1. Full Title: The Association of Systemic inflammation with Mortality Due to Non-Index Cancer in Older Adult Cancer Survivors.

b. Abbreviated Title (Length 26 characters): Inflammation and Mortality

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

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3. Timeline: 6 – 18 months; manuscript submission in Fall 2020

4. Rationale:
With advances in screening, early detection and treatment, cancer mortality rates in the United States have declined in recent decades with a resultant steady increase in the cancer survivor population\textsuperscript{1-3}. 16.9 million cancer survivors are estimated to live in the U.S. and 26.1 million is projected by 2040\textsuperscript{2,4}. But despite gains in survival, cancer survivors suffer short- and long-term adverse outcomes that have significant and lasting impact on their quality of life and may contribute to excess and premature mortality in cancer survivors, compared to persons with no cancer history\textsuperscript{5}.

A recent SEER study showed significant reductions in deaths from index cancers over time, especially for the more survivable cancers of the prostate, breast, colon/rectum, endometrium and bladder\textsuperscript{6}. Conversely, long-term cancer survivors, defined as persons who were alive \geq 5 years post diagnosis, were at higher risk of dying from causes other than their index cancer\textsuperscript{6}. Given that the group of survivors \geq 5 years post diagnosis supposedly represent the successfully treated, excess deaths from causes other than their index cancer earlier are of concern. Excess or
premature deaths from causes other than the index cancer may be due to a high prevalence of shared risk factors for cancer and other causes of death in cancer survivors, the untoward and unintended effects of the cancer treatment(s), possible metabolic and immunologic effects of physiologic dysregulation induced by the cancer itself, or a combination of these factors. Although the mechanistic pathways for the development of these adverse outcomes are not fully understood, inflammation is implicated in their pathophysiology. Inflammation has been linked to cardiovascular disease, depressive symptoms, and cognitive impairment in cancer survivors, and with mortality in most chronic disease states and community dwelling older adults.

Cancer-associated inflammation is known to independently predict disease progression and survival in most cancers. In a recent prospective study of inflammation in long-term cancer survivors, cancer survivors showed worse inflammation profiles compared to individuals with no history of cancer and had 72% higher risk of all-cause mortality. In two meta-analyses, elevated levels of C-reactive protein were associated with deaths from cancer and all-cause mortality. But these studies are limited by the investigation of too few proteins and inclusion of death from all causes. The contribution prospectively-determined systemic inflammation to mortality due to causes other than the index cancer, especially in older adult cancer survivors is unknown. Relatedly, little is known about the specific candidate inflammatory proteins that are the critical drivers of non-cancer mortality in cancer survivors.

Prospective population-based studies of survivors of different cancers, that assay a large array of inflammatory proteins at multiple visits over time can help overcome the limitation of prior studies. Improved understanding of the association of systemic inflammation with non-index cancer mortality in cancer survivors may inform surveillance, risk stratification, and clinical management of inflammation in long-term cancer survivors. Additionally, the identification of key inflammatory signatures underlying non-index cancer mortality may unveil new targets for therapeutic interventions that prolong lives.

The overarching goal of this study is to determine the association of systemic inflammation with mortality from causes other than the index cancer in long-term survivors of the most common survivable cancers – prostate, breast, colorectal, endometrial and bladder cancers; and identify specific inflammatory proteins associated with non-index cancer mortality in cancer survivors. We will analyze data from 633 ≥5-year survivors of the most common survivable cancers - prostate, breast, colorectal, endometrial and bladder; who attended visit 5 (2011-2013), in the Atherosclerosis Risk in Communities (ARIC) Study, in which ~5,000 proteins, including ~350 inflammatory proteins, were assayed in plasma collected at 2 time-points 18 years apart, using a state-of-the-art, highly sensitive aptamer-based protein profiling (SOMAscan® Platform). We will identify outcomes from visit 5 (2011-2013) till the end of 2017.

5. Main Hypothesis/Study Questions:

**Aim 1:** *In long-term cancer survivors,* determine whether levels of circulating inflammatory proteins are associated with death from causes other than the index cancer.

**Hypothesis 1:** In long-term cancer survivors, higher levels of pro-inflammatory proteins and lower levels of anti-inflammatory proteins are associated with increased risk of death from non-cancer causes.

**Aim 2:** *In long-term cancer survivors,* determine whether a higher systemic inflammation score ("I-Score") is associated with death from causes other than the index cancer. *I-Score,* a proteomic measure of systemic inflammation, will be constructed using exploratory factor analysis.

**Hypothesis 2:** In long-term cancer survivors, higher I-Score is associated with death from causes other than the index cancer.

**Aim 3:** *In long-term cancer survivors,* determine whether the association of the circulating inflammatory proteins identified in Aim 1 and I-Score with death from causes other than the index cancer varies by a) major cancer site (prostate and breast), b) sex (for non-sex specific cancers), and c) race.
Hypothesis 3: In long-term cancer survivors, the association of the circulating inflammatory proteins identified in Aim 1 and I-Score with death from causes other than the index cancer will differ by major cancer site, be stronger in males, and Blacks.

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:**

ARIC is an ongoing population-based, prospective, cohort study, which from 1987 to 1989 enrolled 15,792 adults (Fig. 1) between the ages of 45 and 65 years, from communities within the U.S: Washington County, MD; Forsyth County, NC; northwestern suburbs of Minneapolis, MN; and Jackson, MS. In 2012, the ARIC study infrastructure was enhanced to become a full-fledged cancer epidemiology cohort. 15,641 ARIC participants (99% of the total cohort) consented to research on non-CVD outcomes such as cancer (Fig. 1). Among them, information from medical records and state cancer registries, was used to ascertain and adjudicate incident cancer cases. Mortality case files since inception of ARIC in 1987 were generated and updated annually. By 2012, 4743 incident cancers among 4107 participants with up to 25 years of follow-up, were ascertained and characterized; and 1660 cancer-related deaths.
Study participants:

Inclusion criteria: All participants who attended Visit 5 (2011 – 2013) and had inflammatory proteins measured in SomaLogic will be eligible for inclusion in the study. Our study population of cancer survivors and cancer-free individuals will be drawn from visit 5 as the baseline for the proposed study, allowing prospective ascertainment of mortality between visit 5 and administrative censoring (December 2017). For cancer survivors however, we will include only survivors of the more survivable common cancers – prostate, breast, colorectal, endometrial and bladder cancers who are at least 5 years post-diagnosis at the Visit 5 study visit. This inclusion criteria minimizes the likelihood of including survivors who still have active disease in the study. At visit 5 (2011-2013), 1138 (18%) of 6461 participants still alive had a history of cancer after enrollment in ARIC, of which 883 were ≥5 years post-diagnosis (Fig. 2). However, of these 883, only 633 are survivors of the more commonly survivable cancers (Fig. 2). However, these numbers are based on the cancer case files through 2012. Cancer case files have recently been updated through 2015, further increasing the sample size of cancer survivors at visit 5.

Exclusion criteria: We will exclude participants who have no measurements of inflammatory proteins at Visit 5 using the aptamer-based SOMAscan assay. We will exclude participants who are diagnosed with less commonly survivable cancers such as cancers of the lung and pancreas. We will also exclude participants who are <5 years post-diagnosis of a first primary cancer.

Exposure: Our primary exposure is plasma concentrations of inflammatory proteins. In this study, we will use and interrogate an extensive array of ~350 inflammatory proteins included in the broad panel of 5,000 proteins measured at visits 3 and 5 (Fig. 1). These proteins include all known inflammatory proteins in literature, including most of the 194 proteins used in a prior study of inflammation in end stage renal disease, inflammatory proteins that are involved in, or by-products of the nuclear factor kappa beta (NF-κB) pathway, and proteins previously studied in relation to aging-associated outcomes in general populations typically by ELISA. We will model inflammation in four ways; we will examine a) the absolute measure of individual proteins, b) the change in inflammatory protein measures at two critical timepoints 18 years apart (Study visit 3: 1993-95, during which >99% of the cohort had no cancer history; and visit 5, 2011-13, during which >1,000 participants had survived a cancer experience); c) a proteomic inflammatory score (I-Score) that is based on inflammatory protein levels at visit 5 and d) change in I-Score between visit 3 and 5.

Cancer survivor status: The focus of this study is on long-term cancer survivors. Therefore, a long-term cancer survivor at study baseline (Visit 5) is defined as a participant who has had a history of any of the 5 cancers of interest and is at least 5 years post diagnosis as at visit 5 (Fig. 3).
**Outcome:**

**Mortality:** Mortality case files since inception of ARIC in 1987 were generated and updated annually through December 31, 2017. All participants or their proxies are contacted annually by phone. Deaths were identified through records obtained from hospitals in the ARIC surveillance catchment areas, death certificates, and interviews of next of kin for potential out-of-hospital fatal events, or obituaries. Death certificates from state vital statistics offices were obtained on an ongoing basis. Questionnaires were also sent to participants’ physicians to confirm out-of-hospital deaths. Dates and causes of death for study participants were verified by death certificate review. We will extract and classify specific causes of death for all participants after Visit 5 into deaths due to the index-cancer versus causes other than the index cancer. Deaths due to the index cancer is defined as a death in which the primary cause is attributed to the primary cancer which a cancer survivor was diagnosed of. For this analysis, the vital status of study participants will be ascertained from study baseline (Visit 5) through December 31, 2017.

