National Health and Nutrition Examination Survey

2005-2006 Data Documentation, Codebook, and Frequencies

Glycohemoglobin (GHB_D)

Data File: GHB_D.xpt

First Published: January 2008

Last Revised: March 2012

Note: See Analytic Notes section for analysis of Hemoglobin A1c (Glycohemoglobin) data for 1999-2010.

Component Description

Diabetes mellitus will be assessed by measures of blood glycohemoglobin, fasting plasma glucose, 2-hour glucose (Oral Glucose Tolerance Test), serum insulin in participants aged 12 years and over.

Glycohemoglobin measures are available for a full sample. Measures of fasting plasma glucose, 2-hour glucose and serum insulin were measured in the morning examination session only.

Diabetes is a leading cause of disease and death in the United States. Eight million Americans are known to have diabetes, and an approximately equal number have undiagnosed diabetes. In 1993, nearly 18 percent of all deaths for persons over the age of 25 were among people with diabetes. The prevalence of diabetes and overweight (one of the major risk factors for diabetes) continue to increase. Substantial new efforts to prevent or control diabetes have begun, including the Diabetes Prevention Trial and the National Diabetes Education Program.

Diabetes testing provides population data to:

1. determine a national estimate of diabetes disease prevalence (diagnosed and undiagnosed),
2. identify the risk factors of diabetes disease;
3. permit a national cohort to be established for follow-up studies of this condition; and
4. provide critical information to clinicians and public health officials for the development of preventive care and community-based interventions.

Eligible Sample

Participants aged 12 years and older were tested.

Description of Laboratory Methodology

In this assay, the stable (SA1c) and labile (LA1c) A1c forms can be individually resolved on the chromatogram without manual pretreatment, allowing accurate measurement of the stable form of HbA1c. The analyzer dilutes the whole blood specimen with a hemolysis solution, and then injects a small volume of the treated specimen onto the HPLC analytical column. Separation is achieved by utilizing differences in ionic interactions between the cation exchange group on the column resin surface and the hemoglobin components. The hemoglobin fractions (A1c, A1b, F, LA1c, SA1c, A0 and H-Var) are subsequently removed from the column material by step-wise elution using elution buffers each with a different salt concentration. The separated hemoglobin components pass through the photometer flow cell where the analyzer measures changes in absorbance at 415 nm. The analyzer integrates and reduces the raw data, and then calculates the relative percentages of each hemoglobin fraction. Analysis requires three minutes.

A detailed description of the laboratory method used can be found at NHANES web page in the Laboratory Procedures Manual.

Laboratory Quality Assurance and Monitoring

The NHANES quality control and quality assurance protocols (QA/QC) meet the 1988 Clinical Laboratory Improvement Act (CLIA) mandates. Detailed quality control and quality assurance instructions are discussed in the NHANES Laboratory/Medical Technologists Procedures Manual (LPM). Read the LABDOC file for detailed QA/QC protocols.

There were changes to the equipment and lab site from the previous 6 years. Glycohemoglobin measurements for NHANES 1999-2004 were performed by the Diabetes Diagnostic Laboratory at the University of Missouri-Columbia using Primus CLC330 and Primus CLC 385 (Primus Corporation, Kansas City, MO). Glycohemoglobin measurements for NHANES 2005-2006 were performed by the Diabetes Laboratory at the University of Minnesota using Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA). Both assays use a High Performance Liquid Chromatography (HPLC) system.

Analytic Notes

Analytic note for analysis of Hemoglobin A1c (Glycohemoglobin) data for 1999-2010:

Removal of cross-over regression to compare Hemoglobin A1c data from 2005-2006 to 2003-2004:
The recommendation to use the Hemoglobin A1c (Glycohemoglobin) cross-over study regression equation to compare 2005-2006 (GHB_D) data to 2003-2004 (GHB_C) data has been withdrawn. Analyses of Hemoglobin A1c, including trend analysis, should use the original data without the use of the cross-over regression. A correction **to the documentation for 2005-2006 (GHB_D) removing this cross-over regression equation was posted on the NHANES web site in November 2011.**

