1.a. Full Title: Physical Activity and Lifetime Risk of Incident Cardiovascular Disease, and Cancer: the ARIC Study.

b. Abbreviated Title (Length 26 characters): PA & multiple outcomes

2. Writing Group:
   Writing group members: Yasuhiko Kubota, Kelly Evenson, Richard F. Maclehose, Nicholas S. Roetker, Aaron Folsom, others welcome

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

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3. Timeline:
   Data analysis: 1-2 months from manuscript approval date.
   First draft of the manuscript: 2-3 months from manuscript approval date.

4. Rationale:
   Non-communicable diseases (NCD) are responsible for two thirds of 56 million global deaths, and 16 million NCD deaths are premature (1). Most NCD deaths derive from cardiovascular disease (CVD) and cancer (1), and thus it is very important to prevent these two diseases for the prevention of premature deaths.
Physical inactivity is considered as one of the four common lifestyle risk factors for NCD (1) (the others are tobacco use, the harmful use of alcohol and unhealthy diets). Abundant reports have suggested that physical inactivity is associated with increased risks of coronary heart disease (2, 3), stroke (4, 5), heart failure (6), peripheral artery disease (7), atrial fibrillation (8, 9), venous thromboembolism (10), and cancer (11, 12). While tobacco use, harmful drinking, and unhealthy diets may be able to be regulated by policy, physical activity depends on mainly individual consciousness.

One tool that may motivate people to be physically active is an understanding of the lifetime risk for major NCD or mortality according to physical activity levels. Lifetime risk estimates, which are absolute risks assessments at a certain age, may be more easily understood by clinicians and general people than relative risks (13). However, to the best of our knowledge, so far there has been no study estimating lifetime risks for major NCD or mortality according to physical activity levels in middle age.

ARIC has published on many of these outcomes individually, but we believe an overall paper looking at multiple outcomes will be useful. In a sense, this is a “review” of PA and multiple outcomes in ARIC with longer follow-up than previously.

5. Main Hypothesis/Study Questions:
To estimate individual lifetime risks of multiple outcomes: incident CVD (coronary heart disease, stroke, heart failure, peripheral artery disease, atrial fibrillation, and venous thromboembolism), and incident cancer in relation to mid-life physical activity level.

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).

Design
Prospective cohort

Inclusion/exclusion criteria
Inclusion: participants who provided information on physical activity at visit 1.

Exclusion: those who had prevalent CVD or cancer at visit 1.

Main exposure: Physical Activity Levels
Physical activity levels were measured using a modified Baecke physical activity questionnaire at Visit 1 (14, 15). Each of the 150 reported sports and exercises was assigned a specific metabolic equivalent (MET) value according to the Compendium of Physical Activities, where 1.0 MET is considered a resting metabolic rate obtained during quiet sitting. MET values were then multiplied by the time and proportion of the year spent for a final value in units of MET-minutes per week. For comparison we also calculated the MET-minutes per week spent in moderate (3.0–6.0 METs) to vigorous (>6.0 METs) activity, as well as in vigorous activity alone. We will categorize the participants as the following 2 patterns if necessary.
First, we will categorize PA according to the AHA guidelines as “recommended” (≥150 min/wk of moderate intensity or ≥75 min/wk of vigorous intensity or ≥150 min/wk of moderate + vigorous intensity), “intermediate” (1–149 min/wk of moderate intensity or 1–74 min/wk of vigorous intensity or 1–149 min/wk moderate + vigorous intensity), or “poor” (0 min/wk of moderate or vigorous exercise).

Second, we will calculate overall PA in MET*min/week and categorize PA into quartiles.

Covariates
Age, sex, race/ARIC field center, estimated glomerular filtration rate, smoking status and amount, alcohol drinking and amount, daily total energy intake and education at visit 1.

Endpoints
Time to events and lifetime risks of NCD using ARIC visit 1 as baseline.

Statistical analysis
We will calculate hazard ratios (HR) and 95% confidence intervals of incident CVD and cancer and total mortality using Cox proportional hazards models in relation to physical activity levels. We will also compute lifetime risk of NCD outcomes using a macro from Dr. Donald Lloyd-Jones (16). It employs a Kaplan Meier analysis that incorporates competing risks, with deaths from other causes as competing events. Remaining conditional lifetime risk will be calculated at 45, 55, and 65 years. If necessary, we will conduct sex or race-specific analyses.

Limitations
Physical activity was self-reported not directly measured.

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.csc.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)?

Multiple ARIC papers on individual outcomes. For example:

#2432: Life’s Simple 7 (ideal CV risk) and heart failure
#2548: Changes in Physical Activity and the Risk of Incident Heart Failure: The Atherosclerosis Risk in Communities (ARIC) Study
#2631: Physical activity, family history of premature coronary heart disease (CHD), and incident CHD in the Atherosclerosis Risk in Communities (ARIC) study

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* 2006.16)

___   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.csc.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.csc.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 for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC 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 ____ No.

References: