Glycosylated Hemoglobin Testing in the National Social Life, Health, and Aging Project

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Objectives. Longitudinal biometric measures of health are still new in nationally representative social science survey research. Data measuring blood sugar control provide opportunities for understanding the development of diabetes and its complications in older adults, but researchers must be aware that some of the differences across time can be due to variations in measurement procedures. This is a well-recognized issue whenever all samples cannot be assayed at the same time and we sought to present the analytic methods to quantify and adjust for the variation.

Method. We collected and analyzed HbA1C, glycated hemoglobin, a biomarker of average blood sugar concentrations within the past few months. Improvements were made in the collection protocol for Wave 2, and assays were performed by a different lab.

Results. The HbA1C data obtained during Wave 1 and Wave 2 are consistent with the expected population distributions for differences by gender, age, race/ethnicity, and diabetes status. Age-adjusted mean HbA1C declined slightly from Wave 1 to Wave 2 by −0.19 (95% confidence interval [CI]: −0.27, −0.10), and the average longitudinal change was −0.12 (95% CI: −0.18, −0.06).

Discussion. Collection of HbA1C in Wave 2 permits researchers to examine the relationship between HbA1C and new health and social measures added in Wave 2, and to identify factors related to the change in HbA1C. Changes in collection protocol and labs between waves may have yielded small systematic differences that require analysts to carefully interpret absolute HbA1C values. We recommend analytic methods for cross wave differences in HbA1C and steps to ensure cross wave comparability in future studies.

Key words: Biomeasures—Diabetes—Glycated hemoglobin—Health trajectory—Longitudinal.

THE National Social Life, Health, and Aging Project (NSHAP) is an NIA-funded, population-based, longitudinal study of health and aging (O’Muircheartaigh, English, Pedlow, & Kwok, in press). NSHAP is unique among other survey studies of aging in its simultaneous inclusion of both rich social measures and a wide range of biometric measures, several of which are novel in this setting. Wave 1, completed in 2010–2011, provides researchers the opportunity to study the relationships between glycated hemoglobin (HbA1C) and several new health and social measures that were added in Wave 2. It also permits examination of how changes in HbA1C are related both to baseline characteristics and to simultaneous changes in other measures, thereby allowing researchers to study the natural course of prediabetes and diabetes (including how this is related to other age-related health changes) and to focus more precisely on the mechanisms by which social factors are related to HbA1C.

Collecting biometric measures longitudinally presents several challenges, especially within the context of an in-home omnibus study such as NSHAP. New biometric measures and methods for collecting biological samples are continually being developed, which together with improvements based on past experience leads to new protocols being introduced and existing protocols being modified. In addition, the need to integrate individual collection protocols into a unified set of procedures that can be performed quickly and reliably by nonmedically trained interviewers in the home occasionally necessitates changes in one protocol to accommodate changes in another. Finally, changes in laboratory procedures may be required, either because of changes in the organization or assays in the lab(s) or in order to take advantage of improved technologies. Because each of these changes can affect the value of a measure, care is required when analyzing and interpreting data whenever assays cannot be run on all samples at the same time. This is especially true when data from multiple waves are combined, either by comparing the results of cross-sectional analyses between waves or by performing longitudinal analyses.

In NSHAP Wave 2, minor changes to the collection protocol for the dried blood spots (DBS) (from which the HbA1C measure is obtained) were made, and a new lab was chosen to perform the assay because the lab used in Wave 1 occasionally necessitates changes in one protocol to accommodate changes in another. Finally, changes in laboratory procedures may be required, either because of changes in the organization or assays in the lab(s) or in order to take advantage of improved technologies. Because each of these changes can affect the value of a measure, care is required when analyzing and interpreting data whenever assays cannot be run on all samples at the same time. This is especially true when data from multiple waves are combined, either by comparing the results of cross-sectional analyses between waves or by performing longitudinal analyses.