Re-Release of 2007-2010 Hemoglobin A1c data:

Hemoglobin A1c results for 2007-2008 (GHB_E) and 2009-2010 (GHB_F) were temporarily withdrawn in November 2011 to evaluate a shift to the right (increased values) in the distribution of Hemoglobin A1c in 2007-2010 compared to 1999-2006. After careful evaluation of participant data, laboratory quality control data and non-NHANES A1c studies, a cause for this shift in the distribution of Hemoglobin A1c could not be identified. Therefore, the Hemoglobin A1c data for 2007-2008 (GHB_E) and 2009-2010 (GHB_F) were re-released in March 2012 without changes to the data. The user will need to carefully consider the information presented in this analytic note when analyzing Hemoglobin A1c data from 1999-2010.

Background:

Hemoglobin A1c (glycohemoglobin), a diabetes test that reflects plasma glucose for the previous 120 days, has been used to monitor diabetes for many years. In recent years, new clinical recommendations included applying hemoglobin A1c to the diagnoses of diabetes (6.5% or greater) and pre-diabetes (5.7%-6.4%) [Summary of revisions for the 2010 clinical practice recommendations. Diabetes Care 2010;33 Suppl 1:S3. PubMed PMID: 20042773; PubMed Central PMCID: PMC2797388].

In October 2011, an increase in the proportion of Hemoglobin A1c between 5.7-6.4% was noted in NHANES 2007-2010 compared to 1999-2006. Any minimal increase in Hemoglobin A1c would result in a notable increase in the proportion of Hemoglobin A1c between 5.7-6.4% since the lower cut-point (5.7%) is close to the middle of the Hemoglobin A1c distribution for NHANES participants. This increase in Hemoglobin A1c between 5.7-6.4% and the shift to the right (increased values) in the distribution of A1c for 2007-2010 led to a re-evaluation of the previously released NHANES A1c data. The evaluation of trends in NHANES A1c data included the assessment of laboratory instrument changes using cross-over studies, a review of participant Hemoglobin A1c data trends which occurred during NHANES 1999-2010, assessment of internal laboratory quality controls, and examination of external laboratory quality controls such as data from the National Glycohemoglobin Standardization Program (NGSP).

During 1999-2010, there were three Hemoglobin A1c laboratory instruments and two laboratories used in NHANES. Hemoglobin A1c was performed in the first laboratory on the Primus CLC330 (from 1999-2004) and then in the second laboratory on the Tosoh A1C 2.2 Plus (from 2005-2006). From 2007-2010, Hemoglobin A1c was performed in the second laboratory on the Tosoh A1C G7. Laboratory method cross-over studies were conducted at the time of each of the laboratory instrument changes. Both laboratories analyzing NHANES Hemoglobin A1c data from 1999-2010 were standardized by participating in the NGSP.

It was determined that the Hemoglobin A1c cross-over study regression equation to compare NHANES 2005-2006 data to 2003-2004 data resulted in an over-correction of the data and should not be used. The reason for withdrawing this cross-over regression was that the laboratories performing the Hemoglobin A1c were standardized (harmonized) using the NGSP and the laboratories demonstrated acceptable analytical performance using NGSP criteria for bias and imprecision. A correction to the documentation for 2005-2006 (GHB_D) was posted on the NHANES web site in November 2011. If this 2003-2006 cross-over study regression equation correction was used for A1c analyses, a review of any previous analyses should be performed without this cross-over regression equation to assess if there are any significant changes to the findings.

The distributional changes to Hemoglobin A1c between 1999-2006 and 2007-2010 persisted when the cross-over regression between 2003-2004 and 2005-2006 was not used. This change in A1c distributions resulted in higher estimates of the proportion of A1c greater than or equal to 5.7%. From 2005-2006 to 2007-2008, the age-adjusted weighted proportion of A1c between 5.7-6.4% in participants 18 years and older increased from 15.3 to 21.7%. Also, the proportion of A1c greater than or equal to 6.5% increased from 5.8 to 7.3% from 2005-2006 to 2007-2008.

