**ARIC Manuscript Proposal # 1633**

**PC Reviewed: 4/13/10** **Status: A** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

1.**a. Full Title**: Age at menarche and risk of type 2 diabetes

**b. Abbreviated Title (Length 26 characters)**: Age at menarche and type 2 diabetes risk

**2. Writing Group**: Jill Dreyfus, Rachel Huxley, Nora Franceschini, Jim Pankow, Elizabeth Selvin, Pamela Lutsey, Ellen Demerath.

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

**First author: Jill Dreyfus, MPH**
PhD Student
Division of Epidemiology and Community Health
School of Public Health, University of Minnesota
1300 South Second St., Suite 300
Minneapolis, MN 55454-1015
(651) 343-3257 (phone)
(612) 624-0315 (fax)
email: gora0001@umn.edu

**Senior author: Ellen Demerath, Ph.D.**
Associate Professor
Division of Epidemiology and Community Health
School of Public Health, University of Minnesota
1300 South Second St., Suite 300
Minneapolis, MN 55454-1015
(612) 624-8231 (phone)
(612) 624-0315 (fax)
email: ewd@umn.edu

**Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):**
Address: same as above for first author

**3. Timeline**: Analyses will begin immediately upon approval of this proposal.

**4. Rationale**:

Two recent studies have reported that early age at menarche raises the risk for type 2 diabetes[1,2]. Women in the Nurses' Health Study I with age at menarche < or = 11 years had a RR of 1.18 (95% CI 1.10-1.27) for type 2 diabetes compared with women with age at menarche =13 years, after adjusting for potential confounders such as BMI and other social and lifestyle factors[2]. The RR was higher in the younger Nurses Health Study II cohort (1.40, 95% CI 1.24-1.57) after adjusting for the same covariates[2]. In the EPIC-Norfolk study[1], women with age at menarche 15-18 years had an OR of 0.66 (95% CI 0.51-0.86) for type 2 diabetes compared women with menarche onset at age 8-11 year, however the association was completely attenuated after adjustment for adult BMI. There was a stronger association between early age at menarche and diabetes among women with larger waist circumference compared with participants who had small waist circumference[1].

Weaknesses of the aforementioned studies are that they relied on self-reported physician diagnosis of diabetes, and in the case of the Nurses' Health Study I and II, did not have waist circumference data. Although it is not clear whether increasing early childhood obesity is causally responsible for the downward trend in age at menarche in the United States[3,4], it is well established that early menarche is associated with higher adolescent and early adulthood adiposity [6,7,8,9] (and also shown by [1,2]). Early menarche is also associated with greater waist circumference [10]. Proper interpretation of an association between menarche timing and diabetes requires rigorous consideration of its independence from the relationship between menarche and adiposity, and central adiposity, in particular. We propose to assess weight gain from age 25 to baseline, baseline BMI, and waist circumference at baseline as adjustment factors in the ARIC study. Additionally, there remains a lack of knowledge about potential race/ethnicity differences in this association. African-American women have higher risk of type 2 diabetes, higher adiposity, and earlier age at menarche than European American women[5, 11, 12], but lower visceral and subcutaneous abdominal fat mass relative to total adiposity than European women[13]. Given this gap in the literature, our study will explore potential race differences in the association between risk for type 2 diabetes and age at menarche.

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

We will test the hypothesis that age at menarche is associated with prevalent and incident type 2 diabetes, and if this association is independent of adiposity or is modified by race.

**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).**

**Participants:** Women of European and African ancestries with available self-reported information regarding age at menarche, diabetes diagnosis at baseline, and laboratory information on fasting plasma glucose level and diabetes diagnosis during follow-up.

**Variables**: Prevalent diabetes, person years to incident diabetes, fasting plasma glucose measurements. Prevalent diabetes will be defined as self-reported physician diagnosis of diabetes, fasting plasma glucose > or = 126 mg/dl, or self-reported diabetes medication in the last 2 weeks at the baseline visit. Incident diabetes will be defined as fasting plasma glucose > or =

126 mg/dl, self-reported physician diagnosis of diabetes, nonfasting glucose > or = 200 mg/dl, or self-reported diabetes medication in the last 2 weeks at a follow-up visit.

**Inclusion**: all white and African American women with information on diabetes diagnosis, fasting plasma glucose measurements, and age at menarche

**Exclusions:** Women with age at menarche <9.0 or >17.0 years, and race other than black or white.

**Exposure:** Early age at menarche (e.g. <11 years compared to 15+ years).

**Primary analysis:** We will begin by using logistic regression to estimate odds ratios for incident and prevalent diabetes combined (diabetes yes/no), and Cox proportional models to estimate the relative risk for incident type 2 diabetes according to age at menarche category. In a preliminary analysis of the visit 1 data, we identified 487 prevalent diabetes cases among white women, and 517 prevalent cases among black women, after the exclusions listed above. For white women, the prevalence of diabetes differed significantly by age at menarche category (<11, 11.0-11.9, 12.0-12.9, 13.0-13.9, 14.0-14.9, 15+ year) before adjustment for covariates [$\chi^2(5, N = 5,977) = 21.1$, $p < 0.001$]. Diabetes prevalence was highest among women with age at menarche <11. We found no association of age at menarche with diabetes prevalence before adjustment for black women.

