ARIC Manuscript Proposal #2845

PC Reviewed: 9/13/16	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Life's Simple 7 at middle-age and the prognosis after myocardial infarction

b. Abbreviated Title (Length 26 characters): Life's simple 7 and myocardial infarction

2. Writing Group:

Writing group members: Yejin Mok, Yingying Sang, Shoshana Ballew, Casey Rebholz, Gerardo Heiss, Aaron Folsom, Josef Coresh, Kunihiro Matsushita; others welcome

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

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3. Timeline: Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

In 2010 the American Heart Association (AHA) announced the following strategic goal: "By 2020, to improve the cardiovascular health of all Americans by 20% while reducing death from cardiovascular disease and stroke by 20%."[1] To achieve this goal, the AHA recommended focusing on 7 traditional risk factors, total cholesterol, fasting blood glucose, blood pressure, smoking, body mass index, physical activity, and diet (Life's Simple 7).[1, 2] The selection of these 7 factors is primarily based on their contributions to the incidence of cardiovascular disease and efficacy of interventions targeting them.[1]

Of interest, among patients with acute myocardial infarction (MI), a few registry-based studies have reported counterintuitively inverse associations between those traditional factors at the time of MI and prognosis (namely, lower mortality among those with more risk factors than those with less risk factors).[3, 4] These studies speculate unmeasured

confounders and difference in medical management (those with traditional risk factors are likely to receive preventive care like statin more than those without) as potential explanations. However, these studies had data of traditional risk factors only at the presentation of MI (prone to misclassification) and outcomes during hospitalization, limiting their ability to comprehensively assess the contributions of Life's Simple 7 to the prognosis after MI.

Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) Study, we will primarily quantify the associations of Life's Simple 7 evaluated at middle-age with the risk of adverse outcomes after MI occurrence later in the life course. To provide a complete picture, we will secondarily assess the contribution of Life's Simple 7 to incident MI as well. If Life's Simple 7 at middle-age is associated with lower risk of not only incident MI but also adverse outcomes after MI (contradictory to the previous registry studies [3, 4] for traditional risk factors at MI presentation), it would be motivating to keep optimal cardiovascular health although some unfortunately develop MI with no or few traditional risk factors [3, 4].

5. Main Hypothesis/Study Questions:

Cardiovascular health behaviors and factors (Life's Simple 7) will be associated not only with the risk of incident MI but also with that of adverse outcomes after MI.

6. Design and analysis

Design: Prospective cohort study. We will first link Life Simple 7 factors at visit 1 to the risk of incident MI in the entire ARIC cohort and then to the risk of adverse outcomes after incident MI among relevant participants. As detailed below, we will conduct a few sensitivity analyses with updated Life Simple 7 factors using data from other visits, annual phone follow-up, and the medical record during MI hospitalization.

Inclusions: All black and white ARIC subjects who did not have a history of MI at visit 1 will be included in the first prospective analysis. The second analysis (our primary interest) will be restricted to those who developed MI after visit 1.

Exclusions:

1. Ethnicity other than black and white
2. Individuals with missing data on Life's Simple 7 factors (exposures) or outcomes described below
3. Participants who had a history of MI based on self-report or electrocardiogram (ECG)

Exposures:

Individual health behaviors and factors will be categorized as poor, intermediate, or ideal according to the AHA Life's Simple 7 criteria (Table 1). These criteria refer to what have been used in Folsom's paper.[5] The score will be calculated as the sum of the scores for each of 7 individual components and the range will be from 0 to 14, with a lower score being unhealthy.

Table 1. AHA Life's Simple 7 criteria

		Ideal	Intermediate	Poor
Health behaviors	Smoking	Never smoker or former and quit >12 months	former and quit ≤12 months	Current smoker

	BMI	<25 kg/m^2	25-<30 kg/m^2	≥30 kg/m^2
	Physical activity (Modified Baecke questionnaire)[6]	≥150 min/wk moderate or ≥75 min/wk vigorous intensity or ≥150 min/wk combination	1-149 min/wk moderate or 1-74 min/wk vigorous intensity or 1-149 min/2k combination	None
	Diet*(modified 66-item Harvard food frequency questionnaire)[7]	4-5 components	2-3 components	0-1 components
Health factors	Total cholesterol	<200 mg/dl (untreated)	200-239 mg/dl or treated to goal	≥240 mg/dl
	Blood pressure	SBP <120 mmHg and DBP <80 mmHg (untreated)	SBP 120-139 mmHg or DBP 80-89 mmHg or treated to goal	SBP ≥140 mmHg or DBP ≥90 mmHg
	Fasting blood glucose	<100 mg/dl (untreated)	100-125 mg/dl or treated to goal	≥126 mg/dl

