ARIC Manuscript Proposal #3985

PC Reviewed: 12/14/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Chest symptoms and subsequent risk of cardiovascular disease: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Chest symptoms and CVD

2. Writing Group:

Writing group members: Kentaro Ejiri, Yejin Mok, Ning Ding, Elizabeth Colantuoni, Patricia P. Chang, Wayne Rosamond, Amil Shah, Pamela Lutsey, Lin Yee Chen, Michael Blaha, Lena Mathews, Kunihiro Matsushita, Others welcome

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

First author: **Kentaro Ejiri**
Address: Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health
2024 E. Monument Street, B-314D, Baltimore, MD, 21287
Phone: (443) 550-8301
E-mail: kejiri1@jhmi.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
Name: Kunihiro Matsushita
Address: Department of Epidemiology,
Johns Hopkins Bloomberg School of Public Health
2024 E. Monument Street, Suite 2-600, Baltimore, MD, 21287
Phone: (443) 287-8766 Fax: 443-683-8358
E-mail: kuni.matsushita@jhu.edu

3. Timeline: Analysis will begin following proposal approval and completion of visit 1 data cleaning. A manuscript will be completed within 6 months after for the approval of this proposal.

4. Rationale:

Chest pain is one of the most common symptoms related to emergency room visit in US.[1, 2] The management of chest pain is challenging, since chest pain can be caused by various clinical

conditions and some of them are life-threatening and require urgent and specific treatment. To guide the management of chest pain, the American College of Cardiology (ACC) and the American Heart Association (AHA) have recently released the Guideline for the Evaluation and Diagnosis of Chest Pain in 2021.[3] A cornerstone of this new guideline is the risk classification of having coronary artery disease (CAD) including acute coronary syndrome (ACS), according to demographics, clinical conditions, and types of chest symptoms.

This approach of focusing on the probability of having ACS "now" makes sense since ACS is a leading cause of chest pain and requires urgent care. Simultaneously, it is important to understand the long-term prognostic implications of chest pain since some patients with chest symptoms due to non-CAD causes may still benefit from some preventive therapies of cardiovascular disease (CVD). Also, some chest symptoms may be linked to heart failure (HF), another life-threatening cardiac condition, rather than CAD.

In this context, although a number of previous studies explored the association of chest symptoms with subsequent risk of cardiovascular outcomes,[4-9] there are several important caveats in those studies. For example, most studies evaluated CAD and cardiac mortality as outcomes of interest [5-9] but not other relevant CVD events such as HF and sudden cardiac death. Also, those studies focused on typical angina-related chest symptoms (i.e., chest pain on exertion relieved by resting and pain localized at sternum or left anterior chest),[4-9] whereas other chest symptoms (e.g., dyspnea on effort, worsening of symptoms) may provide unique prognostic information. Furthermore, the follow-up period was relatively short (<10 years) in most studies.[5-9]

To overcome these caveats, we aim to comprehensively evaluate different chest symptoms which were reported during study visits and their associations with future risk of different CVD outcomes (CAD, HF, sudden cardiac death, atrial fibrillation, and stroke) and other in the community.

5. Main Hypothesis/Study Questions:

1. Several chest symptoms, even not specific to angina, will be associated with subsequent risk of CVD outcomes
2. Different types of chest symptoms will be associated with different types of CVD

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 population: ARIC participants at Visit 1 (1987-89) (Aged 44-66)

Inclusion: Black and White participants

Exclusion:

- Missing chest symptoms
- Non-Black and White
- Previous history of CAD: History of coronary heart disease was defined as self-reported clinical history, evidence of prior myocardial infarction by electrocardiogram obtained at Visit 1 (i.e., PRVCHD05 = Yes)

- Since the assessment of chest pain can be different according to the presence vs. absence of history of CAD, we will exclude participants with prevalent CAD at baseline.
- As secondary analysis, we will exclude participants with prevalent HF and atrial fibrillation (since stroke itself is unlikely to cause chest symptoms, we will not exclude participants with prevalent stroke).

Exposure: Chest symptoms (there are many options to categorize chest symptoms, but our current primary plan is noted below [we may explore other approaches according to our analyzed results])

1. Established classification of angina-related chest symptoms according to Rose angina questionnaire

   We will follow the previous literature[8, 10-12] and stratify the study population into 4 groups of definite angina, possible angina, chest pain not on exertion, and no chest pain, as summarized in the table below.

Definite angina	Definite angina covers chest pain brought on by exertion and which (i) is situated over the sternum or left anterior chest; (ii) forces a person to slow down or stop; (iii) goes away if the person stands still and (iv) disappears within ten minutes.
Probable angina	Possible angina is defined as chest pain brought on by exertion but not satisfying all four of the additional criteria necessary for a diagnosis of definite angina.
Chest pain not on exertion	Chest pain but not on exertion
No chest pain	

2. A few derivatives from the established angina-related symptoms

   We will explore a few modified versions of angina-related to symptoms as described below.

   i. Incorporating worsening of chest symptoms

   We will subdivide definite angina and probable angina according to the presence or absence of worsening of chest symptoms within 2 months (ARIC variable name: MHXA16, MHXA18, MHXA19, MHXA21, MHXA22, MHXA23 and MHXA24). We will also explore worsening of chest symptoms as an exposure as well (see table below).

