

ARIC Manuscript Proposal # 1271

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Priority: _____

1.a. Full Title: Does the diabetes case definition affect the relationship of incident diabetes and traditional and novel risk factors?

b. Abbreviated Title (Length 26 characters): Diabetes case definition

2. Writing Group:

Writing group members:

Suzette J. Bielinski, James S. Pankow, Elizabeth Selvin, David Couper, Fred Brancati, Christie Ballantyne, Gabriella Vazquez, Sue Duval

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

First author: Suzette J. Bielinski

Address: University of Minnesota
1300 South Second Street, Suite 300
Minneapolis, Minnesota 55116

Phone: 612-624-1899 Fax: 612-624-0315
E-mail: Bielinski@epi.umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

James S. Pankow

Address: University of Minnesota
1300 South Second Street, Suite 300
Minneapolis, Minnesota 55116

Phone: 612-624-2883 Fax: 612-624-0315
E-mail: pankow@epi.umn.edu

3. Timeline:

Starting Analyses: July 1, 2007

First Draft: September 1, 2007

Submission for Publication: October 1, 2007

4. Rationale:

Prospective epidemiological studies have characterized major risk factors for incident diabetes. These studies employ a variety of criteria to determine diabetes status including self-report, medication use, fasting or non-fasting glucose levels, and/or results from an oral glucose tolerance test. Table 1 summarizes the diabetes case definition used by several of the larger epidemiological studies (Add citations).

All the studies listed, with the exception of the Framingham Offspring Study, included self report of physician diagnosed diabetes in the case definition. For Iowa Women's Health Study, NHANES I, and Nurses Health Study, self report was the only criterion used to define diabetes or trigger additional validation. The use of a case definition based solely on self report can be problematic. In general, any individual characteristic that is associated with more frequent glucose screening or medical surveillance could bias the relationship of diabetes and associated risk factors. Using NHANES data from 5 consecutive examinations (1960-2000), Gregg et al observed large increases in diagnosed diabetes in the overweight and obese. These authors speculate that this trend is due to opportunistic screening of obese individuals¹.

Reliance on a self-report only case definition excludes the large population of undetected diabetes cases in the population. Using the standard definition of diabetes employed in the ARIC Study, 34% of the baseline diabetes cases were identified via a single fasting glucose measurement only. Fasting glucose detected diabetes remained the predominant single criterion for incident diabetes diagnosis in all subsequent visits; 81%, 79%, and 69% of cases for visits 2, 3, and 4 respectively. The short-term variability in a single glucose measurement poses important issues for the use of glucose screening alone to define diabetes cases. The use of a single fasting glucose cutoff score of 126 mg/dL is variable and subject to regression to the mean. Indeed, of the incident cases defined solely by fasting glucose for which there is follow-up data, 40% of visit 2 and 28% of visit 3 screened only cases were do not meet the standard ARIC case definition at a subsequent visit.

Whether different case definitions alter the associations of diabetes with risk factors is unknown. Assuming the case definition impacts the magnitude and or direction of

associations between risk factors and diabetes, it is unknown if these differences are important in our understanding of the etiology, treatment, or diagnosis of diabetes. Another important aspect of this issue is whether or not and to what extent the case definition impacts the predictive value of risk factors for incident diabetes.

The ARIC cohort provides a unique opportunity to assess the associations of incident diabetes and risk factors using several different case definitions. We will compare three different case definitions; self report only, ARIC protocol, and multiple evidence. The self report only group consists of anyone in ARIC who answered positively when asked if a doctor has ever said you had diabetes or sugar in the blood. The ARIC protocol case definition is any participant who self reported, used diabetic medication, had a fasting glucose ≥ 126 mg/dL, or a non-fasting glucose of ≥ 200 mg/dL. Finally, the multiple evidence case definition is the most stringent and includes only those people with a minimum of two of the ARIC criteria (i.e. more specific but less sensitive). To assess the impact of the screening cutoff levels, we will investigate the relationship between risk factors and various glucose screening levels in the screened detected only individuals (i.e. 126-129, 130-134, 135-139, ≥ 140).