Models will be run in a series, adding additional covariates, with the exception of adiposity measures. Covariates will include: age at baseline, current smoking, ever smoking, alcohol use, physical activity level, education, parity, parental history of diabetes, and birth weight. We will stratify by race/ethnicity to examine effect modification by race. An interaction term (race*menarche) will test the significance of the effect modification. If the final logistic and Cox proportional hazards models above indicate linear effects of age at menarche, we will continue the analysis using age at menarche as a continuous variable for all remaining analyses.

The models will then be further adjusted by the addition of adiposity related variables (baseline BMI and waist circumference and weight gain from 25-baseline). We also will consider stratifying the results by quintiles of waist circumference to further examine the independence of the menarche-diabetes relationship from current adiposity.

Our focus in the analysis will be on whether adjusting for waist circumference attenuates any association between menarche timing and type 2 diabetes, and to assess whether race/ethnicity differences in the association exist, and are explained by differences in waist circumference.

If independent effects of age at menarche are identified in the above analyses, we will contextualize the findings by comparing the RRs of diabetes in women with early menarche to those of women with a family history of diabetes, and with elevated BMI and waist circumference.

**Covariates: (listed above)**

**Statistical significance:** Statistical tests will be 2-sided and significance will be defined at $\alpha$=0.05

**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 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 __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 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.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)?**

**ARIC Manuscript Proposal # 678.** Reproductive history and late life health status among older African-American and White women. Independent variables were parity, pregnancy loss, use of oral contraceptives, age at menarche, and menopausal status. Dependent variables include physical and psychological health later in life.

**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. **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.**

**References:**


1. Lakshman R, Forouhi N, Luben R, Bingham S, Khaw K, Wareham N, Ong KK. Association between age at menarche and risk of diabetes in adults: results from the EPIC-Norfolk cohort study. Diabetologia. 2008;51(5):781-6. Epub 2008 Mar 5.
2. He C, Zhang C, Hunter DJ, et al. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. Am J Epidemiol. 2010;171:334-44.
3. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. Trends Endocrinol Metab. 2009 Jul;20(5):237-42. Epub 2009 Jun 21.
4. Himes JH. Examining the evidence for recent secular changes in the timing of puberty in US children in light of increases in the prevalence of obesity. Mol Cell Endocrinol. 2006 Jul 25;254-255:13-21.
5. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. Relation of age at menarche to race, time period, and anthropometric dimensions: the Bogalusa Heart Study. Pediatrics. 2002;110:e43.
6. Himes, J.H., Obarzanek, E., Baranowski, T., Wilson, D.M., Rochon, J., McClanahan, B.S., 2004. Early sexual maturation, body composition, and obesity in African-American girls. Obes. Res. 12 (Suppl.), 64S–72S.
7. Demerath, E.W., Li, J., Sun, S.S., Chumlea, W.C., Remsberg, K.E., Czerwinski, S.A., Towne, B., Siervogel, R.M., 2004a. Fifty-year trends in serial body mass index during adolescence in girls: the Fels Longitudinal Study. Am. J. Clin. Nutr. 80, 441–446.
8. Garn, S.M., Haskell, J.A., 1960. Fat thickness and developmental status in childhood and adolescence. Am. J. Dis. Child. 99, 746–751.
9. Adair LS, Gordon-Larsen P. Maturational timing and overweight prevalence in US adolescent girls. Am J Public Health. 2001 Apr;91(4):642-4.
10. Kivimäki M, Lawlor DA, Smith GD, Elovainio M, Jokela M, Keltikangas-Järvinen L, Vahtera J, Taittonen L, Juonala M, Viikari JS, Raitakari OT. Association of age at menarche with cardiovascular risk factors, vascular structure, and function in adulthood: the Cardiovascular Risk in Young Finns study. Am J Clin Nutr. 2008 Jun;87(6):1876-82.
11. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. JAMA. 2000;283(17):2253-9.
12. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, Hu FB. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care. 2006;29(7):1585-90.
13. Katzmarzyk PT, Bray GA, Greenway FL, Johnson WD, Newton RL Jr, Ravussin E, Ryan DH, Smith SR, Bouchard C. Racial differences in abdominal depot-specific adiposity in white and African American adults. Am J Clin Nutr. 2009; Oct 14.