1.a. **Full Title**: Potential future benefits of cardiovascular risk factor control in today’s young adults (R01HL107475-04)

b. **Abbreviated Title (Length 26 characters)**: Value of early CVD prevention in young adults

2. **Writing Group**: No standing ARIC writing group applies to this study’s topic.

Writing group members: Andrew E. Moran (PI); Mark Pletcher; Eric Vittinghoff; Elizabeth Oelsner

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. confirmed--AEM

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3. **Timeline**: November 1, 2016 to March 31, 2019
4. **Rationale:**

Primary prevention—recognition and control of risk factors like high blood pressure (BP) and low density lipoprotein cholesterol (LDL-C) before cardiovascular disease (CVD) develops—has contributed to declining CVD death rates. Along with diabetes, “prediabetes” (fasting glucose ≥100 and <126 mg/dl or hemoglobin A1c 5.7-6.4%) has increased in prevalence, and is associated with higher CVD risk. An important mechanism for implementing primary prevention in clinical practice has been national risk factor control guidelines, which increasingly define the standard of quality care and reimbursement.

Current hypertension and cholesterol treatment guidelines recommend few young adults (aged 20-39 years) for treatment, and few young adults with high BP or LDL-C have these risk factors treated or controlled. 2014 hypertension guidelines strongly recommended treating raised diastolic BP in young adults aged ≥30 years but only weakly recommended treatment in those aged 18-29 years. 2013 cholesterol guidelines based treatment on 10-year CVD risk in most patients. Few young adults with moderately high LDL-C (≥130 and <190 mg/dl) were deemed eligible for treatment because almost all are below the 10-year risk threshold—treatment is therefore focused almost exclusively on adults aged ≥40 years. Hypertension and cholesterol guidelines base treatment on current BP and LDL-C and did not consider cumulative lifetime exposures. Both the hypertension and lipid treatment guidelines recommended aggressive risk factor control in patients with diabetes, but did not recommend accounting for prediabetes status when considering BP or LDL-C treatment.

Accumulating epidemiologic evidence has demonstrated that lasting atherosclerotic damage is caused by early life BP and LDL-C exposures. Our group analyzed CVD risk factor exposures and outcomes from age 20 years until death or old age in Framingham Offspring cohort data. The results suggest that cumulative high diastolic BP and LDL-C exposures during ages 20-39 years are independent predictors of later life CVD risk, implying that young adults may benefit from early BP and LDL-C control. We propose to extend our statistical analyses and incorporate them into a new CVD microsimulation model that tracks life course risk factor trajectories, prediabetes incidence, and cumulative risk factor exposures (“mmHg-years” of BP and “mg/dl-years LDL-C”—analogous to cigarette “pack-years”). Using these tools, we will simulate the lifelong benefits and risks of early prevention and re-evaluate the potential health impacts of interventions to control high LDL-C and BP in young adults, especially in the growing number of higher risk young adults with prediabetes.

5. **Main Hypothesis/Study Questions:**

**Aim 1.** Estimate the potential life years gained from BP and LDL-C control during young adulthood (early prevention), accounting for cumulative atherosclerotic damage from young adulthood exposures

*We hypothesize that 1) control of elevated diastolic BP (≥90 mmHg) and LDL-C (≥130 mg/dl) before age 40 years would yield superior lifetime gains in quality-adjusted life years compared with controlling BP and cholesterol according to 10-year risk after age 40 years, and that millions of young adults could potentially benefit from early adult risk factor control, but that 2) these benefits will be very sensitive to adverse event rates and any potential quality of life decrement associated with taking preventive medications on a daily basis.*

**Aim 2.** Project life years gained, as above, of early treatment young adult raised BP and LDL-C through 2050 in young adults with prediabetes

*We hypothesize that the number of young adults with prediabetes will grow in coming decades, and that aggressive BP and LDL-C control during the young adult years in these patients would gain more quality-adjusted life years and be more cost-effective than deferred/later treatment in this group.*
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).

1. **Data:** We propose to harmonize and pool individual-level data from the main ARIC study with similar data from several other NIH-funded prospective cohort studies (related ancillary study proposals in progress for CHS, CARDIA, MESA, Framingham Offspring, Health ABC, Hispanic Community Health Study/Study of Latinos, Jackson Heart Study, and Strong Heart Study). The pooled data will permit us to model risk across the adult years, and will provide a sufficient number of CVD events to support robust inferences that may be generalizable to the entire adult U.S. population. Inclusion of ARIC in this work is particularly important given its robust data in middle aged and older adults, racial/ethnic diversity, meticulous follow-up, and gold-standard measures of CVD risk.