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1 no longer existed. In this paper, we compare the distribution of HbA1C values from Wave 2 to that from Wave 1 and from the National Health and Nutrition Examination Survey (NHANES). While we find that any systematic difference in HbA1C due to procedural changes between waves is at most modest, we discuss the implications of such differences for specific types of analyses and make suggestions for Wave 3 to ensure continued comparability in HbA1C. This paper can thus serve as a guide for those working with other longitudinally collected biomarkers where changes in the collection and/or assay procedures have been made.

**METHOD**

**HbA1C**

Glucose, a sugar, circulates in one’s blood until it is used by cells for energy, stored in the form of glycogen, or excreted from the body. The concentration of glucose normally fluctuates throughout a day in response to food, physical activity, and fasting. Individuals with diabetes most commonly have chronically high blood concentrations of glucose due to insulin resistance and/or failure to produce adequate amounts of insulin. Insulin resistance is the pathophysiologic origin for individuals living with type 2 diabetes, the dominant form of diabetes. Diabetes is associated with an elevated risk of microvascular and cardiovascular complications (Huang, Liu, Moffet, John, & Karter, 2011). HbA1C is a measure of average blood sugar concentrations within the past few months (Nathan et al., 2008).

Normally, a small percentage of the hemoglobin molecules in red blood cells become glycated (that is, chemically linked to glucose without enzyme activity). Over the three to four month life of a red blood cell, the percentage of glycated hemoglobin increases and does so faster the more glucose in one’s blood. Glycated hemoglobin thus can be used to indicate blood sugar levels in the recent past (the last 2 to 3 months). HbA1C is classically used to measure long-term blood glucose control—useful as a marker of blood sugar regulation, diabetes, or how well diabetes is being managed. More recently, HbA1C has been recommended as an additional approach to diagnosing diabetes (“Diagnosis and classification,” 2010; “International Expert Committee report,” 2009; World Health Organization, 2011). Unlike methods such as the oral glucose tolerance test, a reliable measure of HbA1C does not require fasting.

**NSHAP Protocol**

The NSHAP HbA1C biomasure is an assay of DBS collected by the field interviewers. The use of DBS is a departure from the typical HbA1C assay used in clinical practice which is based on whole blood. In the following paragraphs, we describe how the data collection and assay methods evolved from Wave 1 to Wave 2. In both waves, NSHAP respondents were not informed of their biomarker results.

**Collection, Storage, and Shipping**

In Wave 1, the field interviewer collected blood from a respondent on a Whatman 903 filter paper that had been treated with a proprietary solution to facilitate rehydration (Williams & McDade, 2009). After collection, the filter paper was allowed to air-dry until the end of the interview. All DBS analyses are based on the use of filter paper. The field interviewer sealed the paper in a Ziploc bag containing a desiccant. Once the field interviewer returned to his or her own home, the filter paper was removed from the Ziploc bag and placed in a clear, breathable plastic container with the cover flipped up. A desiccant pack was placed in the container which was then closed overnight and left at room temperature to ensure drying of the blood spots. In the morning, the filter paper was stored in a sealed Ziploc bag along with the desiccant pack and placed in a storage container. The storage container was kept in the refrigerator at 4°C until the next shipping day. Every week, collected filter papers were shipped at room temperature to Northwestern University, where they were forwarded to Flexsite Diagnostics in Palm City, Florida. Upon arrival at the laboratory, the filter papers were catalogued and frozen at −25°C until analysis.

In Wave 2, the field interviewer collected the respondent’s blood on Whatman 903 paper that was pretreated with 20 μl of a modified citrate buffer (0.5 molar, pH 4.5) containing aniline (60 mmol/l) and semicarbazide (25 mmol/l) using a 20 μl pipet with plastic tip according to a protocol developed and validated by (Petranyi, Petranyi, Sharpe, & Alberti, 1986). The pretreated cards were allowed to dry at room temperature for 24 hr. The DBS collection procedures were similar across waves, but some refinements were introduced in order to increase respondent blood flow and maximize collection such as selecting a new lancet and adding a hand warmer (see O’Doherty et al.). The storage and shipping procedures were identical to Wave 1, except that the filter papers were shipped to the University of Washington (UW), Department of Medicine Biomarker Analysis Laboratory. At the laboratory, filter paper and desiccant packer were placed in a Ziploc bag and stored at −70°C until processing.

