ARIC Manuscript Proposal #2303

PC Reviewed: 2/11/14 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title:

Diabetes, hyperglycemia, and the burden of frailty syndrome in the Atherosclerosis Risk in Communities Study

1.b. Abbreviated Title (Length 26 characters):

Diabetes and frailty syndrome

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal: JGG

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3. Timeline:

All data for the proposed analyses are currently available. We aim to complete this manuscript within a year after approval of this proposal.

4. Rationale:

The health burden attributable to diabetes is substantial, accounting for a significant amount of morbidity as the result of both microvascular (e.g., diabetic retinopathy, nephropathy, and neuropathy) and macrovascular (e.g., coronary heart disease, peripheral arterial disease, and stroke) complications[1–3]. A growing body of research has focused on understanding the relation between diabetes and the development of frailty syndrome in older adults[4,5]. Frailty syndrome is most often characterized by a biological state of increased vulnerability to acute or chronic stressors that results from a decrease in physiological reserve and an increase in multisystem dysfunction that accompany aging[6,7]. Frailty is associated with increased risk of disability, hospitalization, and mortality[8,9].

The most extensively used operational definition of frailty was developed by Fried et al., and it comprises a specific phenotype that includes the presence of at least three of five components: 1) weight loss, 2) slowness, 3) exhaustion, 4) weakness, and 5) low physical activity[6,10]. The presence of one or two components constitutes a prefrail state associated with increased risk of developing the syndrome[6]. In studies that have defined frailty according to the aforementioned criteria, prevalence estimates among adults aged 65 years or older have ranged from 4% to 17%[11].

In the Cardiovascular Health Study, the Women's Health and Aging Studies, and the Health and Retirement Study, frailty syndrome as defined by Fried et al. was found to be associated with prevalent diabetes[6,12,13]. Several other studies have reported independent associations between each of the five components of frailty and diabetes[5]. It has been further demonstrated that insulin resistance, hyperglycemia below the threshold for diagnosis of diabetes, and inflammation are also related to the burden of frailty[13–15]. Thus, it has been postulated that diabetes and prediabetes may directly contribute to the development of frailty through metabolic pathways, or they may contribute to the syndrome through comorbid microvascular and macrovascular complications[5]. Previous investigations have not extensively explored the extent to which the association between diabetes and frailty can be explained by other diseases and disorders. Additionally, the influence of duration of diabetes or glycemic control on the burden of frailty has yet to be examined. Further research into each of these areas will help to more accurately establish the burden of frailty associated with diabetes and may help elucidate mechanisms by which chronic hyperglycemia increases the risk of frailty.

In the ARIC study, we have the opportunity to 1) rigorously quantify and characterize the burden of frailty syndrome associated with diabetes and prediabetes and 2) determine the extent to which comorbidities, duration of diabetes, and hyperglycemia that is below the threshold for a diagnosis of diabetes contribute to frailty in a population-based cohort of men and women. The findings from this study will have important clinical and public health implications that could

affect prevention strategies and inform the ongoing debate regarding the relative importance of tight glycemic control in older adults with diabetes.

5. Main Hypothesis/Study Questions:

Question 1

Are diabetes and prediabetes associated with a higher prevalence of frailty syndrome in older, community-dwelling adults?

Hypothesis 1.1

We hypothesize that individuals with diabetes and prediabetes have a significantly higher burden of frailty compared to those who are normoglycemic.

Question 2

To what degree do comorbidities explain any excess burden of frailty in those with diabetes and prediabetes compared to those who are normoglycemic?

Hypothesis 2

We hypothesize that comorbidities partially explain the association of diabetes and prediabetes with frailty.

Question 3

Among those with diabetes, is duration of diabetes or glycemic control associated with frailty?

Hypothesis 3

We hypothesize that longer duration of diabetes and poorer glycemic control are associated with a higher likelihood of being frail.

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

We will conduct a cross-sectional study of the association of diabetes and prediabetes with disability at visit 5. Duration of diabetes will be assessed using historical data.

Exclusions

Participants with missing data on diabetes status (based on self-reported diagnosis, glucose, and/or HbA_{1c}) or frailty syndrome will be excluded from the analyses. In the event that there is a substantial amount of missing data, we will determine its nature and will come to a consensus on the most appropriate way of dealing with it.