The age-adjusted weighted Hemoglobin A1c (%) distribution for participants 18 years and older was the following:

Percentiles

Years	n	Mean	5th	25th	50th	75th	95th
1999-2000	4711	5.38	4.6	5	5.2	5.5	6.8
2001-2002	5297	5.47	4.8	5.1	5.3	5.5	6.7
2003-2004	5048	5.48	4.8	5.1	5.3	5.6	6.7
2005-2006	5022	5.44	4.6	5	5.3	5.6	6.6
2007-2008	5610	5.58	4.8	5.2	5.4	5.7	6.9
2009-2010	6029	5.62	4.8	5.2	5.5	5.8	6.9

On 11/04/2011, Hemoglobin A1c data for NHANES 2007-2008 (GHB_E) and 2009-2010 (GHB_F) were temporarily withdrawn from the public data release in order to further evaluate the possible reason for the increased Hemoglobin A1c.

Participant data for Hemoglobin A1c from 1999-2010 were then reviewed to determine if survey design changes were the reason for the increase of A1c in 2007-2010. Unweighted and weighted analyses of Hemoglobin A1c by specific age groups, gender, race/ethnic and body mass index (BMI) categories showed shifts to the right (increased values) between 1999-2006 compared with 2007-2010 in the Hemoglobin A1c distribution, and increases in the proportion of A1c between 5.7-6.4%. This change in the A1c distribution was seen in most subgroups which suggested a possible laboratory method etiology and not a survey design issue. The change in the A1c distribution from 2005-2006 to 2007-2008 included subgroups such as participants with normal BMI and younger participants, where increases in Hemoglobin A1c values would not be expected over a relatively short time. In addition, the participant trends in fasting plasma glucose (FPG) and 2-hour oral glucose tolerance test (OGTT) data were examined to see if they correlated with increased trends in Hemoglobin A1c. The NHANES FPG (2005-2010) and OGTT (2005-2010) were relatively stable and did not show the same magnitude of increase in 2007-2010 as Hemoglobin A1c, and would possibly suggest that the increase in Hemoglobin A1c was a laboratory method issue.

Internal and external laboratory quality controls were evaluated to determine if laboratory method changes were the reason for the increased Hemoglobin A1c. These included evaluation of the internal "bench" quality controls for imprecision. For 2007-2010, the internal quality control coefficients of variation ranged from 1.2-1.5% for Hemoglobin A1c concentration range of 5.3-5.4%. The laboratories performing NHANES Hemoglobin A1c from 1999-2010 participated in the NGSP, an external standardization program that certifies the laboratories for bias and precision for Hemoglobin A1c. The NGSP sends to each laboratory monthly a set of 10 whole blood specimens (Hemoglobin A1c range from 4-10%) and the specimens are analyzed in singlet for 2 days. The NSGP laboratories are compared to a central primary reference lab and to other similarly certified laboratories. The NGSP criteria for acceptable A1c bias is +/- 0.35% and the acceptable precision is not to exceed a standard deviation of 0.229, based on the difference of sample replicates. From 1999-2010, both NHANES laboratories did not exceed the NGSP Hemoglobin A1c criteria for bias or precision in any month. For 2007-2010, the NHANES laboratory had an average yearly A1c bias ranging from -0.10 to +0.02% from the NGSP central primary reference laboratory (yearly mean A1c ranged from 7.5 to 8.1% for the central primary reference laboratory). It would be expected that the NGSP bias would be more positive based on the increased Hemoglobin A1c seen in the NHANES participant data from 2007-2010. In addition, for 2005-2010, the NHANES laboratory's bias compared well to other similarly certified NGSP (secondary reference) laboratories that used other types of Hemoglobin A1c methods. Another external comparison performed by the NHANES laboratory used in 2005-2010 was the analysis of specimens obtained biannually from the International Federation of Clinical Chemistry (IFCC). The IFCC laboratory is used to confirm the "master" equation that relates Hemoglobin A1c values in the United States to the rest of the world. The NHANES laboratory and the NGSP central reference laboratory correlated well to the IFCC A1c values. In conclusion, the NHANES laboratory used from 2005-2010 had acceptable analytical performance for bias and precision.

