand and identify patterns that support health or predispose to obesity and chronic disease. Moreover, findings from the joint patterning exploration may address the gap identified in the systematic review and if the joint effects are demonstrated, then the findings should be further confirmed through randomized controlled trials which can manipulate the time of day of these behaviors while controlling for both dietary intake and activity. Results from these controlled

trials would help ascertain whether observed associations with health outcomes, as seen in findings from Chapters 2 and 3, may be explained by personal, environmental, or behavioral factors or whether there is a true causal relationship between time of day of these events and health.