1.a. Full Title: Tracking of HbA1c from Two Visits 14 years Apart in a Community-based Population: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Elizabeth Selvin, PhD, MPH; Kunihiro Matsushita, MD, PhD; Michael W. Steffes, MD, PhD; Frederick L. Brancati, MD, MHS; Josef Coresh, MD, PhD

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

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3. Timeline: Data on the primary variable of interest --measurements of HbA1c from Visit 2 have recently been completed. We anticipate this manuscript will be completed <1 year from receiving the data.

4. Rationale:
   Hemoglobin A1c (HbA1c) is a measure of long-term glycemic control, reflecting glucose exposure over the previous 2-3 month period. HbA1c is central to the clinical management of diabetes and is an important epidemiologic measure in clinical and population-based studies of diabetes. As HbA1c reflects average glucose levels, it is more stable (has lower within-person variability) than other glycemic measurements
including fasting or 2 hour glucose (1). We have previously demonstrated that the short-
term (~2 week) within-person variability in HbA1c levels in persons without diabetes is 
small (CV=4%)(1). Variability in HbA1c levels over the long-term is less well 
characterized.

In persons with diabetes, HbA1c levels are influenced by glucose lowering 
strategies, particularly medication use. In persons without diabetes, HbA1c represents a 
largely un-manipulated entity. Few studies of non-diabetic individuals have repeat 
measurements of HbA1c. To our knowledge, only a single previous study has examined 
the tracking of HbA1c over the long-term among an unselected sample of persons 
without diabetes (2). In this study, Meigs et al compared HbA1c values measured 4-6 
years apart in presumptive non-diabetic participants in the original cohort of the 
Framingham Heart Study. The authors found that change in HbA1c was associated with 
baseline age and BMI; but, overall, HbA1c was fairly reliable over this period with 91% 
of measurements staying within +/-20% of the baseline value.

The objective of the present study is to characterize changes in HbA1c levels in 
ARIC participants during 14 years of follow-up. We will assess change in HbA1c overall 
and compare the tracking of HbA1c among persons who remain non-diabetic during this 
period, persons who develop diabetes during this period, and persons who remain 
diabetic during this period. A recent study reported that “pre-diabetes” affects an 
estimated 40% of adults over 65 years of age and the combined prevalence of diabetes 
(diagnosed and undiagnosed) and pre-diabetes in the general U.S. population aged 65 and 
older is 72% (3). A goal of the present proposal is to characterize the “natural” 
progression in HbA1c (from middle-age to older) among persons without diabetes at 
baseline.

5. Main Hypothesis/Study Questions:

Hypothesis 1: The well-documented increase in HbA1c with age among initially non-
diabetic individuals may be largely explained by the transition of those in the highest 
quintile of baseline HbA1c to diabetes during the 14 year interval.

Hypothesis 2: Greater increases in HbA1c will be associated with older age, Black 
race/ethnicity, higher body mass index, dyslipidemia, and smoking status at baseline. 
Additional exploratory analyses will be conducted to characterize the subgroup of 
individuals who have the most rapid increase (steepest slope) in HbA1c and to relate 
change in HbA1c to change in BMI, fasting glucose, and lipids.

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: The study population will be limited to the subsample of ARIC 
CARMRI participants who had HbA1c measurements at both the second examination in 
1990-92 (Visit 2) and at the CARMRI examination (Visit 5). We will compare HbA1c
levels at the second ARIC examination (Visit 2) with HbA1c levels at the ARIC MRI examination (Visit 5), the only two time points at which HbA1c levels were measured.

**Statistical Analyses:** The main outcome of interest will be the absolute and percentage change in HbA1c from baseline (Visit 2) among persons without diagnosed diabetes at baseline.

Additional analyses will be conducted stratified by diabetes status at baseline and follow-up (i.e., diabetes at baseline, developed diabetes during follow-up, non-diabetic for the duration). Among persons with diagnosed diabetes, we will further stratify by glucose-lowering medication use. However, it is recognized that trends in treated diabetes may be stunted due to the increased availability of oral diabetes agents and more aggressive approaches to treatment in clinical practice (note: this analysis will be limited by the small sample size of treated diabetics).

We will calculate the within-person coefficient variation and reliability coefficients for HbA1c in initially non-diabetic individuals and other groups of interest. Scatter- and Bland-Altman plots will be generated to visually display the change in HbA1c levels across the range of values. We will also calculate intra-class and Pearson’s correlation coefficients and percentage of measurements which were within 20 and 30% of the baseline value (cut-points chosen for comparability to previous studies) to quantify “tracking” of HbA1c over this time period.

We will assess predictors of change in HbA1c level in multivariable linear regression analyses of absolute and percent change from baseline. We will use logistic regression models to examine baseline predictors of large absolute increases in HbA1c over the 14 year period (e.g., highest vs. lowest 4 quintiles). Covariates of interest include age, sex, race/center, hypertension status, body mass index, smoking status, lipid levels, and glucose levels/impaired fasting glucose status.

Subsidiary analyses will be conducted to explore the following questions which lack pre-specified hypotheses:
- Who are the individuals with the largest increases and decreases in HbA1c level?
- Which covariate(s) predict the largest changes in HbA1c?
- Who are the people that decrease? (without glucose-lowering drugs)

**Sensitivity analyses:** We will conduct sensitivity analyses utilizing information on diabetes diagnosed during the follow-up period (from Visits 3 and 4 and AFU data) to classify duration of diabetes among those persons “newly” detected at the ARIC CARMRI visit. In analyses of predictors of change in HbA1c level, we will also compare models with and without updated covariate information and also consider analyses assessing change in covariates as predictors of HbA1c change. Additional sensitivity analyses will be conducted incorporating sampling weights to assess possible effects of CARMRI stratified sampling design (high IMT and non-high IMT).
**Limitations:** HbA1c measurements are available at only two time points (Visit 2 & CARMRI), 14 years apart. Our analysis is thus limited to CARMRI participants, a non-random sub-sample of the ARIC Cohort who did not have events during the 14 year follow-up interval. While we can compare baseline characteristics of those individuals who died prior to the CARMRI follow-up to those who attended the visit, informative censoring is a serious limitation of this 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 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  __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

8.c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group? ____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.csec.unc.edu/ARIC/search.php](http://www.csec.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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  __X__ Yes  ____ No
11.b. If yes, is the proposal

_X__ A. primarily the result of an ancillary study (list number* ___2003.05
and 2006.15_______)

___ 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/

12. 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. _ES_

Reference List

1. Selvin E, Crainiceanu CM, Brancati FL, Coresh J: Short-term Variability in
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3. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE,
Gregg EW, Bainbridge KE, Saydah SH, Geiss LS: Full Accounting of Diabetes and
32:287-294, 2009