1.a. Full Title: Relative risk regression model with inverse polynomials.

b. Abbreviated Title (Length 26 characters): inverse polynomials

2. Writing Group:
   Writing group members:
   Yang Ning, Mark Woodward

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

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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).

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3. Timeline:
   Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

Clinical guidelines abound with apparently-exact risk thresholds for continuous risk factors, for which definitive evidence is lacking. Examples include the lower risk thresholds for body mass index of 18.5 kg/m^2 and of 115/75 mm Hg for blood pressure. Such thresholds are interpreted as the lowest level that a particular risk factor can go
without risk increasing thereafter, and arise because of the apparent biological truth that many risk factor-disease associations, at least in chronic disease, have a so-called "J-shaped" association. This idea is enshrined within the World Health Organization's Global Burden of Disease project, which estimates country-specific burden in relation to an assumed ideal value of a risk factor: the "theoretical-minimum-risk exposure". Two specific examples of current concern in medicine, where concepts of suitable clinical thresholds are being questioned, are how far can levels of glycemia be safely lowered, to prevent cardiovascular and other complications, without causing deleterious effects, and what is the lowest appropriate threshold in defining new stages of chronic kidney disease?

Epidemiological and clinical studies which address the issue of thresholds generally rely on Cox proportional hazards models, fitting data on the index continuous risk factor after it has been categorized, typically according to its quantiles. More recently, spline models have become recognized as more informative in exploring non-linearity. Clearly, neither can identify the best estimate of the minimum, should one exist. To do this, a parametric non-linear survival model, which can deal with asymmetry, is required. In this manuscript we suggest such a model and illustrate its use, not only to estimate minima, but more generally to understand non-linear risk factor-outcome responses across the entire range of data.

5. Main Hypothesis/Study Questions:

The association of impaired eGFR with all cause mortality outcomes will be modeled by inverse polynomials.

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).

Data:

Exposure Variables from ARIC visit 4:
- eGFR (serum creatinine). eGFR will be assessed by CKD-EPI epi equation.11
- Albuminuria (urinary albumin-to-creatinine ratio). Albuminuria will be expressed as urinary albumin-to-creatinine ratio (ACR).

Interacting/Confounding Variables from ARIC visit 4 or closest exam:
- Age, sex, race, hypertension, diabetes.
- Other established cardiovascular risk factors: history of cardiovascular disease (myocardial infarction, bypass grafting, percutaneous coronary intervention, heart failure or stroke), dummy variable hypercholesterolemia, cholesterol levels (total, HDL, LDL), triglycerides, diabetes mellitus, glucose levels with fasting status, smoking (current, former, never), BMI (height, weight), systolic blood pressure, diastolic blood pressure.
- Interfering medication (blood pressure including ACE inhibitors/ARB, Statins, as well as glucose lowering medication).
Outcome Variables:
- All cause mortality + Follow-up time.

Analysis plan and methods:
Various cohorts from North America, Europe, Asia, and Australia will be pooled on individual participant level. Continuous representations of eGFR and other cardiovascular risk factors will be explored, using inverse polynomial relative risk models.

Summary/conclusion:
The inverse polynomials could model various bounded asymmetric relative hazard functions. The estimated hazard function of all cause mortality by inverse polynomials is close to the spline estimate, shows narrower confidence intervals, and provides accurate inference on the minimum hazard threshold.

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 ICTDER03 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.cscce.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)?

MP1449: Comparison of a novel equation for estimated glomerular filtration rate with a conventional one regarding the association with coronary heart disease, stroke, and all-cause mortality: The Atherosclerosis Risk in Communities (ARIC) Study; Matsushita, K.
MP1362: Chronic kidney disease and risk of end-stage renal disease: The Atherosclerosis Risk in Communities Study; Bash, L.

MP1123: Albuminuria and kidney function as predictors of cardiovascular events mortality; Astor, B.

These would be most relevant proposals.

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/

11. 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.