ARIC Manuscript Proposal #4172

PC Reviewed: 12/13/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Associations between Physical Activity and Continuous Glucose Monitoring Metrics in Older, Community-Dwelling Adults: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): PA and CGM Characteristics

2. Writing Group:
Writing group members: Joseph Sartini, Michael Fang, Mary Rooney, Jen Schrack, Josef Coresh, Scott Zeger, Elizabeth Selvin

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __JS_ **[please confirm with your initials electronically or in writing]**

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3. Timeline:
December 2022-January 2023: Based on preliminary visit 9 data (including N~900 participants who have worn continuous glucose monitoring sensors (CGM) and Actigraph sensors concurrently), we will prepare an abstract.

Early 2023: Once visit 9 data are finalized (including up to N~1,100 participants who will wear CGM and Actigraph sensors concurrently), we will prepare for publication both a full-length manuscript describing results, as well as a methodology paper describing the processes used to arrive at these results.

4. Rationale:

Engaging in routine physical activity (PA) is often recommended for people with type 2 diabetes to aid in self-regulation of glycemic variability and manage diabetes. This common recommendation stems from the consensus that PA improves insulin sensitivity. Bouts of PA result in short term increase in glucose uptake by the contracting muscles, and there is also evidence to support that muscles which are frequently trained are more responsive to insulin [2,3].

However, there have been few analyses of the effect of PA on diabetes management in older adults. The American Diabetes Association (ADA) recommends that older adults with type 2 diabetes engage in PA, if it is safe for them to do so. This recommendation aims to not only strengthen self-regulation of glycemic variability and manage diabetes, but also to combat muscle loss and development of frailty [1]. This recommendation is based upon results found in the Look AHEAD (Action for Health in Diabetes) trial. This trial found that, while exercise did not reduce the incidence of cardiovascular diseases, exercise as part of a group of lifestyle interventions is effective in producing other clinical benefits, such as weight loss, reduced A1C levels, lowered systolic blood pressure, among others [7]. While Look AHEAD was quite comprehensive, the trial did not include adults older than 75, and it relied upon solely HbA1c to assess participant's glycemic status [7]. As such, little is known about how PA could potentially reduce glycemic variability, and at what levels of PA these types of benefits might be seen, if at all, in adults older than 75 who generally engage in little routine PA.

Older adults with type 2 diabetes, especially those who are on certain glucose-lowering medications, are at an increased risk of hypoglycemia during and after engaging in PA [8]. This effect is exaggerated by the decreased awareness of hypoglycemia experienced by this group, believed to be due to "alterations in release of counterregulatory hormones and psychomotor performance" [6]. The Look AHEAD trial did capture mild and severe hypoglycemia using self-report and serious adverse event reports. These methods were oriented toward detection of hypoglycemia through symptoms. The findings of the Look AHEAD study indicated that, in the Intensive Lifestyle Intervention (ILI) group which participated in greater PA, the risk of hypoglycemic events was significantly higher ($p = 0.008$) than the baseline Diabetes Support and Education (DSE) group during the first year of the study, when the ILI group experienced the greatest weight loss due to the assigned PA routine and was continuing to use insulin at the same rate as the DSE group. This result, according to the study, indicated evidence for a recommendation of reduction in insulin use during periods of great weight loss and PA to minimize risk for hypoglycemic events [4].

The Look AHEAD trial has provided evidence for a link between weight loss and instances of severe hypoglycemia, but the direct, temporal association between PA and bouts of hypoglycemia in older adults with diabetes is not well characterized. The use of CGM sensors in a population of people with type 2 diabetes at this age would allow for a comprehensive and safe ascertainment of hypoglycemic episodes, particularly those which go unnoticed by participants. These sensors also facilitate timestamp analysis, allowing linking of hypoglycemic events to activities undergone by the participants.