*Fruits and vegetables ≥4.5 cups/day (approximated as ≥4.5 sevings/day); Fish ≥3.5 oz servings/wk servings/wk (approximated ≥2 3- to 5-oz servings/wk); Whole grain ≥3 1 oz serving or 1.1 g/10g carbohydrates servings/day (approximated as ≥3 servings/day); Sodium ≤1500 mg/day; Sugar Sweetened beverages <450 kcal or 36 oz/wk (approximated as ≤4 glasses/wk)

Covariates:
Age, gender, race/ethnicity, body mass index, HDL-cholesterol, LDL-cholesterol, triglyceride, ECG, prior heart failure, prior stroke and revascularization procedure

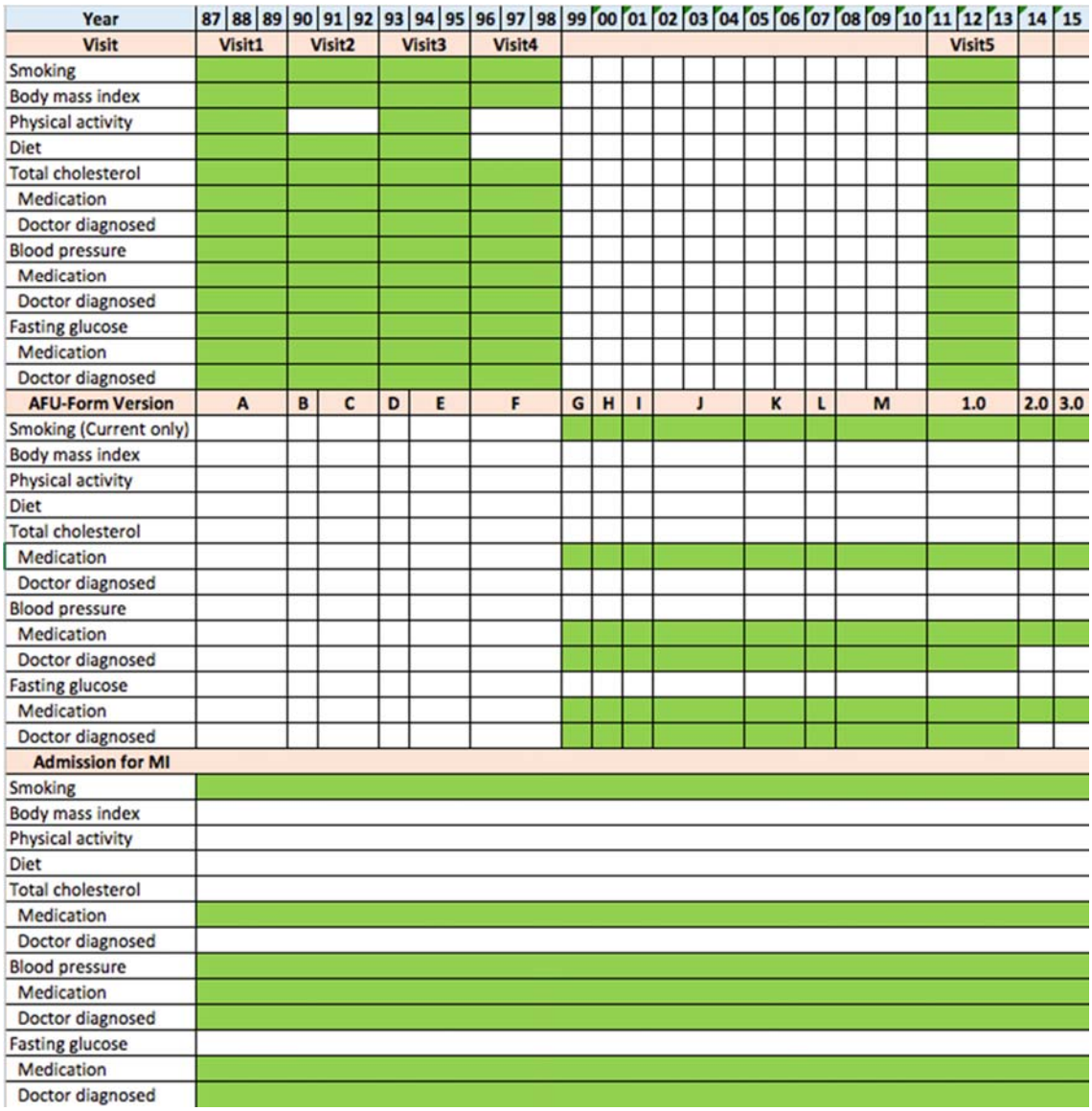
Outcomes:
For the first analysis, definite and probable MI cases adjudicated by the ARIC physician panel will be the outcome of interest. To evaluate the possibility of selection bias in the second analysis (our primary interest) due to MI deaths out of hospital, we will also explore all-cause mortality and cardiovascular mortality. The second analysis will include all-cause mortality, cardiovascular mortality, recurrent MI, heart failure, and stroke after incident MI.

