**Manuscript Proposal, CARDIA Study**

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| **Date Submitted: 12/03/20** |

**Review Instructions (page 2) prior to completing/submitting proposal.**

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| **I. Title:** | The association of 20-year longitudinal declines in cardiorespiratory fitness with all-cause and cardiovascular disease related morbidity and mortality: CARDIA |
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| **II. Abbreviated Title:** | 20-year fitness changes and endpoints |

**Select the type of manuscript:** **type an “X” in the box to the “RIGHT” of the type** (these are not check-boxes)

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| **III.** | **Data: Core**: | **x** | **Ancillary**: | **x** | **Substudy**: |  | **Genetic:** |  |  |
|  | ***Include study name below, as applicable:*** | | | | | | | | |
|  | Ancillary Study: CARDIA Fitness Study | | | | | | | | |
|  | Substudy: | | | | | | | | |
|  | Keywords: fitness, aging, clinical outcomes | | | | | | | | |

***Reminder: Identify your keywords!***

**Select data years to be used in proposal: type an “X” in the box to the “RIGHT” of exam** (these are not check-boxes)

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| **IV.** | **Year 0** | | **Year 2** | | **Year 5** | | **Year 7** | | **Year 10** | | **Year 15** | | **Year 20** | | **Year 25** | | **Year 30** | |
| **Data:** | **Exam 1** | **x** | **Exam 2** | **x** | **Exam 3** | **x** | **Exam 4** | **x** | **Exam 5** | **x** | **Exam 6** | **x** | **Exam 7** | **x** | **Exam 8** | x | **Exam 9** | **x** |
|  | **1985-86** | | **1987-88** | | **1990-91** | | **1992-93** | | **1995-96** | | **2000-01** | | **2005-06** | | **2010-11** | | **2015-16** | |

**V. Writing Group**

* **Core and Ancillary Study manuscript proposals:** Include **ALL** authors in the area below; **DO NOT** type their names here.
* **Genetics manuscript proposals only:** Include in authors area below: (1) first 3 authors, (2) CARDIA Representative, (3) all CARDIA authors, and (4) last author
* **As of Apr 6, 2016: “Proposals submitted to P&P should have at most five (5) co-authors from one center (and preferably fewer), and no more than nine (9) total authors, to allow for collaborators from other centers to join**.”

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Example: Coordinating Center, Birmingham Field Center, Echo Reading Center, etc.

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\*A Representative is a CARDIA Investigator who is Steering Committee approved to represent CARDIA in publications and who works closely with you on this manuscript. See instructions for link to “Representatives” list.

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**VI. Background**

Cardiorespiratory fitness (henceforth: fitness) is an important attribute that requires coordination across multiple anatomical systems including the cardiovascular, respiratory, and musculoskeletal systems. Substantial evidence accumulated over the past several decades supports the strong association of low fitness with risk of premature mortality and non-fatal and fatal cardiovascular disease (CVD).1-12 Further, epidemiological evidence suggests that fitness is potentially a stronger predictor of mortality compared to more established risk factors including smoking, hypertension, high cholesterol and type 2 diabetes mellitus.13

While several classic landmark population-based studies have demonstrated an inverse association of fitness with all-cause and cause-specific morbidity and mortality (e.g., CVD, cancer), most have examined this association using a single exposure estimate of fitness most often ascertained during midlife.14,15 However, with the single-time assessment, it is difficult to discern if observed findings are influenced by genetics, subclinical disease, or changes in physical activity and body weight.14 Far fewer population-based studies have reported on the association of fitness changes and mortality.14,16,17 Of these, all were conducted in homogeneous study samples consisting of white men only, which limits potential generalizability of findings; two of the studies utilized Norwegian and Finnish study samples.16,17 Further, all studies conceptualized fitness change based on two assessments that ranged approximately 514 to 1117 years apart and two studies utilized cycle ergometer protocols16,17, which has been shown to result in lower fitness measures compared to the treadmill. Nonetheless, findings from these studies supported a lower mortality risk among those men who increased fitness, or moved to a higher fitness category, over the exposure assessment period.14,16,17