Beyond the risks of hypoglycemia, existing PA recommendations for older adults with type 2 diabetes may be too strenuous for some older adults. The Look AHEAD trial tested the benefit

of implementing lifestyle intervention with the goal of 175 minutes of moderate PA per week [7], which is much more intense and longer in duration than most older adults with type 2 diabetes currently undergo [5]. It is expected that PA for adults in this age range who have type 2 diabetes, which itself is a risk factor for frailty [1], will be rather limited, likely occurring in small bursts at relatively low intensities [5]. This type of activity is normally difficult to accurately quantify, but use of accelerometers to measure daily movement provides unique opportunities to understand patterns and trends of daily PA. As such, analyzing a population of adults over 75 who wore these devices makes it possible to discern the characteristics of activities that are beneficial in managing glycemic variability.

The ARIC study has gathered novel data that will facilitate rigorous evaluation of the associations between PA and glucose patterns in older adults both with and without type 2 diabetes. Participants who attended ARIC visit 9 wore an Actigraph (GT9X) accelerometer and CGM (Abbott Freestyle Libre Pro) sensors concurrently for up to 7 days. Using the ARIC visit 9 data, we will (1) evaluate the associations of intensity, volume, and fragmentation of PA with traditional CGM metrics among the older adult community-dwelling study participants. For this same population, we will also (2) ascertain the associations of the same intensity, volume, and fragmentation PA metrics with glucose excursions, and we will (3) define the temporal extent of the influence PA has on the glucose time series, or the nature of how PA instances cause the CGM patterns to deviate from normal.

5. Main Hypothesis/Study Questions

Aim #1: Evaluate the cross-sectional association between relevant PA metrics for older adults (all indicated via Actigraph sensor) and traditional CGM metrics assessing glycemic levels and glycemic variability, stratified by diabetes status.

H1.1: Higher average volume, greater maximum intensity, and lower fragmentation of PA will be associated with lower HbA1c, lower CGM mean glucose, lower CV of CGM glucose, and higher CGM Time-in-Range for those participants with type 2 diabetes.

H1.2: Higher levels of PA and PA capacity (higher maximum intensity and lower fragmentation) will have little to no association with any glycemic measures, CGM-based or otherwise, in those participants without diabetes.

Aim #2: Determine the association between PA characteristics and glucose excursions (hyper- and hypoglycemic) in those with and without diabetes.

H2.1: Increasing PA volume and higher capacity for PA (higher maximum intensity and lower fragmentation) will be associated with reduced hyperglycemic excursions in a dose response manner, regardless of diabetes status

H2.2a: There will be no association between PA and hypoglycemic excursions for those without diabetes

H2.2b: Higher volume in conjunction with lower maximum intensity and greater fragmentation of PA will be associated with a higher likelihood of hypoglycemic events in those with diabetes

Aim #3: Examine how the association between PA and glucose excursions varies temporally after bouts of PA, if at all.

H3: After bouts of PA, individuals will experience prolonged damping of their glucose excursions, potentially lasting more than a day, regardless of diabetes status.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design

Cross-sectional analyses of data collected at visit 9.

Study population

Inclusion: ARIC participants with ≥5 days of analyzable, matched CGM and Actigraph data.
Exclusion: Participants with missing covariates of interest.

Exposures

Participants were asked to wear the CGM sensor for 14 days, of which the Actigraph was to be worn concurrently for 7 days.

PA: Data are available on incidences of PA as collected by the Actigraph sensor. These data, which serve to characterize general and granular PA levels, are summarized in the following table.

Metric	Measured Quantity	Aggregation Level	Units
Number of Active Bouts	Instances of determined PA	Daily	Counts
Total Active Time	Total time spent in active state	Daily	Minutes
Activity Counts	Duration and intensity of PA	Minute	Vectorized Counts
Max 10 Minutes (M10)	Average activity count over most active 10 minutes	Daily	Vectorized Counts
Active-to-Sedentary Transition Probability (ASTP)	Likelihood of moving from active to sedentary state at each measurement; reciprocal of average PA bout length	Full Period	Unitless

Note that an activity contributing to activity counts are defined accelerations along a certain axis, such that the vector magnitude of activity counts is accumulated over the aggregation

period and calculated as the square root of the sum of squares across the three axes. These counts are meant as a proxy for movements, such that larger values would indicate higher intensity activity. A bout, on the other hand, is a prolonged period of movement of a certain intensity. In summary, the daily volume of PA, the maximum intensity, and the fragmentation metrics can be used as proxies for PA engagement and capacity, and the time series of activity counts can be used directly in the more granular analyses.