**Assays**

For Wave 1, Flexsite Diagnostics assayed the DBS using the Roche Unimate immunoassay and Cobas Integra Analyzer. The immunoassay incorporates a latex-enhanced competitive turbidimetric immunoassay, which determines HbA1C concentration, with a colorimetric quantification of total hemoglobin. The Cobas Integra analyzer, which is National Glycohemoglobin Standardization Program (NGSP)-certified, was calibrated using a synthetic HbA1C standard (http://biomarkers.uchicago.edu/pdfs/TR-HbA1c.pdf).

By the time of Wave 2, Flexsite Diagnostics no longer existed as an independent company. As a result, NSHAP investigators selected UW, Department of Medicine Biomarker Analysis Laboratory to perform DBS assays. The UW HbA1C assay...
uses an automated ion-exchange high-performance liquid chromatography (IE-HPLC) system to measure the percentage of glycated hemoglobin in DBS samples. A punch from a DBS card containing a patient blood sample is eluted in a buffer solution. The elution solution is transferred to a sample vial, diluted and analyzed on an NGSP-certified Bio-Rad Variant II Hemoglobin Testing System.

For Wave 2, the data include a raw measure of HbA1C for the DBS as well as a whole blood equivalent calculated using the formula \( WB = -1.786 + 1.302 \text{DBS} \). For Wave 1, the vendor only supplied the whole blood equivalent numbers—we have neither the measure for the DBS nor the equation Flexite used to convert the dried blood measure to its whole blood equivalent.

In each wave, the protocol and miscalibration of the assay instruments could have caused a shift up or down, widening or narrowing of range, or nonlinear changes. Unfortunately, we cannot correct for this variation because details of Flexite’s calibration process no longer exist and Wave 1 samples were not stored in a manner that allowed for calibration across waves.

**Data Analysis**

The distributions of HbA1C in NSHAP Waves 1 and 2 were compared numerically using the mean, standard deviation, range and percentiles, and graphically using histograms. Linear regression models were fit to HbA1C separately for both waves, including gender, age, race/ethnicity and self-reported diabetic status as covariates (Weisberg, 2013). Diabetic status was assessed using the question: “Has a doctor ever told you that you have diabetes or high blood sugar?” Interaction terms among these covariates were also examined, and residual plots were used to verify the adequacy of the model. For comparison, parallel analyses were performed using data from NHANES collected in 2005–2006 and 2009–2010, corresponding to the Wave 1 and Wave 2 field periods, respectively (Table 1).

The change in HbA1C from Waves 1 to 2 was computed for all respondents who provided blood spots in both waves, and a paired \( t \)-test was used to obtain a 95% confidence interval for the mean difference. This analysis was then repeated separately within clinical subgroups defined according to changes in diabetic status between waves: (a) those who were nondiabetic at both waves, (b) those who were nondiabetic at Wave 1 but were diagnosed with diabetes prior to Wave 2, (c) those who were undiagnosed diabetics at Wave 1 (defined as having an HbA1C greater than 6.5) and remained undiagnosed at Wave 2, (d) those undiagnosed diabetics at Wave 1 who were diagnosed with diabetes prior to Wave 2, and (e) those who were already diagnosed with diabetes at Wave 1. In addition, a Bland–Altman plot (Altman & Bland, 1983) was used to examine the relationship between the change in HbA1C between waves and the average HbA1C across both waves, augmented by a LOcally WEighted Scatterplot Smoother (LOWESS).

| Table 1. Distribution of HbA1C Among NSHAP Wave 2 and NHANES 2009–2010, Comparing Participants Reporting a Diabetic Diagnosis (Diabetic Dx) to Those Who Did Not (Nondiabetic) |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | NSHAP Wave 2    | NHANES 2009–2010|                 |
|                                 | Nondiabetic     | Diabetic Dx     | Nondiabetic     | Diabetic Dx     |
| Mean                            | 5.6             | 6.8             | 5.7             | 7.0             |
| SD                              | 0.6             | 1.3             | 0.5             | 1.4             |
| Range                           | 3.6–11.2        | 4.6–14.4        | 4.0–12.0        | 4.7–13.5        |
| 25th percentile                 | 5.2             | 6.0             | 5.4             | 6.1             |
| Median                          | 5.5             | 6.5             | 5.7             | 6.8             |
| 75th percentile                 | 5.9             | 7.2             | 5.9             | 7.5             |
| \( N \)                         | 2,180           | 684             | 1,266           | 383             |