Worsening	This covers worsening of chest symptoms within 2 months which (i) is more often; (ii) is more severe; (iii) is lasted longer; (iv) is required more nitroglycerin to relieve it; (v) is started by less exertion; (vi) is started by even when sitting still; or (vii) is started when sleeping.
Stable	Any chest symptoms without worsening within 2 months.
Asymptomatic	

   ii. Incorporating dyspnea

We will subdivide definite angina and probable angina according to the presence or absence of dyspnea on exertion (ARIC variable name: PRAA22, PRAA23, PRAA24, PRAA25 and PRAA26). We will also explore dyspnea on exertion as an exposure as well (see table below).

Dyspnea on daily activity	This covers dyspnea on exertion which (i) ever stop for breath after walking about 100 yards (or after a few minutes) on the level or (ii) is too breathless to leave the house or breathless on dressing or undressing.
Dyspnea required walking slower or stopping while walking	This covers dyspnea on exertion which (iii) is to walk slower than people of his/her age on the level because of breathlessness or (iv) ever to stop for breath when walking at his/her pace on the level but not satisfying the criteria of dyspnea on daily activity.
Dyspnea on the level or a slight hill	This covers dyspnea on exertion (v) when hurrying on the level or walking up a slight hill but not satisfying the criteria of dyspnea on daily activity and dyspnea required walking slower or stopping while walking.
Dyspnea only with strenuous exercise	

2. Exploration of different chest symptoms
   Leveraging rich data on chest symptoms in ARIC (see Appendix on pages 9-10 below), we will explore various chest symptoms and their associations with different CVD outcomes. We will use machine learning approach as described below in "**Analysis plan**".

Other variables

- Sociodemographic: age, race, sex, education level, study site
- Physical information: body mass index, waist circumference, blood pressure, heart rate
- Lifestyle: smoking status, alcohol habit, and physical activity
- Medication: antihypertensive drugs, antidiabetic drugs, statins and antithrombotic agents
- Diabetes: Defined as fasting glucose concentration 126 ≥mg/dL (7.0 mmol/L), non-fasting glucose ≥200 mg/dL (≥11.1 mmol/L), self-reported physician diagnosis of diabetes, or use of anti-diabetic drugs.
- Total and high-density lipoprotein cholesterol
- Estimated glomerular filtration rate
- History of stroke was defined as self-reported clinical history at Visit 1.
- History of HF was defined according to Gothenburg criteria and as self-reported use of diuretics at Visit 1 (i.e., PREVHF01 = Yes)
- History of atrial fibrillation was defined by electrocardiogram, which a 10-second 12-lead electrocardiogram with MAC PC cardiograph (Marquette Electrocics Inc, Milwaukee, WI) were performed at visit 1. An automatically coding of atrial fibrillation by electrocardiogram was sent to ARIC Reading Center and was confirmed through visually checked by a cardiologist.[13]

Outcomes:
We defined the outcomes in this study according to previous publications.

- CAD: definite or probable myocardial infarction, definite cardiac death or coronary revascularization procedure.[14, 15]
- HF: hospitalization or death with diagnostic code (*ICD-9* 428 or ICD-10 I50).
- Sudden cardiac death: Adjudicated cases of sudden cardiac death.[15]
- Atrial fibrillation is defined by electrocardiogram, hospital discharge codes and death certificates.[13] A 10-second 12-lead electrocardiogram with MAC PC cardiograph (Marquette Electrocics Inc, Milwaukee, WI) were performed at each study visit. An automatically coding of atrial fibrillation by electrocardiogram was sent to ARIC Reading Center and was confirmed through visually checked by a cardiologist. Additionally, hospitalization or death with diagnostic code (*ICD-9 clinical modification code 427.31 or 427.32)* was identified as atrial fibrillation.
- Stroke was definite or probable ischemic stroke cases which were adjudicated by the ARIC MMCC.[16]
- All-cause death (since CVD is the leading cause of death in the US, we will secondarily analyze all-cause mortality).