Outcomes

CGM: The CGM devices sample interstitial glucose every 15 minutes, painting a detailed picture of the individual's glucose profile over the observation period. The measures derived from this data are summarized in the table below.

Metric	Calculation	Associated Aims
Mean Glucose	Simple mean of all CGM values collected during observation	1
Coefficient of Variation (CV)	Standard deviation of CGM values over the observation period, divided by mean glucose	1
Time in Range (TIR)	Percentage of CGM measurements in the 70-180 mg/dL range	1
Number of Hypoglycemic Periods	Unique periods of contiguous CGM under 70 mg/dL	2,3
Magnitude of Hypoglycemic Excursion	Minimum CGM value attained during hypoglycemic event	2,3
Number of Hyperglycemic Periods	Distinct periods of contiguous CGM over 180 mg/dL	2,3
Area under the Curve (AUC) of Hyperglycemic Excursion	Area under the CGM signal curve during hyperglycemic event	2,3

Hypoglycemia Reports: In conjunction with the CGM-based assessment of hypoglycemia, all participants have self-report data indicating their history of severe hypoglycemia, which includes events leading to hospitalizations, as well as self-reported hypoglycemia symptoms during their two-week CGM wear period. This supplemental data will assist in ascertaining the occurrence and severity of analyzed hypoglycemic events.

Covariates

Age, sex, diabetes status, race, study center, educational attainment, BMI, Sulfonylurea use, Non-sulfonylurea diabetes medication use, SBP, DBP, frailty

For Aim #1, Aim #2, and Aim #3, covariates will be based on visit 9 data.

Data analysis

We will report the characteristics of the participants who wore both the Actigraph and continuous glucose monitoring sensor time-series at visit 9 stratified by diabetes status. For Aim #1, general linear models will be used to assess the associations between PA metrics and glycemic variability. In this model, number of active bouts and total active time will be used as proxies for physical activity volume, Max10 will be used to indicate capacity for exercise intensity, and ASTP will be used to indicate general endurance, while glycemic variability will be assessed using time-in-range, number of hyperglycemic excursions, mean amplitude of hyperglycemic excursion, and glucose variability through CV (see table). These measures will be collected through aggregation over the entire concurrent-wear period for each participant. Covariates will be included in this linear model according to the following hierarchy.

- Model 1 = age, race, sex
- Model 2 = Model 1 + study center, educational attainment, BMI, diabetes medication use
- Model 3 = Model 2 + SBP, DBP

For Aim #2, we will mark all individual glucose excursions, defined to be periods where the glucose signal exceeds 180 mg/dL or drops below 70 mg/dL, for each participant, collecting the average magnitude and duration along with the total number of excursions. Then, the same active bouts, total counts, Max10, and ASTP metrics for PA will be used to assess volume, intensity capacity, and endurance for each participant. Finally, we will use a generalized linear model (including the same covariates as in Aim #1) to evaluate the associations between these PA metrics and the intensity/length of glucose excursions.

For Aim #3, granular associations between PA and CGM will be addressed first using varying-order Vector Auto-Regressive (VAR) models, Functional Regression, and Structural Equations Models fit to the two time series, allowing for evaluation of the association between PA and later changes in the sensor glucose readings. The VAR model will be fit on an individual basis, and the distributions of the resulting coefficients will be presented both overall and collated by diabetes status and age quartile. The Functional Regression and Structural Equations models, on the other hand, will be fit to the full population of data for the purposes of estimation. These models will also be fit to data from each part of the day to account for diurnal differences in both glucose and PA, and to data around estimated meal consumption, which will facilitate investigation of how PA affects the post-meal glucose response.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

___X___ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#3792

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* ___3792_____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to

publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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