A laboratory group from the NGSP system was consulted by NCHS in February 2012 to review the NHANES laboratory and participant Hemoglobin A1c data. The NGSP group concluded that both NHANES laboratories met NGSP criteria for bias and precision from 1999-2010. In addition, the EDIC (Epidemiology of Diabetes Interventions and Complications) study, a longitudinal study of type 1 diabetic persons that had Hemoglobin A1c performed in the same NHANES laboratory during 2005-2010, was evaluated to see if similar increases in Hemoglobin A1c occurred. For the EDIC participants in the lower 10th percentile (similar Hemoglobin A1c values to NHANES), the A1c values were relatively stable, but the sample size was small (less than 200 participants). Other laboratory factors including pre-analytical issues (sample collection and anticoagulants) and commutablility (caused by differences in sample matrix between participants and laboratory controls) were considered but determined not likely to contribute to the increase in Hemoglobin A1c seen in 2007-2010. The NGSP laboratory group felt that the NGSP system currently had insufficient precision at the lower pre-diabetes cut-point of 5.7% to detect the Hemoglobin A1c changes seen in NHANES 2005-2010.

In conclusion, the increase in Hemoglobin A1c in 2007-2010 seen in NHANES participants by age, gender, race/ethnicity and BMI and not seen to the same magnitude in participant fasting plasma glucose and oral glucose tolerance test values suggested a possible laboratory method etiology. However, the laboratory's internal quality control, external NGSP data, and Hemoglobin A1c data performed for non-NHANES studies during 2007-2010 suggested no laboratory method issues related to the shift to the right (increased values) of the Hemoglobin A1c distribution and the proportion of A1c between 5.7-6.4%. In summary, despite intensive studies to determine the etiology of the A1c trend increase, it was not possible to determine if laboratory method, survey design effect or population changes caused the increase in the Hemoglobin A1c. Therefore,

after careful evaluation of participant data and data from the laboratory performing the Hemoglobin A1c, the Hemoglobin A1c data for 2007-2008 (GHB_E) and 2009-2010 (GHB_F) were re-released in March 2012 without changes to the data. The user will need to carefully consider the information presented in this analytic note when analyzing Hemoglobin A1c data from 1999-2010.

NHANES 2005-2006 Survey Design:

The analysis of NHANES 2005-2006 laboratory data must be conducted with the key survey design and basic demographic variables. The NHANES 2005-2006 Household Questionnaire Data Files contain demographic data, health indicators, and other related information collected during household interviews. They also contain all survey design variables and sample weights for these age groups. The phlebotomy file includes auxiliary information such as the conditions precluding venipuncture. The household questionnaire and phlebotomy files may be linked to the laboratory data file using the unique survey participant identifier SEQN.

References

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- Steffes M, Cleary P, Goldstein D, et al. Hemoglobin A1c Measurements over Nearly Two Decades: Sustaining Comparable Values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study. Clin Chem 2005; 51:4.
- Tosoh A1c 2.2 Plus Glycohemoglobin Assay Application Instruction Guide, 1998. PN 990233 Version 1.2. Tosoh Medics, Inc.
- Tosoh A1c 2.2 Plus Operator’s Manual, 1998. PN 990228 Version 1.2. Tosoh Medics, Inc., 347 South San Francisco, CA 94080.
- Trivelli LA, Ranney HM, Lai H-T. Hemoglobin components in patients with diabetes mellitus. NEJM 1971; 284(7):353.

Codebook and Frequencies

SEQN - Respondent sequence number

Variable Name:	SEQN
SAS Label:	Respondent sequence number
English Text:	Respondent sequence number.
Target:	Both males and females 12 YEARS - 150 YEARS

LBXGH - Glycohemoglobin (%)

Variable Name: LBXGH

SAS Label: Glycohemoglobin (%)

English Text: Glycohemoglobin (%)

Target: Both males and females 12 YEARS - 150 YEARS

Code or Value	Value Description	Count	Cumulative	Skip to Item
3.8 to 15.6	Range of Values	6493	6493	
.	Missing	487	6980	