ARIC Manuscript Proposal #2304

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

1.a. Full Title:

Diabetes, hyperglycemia, and the burden of functional disability in the Atherosclerosis Risk in Communities Study

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

Diabetes and functional disability

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 prevalence of diabetes and prediabetes are rising rapidly in the United States[1]. According to the most recent available data, approximately 11% of all adults aged 20 years or older have diabetes and 35% have prediabetes[2]. These estimates are substantially higher among those aged 65 years or older (27% and 50% respectively)[2], and both the prevalence and incidence of diabetes and prediabetes are predicted to increase as the population ages[1]. The health burden attributable to diabetes is particularly great, 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[3–5].

Many of the complications of diabetes can lead to functional disability[6–8], which is often defined as difficulty or dependency in performing tasks essential to independent living[9,10]. For example, diabetic neuropathy may decrease lower extremity mobility (LEM; e.g., walking up 10 steps without resting) and ability to engage in general physical activities (GPAs; e.g., lifting or carrying something as heavy as 10 pounds). Similarly, an occurrence of stroke may hinder ability to perform activities of daily living (ADLs; e.g., dressing, including tying shoes, working zippers, and doing buttons), and impede capacity to perform instrumental activities of daily living (IADLs; e.g., managing money).

Several studies have examined the association between diabetes and functional disability. A recent systematic review and meta-analysis identified 26 studies that assessed measures of LEM, ADLs, and IADLs in older adults[8]. Pooled odds ratios (OR) from 12 cross-sectional studies showed that those with diabetes had increased odds of a disability defined by LEM compared to those without diabetes (OR 1.71, 95% confidence interval [CI] 1.53 to 1.91)[8]. Pooled point estimates from 12 and 10 cross-sectional studies similarly showed that having diabetes was associated with increased odds of disability related to ADLs (OR 1.87, 95% CI 1.66 to 2.10) and IADLs (OR 1.67, 95% CI 1.57 to 1.77), respectively[8].

Despite this growing body of research, the extent to which the association between diabetes and functional disability can be explained by comorbid microvascular and macrovascular complications remains unclear[8,11]. Some previous studies of diabetes and disability have attempted to evaluate the extent to which other diseases and disorders explain the association[7,8]. However, none has done so comprehensively and with high-quality characterization of comorbidities[8]. Still fewer studies have examined the influence of duration of diabetes or glycemic control on the burden of disability, and those that have report inconsistent results[7,12,13]. Additionally, only two studies to date have assessed the association between prediabetes and disability, and their findings are conflicting[14,15]. Further research into each of these areas will help to more accurately establish the burden of disability associated with diabetes and may help elucidate mechanisms by which chronic hyperglycemia increases the risk of disability.

In the ARIC study, we have the opportunity to 1) rigorously quantify and characterize the burden of functional disability 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 disability 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 functional disability in older, community-dwelling adults?

Hypothesis 1.1

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

Question 2

To what degree do comorbidities explain any excess burden of disability 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 disability.

Question 3

Among those with diagnosed diabetes, is duration of diabetes or glycemic control associated with functional disability?

Hypothesis 3

We hypothesize that longer duration of diabetes and poor glycemic control are associated with a higher likelihood of being functionally disabled.

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 functional disability 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 $\geq$ 126 mg/dL (7.0 mmol/l), or 4) $HbA_{1c} \geq 6.5\%$ (48 mmol/mol)[5]. Prediabetes will be defined by a fasting plasma glucose level $\geq$ 100 mg/dL (5.6 mmol/l) and $\leq$ 125 mg/dL (6.9 mmol/l) or an $HbA_{1c} \geq 5.7\%$ (39 mmol/mol) and $\leq$ 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 $\geq$ 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.