Variables

Diabetes and prediabetes. Participants who meet any of the following criteria at visit 5 will be characterized as having diabetes: 1) self-report of a physician diagnosis of diabetes, 2) self-report

of use of anti-diabetic medication, 3) fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/l), or 4) HbA_{1c} ≥ 6.5% (48 mmol/mol)[5]. Prediabetes will be defined by a fasting plasma glucose level ≥ 100 mg/dL (5.6 mmol/l) and ≤ 125 mg/dL (6.9 mmol/l) or an HbA_{1c} ≥ 5.7% (39 mmol/mol) and ≤ 6.4% (48 mmol/mol)[5]. We may also utilize a stringent definition of undiagnosed diabetes that will require both an elevated fasting plasma glucose level and HbA_{1c}. Furthermore, among individuals who did not fast for 8 or more hours prior to having their blood drawn, we may define undiagnosed diabetes by a non-fasting glucose ≥ 200 mg/dL (11.1 mmol/l).

Duration of diabetes. Calculated as 1) the time since self-report of a physician diagnosis of diabetes or use of anti-diabetic medication at an earlier visit or during one of the annual telephone calls, or 2) current age minus reported age at diagnosis if diabetes was prevalent at visit 1.

Glycemic control. Assessed using HbA_{1c} measured at visit 5.

Frailty syndrome. Characterized by the presence of at least three of five components: 1) weight loss, 2) slowness, 3) exhaustion, 4) weakness, and 5) low physical activity (Table1). The presence of one or two components constitutes a prefrail state[6,10].

Table 1 Frailty syndrome: potential measures and suggested classifications to determine the presence of at least three of five components of frailty.

Component	Measure	Classification
1) Weight loss	a) In the last year, have you lost more than 10 pounds unintentionally (that is, not due to dieting or exercise)?	a) Yes
2) Exhaustion	a) I felt everything I did was an effort b) I could not get "going" c) Did you have a lot of energy?	a) Some of the time or most of the time b) Some of the time or most of the time c) A little of the time or none of the time
3) Low physical activity	a) ARIC/Baecke Physical Activity Questionnaire	a) Less than one hour per week of activity for 10 or more months
4) Slowness	a) 4m walk test	a) Women speed <= 4.57/7 m/s for height <= 159 cm speed <= 4.57/6 m/s for height > 159 cm Men speed <= 4.57/7 m/s for height <= 173 cm speed <= 4.57/6 m/s for height > 173 cm
5) Weakness	a) Grip test	a) Women <= 17 kg for BMI <= 23 <=17.3 kg for BMI 23.1 - 26 <= 18 kg for BMI 26.1 - 29 <= 21 kg for BMI > 29 Men <= 29 kg for BMI <= 24 <= 30 kg for BMI 24.1 - 26 <= 30 kg for BMI 26.1 - 28 <= 32 kg for BMI > 28

Other covariates of interest. Demographics (age, sex, field center/race, education, income, marital status, and employment status at the most recent time data are available); health behaviors (smoking status, alcohol consumption, physical activity, and sedentary behavior); and comorbidities and health status variables (body mass index [BMI], blood pressure, reduced kidney function defined by estimated glomerular filtration rate, history of chronic kidney disease, peripheral arterial disease, coronary heart disease, heart failure, stroke, or fracture-related hospitalization at or prior to visit 5, self-reported health status, medication use, functional

disability as defined by Kuo et al.[16,17], need for special assistance from an individual or device, and history of falls).

Statistical Analyses

Statistical tests will be two-sided and based on an α-level of 0.05. Descriptive statistics (proportions, means, and standard deviations) will be used to describe demographics, health behaviors, and risk factors and comorbidities among participants with and without diabetes (and groups characterized by normoglycemia or prediabetes). Differences between groups will be assessed using chi-square tests for categorical variables and two sample t-tests or analysis of variance for continuous variables as is appropriate (if assumptions of these tests are not met, then non-parametric equivalents will be used).

The association between diabetes (and groups characterized by normoglycemia or prediabetes) and functional disability will be assessed using log-binomial regression to estimate prevalence ratios (PR). We will compare models with adjustment for the following categories of variables (as described above):

Model 0: Diabetes
Model 1: Model 0 + Demographics
Model 2: Model 1 + Health behaviors
Model 3: Model 2 + Comorbidities

The excess prevalence of disability accounted for by comorbidities will be calculated as follows: [(Model 2 – Model 3) / (Model 2 – 1)] x 100. Log-binomial regression will also be used to determine the associations of duration of diabetes and glycemic control with disability among those with diagnosed diabetes.

We will test for interactions by age (older vs. younger [or continuously]), sex (male vs. female), field center/race (indicator variable for Minnesota white, Mississippi black, Maryland white, North Carolina black, North Carolina white), BMI (higher vs. lower [or continuously]), and smoking status (non-smoker vs. ever smoked) by including each variable as an interaction term in the models. The interaction term will be considered statistically significant at an α-level of 0.10. If significant interactions are observed, stratified results will be reported, although interpretations will be guided by the cell sizes and precision of effect estimates.