**Notes.** Estimates weighted to account for differential probabilities of selection and nonresponse. NSHAP participants were born between 1920 and 1947, who were between the ages of 62 and 91 at the time of Wave 2.NHANES participants were 62 and older at the time of the 2009–2010 survey.


**Results**

Overall, the distribution of HbA1C in NSHAP is similar across waves and corresponds closely to that of NHANES. Although the mean value for Wave 2 is slightly lower (−0.20%) than for Wave 1, the spread and shape of the distributions are similar (Figure 1). When compared with the distribution from the 2009–2010 NHANES, the Wave 2 distribution again has a slightly lower mean and median, but the standard deviation and range match well (Table 2).

Table 2 shows regression models of HbA1C fit separately to NSHAP Waves 1 and 2 and to NHANES data from the same periods. In general, results are quite similar across the four datasets. As expected, those reporting a diagnosis of diabetes have an average HbA1C that is 1.18%–1.28% higher than nondiabetics (Figure 2). But while HbA1C is estimated to increase with age by approximately 0.03%–0.04% per decade among nondiabetics (Pani et al., 2008), it is estimated to decrease by between 0.15% and 0.33% per decade among diabetics. As has been demonstrated
previously, both blacks and Hispanics have higher HbA1C than whites (Herman et al., 2007; Kirk et al., 2006). In addition, women have lower values on average than men, though within the context of this model the differences are not statistically significant (Yang, Lu, Wu, & Chang, 1997). Finally, the constant for Wave 2—representing the average HbA1C for a 70 year old, nondiabetic white man—is −0.19% (95% confidence interval [CI]: −0.27, −0.10) lower than for Wave 1. This difference is nearly identical in magnitude to the increase observed in NHANES over the same period (5.55–5.72).

Changes in HbA1C Over Time

Among all respondents with HbA1C values for both Waves 1 and 2, the mean within-respondent change was −0.12% (95% CI: −0.18, −0.06). Table 3 shows the mean changes separately by clinical subgroup. All groups except one declined on average. The largest declines were among those classified as undiagnosed diabetics (HbA1C greater than 6.5 but without a clinical diagnosis of diabetes) in Wave 1; this likely reflects some regression toward the mean, together with the effects of medical treatment among those who were newly diagnosed following Wave 1. Notably, the mean change among those with a diabetes diagnosis in Wave 1 (and therefore likely to benefit from treatment between waves) was nearly the same as for those without a diabetes diagnosis at either wave or undiagnosed diabetics in Wave 1 (−0.11 vs 0.10, respectively).

Figure 3 shows the relationship between the observed changes and the average HbA1C across waves. The deviation of the mean difference (represented by the LOWESS curve) from zero is very small compared to the total variation in the individual differences. Although there is a slight tendency for the mean difference to increase with average HbA1C, this is restricted to those with the lowest and highest average values, with the mean difference remaining constant from about 5.5% to 8.5%.

Implications of a Systematic Difference Due to Changes in Measurement

Although the data we present here are not sufficient to establish or rule out a possible systematic difference due to changes in measurement between Waves 1 and 2, they do suggest that any such difference, if present, is likely to be small. Still, it is useful to consider what effects such a difference might have on the results of analyses using these data. Two important cases to consider are (a) comparison of results between waves from cross-sectional models of HbA1C, and (b) longitudinal analyses of changes in HbA1C between waves. For this discussion,

Figure 1. Distribution of HbA1C in Waves 1 and 2 of the National Social Life, Health, and Aging Project.