CARDIA can contribute to the existing knowledge base in several ways, including:

1. Fitness was ascertained using a symptom-limited graded exercise treadmill test (GXT) at baseline (Year 0; 1985-86), and the Year 7 (1992-93) and 20 (2005-06) follow-up exams. ***CARDIA will be the first study to report on the associations of fitness change with morbidity and mortality endpoints using three timepoints spanning 20 years that reflect the young adult to early midlife transition.***
2. CARDIA is a diverse and well-characterized biracial cohort. ***CARDIA will be the first study to examine potential differences in these associations by race and sex.***
3. Use of more sophisticated statistical approaches including linear mixed models. Prior studies either utilized exposures based on absolute difference in fitness or changes in fitness category (quartiles or quantiles), overtime.

We leverage these data to examine the associations of 20-year fitness changes with all-cause and CVD related morbidity and mortality.

**VII. Main Study Questions and Hypotheses**

**Aim 1:** To examine the associations of 20-year fitness changes with all-cause mortality and CVD related morbidity and mortality in the entire cohort and within and across race/sex groups.

***Hypothesis 1a:*** Declines in fitness over 20 years will be associated with a high risk of all-cause and CVD related morbidity and mortality

***Hypothesis 1b:*** The observed association will persist in all four represented race/sex groups.

***Hypothesis 1c:*** When compared to white women, the magnitude of the association will be strongest in black men, followed by white men and black women.

**CARDIA data to be used (Required: Exam year(s):** Y20, Y25; **etc.) - See page 2 for instructions.**

Blood Pressure (Form 2; Years 0-20); Sociodemographics (Form 3; Years 0-20); Fasting Blood Draw (total cholesterol, LDLc, HDLc, triglycerides, insulin and glucose; Years 0-20; Alcohol Use Questionnaire (Form 7; Years 0-20); Medical History Questionnaire (Form 8; Years 0-20); Tobacco Use Questionnaire (Form 10; Years 0-20); Physical Activity History (Form 18; Years 0-20); Anthropometry (Form 20; Years 0-20); Graded Exercise Test Rescheduling and Exclusion Criteria Form (Form 21; Years 0, 7, and 20); Treadmill Exercise Test Form (Form 22; Years 0, 7, and 20); Clinical endpoints (396 mo update).

**IX. Analytic Plan**

**Exposure variable (fitness):** total test duration (maximal)

**Outcome variables (endpoints):** all-cause mortality and CVD-related morbidity and mortality (pooled estimates, not by disease type). **Note:** We realize that we will need sufficient cases of CVD since Year 20 to conduct this analyses. We will assess statistical power with the most recent adjudicated datasets, and delay the analysis if additional cases need to accumulate.

**Covariates:** sex, race, participating center, marital status, difficulty paying for basics, tobacco use, alcohol use, physical activity, obesity, systolic blood pressure, LDL-c, HDL-c, triglycerides, family history of CVD, co-morbidities (0, 1, ≥2).

Initial statistical analyses stages will involve data cleaning and variable construction for our primary and covariate measures, beginning with a descriptive content analysis. This descriptive analysis will include frequency distributions, as well as measures of central tendency and variability.

Participants will be excluded if they have missing age, fitness data at all three time points (i.e., Y0, Y7, and Y20), and/or had a CVD event prior to Year 20. Baseline characteristics of the included versus excluded participants will be compared using appropriate bivariable statistics (i.e., Chi-squared tests, Student t-tests, Wilcoxon Rank Sum).

We will use two approaches to address the study hypotheses. For the first approach we will use a binary mixed effects regression model with all-cause mortality and CVD-related morbidity and mortality as the binary outcome and age, maximal fitness, and age\*maximal fitness as the exposures. For the second approach, we will use a linear mixed effects regression model to create summaries of participants fitness from Y0 to Y20, and then fit a Cox proportional hazards (Cox PH) model that would have a regression equation similar to this: CVD risk after Y20 ~ decline in max fitness from Y0 to Y20. For this approach, we will fit a linear mixed model to the fitness data and use subject-specific random intercepts and slopes as the exposures for the models.