Analysis plan:

- Baseline characteristics will be summarized by the groups of chest symptoms as noted in "**Exposures**" above.
- Continuous variables will be presented as mean (SD) or as median with interquartile interval (IQI); categorical variables are presented as numbers and ratios (%). Statistical difference among groups were examined using the analysis of variance for continuous variables and the chi-square test for categorical variables.
- We will estimate cumulative incidence of different CVD outcomes by the groups of chest symptoms using the Kaplan-Meier method and assess statistically significant difference using the log-rank test.
- We will estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of CVD outcomes according to chest symptoms using Cox proportional hazards models.
- To explore potential confounders, we will implement the following models: Model 1, unadjusted; Model 2, adjusted for age, sex, race, and study site; and Model 3, further adjusted for education level, body mass index, smoking status, diabetes and estimated glomerular filtration rate; Model 4, additionally adjusted for history of CVD (i.e., HF, atrial fibrillation, and stroke).
- We will conduct subgroup analysis by age (above or below median), sex, race, education level, body mass index, smoking status, diabetes, estimated glomerular filtration ($<$ vs. $\geq$60), and history of CVD (either HF, stroke or atrial fibrillation). The statistical interaction will be tested by likelihood ratio test.
- We will also explore risk prediction of CVD outcomes by combining chest symptoms and demographic and clinical factors. We will explore c-statistics as a measure of discrimination and evaluate calibration by calibration plots and Hosmer-Lemeshow chi-square.
- Lastly, we will derive a prediction model using a classification tree (a machine learning approach).[17] We prefer this approach to other machine learning approaches (e.g., random

forest) since it will allow us to visualize and program a simple, single model, which will be important for usability in other studies and clinical practice. Nonetheless, we will explore other approaches as well, particularly if the performance of the prediction model based on a classification is not optimal. The classification tree will be trained on a random 70% sample and evaluated on the remaining 30% sample. The classification tree will enable us to detect the presence of higher order interactions, which may improve the accuracy of our prediction model but are not considered in the parametric approach. The prediction model derived using the multinomial modeling approach will be updated if we observe a significant improvement (e.g., more than 3%) in accuracy.

Limitations:

- Only Black and White populations.
- Only 44-66 aged population at baseline.
- Residual confounding is inevitable.
- Potential misclassification of chest symptoms (e.g., different definitions of chest symptoms and care seeking behaviors)
- Acute chest symptoms were not necessarily assessed.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __x_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/aricproposals/dtSearch.html

___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)?
Based on our search, we did not find any proposals investigating the association of chest symptoms with the subsequent risk or CVD outcomes.

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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

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Appendix. List of ARIC variables related to chest symptoms

Variable name	Variable definition or exact question	Answer option
MHXA04	Chest pain or discomfort?	Yes/No/Missing
MHXA05	Do you get it when you walk uphill or hurry?	Yes/No/Never hurries or walks uphill/Missing
MHXA06	Do you get it when you walk at an ordinary pace on the level?	Yes/No/Missing
MHXA07	What do you do if you get it while you are walking?	Stop or slow down/Carry on/Missing
MHXA08	If you stand still what happens to it?	Relieved/Not relieved/Missing
MHXA09	How soon?	More than 10 minutes/10 minutes or less/Missing
MHXA10A	Sternum (upper or middle)	Yes/No/Missing
MHXA10B	Sternum (lower)	Yes/No/Missing
MHXA10C	Left anterior chest	Yes/No/Missing
MHXA10D	Left arm	Yes/No/Missing
MHXA10E	Other	Yes/No/Missing
MHXA10F	Location of Q10e other chest pain	Text suppressed/Missing
MHXA11	Chest pain anywhere else?	Yes/No/Missing
MHXA12	Did you see a doctor because of this pain or discomfort?	Yes/No/Missing
MHXA13	Doctor diagnosis of chest pain	Angina/Heart attack/Other heart disease/Other/Missing
MHXA14	Hospitalized for this chest pain?	Yes/No/Missing
MHXA15	How long ago did you start getting this pain?	1 month/6 months/1 year/2 years/over 2 years ago/Missing
MHXA16	Within the past 2 months, has your chest discomfort occurred more often?	Yes/No/Missing
MHXA17	Has it occurred at least twice as often as before?	Yes/No/Missing
MHXA18	Within the past 2 months, has the pain become more severe?	Yes/No/Missing
MHXA19	Within the past 2 months, has the pain lasted longer when it occurs?	Yes/No/Missing
MHXA20	Use Nitroglycerin to relieve the pain?	Yes/No/Missing
MHXA21	With the past 2 months, has the pain required more nitroglycerin to relieve it?	Yes/No/Missing
MHXA22	Within the past 2 months have you started getting the pain with less exertion?	Yes/No/Missing

MHXA23	Within the past 2 months, have you started getting the pain when sitting still?	Yes/No/Missing
MHXA24	Within the past 2 months, have you started getting the pain when sleeping?	Yes/No/Missing
MHXA25	Have you ever had a severe pain across the front of your chest lasting for an hour or more?	Yes/No/Missing
PRAA21	Are you disabled from walking by any condition other than heart or lung disease?	Yes/No/Missing
PRAA22	Are your troubled by shortness of breath when hurrying on the level or walking up a slight hill?	Yes/No/Missing
PRAA23	Do you have to walk slower than people of your age on the level because of breathlessness?	Yes/No/Missing
PRAA24	Ever have to stop for breath when walking at our own pace on the level?	Yes/No/Missing
PRAA25	Ever stop for breath after walking about 100 yards (or after a few minutes) on the level?	Yes/No/Missing
PRAA26	Too breathless to leave the house or breathless on dressing or undressing?	Yes/No/Missing