Statistical Analysis:

1. We will summarize basic characteristics by the score based on Life's Simple 7 (0-7, 8-9, and 10-14)[8] at baseline (Visit 1).
2. In terms of longitudinal analysis, we will first quantify the association of Life's Simple 7 (summary score as well as individual factors) with the risk of incident MI, using Kaplan-Meier method as well as Cox proportional hazards regression models accounting for covariates.
3. Subsequently, among those who had incident MI during follow-up, we will similarly evaluate the association of Life's Simple 7 (summary score as well as individual factors) with adverse events (all-cause mortality, cardiovascular mortality, recurrent MI, heart failure, and stroke) after incident MI, using Kaplan-Meier method as well as Cox proportional hazards regression models accounting for covariates.

4. For our primary analysis after MI, we will conduct a few sensitivity analyses:
    a. We will repeat analysis in several subgroups by race and gender.
    b. To assess for the appropriateness of censoring at time for non-cardiovascular death, competing risk analyses will be performed using Fine and Gray's method.[9]
    c. As the time between the evaluation of Life's Simple 7 and MI occurrence may influence the associations of Life Simple 7 with adverse events (e.g., Life's Simple 7 factors 20 years prior to MI may not be that prognostic and the opposite for Life's Simple 7 assessed a few months prior to MI), we will restrict to MI cases between 3 and 9 years after visit 1.
    d. We will also evaluate whether updated Life's Simple 7 factors at subsequent visits, annual follow-up, and admission for MI have similar associations with adverse events after MI. Table 2 summarizes Life's Simple 7 factors we will be able to update accordingly.

Table 2. Availability of Life's simple 7 through the study



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)?
MP #2773 "Risk of recurrent ischemic complications in myocardial infarction (MI) and peripheral arterial disease (PAD)" looks most relevant in the sense of assessing adverse outcomes after MI in the context of traditional risk factors in the ARIC cohort. However, that proposal focuses on clinical factors at the time of MI and does not include several factors in Life's Simple 7 (BMI, physical activity, diet, and total cholesterol) as exposure of interest. Moreover, key authors of MP #2773, Yejin Mok, Shoshana Ballew, Josef Coresh, and Kunihiro Matsushita will also play important roles in the present proposal.

MP #528 "Is diabetes an independent risk factor for mortality after MI?" is also somewhat relevant but this focuses on diabetes at MI presentation. Most importantly this study has been published (Acta Diabetol 2004;41:77–83) and thus our proposal will not jeopardize.

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ 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.

References

1. Lloyd-Jones, D.M., et al., *Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond.* Circulation, 2010. **121**(4): p. 586-613.
2. Sacco, R.L., *The new American Heart Association 2020 goal: achieving ideal cardiovascular health.* J Cardiovasc Med (Hagerstown), 2011. **12**(4): p. 255-7.
3. Roe, M.T., et al., *Documented traditional cardiovascular risk factors and mortality in non-ST-segment elevation myocardial infarction.* Am Heart J, 2007. **153**(4): p. 507-14.
4. Canto, J.G., et al., *Number of coronary heart disease risk factors and mortality in patients with first myocardial infarction.* JAMA, 2011. **306**(19): p. 2120-7.
5. Folsom, A.R., et al., *Community prevalence of ideal cardiovascular health, by the American Heart Association definition, and relationship with cardiovascular disease incidence.* J Am Coll Cardiol, 2011. **57**(16): p. 1690-6.
6. Baecke, J.A., J. Burema, and J.E. Frijters, *A short questionnaire for the measurement of habitual physical activity in epidemiological studies.* Am J Clin Nutr, 1982. **36**(5): p. 936-42.
7. Willett, W.C., et al., *Reproducibility and validity of a semiquantitative food frequency questionnaire.* Am J Epidemiol, 1985. **122**(1): p. 51-65.
8. Nayor, M., et al., *Cardiovascular Health Status and Incidence of Heart Failure in the Framingham Offspring Study.* Circ Heart Fail, 2016. **9**(1): p. e002416.
9. Fine, J.P. and R.J. Gray, *A proportional hazards model for the subdistribution of a competing risk.* J Am Stat Assoc, 1999. **94**: p. 496-509.