**Other covariates:**

Demographic and clinical variables of interest such as age, sex, race, education, body mass index (BMI), collected at baseline and updated as needed during follow-up will be extracted. Additionally, laboratory and physiologic data, including systolic and diastolic blood pressures, total/high density lipoprotein cholesterol, triglycerides and waist circumference will be extracted from all study visits for which they were collected. Cancer diagnosis, shared cancer and cardiovascular disease risk factors, such as cigarette, alcohol use/intake, physical activity, and diabetes, and other disease information (such as cardiovascular disease, hypertension, coronary heart disease, heart failure), and medication use will also be extracted from Visits 1, 2, 3, 4, 5 and 6. Information about liver function will be determined by liver function tests. We will adjust for age, sex, race, and education as confounders of the association of inflammation and deaths due to causes other than the non-index cancer.

**Statistical Analysis**

The overall strategy for this analysis is to apply regression methods to understanding the association of systemic inflammation with death from causes other than the index cancer in cancer survivors; and identifying candidate inflammatory proteins that are critical to these outcomes. We will investigate the contribution of specific inflammatory proteins and a proteomic inflammatory index (the I-Score) which will be developed by exploratory factor analysis. We will evaluate both measures at study baseline (visit 5), as well as an 18-year change in both measures between visit 3 and 5. While the I-Score serves as a measure of overall systemic inflammation which may have potential prognostic value in cancer survivors, the identification of a specific inflammatory signature may enhance our knowledge of the etiology of these outcomes in cancer survivors. Subsequently, we will test whether our findings differ in persons with no cancer history.

**Aim 1:** Are levels of circulating inflammatory proteins associated with death from causes other than the index cancer?

Using Cox proportional hazards models, we will evaluate the association of systemic inflammation and mortality from causes other than the index cancer in cancer survivors. Our exposure - systemic inflammation will be evaluated in 2 ways: a) Specific inflammatory proteins measured at Visit 5, and b) Change in inflammatory proteins from visit 3 to visit 5. Thus, for Models 1a – 6a (Table 2), we will fit Cox regression models among eligible cancer survivors using log-transformed inflammatory proteins measured at Visit 5 and modelled as continuous variables. For Models 1b – 6b, we will fit Cox models among a slightly smaller sub-group of cancer survivors who were cancer free at visit 3.
We will model the hazard of death between visit 5 (study baseline) and the end of follow up as a function of 18-year change in each systemic inflammation protein between visit 3 (1993-95), during which participants were mid-life and cancer-free; and visit 5 (2011-2013) when they were at least 5 years post cancer diagnosis (Figs. 1 and 3). Our outcome of interest is mortality from causes other than the index cancer, defined as any death occurring during follow up with a primary cause that is different from a primary cancer diagnosis. Our study baseline is visit 5. Therefore visit 5 is considered time 0 or the study origin, and time since visit 5 is our time scale (Fig. 3). Participants will be followed from Visit 5 till a report of death or the end of study follow up in December 2017. Participants will be censored at the time of death from causes other than the index cancer. Deaths with primary causes attributed to the index cancer will be treated as competing risks (Fig. 3). Thus, all Cox regression models will evaluate the cause-specific hazard death due to causes other than the index cancer. In Models 1a-b (Table 2) we will adjust for age, sex, race-center (Maryland white; Minnesota white; North Carolina white; North Carolina African American; Mississippi African American), and time since diagnosis. Models 2a-2b will be additionally adjusted for cancer risk factors (BMI, waist circumference, diabetes, cigarette smoking, alcohol use and physical inactivity). This model allows us test whether the association of inflammatory proteins with mortality in cancer survivors is independent of cancer risk factors. We will evaluate model fit using likelihood ratio tests and Akaike Information Criteria (AIC). We will test the validity of the proportional hazards assumption using statistical tests and graphical diagnostics based on scaled Schoenfeld residuals. If we find that the hazards are not proportional, we will fit non-proportional hazards or generalized gamma models. To account for multiple comparisons, we will apply Bonferroni or false discovery rate (FDR) correction methods. Inflammatory proteins that are significantly associated with our outcomes at the FDR/Bonferroni-corrected level of significance will be depicted using volcano plots. To estimate whether inflammatory proteins are associated with faster time to death from causes other than the index cancer, we will identify quartiles (minimum – 25th, 25th – 50th, 50th – 75th and 75th – maximum) of log-transformed distributions of each inflammatory protein identified as critical to deaths from causes other than the index cancer. We will then create Kaplan-Meier plots that compare time to death in survivors in the highest and lowest quartiles. We may also compare time to death between survivors who remained in the lower quartiles of inflammation at visits 3 and 5.
and those who remained in the higher quartile or transitioned from lower to higher quartiles over the 18-year period.