Table 2. Regression Models of HbA1C Fit Separately to NSHAP Waves 1 and 2 and NHANES 2005–2006 and 2009–2010 (95% Confidence Intervals in Parentheses)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>NSHAP</th>
<th></th>
<th>NHANES</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Ref.</td>
<td>−0.08 (−0.17, &lt;0.01)</td>
<td>Ref.</td>
<td>−0.01 (−0.07, 0.04)</td>
</tr>
<tr>
<td>Female</td>
<td>−0.08 (−0.17, &lt;0.01)</td>
<td>Ref.</td>
<td>−0.01 (−0.07, 0.04)</td>
<td>Ref.</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>0.53 (0.19, 0.86)</td>
<td>0.36 (0.22, 0.50)</td>
<td>0.36 (0.17, 0.55)</td>
<td>0.12 (−0.03, 0.27)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.34 (0.16, 0.52)</td>
<td>0.22 (0.04, 0.39)</td>
<td>0.30 (0.13, 0.47)</td>
<td>0.26 (0.15, 0.36)</td>
</tr>
<tr>
<td>Other</td>
<td>0.50 (−0.11, 1.11)</td>
<td>0.24 (−0.06, 0.54)</td>
<td>0.26 (−0.08, 0.60)</td>
<td>0.28 (0.03, 0.52)</td>
</tr>
<tr>
<td>Diabetic diagnosis (self-reported)</td>
<td>1.28 (1.13, 1.43)</td>
<td>1.18 (1.01, 1.35)</td>
<td>1.23 (0.95, 1.50)</td>
<td>1.26 (1.10, 1.42)</td>
</tr>
<tr>
<td>Age (decades)</td>
<td>0.05 (0.01, 0.09)</td>
<td>0.02 (−0.02, 0.07)</td>
<td>0.03 (−0.02, 0.07)</td>
<td>0.05 (0.01, 0.09)</td>
</tr>
<tr>
<td>Diabetic × Age</td>
<td>−0.28 (−0.52, −0.03)</td>
<td>−0.15 (−0.30, −0.01)</td>
<td>−0.24 (−0.43, −0.06)</td>
<td>−0.33 (−0.58, −0.07)</td>
</tr>
<tr>
<td>Constant</td>
<td>5.74 (5.68, 5.81)</td>
<td>5.55 (5.50, 5.60)</td>
<td>5.55 (5.43, 5.66)</td>
<td>5.72 (5.64, 5.80)</td>
</tr>
</tbody>
</table>

Notes. Estimates weighted to account for differential probabilities of selection and nonresponse. Confidence intervals utilize design-based standard errors.

*Restricted to participants of NSHAP Wave 1, born between 1920 and 1947, ages 57–85 at the time of survey.

*Restricted to participants of NSHAP Wave 2, born between 1920 and 1947, ages 62–91 at the time of survey.

*Age is centered at 70, so the constant estimates the mean HbA1C for 70 year old, nondiabetic, white men.
we’ll assume that any systematic changes in measurement can be represented by a linear transformation, or in other words, that an HbA1C value $Y_1$ measured in Wave 1 would, if measured in Wave 2, be equal to $Y_2 = \theta + \lambda Y_1$ where $\theta \neq 0$ represents an additive shift and $\lambda \neq 1$ represents a multiplicative shift. Here we make no assumption about which value, $Y_1$ or $Y_2$, is more accurate in an absolute sense.

Regarding the first case, if $\lambda$ is not equal to one, then a cross-sectional regression model of HbA1C in Wave 2 will have coefficients which differ from those in Wave 1 by a factor of $\lambda$. Comparing the coefficients in Table 2 for Wave 2 to those from Wave 1 (excluding the constant), we see that the Wave 2 coefficients differ by an overall factor of 0.80 (95% CI: 0.60, 0.99), or in other words, are 20% smaller overall. Yet while this is consistent with the possibility of a small, multiplicative shift, the confidence interval barely excludes 1, and the overall similarity in the coefficients across all four datasets suggests that any shift between Waves 1 and 2 is, at most, modest. Similarly, while a nonzero value of $\theta$ would produce an additive shift in the constant term, the observed difference in the constants between Waves 1 and 2 may also be due in part to real changes in glycemic control in the population, and as noted above, is similar in magnitude to the change in the constant observed between 2005–2006 and 2009–2010 of NHANES (albeit in the opposite direction).

