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Original article

Blood spot–based measures of glucose homeostasis and diabetes prevalence in a nationally representative population of young US adults

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ABSTRACT

Purpose: We investigated understudied biomarker-based diabetes among young US adults, traditionally characterized by low cardiovascular disease risk.
Methods: We examined 15,701 participants aged 24 to 32 years at Wave IV of the National Longitudinal Study of Adolescent Health (Add Health, 2008). The study used innovative and relatively noninvasive methods to collect capillary whole blood via finger prick at in-home examinations in all 50 states.
Results: Assays of dried blood spots produced reliable and accurate values of HbA1c. Reliability was lower for fasting glucose and lowest for random glucose. Mean (SD) HbA1c was 5.6% (0.8%). More than a quarter (27.4%) had HbA1c-defined prediabetes. HbA1c was highest in the black, non-Hispanic race/ethnic group, inversely associated with education, and more common among the overweight/obese and physically inactive. The prevalence of diabetes defined by previous diagnosis or use of antidiabetic medication was 2.9%. Further incorporating HbA1c and glucose values, the prevalence increased to 6.8%, and among these participants, 38.9% had a previous diagnosis of diabetes (i.e., aware). Among those aware, 37.6% were treated and 64.0% were controlled (i.e., HbA1c $< 7\%$).
Conclusions: A contemporary cohort of young adults faces a historically high risk of diabetes but there is ample opportunity for early detection and intervention.

Introduction

In 2012, economic costs of diagnosed diabetes totaled $245 billion, including $176 billion in direct medical costs and $69 billion in reduced productivity [1]. The 2012 economic burden represents a 41% increase from $174 billion in 2007. The largest components of medical expenditures for diabetes include hospital inpatient care (43%) and prescription medications for diabetes complications (18%). Type 2 diabetes onset at age 20 years is associated with a 15-year reduction in life expectancy, increased risk of severe, chronic diabetes complications by age 40 years, and worse education attainment and employment outcomes [2,3]. As such, diabetes in the first few decades of life is clinically, economically, and societally burdensome [3–6].

However, little is known about diabetes prevalence in contemporary populations of young adults in the United States,

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traditionally characterized by low cardiovascular disease risk. Given that 28% of the US population is unaware of their diabetes, exam-based assessments such as those from the National Health and Nutrition Examination Survey (NHANES) provide valuable information on the full burden of diabetes [7–10]. Besides NHANES, to our knowledge, the National Longitudinal Study of Adolescent Health (Add Health) is the only other study from which it is possible to estimate biomarker-based prevalence of diabetes among contemporary US young adults in their 20s.

Add Health—widely used in social, behavioral, and health science research [11]—is notable for its national probability sampling strategy, oversampling of typically underrepresented groups, and high response rate. Add Health is uniquely suited for examinations of the transition to adulthood. The larger sample of young adults (15–20 times the size of one NHANES cohort of young adults) enables potentially more precise estimates and comprehensive analysis of subgroup differences (e.g., incorporating finer racial/ethnic categorizations) [12–14]. Additionally, the measurement of diabetes in field studies such as Add Health is distinct from and potentially more complicated than that in examination center-based studies, requiring adaptation of biomarker collection to more variable home environments and using many more field staff.

In Add Health, measures of glucose homeostasis were obtained via an innovative and relatively noninvasive collection of capillary whole blood via finger prick. Although these relatively recently developed methods of evaluating glucose homeostasis have been used in the Moving to Opportunity housing experiment, Health and Retirement Study, National Social Life, Health, and Aging Project, and Los Angeles Family and Neighborhood Survey, little information is available on the validity and reliability of the measurements they generate [15–17]. We therefore examined these properties in the larger Add Health sample. Addressing gaps in the literature, the objectives of this study were to first assess the quality of measures of glucose homeostasis derived from dried blood spot (DBS) technology and then to quantify diabetes prevalence overall and by important demographic, social, clinical, and behavioral risk factors, thereby allowing assessments of health disparities.

Methods

Add Health study design and data collection

Add Health enrolled a national probability sample of 20,745 US adolescents in grades 7 through 12 during the 1994 to 1995 school year (Wave I response rate: 79%) [18]. The Add Health cohort has been followed for over a 13-year period and represents more than 22 million individuals. Three in-home follow-up interviews have been completed: Wave II in 1996 (88% of the eligible cohort at Wave I), Wave III in 2001 to 2002 (77%), and Wave IV in 2008 (80%). Each wave of the study was approved by the University of North Carolina Public Health-Nursing Institutional Review Board (Chapel Hill, NC).