**Aim 2:** Is a proteomic measure of inflammation (I-Score) associated with death from causes other than the index cancer?

We will perform Exploratory Factor Analysis (EFA) to find combinations of inflammatory markers at each visit that explain a significant proportion of the variance in the inflammatory proteins. EFA[^20] is a mathematical data reduction procedure that uses the linear relationships among variables to find a smaller set of factors that explain most of the variance in the original variables and depict the underlying structure of the phenomena (in this case, inflammation). We will select inflammatory proteins to be included in the EFA based on the variability of each protein in cancer survivors and the correlation of proteins within the same class. EFA assumes that the linear intercorrelations between measured variables reflect a smaller number of latent processes, which can be described by a weighted linear combination of the original variables. Weights from each component represent the magnitude and direction of the relationship between each inflammatory protein and inflammation. We will decide on component(s) to retain based on eigen values, scree plots, parallel analysis and the underlying biology. In parallel analysis, eigenvalues from our data set will be compared with those from a matrix of random values of the same dimensionality and components as our data. Factors with eigenvalues greater than those from the corresponding random data will be retained[^21,^22]. We will estimate inflammatory scores (I-scores) at visit 3 and 5. We will develop I-Scores using proteins at one visit (Visit 3 or 5) and then extend derived weights to creating an equivalent weight at the other visit. An individual’s inflammatory score (I-score) will be equivalent to factor scores for the individual, derived as the sum of weighted inflammatory proteins at that visit, where the weights are the loadings for significant component(s) from EFA.

To determine whether higher levels of I-Scores are associated with mortality from causes other than the index cancer in cancer survivors, we will evaluate the effect of absolute I-Scores at visit 5 (Models 1c-6c), and 18-year change in I-Scores between visits 3 and 5 (Models 1d-6d). With the exception of the inflammatory measure, all models will be constructed as in Aim 1. As done in Aim 1, we will identify quartiles of the I-Score distribution and create Kaplan-Meier plots estimating time to death from causes other than the index cancer in cancer survivors for cancer survivors who have the highest and lowest quartiles of I-Scores.

**Aim 3:** Does the association of systemic inflammation (inflammatory proteins and I-Score) with death from causes other than the index cancer vary by a) major cancer site (prostate and breast), b) sex (for non-sex specific cancers), and c) race?

To evaluate potential differences by race and sex in the association of inflammatory proteins with death from causes other than the index cancer, we will extend Models 2a-b to include an inflammatory marker and race interaction term (Models 3a-b), and an inflammatory marker and sex interaction term (Models 4a-b) as shown in Table 1. However, the model evaluating effect measure