In the case of a regression analysis of within-respondent changes from Waves 1 to 2, a $\lambda$ different from one will also yield bias in the coefficients, though by an amount that depends not only on $\lambda$ but also on the correlation between Wave 1 HbA1C and the covariate(s). The lack of an obvious nonzero slope in Figure 2 suggests again that any difference of $\lambda$ from one is in this case likely small. As in the first case, a nonzero value of $\theta$ would yield an additive shift in the constant term thereby biasing estimates of the absolute amount of within-respondent change.

In sum, for both cross-sectional and longitudinal analyses, values of $\theta$ different from zero will introduce bias into estimates of the constant terms, while values of $\lambda$ different from one will introduce bias into estimates of the other coefficients. Regarding the latter, tests of the null hypothesis of no association are likely to remain valid if the differences in measurement are not too large.

**Discussion**

By continuing to measure HbA1C in Wave 2, NSHAP permits researchers to examine how HbA1C is related to several new health and social measures introduced in Wave 2, as well as to study for the first time how within-respondent changes in HbA1C are related to social factors among the U.S. population of older adults. HbA1C also provides an additional way of identifying individuals with diabetes that complements diagnoses based on self-report and medication usage. HbA1C is relevant beyond the study of diabetes, as it has also been found to be an independent predictor of health outcomes like cardiovascular events and mortality in individuals with and without diabetes (Selvin, 2010).

Social scientists involved in longitudinal studies are quite familiar with the instrument effects that occur with changes in survey methodology over time. As we have highlighted in this discussion of HbA1C, the same instrument effects can also occur with biomeasures even those that are well established and subjected to national standardization protocols. NGSP certified laboratories, an international program for harmonizing HbA1C assays, have undergone a rigorous process that includes the use of certified reagents/protocols and comparison of analysis of a set number of samples with a secondary reference laboratory.

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![Figure 2](https://academic.oup.com/psychsocgerontology/article-lookup/69/Suppl_2/S198/605504)

Figure 2. Comparison of the distributions of HbA1C in participants with and without a diabetes diagnosis.

<table>
<thead>
<tr>
<th>Wave 1 diabetes status</th>
<th>Diabetes diagnosis at wave 2</th>
<th>Wave 1 mean</th>
<th>Wave 2 mean</th>
<th>Mean change</th>
<th>95% CI</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiabetic</td>
<td>No</td>
<td>5.66</td>
<td>5.56</td>
<td>−0.10</td>
<td>−0.14, −0.05</td>
<td>873</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>5.82</td>
<td>5.96</td>
<td>0.14</td>
<td>−0.07, 0.35</td>
<td>47</td>
</tr>
<tr>
<td>Undiagnosed diabetic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No</td>
<td>7.00</td>
<td>6.65</td>
<td>−0.35</td>
<td>−0.79, 0.08</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>7.83</td>
<td>6.62</td>
<td>−1.20</td>
<td>−1.89, −0.51</td>
<td>24</td>
</tr>
<tr>
<td>Diagnosed diabetic</td>
<td>Not applicable</td>
<td>6.99</td>
<td>6.88</td>
<td>−0.11</td>
<td>−0.34, 0.12</td>
<td>259</td>
</tr>
</tbody>
</table>

*Notes.* Estimates weighted to account for differential probabilities of selection and nonresponse. Confidence intervals utilize design-based standard errors.

<sup>a</sup>Defined as having an HbA1C value greater than 6.5 in Wave 1.
GLYCOSYLATED HEMOGLOBIN TESTING

In order to be certified, laboratories must produce results with the samples that meet criteria for precision, bias, and outliers. Both labs involved in HbA1C testing used NGSP certified laboratory assays. However, data collection procedures were not certified and differences in data collection may have introduced the small shift from one wave to the next. Ideally the data collection and assay should be NGSP certified.

The unavoidable change in lab for Wave 2 raises the possibility that the Wave 2 values may differ systematically from the Wave 1 values, which would have consequences for how the results of analyses using the data from both waves—either repeated cross-sectional or longitudinal analyses—should be interpreted. The data presented here suggest that such measurement differences, if present, are likely to be small relative to the variability in HbA1C in the population. Still, researchers using the data from both waves should be aware of the way in which such differences might affect their results, as described above.