Both approaches will be conducted using the entire analytic sample (Hypothesis 1a) and within each of the four race/sex groups (Hypothesis 1b). We will test for interactions by race and sex (fitness change\*race/sex) to address Hypothesis 1c.

**X. Timeline**

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|  | **Dec-Jan** | **Feb-Mar** | **Apr-May** | **Jun-Jul** | **Aug-Sept** | **Oct-Nov** |
| Manuscript approval from CARDIA | x |  |  |  |  |  |
| Data request | x | x |  |  |  |  |
| Statistical analysis |  | x | x |  |  |  |
| Manuscript Preparation / Revision |  |  | x | x | x |  |
| Submit manuscript for P&P approval |  |  |  |  |  | x |
| Submit to peer-reviewed journal |  |  |  |  |  | x |

**Note.** We realize that we will need sufficient cases of CVD since Year 20 to conduct this analyses. We will assess statistical power with the most recent adjudicated datasets, and delay the analysis if additional cases need to accumulate.

**References (limit: one page)**

1. Bruce RA. Exercise, functional aerobic capacity, and aging--another viewpoint. *Med Sci Sports Exerc.* 1984;16(1):8-13.

2. Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med.* 1988;319(21):1379-1384.

3. Erikssen J. Physical fitness and coronary heart disease morbidity and mortality. A prospective study in apparently healthy, middle aged men. *Acta Med Scand Suppl.* 1986;711:189-192.

4. Lie H, Mundal R, Erikssen J. Coronary risk factors and incidence of coronary death in relation to physical fitness. Seven-year follow-up study of middle-aged and elderly men. *Eur Heart J.* 1985;6(2):147-157.

5. Sandvik L, Erikssen J, Thaulow E, Erikssen G, Mundal R, Rodahl K. Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. *N Engl J Med.* 1993;328(8):533-537.

6. Hein HO, Suadicani P, Gyntelberg F. Physical fitness or physical activity as a predictor of ischaemic heart disease? A 17-year follow-up in the Copenhagen Male Study. *J Intern Med.* 1992;232(6):471-479.

7. Peters RK, Cady LD, Jr., Bischoff DP, Bernstein L, Pike MC. Physical fitness and subsequent myocardial infarction in healthy workers. *JAMA.* 1983;249(22):3052-3056.

8. Slattery ML, Jacobs DR, Jr., Nichaman MZ. An assessment of caloric intake as an indicator of physical activity. *Prev Med.* 1989;18(4):444-451.

9. Slattery ML, Jacobs DR, Jr., Nichaman MZ. Leisure time physical activity and coronary heart disease death. The US Railroad Study. *Circulation.* 1989;79(2):304-311.

10. Sobolski J, Kornitzer M, De Backer G, et al. Protection against ischemic heart disease in the Belgian Physical Fitness Study: physical fitness rather than physical activity? *Am J Epidemiol.* 1987;125(4):601-610.

11. Wilhelmsen L, Bjure J, Ekstrom-Jodal B, et al. Nine years' follow-up of a maximal exercise test in a random population sample of middle-aged men. *Cardiology.* 1981;68 Suppl 2:1-8.

12. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation.* 2008;117(5):614-622.

13. Ross R, Blair SN, Arena R, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation.* 2016;134(24):e653-e699.

14. Blair SN, Kohl HW, 3rd, Barlow CE, Paffenbarger RS, Jr., Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA.* 1995;273(14):1093-1098.

15. Imboden MT, Harber MP, Whaley MH, Finch WH, Bishop DL, Kaminsky LA. Cardiorespiratory Fitness and Mortality in Healthy Men and Women. *J Am Coll Cardiol.* 2018;72(19):2283-2292.

16. Erikssen G, Liestol K, Bjornholt J, Thaulow E, Sandvik L, Erikssen J. Changes in physical fitness and changes in mortality. *Lancet.* 1998;352(9130):759-762.

17. Laukkanen JA, Zaccardi F, Khan H, Kurl S, Jae SY, Rauramaa R. Long-term Change in Cardiorespiratory Fitness and All-Cause Mortality: A Population-Based Follow-up Study. *Mayo Clin Proc.* 2016;91(9):1183-1188.

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