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<table>
<thead>
<tr>
<th>Models*</th>
<th>Covariates</th>
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<tr>
<td>Models 1c-d</td>
<td>Age, sex, race-center, time since cancer diagnosis</td>
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<tr>
<td>Models 2c-d</td>
<td>Age, sex, race-center, time since cancer diagnosis, cancer risk factors</td>
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<tr>
<td>Models 3c-d</td>
<td>Age, sex, race-center, time since cancer diagnosis, cancer risk factors</td>
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<tr>
<td>Models 4c-d</td>
<td>Inflammatory marker*race interaction term</td>
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<tr>
<td>Models 5c-d (prostate cancer)</td>
<td>Age, race-center, time since cancer diagnosis, prostate cancer-specific risk factors</td>
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<tr>
<td>Models 6c-d (breast cancer)</td>
<td>Age, race-center, time since cancer diagnosis, breast cancer-specific risk factors</td>
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*Models 1c-d and 2c-d apply to Aim 2
*Models 3c-d – 6c-d apply to Aim 3
*Model 3 will be limited to survivors of non-sex specific cancers
*c-models: I-Scores at visit 5
*d-models: Change in I-Scores between visit 3 and 5
modification by sex will be limited to survivors of non-sex specific cancers (colorectal and bladder). To determine whether the association of systemic inflammation with death from causes other than the index cancer in cancer survivors varies by major cancer site ~ prostate and breast, we will perform sub-group analyses in 276 prostate cancer survivors (Models 5a-b) and 189 breast cancer survivors (Models 6a-b), excluding the sex term in the adjustment covariates. For these cancer-specific models, we will adjust for risk factors that are specific to each cancer. Similarly, to evaluate potential differences by race and sex in the association of the systemic inflammation measured by the I-Scores on mortality from causes other than the index cancer in cancer survivors, we will extend Models 2c-d to include an I-Score and race interaction term (Model 3c-d), and an I-Score and sex interaction term (Model 4c-d) as shown on Table 2. To determine whether the association of I-Scores with mortality from causes other than the index cancer in cancer survivors varies by major cancer site ~ prostate and breast, we will perform sub-group analyses in ~276 prostate cancer survivors (Models 5c-d) and 189 breast cancer survivors (Models 6c-d), excluding the sex term in the adjustment covariates.

With linkages to CMS data for a subset of ARIC participants enrolled in Medicaid at the time of their cancer diagnosis, we may be able to evaluate the effect of treatment (chemotherapy, surgery, radiotherapy or combination therapy) in this subset of cancer survivors. However, given our sample size, we may have insufficient power to detect significant differences by treatment type. If this happens, we will interpret findings with caution and plan to explore treatment effect in future other cohorts sufficiently powered for determination of treatment effect.

**Power calculations**

Under the following assumptions: a) that ~5% of deaths are due to the primary cancer, b) a standard deviation of 0.5, and c) an alpha of 0.05, our sample size of 633 cancer survivors has 78%, 90%, 96% and 98% power to detect a hazard ratio of 1.2, 1.3, 1.35 or 1.40 respectively, per standard deviation increase in inflammatory scores using Cox regression models.

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<tr>
<th>Hazard Ratio</th>
<th>Power</th>
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<tr>
<td>1.25</td>
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<td>1.30</td>
<td>0.90</td>
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<td>1.35</td>
<td>0.96</td>
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<tr>
<td>1.40</td>
<td>0.98</td>
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**Sensitivity analyses:**

Given that circulating inflammatory proteins are largely synthesized by the liver, participants with compromised liver function may have altered levels of inflammatory proteins independent of other causes. We will determine the sensitivity of our findings to compromised liver function by excluding participants with a history of liver disease and repeating the analysis in a smaller subset of cancer survivors who have no history of liver disease.

**Power for sub-group analyses:**

Given the role of the liver and kidney in the synthesis and regulation of circulating inflammatory proteins, participants with compromised liver or kidney function may have altered levels of inflammatory proteins independent of other causes. We will determine the sensitivity of our findings to compromised liver and kidney function by excluding participants with a history of liver/kidney disease and repeating the analysis in a smaller subset of cancer survivors who have no history of liver or kidney disease. We will also adjust for markers of liver and kidney function and evaluate the robustness of findings before and after these adjustments.

7.a. Will the data be used for non-CVD analysis in this manuscript? [ ] Yes [ ] 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 √ 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

√ 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# 3327. A proteomic analysis of incident dementia: The ARIC Study
   • MP# 3051. The association of middle and late-life blood pressure with conversion to MCI and dementia: The ARIC Study
   • MP# 3058. The association of late-life glycemia status with 3-year late-life cognitive decline and incident MCI/dementia: The ARIC Study
   • MP# 3903. Multi-omic data integration using systems approaches for mechanistic understanding of disease 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? __√__ Yes ____ No

11.b. If yes, is the proposal _NO_ A. primarily the result of an ancillary study (list number* _________) _YES_ 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 ____ No.

References


of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. Lancet. 2010;375(9709):132-
140. doi: 10.1016/S0140-6736(09)61717-7 [doi].

Atherosclerosis. 2017;259:75-82. doi: S0021-9150(17)30055-2 [pii].

19. The atherosclerosis risk in communities (ARIC) study: Design and objectives. the ARIC investigators. Am J


Heidelberg: Springer Berlin Heidelberg; 2011:1094-1096. https://doi.org/10.1007/978-3-642-04898-2_455. 10.1007/978-
3-642-04898-2_455.

23. Franklin SB, Gibson DJ, Robertson PA, Pohlmann JT, Fralish JS. Parallel analysis: A method for determining