The fact that the mean within-person change in HbA1C among nondiabetics was negative is inconsistent with results previously reported which suggest that HbA1C gradually increases over time among this subgroup. From both cross-sectional and longitudinal analyses, we expect that HbA1C should increase by about 0.01 to 0.04 per year among those without diabetes (Glei, Goldman, Lin, & Weinstein, 2011; Pani et al., 2008; Ravikumar, Bhansali, Walia, Shannugasundar, & Ravikiran, 2011). This inconsistency suggests that the average decrease in the mean in NSHAP may have been due, at least in part, to the changes in the collection protocol and/or lab. However, the data presented here are not sufficient to draw firm conclusions about the magnitude of such an effect, since several factors may contribute to the apparent discrepancy including nonresponse bias (e.g., those who declined to participate in NSHAP may be more likely to experience an increase in HbA1C) and nonrandom dropout (e.g., those Wave 1 respondents who died or became too ill to participate in Wave 2 may also have been more likely to experience an increase). Accurate estimation of the absolute change within-respondent in HbA1C requires taking careful steps to ensure precise calibration between waves (see below). However, as described above, regression models of the change continue to be unbiased as long as there is no systematic multiplicative difference between waves (except for the constant, which will be biased by an amount equal to the measurement effect).

It may be tempting to compare the differences in the estimated constants in Table 2 and speculate about which dataset(s) have greater bias, as well as the direction of that bias. However, we caution the reader about drawing such conclusions, which we believe are unwarranted on the basis of these data alone. For example, the difference from Waves 1 to 2 in NSHAP (5.74–5.55) is nearly the same as the difference between NHANES 2005–2006 and 2009–2010 (albeit in the opposite direction). The CDC studied the (unexpected) increase over this period in NHANES HbA1C, only to conclude that they could offer no reason for the difference based on differences in laboratory procedures. In addition, a 2004 study on inter-laboratory variations by the NGSP, a collaborative of reference laboratories, found that laboratories varied in their measurements of low, mid, and high reference samples by standard deviations of about 0.6% (Goodall, 2005). Thus, the differences between NSHAP and NHANES and between the two waves of NSHAP are well within the accepted range for NGSP-certified laboratories, and should not be interpreted as evidence of a deficiency with any particular dataset. Given these differences, however, researchers using such datasets should be cautious about over interpreting small differences in the constants between different datasets or in comparing individual values to a specific threshold (e.g., >6.5%), which may involve a small amount of misclassification near the cutoff. This is also the case clinically, where multiple measures confirm a diagnosis.

Finally, as NSHAP investigators, we plan to undertake a number of steps in Wave 3 to permit precise between-wave calibration in HbA1C and the other DBS measures. First, we shall establish a repository of stabilized samples for cross-calibration between waves. Second, while Wave 3 is being fielded, whole blood samples and DBS will be collected from an auxiliary sample of participants. The whole blood will be immediately analyzed, while the blood spots will be processed through the normal survey protocol. This comparative method will allow for the estimation of collection, shipping and storage effects. Such procedures could be used by any study employing longitudinal biomarkers.

Figure 3. Relationship between the observed changes and the average HbA1C across waves of the National Social Life, Health, and Aging Project.

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**Key Points**

- Longitudinal biomasures of health can greatly enhance the value of survey research, but instrument effects can occur with biomasures as they do with survey questions.
- A small shift in mean HbA1C levels occurred between NSHAP waves that is similar in size to unexplained shifts observed across waves of NHANES, both within the accepted range of variation for NGSP-certified laboratories.
- Researchers using such datasets should be cautious about over interpreting small differences in the constants between different datasets or in comparing individual values to a specific threshold (e.g., >6.5%), which may involve a small amount of misclassification near the cutoff as is the case clinically.
- For future collection of biomasures, researchers should store stabilized samples for cross-calibration between waves. Whole blood samples and DBS should be collected from an auxiliary sample of participants.

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