Table 1 Summary of Case definition criteria by Study

Study Name	N	Diabetes Case Definition
ARIC	15,792	Self report of physician diagnosed diabetes, diabetic medication use, non-fasting glucose ≥ 200 mg/dL, or fasting glucose ≥ 126 mg/dL
Framingham Offspring Study ²	2,527	<ul style="list-style-type: none"> • Diabetic medication use, plasma glucose ≥ 200 mg/dL at any examination, or plasma glucose ≥ 200mg/dL 1 hour after a 50-g oral glucose tolerance test • Fasting plasma glucose level ≥ 140 mg/dL or diabetic medication use • OGTT detected by fasting or 2-hour post-challenge ≥ 140 mg/dL
Iowa Women's Study ³	41,836	Self reported physician diagnosed
National Health and Nutrition Examination Survey ¹	I = 12,900 II = 11,761 III = 14,301 1999-2000 = 3,598	Self reported physician diagnosed. For NHANES II, III, and 1999-2000, fasting glucose was measured on a randomly assigned subset.
Nurses Health Study ⁴	121,701	Self reported physician diagnosed with further validation

5. Main Hypothesis/Study Questions:

1. What patterns of disease confirmation emerge for each case definition and fasting glucose cutoff levels? (i.e. To what extent are incident cases confirmed in subsequent visits)
2. Do baseline characteristics of incident diabetes cases differ by case definition?
3. Do incidence rates of diabetes differ by case definition?
4. Do the associations of risk factors for incident diabetes differ by case definition?
5. Do baseline characteristics differ between four fasting glucose levels (126-129, 130-134, 135-139, ≥ 140) for individuals identified as cases via this single criterion?

6. Data (variables, time window, source, inclusions/exclusions):

Design: Prospective

Outcome: Incident diabetes (3-case definitions and 4 screening ranges)

Exposure: Sex, age, race, BMI, WHR, baseline fasting glucose, parental history, hypertension, lipid levels

Novel Risk Factors: adiponectin, CRP, WBC

The date of diabetes incidence will be estimated by linear interpolation using glucose values at the ascertaining visit and the previous one, as previously described⁵. Cox regression will be used to test the null hypothesis that the hazard rate of diabetes is the same across levels or categories of risk factors for the three case definitions (See Table 2). Multivariate linear regression will be used to test the null hypothesis that baseline characteristics are the same across four fasting glucose levels (i.e. 126-129, 130-134, 135-139, ≥ 140). Cox regression will be used to test the null hypothesis that the hazard rate of diabetes is the same across levels or categories of risk factors for the four fasting glucose levels.

Table 2 Hazard ratios for main risk factors by diagnostic criteria

	Self-Report	ARIC	Multiple Evidence
<i>Gender</i>			
▪ Female	1.0	1.0	1.0
▪ Male			
<i>Baseline Age</i>			
▪ Age 45-49	1.0	1.0	1.0
▪ Age 50-54			
▪ Age 55-59			
▪ Age 60-64			
<i>Race</i>			
▪ White	1.0	1.0	1.0
▪ Black			
<i>BMI</i>			
▪ Normal (18.5-25)	1.0	1.0	1.0
▪ Overweight (25-30)			
▪ Obese (30-40)			
▪ Morbid Obese (> 40)			
<i>Waist to Hip Ratio</i>			
▪ Q1	1.0	1.0	1.0
▪ Q2			
▪ Q3			
▪ Q4			
▪ Q5			
<i>Baseline Fasting Glucose</i>			
<i>Parental History of Diabetes</i>			
▪ Neither, %	1.0	1.0	1.0
▪ Mother, %			
▪ Father, %			
▪ Both, %			
<i>Systolic Blood Pressure</i>			
▪ Normal (< 120)	1.0	1.0	1.0
▪ Elevated (121 – 140)			
▪ High (> 140)			

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 ICTDER02 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 ICTDER02 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 ICTDER02 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.csc.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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ☒ Yes ☐ 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)* 1995.09)

*ancillary studies are listed by number at <http://www.csc.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.

1. Gregg EW, Cadwell BL, Cheng YJ, Cowie CC, Williams DE, Geiss L, Engelgau MM, Vinicor F. Trends in the prevalence and ratio of diagnosed to undiagnosed diabetes according to obesity levels in the U.S. *Diabetes Care*. 2004;27:2806-2812.
2. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes*. 2000;49:2201-2207.
3. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, Sellers TA, Lazovich D, Prineas RJ. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2000;160:2117-2128.
4. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am J Epidemiol*. 1997;145:614-619.
5. Duncan BB, Schmidt MI, Pankow JS, Ballantyne CM, Couper D, Vigo A, Hoogeveen R, Folsom AR, Heiss G. Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes*. 2003;52:1799-1805.