Functional disability. Characterized by self-report of difficulty performing 12 tasks classified into the following four functional domains: 1) activities of daily living, 2) instrumental activities of daily living, 3) general physical activities, and 4) lower extremity mobility (Table 1). Consistent with previous research, difficulty performing any task within any functional domain will constitute disability (i.e., "No difficulty" = no disability; "Some difficulty" to "Unable to do" = disability)[7,9,10].

Table 1 Functional disability: self-report of difficulty performing tasks as measured in the Physical Ability Questionnaire.

Questions: How much difficulty do you have…?	
Task	**Domain**
1) Walking from one room to another on the same level?	Activities of daily living
2) Getting in or out of bed?	
3) Eating, including holding a fork, cutting food or drinking from a glass?	
4) Dressing yourself, including tying shoes, working zippers and doing buttons?	
5) Doing chores around the house (like vacuuming, sweeping, dusting or straightening up?	Instrumental activities of daily living
6) Preparing your own meals?	
7) Managing your money (such as keeping track of your expenses or paying bills)?	
8) Stooping, crouching or kneeling?	General physical activities
9) Lifting or carrying something as heavy as 10 pounds?	
10) Standing up from an armless chair?	
11) Walking for a quarter of a mile (that is about 2 or 3 blocks)?	Lower extremity mobility
12) Walking up 10 steps without resting?	
Responses: "No difficulty", "Some difficulty", "Much difficulty", "Unable to do", or "Don't know or do not do".	

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, frailty syndrome as described by Fried and collegues[16], 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 comorbidities and health status variables 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. Lastly, our assessment of functional disability does not include difficulty with leisure and social activities, which have previously been included within in the conceptual framework of disability[9,10].

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.

References

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2. Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011*. (2011). at <http://www.cdc.gov/diabetes/pubs/factsheets.htm>

3. Stratton, I. M. *et al.* Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *BMJ* **321,** 405–412 (2000).

4. Van Dieren, S., Beulens, J. W. J., van der Schouw, Y. T., Grobbee, D. E. & Neal, B. The global burden of diabetes and its complications: An emerging pandemic. *Eur. J. Cardiovasc. Prev. Rehabil.* **17 Suppl 1,** S3–8 (2010).

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

6. Gregg, E. W. *et al.* Diabetes and physical disability among older U.S. adults. *Diabetes Care* **23,** 1272–1277 (2000).

7. Kalyani, R. R., Saudek, C. D., Brancati, F. L. & Selvin, E. Association of diabetes, comorbidities, and A1C with functional disability in older adults: results from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. *Diabetes Care* **33,** 1055–60 (2010).

8. Wong, E. *et al.* Diabetes and risk of physical disability in adults: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* **1,** 106–114 (2013).

9. 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).

10. Kuo, H.-K., Bean, J. F., Yen, C.-J. & Leveille, S. G. Linking C-reactive protein to late-life disability in the National Health and Nutrition Examination Survey (NHANES) 1999-2002. *J. Gerontol. A. Biol. Sci. Med. Sci.* **61,** 380–7 (2006).

11. Gregg, E. W. Diabetes-related disability as a target for prevention. *Lancet Diabetes Endocrinol.* **1,** 81–82 (2013).

12. Gregg, E. W. *et al.* Diabetes and Incidence of Functional Disability in Older Women. *Diabetes Care* **25,** 61–67 (2002).

13. Wu, J. H. *et al.* Diabetes as a Predictor of Change in Functional Status Among Older Mexican Americans: A population-based cohort study. *Diabetes Care* **26,** 314–319 (2003).

14. Sayer, A. A. *et al.* Type 2 Diabetes, Muscle Strength, and Impaired Physical Function: The tip of the iceberg? *Diabetes Care* **28,** 2541–2542 (2005).

15. Hiltunen, L., Keinänen-Kiukaanniemi, S., Läärä, E. & Kivelä, S. L. Functional ability of elderly persons with diabetes or impaired glucose tolerance. *Scand. J. Prim. Health Care* **14,** 229–37 (1996).

16. 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).