Limitations

We will be unable to clearly establish the temporality of the observed associations due to the cross-sectional nature of the analyses. Also, for several important measures (e.g., smoking status, alcohol consumption, physical activity, and sedentary behavior), we will be relying entirely on self-reported information which may be associated with more misclassification than if objective measurements were obtained.

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

___ Yes X No

7.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)?

1. Christman AL, Matsushita K, Gottesman RF, Mosley T, Alonso A, Coresh J, et al. Glycated haemoglobin and cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. Diabetologia. 2011 Jul;54(7):1645–52.

2. Schneider ALC, Pankow JS, Heiss G, Selvin E. Validity and reliability of self-reported diabetes in the atherosclerosis risk in communities study. Am. J. Epidemiol. 2012 Oct 15;176(8):738–43.

3. Bower JK, Appel LJ, Matsushita K, Young JH, Alonso A, Brancati FL, et al. Glycated hemoglobin and risk of hypertension in the atherosclerosis risk in communities study. Diabetes Care. 2012 May;35(5):1031–7.

4. Schneider ALC, Williams EK, Brancati FL, Blecker S, Coresh J, Selvin E. Diabetes and risk of fracture-related hospitalization: the Atherosclerosis Risk in Communities Study. Diabetes Care. 2013 May;36(5):1153–8.

5. MP1602: Race, Socioeconomic Status, and Mobility: the ARIC Study

6. MP1603: Race, Lung Function, and Mobility: the ARIC Study

7. MP1697: Functional status and cardiovascular disease

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/

12.a. 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.

12.b. 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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3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* **36 Suppl 1,** S67–74 (2013).

4. Atienzar, P., Abizanda, P., Guppy, A. & Sinclair, a. J. Diabetes and frailty: an emerging issue. Part 1: Sarcopaenia and factors affecting lower limb function. *Br. J. Diabetes Vasc. Dis.* **12,** 110–116 (2012).

5. Atienzar, P., Abizanda, P., Guppy, A. & Sinclair, a. J. Diabetes and frailty: an emerging issue. Part 2: Linking factors. *Br. J. Diabetes Vasc. Dis.* **12,** 119–122 (2012).

6. Fried, L. P. *et al.* Frailty in Older Adults: Evidence for a Phenotype. *Journals Gerontol. Ser. A Biol. Sci. Med. Sci.* **56,** M146–M157 (2001).

7. Xue, Q.-L. The frailty syndrome: definition and natural history. *Clin. Geriatr. Med.* **27,** 1–15 (2011).

8. Zaslavsky, O. *et al.* Frailty: a review of the first decade of research. *Biol. Res. Nurs.* **15,** 422–32 (2013).

9. Shamliyan, T., Talley, K. M. C., Ramakrishnan, R. & Kane, R. L. Association of frailty with survival: a systematic literature review. *Ageing Res. Rev.* **12,** 719–36 (2013).

10. De Vries, N. M. *et al.* Outcome instruments to measure frailty: a systematic review. *Ageing Res. Rev.* **10,** 104–14 (2011).

11. Collard, R. M., Boter, H., Schoevers, R. a & Oude Voshaar, R. C. Prevalence of frailty in community-dwelling older persons: a systematic review. *J. Am. Geriatr. Soc.* **60,** 1487–92 (2012).

12. Cigolle, C. T., Ofstedal, M. B., Tian, Z. & Blaum, C. S. Comparing models of frailty: the Health and Retirement Study. *J. Am. Geriatr. Soc.* **57,** 830–9 (2009).

13. Blaum, C. S. *et al.* Is Hyperglycemia Associated with Frailty Status in Older Women? *J. Am. Geriatr. Soc.* **57,** 840–847 (2009).

14. Walston, J. Frailty and Activation of the Inflammation and Coagulation Systems With and Without Clinical Comorbidities<subtitle>Results From the Cardiovascular Health Study</subtitle>. *Arch. Intern. Med.* **162,** 2333 (2002).

15. Barzilay, J. I. *et al.* Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Arch. Intern. Med.* **167,** 635–41 (2007).

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17. Kuo, H.-K. *et al.* Exploring how peak leg power and usual gait speed are linked to late-life disability: data from the National Health and Nutrition Examination Survey (NHANES), 1999-2002. *Am. J. Phys. Med. Rehabil.* **85,** 650–8 (2006).