Detailed information on Add Health's measures of glucose homeostasis has been published elsewhere [19]. Briefly, all 15,701 Wave IV Add Health participants were asked whether a health care professional ever told them they had high blood sugar or diabetes (i.e., self-reported history of diabetes). Women were asked to exclude diagnoses during pregnancy. Antidiabetic medication use within the preceding 4 weeks was inventoried by visually inspecting participant-assembled medication containers and categorizing their contents in real-time using Lexicon Plus (Lexi-Comp, Inc.; Hudson, OH).

Capillary whole blood was collected via finger prick from voluntarily fasting (≥8 hours) and nonfasting participants onto seven-spot, Whatman 903 Protein Saver cards by trained and certified field interviewers, subjected to *in situ* desiccation, then shipped to FlexSite Diagnostics, Inc. (Palm City, FL) for assay of HbA1c (%), and to the University of Washington Department of Laboratory Medicine (Seattle, WA) for assay of glucose (milligram per deciliter). The analytical sensitivity, within- and between-assay coefficients of variation (CV) were 3.0%, 2.2%, and 2.4% for HbA1c and 22 mg/dL, 4.4%, and 4.8% for glucose. In paired whole blood and blood spots ($n = 80$), HbA1c values were strongly associated (Pearson $r = 0.99$). Associations in paired serum and blood spots ($n = 83$) were equally strong for glucose concentrations (Pearson $r = 0.97$).

Test-retest reliability analysis in Add Health

In a quality control study conducted over the course of field work, the short-term retest reliability of HbA1c and glucose was assessed in a race/ethnicity- and sex-stratified random sample of 100 Add Health Wave IV participants (mean age 29 years; 50% female; 64% non-Hispanic white; 16% non-Hispanic black; 12% Hispanic/Latino; and 8% other) examined twice, 1 to 2 weeks (mean: 8.6 days) apart. At the two examinations, biospecimens were collected typically by the same field interviewer (84% of participants) and at approximately the same time of day (mean |difference|: 52 minutes; range 0–302 minutes).

The variance in measures of HbA1c (and separately, glucose) was partitioned in a random effects model by letting Y_{ij} be the measure on the ith participant at the jth visit: $Y_{ij=\mu+P_i+m_{j(i)}+e_{ij}}$, where μ is the sample mean and P_i, $m_{j(i)}$, and e_{ij} are the normally distributed participant, measurement, and error effects with mean zero and variance σ_p^2, σ_m^2, and σ_e^2, respectively. Assuming the variance components are independently distributed, the total variance of $Y(\sigma_T^2)$ is $\sigma_T^2 = \sigma_p^2 + \sigma_m^2 + \sigma_e^2$. Reliability was then estimated as the ratio of the between-participant-to-total variance: σ_p^2/σ_T^2, that is an intraclass correlation coefficient (ICC) with 95% confidence intervals (CIs) estimated using the delta method [20]. The ICC represents the proportion of variance not due to measurement variance. Random effects models were implemented in SAS 9.1 (SAS Institute Inc., Cary, NC) using Proc Mixed and the restricted maximum likelihood method.

Validity analysis in Add Health

In a separate quality control study conducted over 10 weeks of field work, a DBS from each of three donors was shipped twice weekly to FlexSite Diagnostics, Inc. ("Lab A") and assayed by laboratory staff masked to the origin of the samples. The 60 returned values of HbA1c were compared with values of HbA1c conventionally assayed in paired whole blood from the same donors on a G7 Automated HPLC-HbA1c Analyzer (Tosoh Bioscience, Inc., San Francisco, CA) by Duke University Health System Laboratories (Durham, NC) ("Lab B"). Accuracy was computed as the Lab A minus Lab B difference (bias, percentage) and its ratio with respect to the criterion standard (relative bias = 100 × bias/Lab B).

Identification of diabetes and its medical management

Diabetes was identified by incorporating self-reported history, antidiabetic medication use, and abnormality of HbA1c and/or glucose identified by American Diabetes Association (ADA) diagnostic thresholds [21]: (1) HbA1c ≥ 6.5%, (2) nonfasting glucose of 200 mg/dL or more, and/or (3) fasting glucose of 126 mg/dL or more. Prediabetes (HbA1c = 5.7%–6.4%) also was identified. Among those with diabetes, awareness was defined as reporting a previous diagnosis. Among those aware, treatment was defined as taking antidiabetic medications, and control of diabetes was defined as HbA1c of less than 7%, according to ADA guidelines [22].

Covariates

Subgroups were defined by the following characteristics: sex (male and female), race/ethnicity (non-Hispanic whites, blacks, and