**Table 1.** ARIC study variables (to be considered as co-variates in statistical models)

<table>
<thead>
<tr>
<th>ARIC Variable</th>
<th>Demographic variables</th>
<th>Anthropometric variables</th>
<th>Lipid variables</th>
<th>Blood pressure variables</th>
<th>Other clinical variables</th>
<th>Outcomes variables</th>
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<tbody>
<tr>
<td></td>
<td>Study site</td>
<td>Self-reported ethnicity</td>
<td>Total cholesterol</td>
<td>Mean systolic BP</td>
<td>Active smoking status</td>
<td>Coronary heart disease death</td>
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<td>Baseline age</td>
<td>Self-reported race</td>
<td>LDL cholesterol</td>
<td>Mean diastolic BP</td>
<td>Date of smoking initiation</td>
<td>Acute myocardial infarction (MI)</td>
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<td></td>
<td>Sex</td>
<td>Level of education (years, or highest level attained)</td>
<td>HDL cholesterol</td>
<td>Self-reported diagnosis of hypertension</td>
<td>Date of smoking cessation</td>
<td>Angina pectoris</td>
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<td>Triglycerides</td>
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<td>Coronary revascularization with or without MI</td>
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<td>Stroke death</td>
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<td>Ischemic stroke</td>
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<td>Hemorrhagic stroke</td>
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<td>Heart failure</td>
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</tbody>
</table>

Table 1. ARIC study variables (to be considered as co-variates in statistical models)
Non-cardiovascular deaths

Disease history variables
- History of chronic kidney disease
- History of stroke
- History of diabetes mellitus
- History of heart failure
- History of coronary heart disease

2. Analysis plan and methods:

Statistical analyses. For this study, we will improve upon our past statistical analysis of young adult exposures in the Framingham Offspring cohort, with coronary heart disease as the outcome (Pletcher et al., PLOS One, 2016). In that study, time-weighted average diastolic BP and LDL-C during ages 20-39 years were strongly associated with later life (after age 40 years) coronary heart disease, even after adjusting for later life diastolic BP or LDL-C. Compared with diastolic BP<=70 mmHg, adjusted hazard ratios (HRs) were 2.1 (95% confidence interval: 0.8-5.7) for diastolic BP=71-80, 2.6 (0.9-7.2) for diastolic BP=81-90, and 3.6 (1.2-11) for diastolic BP=>90 (p-trend=0.019). Compared with LDL-C<=100 mg/dl, adjusted hazard ratios were 1.5 (0.9-2.6) for LDL-C=101-130, 2.2 (1.2-4.0) for LDL-C=131-160, and 2.4 (1.2-4.7) for LDL-C>160 (p-trend=0.009). Early adult exposures to systolic BP and HDL-C were not independently associated with future coronary heart disease events.

The proposed study will repeat this analysis in a dataset of pooled NHLBI cohorts data (as described above). We will apply mixed effects modeling to available demographic and longitudinal cardiovascular risk factor measurements in order to obtain best linear unbiased estimates of individual cardiovascular risk factor exposure “histories” for all participants, extending from age 20 years until death, including body mass index (BMI), high density lipoprotein cholesterol (HDL-C), calculated LDL-C, and systolic and diastolic BP. We will also calculate cumulative pack-years of smoking exposure at every age. Following initial imputation of BMI, age at diabetes onset as well as starting or stopping medication use, risk factor trajectories will be flexibly modeled using restricted 3-knot cubic splines in with knots at approximately ages 20, 40 and 60 years. Fixed effects will capture the average trajectory for each risk factor pattern and random effects will capture individual departures from the average. Models for cholesterols and blood pressure will control for sex, BMI and diabetes status (as time-dependent covariates), and response to medication, which will be treated as a random effect.

Individual trajectories will be used to estimate time-weighted average exposures (similar to “pack years” of tobacco exposure). Young adult risk factor exposure was calculated as the time-weighted average over the ages 20-39 years. Cox proportional hazards models will be used to incorporate the effects of time-weighted average exposure to BP and LDL-C in the same survival models as “current” risk factors (the most recent directly measured value carried forward) in order to estimate the independent effect of young adult risk factors on later life risk for incident (first-ever) coronary heart disease, stroke, and heart failure events. To fit the needs of the computer simulation model, which simulates discreet incident CVD outcomes and disease states, a separate risk function will be fit for incident events for each outcome, censoring on first occurrence of either other two CVD outcomes or non-CVD death. Models will adjust for age, socio-demographics, clinical factors and vascular risk covariates in Table 2. All analyses will use SAS or STATA software.

Computer Simulations: We will use the microsimulation version of the CVD Policy Model,4-6 programmed in TreeAge 2014 software. Based on the above described trajectories analysis we will simulate risk factor trajectories and tabulate individual exposures to BP and LDL-C and other risk factors from age 20 years until death in a computer simulation model of U.S. adults and incorporate young adult and later life BP and LDL-C effects on later life CVD risk. We will simulate and compare the potential life years gained from young adult BP and LDL-C treatment (early treatment) compared with later life, 10-year risk based treatment (late
treatment). Last, we will compare potential life years gained from early vs. late BP or LDL-C treatment in young adults with prediabetes from now until the year 2050. Treatment simulations will account for a range of probabilities or adverse medication events and decrements in quality of life related to long term pharmacologic and lifestyle interventions.

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)?  Not applicable

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.
References:


