Measured and Diagnosed Diabetes and Mortality in the United States

ABSTRACT

Objectives: This study investigates the impact of diabetes on all cause-mortality using two different criteria- one based on HbA1c-level and the other based on self-reported diagnosed diabetes. In specific, the current study examines how the relative risk of death associated with diabetes at baseline diagnosed based on HbA1c levels varies by a previous diagnosis of diabetes.

Methods: Data are from the National Health and Nutrition Examination Survey 1997-2010 and Linked Mortality Files. Adults aged 40-84 are grouped by the HbA1c cutoff level of $\geq 6.5\%$ and self-reported diagnosed diabetes. Hazard ratios of death during follow-up period are estimated by diabetes status defined both by HbA1c and diagnosed diabetes.

Results: Adults with diagnosed diabetes show a higher risk of dying than individuals without diagnosed diabetes, irrespective of their HbA1c level at baseline. Baseline HbA1c contribute little to the risk of death after controlling for self-diagnosed diabetes.

Conclusions: Mortality differentials are more pronounced based on a self-reported previous diagnosis of diabetes rather than when based on baseline HbA1c level. Thus, researchers and health practitioners should consider previously diagnosed diabetes when investigating in the impact of diabetes on mortality.

Introduction

A growing body of literature consistently shows that individuals with diabetes/prediabetes are more likely to have a wide array of diseases than people without diabetes, including cardiovascular diseases, renal diseases, stroke, cognitive impairment and kidney damage (Morgan et al., 2000, Center for Disease Control & Prevention, 2011; Seshasai et al 2014). Individuals with diabetes is also at an increased risk of death from all-cause (Saydah, Tao, Imperatore, & Gregg, 2009; Shen et al., 2014; Stokes & Preston, 2017) and specific-causes mortality, including cardiovascular diseases, cancer, respiratory diseases and diabetes itself (Seshasai et al 2014; Oba et al 2008;Alegre-Diaz et al., 2016; Fox, Sullivan, D'Agostino, & Wilson, 2004). From a population perspective, previous studies demonstrated that the fraction of all deaths attributable to diabetes in the U.S. was 3.6% -11.7% in adults ages 30-74 in 1976-1992 and 1997-2009, respectively (Saydah, Eberhardt, Loria, & Brancati, 2002; Stokes & Preston, 2017). Diabetes prevalence among US adults has been increasing in the last decade, while the impact of the disease on mortality risk has been reduced in the same period, indicating US adults are expected to live longer with the disease today in the past (Gregg et al., 2018). At the same time, as diabetes prevalence and incidence increases in the US, the number of health problems and deaths attributable to diabetes is also expected to increase in the future (Linda, Wang, Yiling, Theodore, & Lawrence, 2014).

In the investigation of the impact of diabetes on excess death, many scholars have typically identified diabetes measured by a standard clinic examination, such as, fasting plasma glucose (FPG), 2-hour fasting glucose and oral glucose tolerance test. For instance, patients who had an FPG level of 126 mg/dL or greater, or a 2-hour PG level of 200 mg/dL or greater at enrollment are identified as diabetic. In addition to these traditional biochemical measures, more scholars have recently advocated the use of glycated Hemoglobin (HbA1c) to diagnose diabetes due to its several advantages (Cowie et al., 2009; Fox, Sullivan, D'Agostino, & Wilson, 2004; Saydah et al., 2004). In research using prospective cohorts from national representative health survey, on the other hand, many scholars used diabetes diagnosed previously by doctors or health professional and reported by participants at a survey, which is often

referred to as self-reported diagnosed diabetes (Gregg et al., 2012; Roglic et al., 2005). Some researchers employed both biomarkers and self-reported diagnosed diabetes (Sreenivasa et al 2011). Whatever diagnostic approaches are chosen by scholars, most of them found a positive and significant impact of diabetes on the risk of death.

However, people who are identified as having or not having diabetes based on biomarkers may have different risks of mortality by their previous diagnosis of diabetes. This is because diabetes is a disease that affects mortality both directly and indirectly through multiple health behaviors (i.e., smoking and dietary), response to treatment, life-threatening health complications and combination of these. Also, the impact of diabetes and potential complications are cumulative and affects cardiovascular problems and kidney years after the onset of diabetes. There is little information whether people who were able to lower blood sugar level after being diagnosed with diabetes have a similar mortality risk with those who were never been diagnosed. Despite observed substantial impact of measured and self-reported diagnosed diabetes on mortality, researchers tend to use these two diagnostic tools interchangeably and their independent effect on mortality has rarely been recognized.

In this study, I examine mortality pattern of national representative sample of US adults ages 40 – 84 with special attention to the dynamics of measured and diagnosed diabetes. In analysis, the sample adults are classified by HbA1c level criteria ($\geq$ 6.5%) and self-reports of diagnosed diabetes. Overall, results show the pronounced impact of self-reported diagnosed diabetes in estimating mortality and diabetes diagnosed based on baseline HbA1c level has little impact once self-reported diagnosed diabetes is considered.

Literature Review

Measured and Diagnosed Diabetes and Mortality

In order to identify person with diabetes, scholars in research community and health practitioners have focused on standard clinical measures for diagnosing diabetes that are often obtained from blood sugar level test including FPG, 2-hour plasma glucose (2-h OGTT), oral glucose tolerance test and HbA1c (An et al., 2015; Saydah et al., 2004). While researchers tend to use one of these biomarkers to diagnose diabetes, others sometimes used more than one indicators, applying a more conservative criteria for detecting diabetes (Menke, Casagrande, Geiss, & Cowie, 2015). On the other hand, several studies assign individuals who are taking antidiabetic drugs or insulin as diabetic even though they do not meet the cutoff value of diagnostic test because people on diabetes treatment were typically already diagnosed with diabetes in the past and the use of such medications is expected to low blood glucose level at baseline (Almdal, Scharling, Jensen, & Vestergaard, 2004; Fishman, Stokes, & Preston, 2014; Fox, Sullivan, D'Agostino, & Wilson, 2004b).

Of these biochemical indicators, HbA1c has been increasingly advocated by health providers and researchers over other traditional biomarkers due to its high repeatability, reliability, little intra-person variation and availability during non-fasting state (Committee & Classification, 2010; International Expert Committee, 2009). While HbA1c is strongly associated with FPG and 2-h OGTT (Davidson, Peters, & Schriger, 1995; Elizabeth, 2010), many scholars recommended HbA1c in screening and diagnosing diabetes (Davidson, Peters, Schriger 1995; Adams et al., 2009; Guo, Moellering, & Garvey, 2014). Furthermore, Hb1ac shows better explanatory power compared with fasting glucose levels in estimating mortality from all-cause and specific causes (Bancks et al 2014; Selvin 2005). Some articles, however, have reported the disadvantages of HbA1c as a diagnostic test for diabetes. For instance, HbA1c shows low sensitivity in diagnosing diabetes than other biomarkers including FPG and 2-h OGTT, resulting in relatively low prevalence and high undiagnosed diabetes when diabetes is identified based on HbA1c cutoff value of 6.5% (Guo et al., 2014).

Focusing on HbA1c, many studies have investigated the association between HbA1c levels and mortality in individuals with and without diabetes. Although prior evidence in general shows that

mortality risk increases with HbA1c levels, some studies reported a nonlinear relationship in certain HbA1c levels (Bancks et al., 2014; Carson et al., 2010; Palta, Huang, Kalyani, Golden, & Yeh, 2017). For instance, Selvin et al (2011) found a significant association between HbA1c and mortality from all-cause in HbA1c levels higher than 5.5%, but the excess risk of death decreases as HbA1c increases at HbA1c levels below 5.5%, reporting a J-shaped pattern. This J-shaped, or sometimes a U-Shaped pattern, is also observed in other HbA1c levels, but mostly in a left tail of HbA1c distribution. Same pattern is observed with other biomarkers, including FPG (Sreenivasa et al 2011). However, one prospective cohort study of New Zealand shows conflicting findings; non-linear association is observed in HbA1c levels greater than 6.5% while linear association in the low to normal HbA1c levels (Brewer et al., 2008).

Along with the biomarkers, diabetes has been diagnosed based on a prior diagnosis of diabetes using a survey question asking whether participants have ever been told that they have diabetes/prediabetes (or sometimes sugar diabetes) by a doctor or health professional (Shen et al 2014). Because of its nature of self-reported event occurred in the past, self-reported diagnosed diabetes is subject to recall error and selection bias that affects validity and reliability. In addition, a previous diagnosis of diabetes has limitation to reflect current diabetes status especially when individuals were diagnosed a long-time ago. However, previous evidence shows that these potential biases are not a major concern; self-reported diabetes shows relatively high sensitivity and specificity (Sayhah et al 2004). Furthermore, other studies that employed both diagnosed and measured diabetes reported similar prevalence of diabetes and estimates associated with mortality (Stokes & Preston, 2017). One study suggests that the high sensitivity and specificity of self-reports of diabetes is due to the substantial improvement of diabetes screening, clear diagnostic criteria for diabetes and increasing attention to diabetes (Midthjell et al 1992).

Similar to the evidence on HbA1c, previous articles found that individual with a previous diagnosis of diabetes have increased risk of death compared to people without diagnosed diabetes (Saydah, Tao, Imperatore, & Gregg, 2009; Stokes & Preston, 2017). For instance, Saydah et al (2002)

found a relative hazard of 1.90 for all-cause mortality in adults ages 30-74 with diagnosed diabetes compared with those without diabetes using national representative survey data in 1976-1992. Similar relative risks are observed in other studies using self-reported diagnosed diabetes, ranging from 1.80 to 2.00 (K et al., 2014). One study conducted by Stokes and Preston (2017) reported a hazard ratio of 1.88 (95% CI: 1.63-2.16). When examining death from cardiovascular and coronary heart diseases, reported relative risk associated with diabetes is slightly higher than death from all-cause, but lower relative risk is reported for deaths from cancer and other causes (Oba 2008; Shen et al., 2014).

The two types of diagnostic approaches are often used together in the investigation of undiagnosed diabetes (Gregg et al., 2004; Menke, Casagrande, Geiss, & CC, 2015). In the studies, undiagnosed diabetes is identified as an individual who meet biomarker criteria for diabetes (i.e., HbA1c level of 6.5% or greater), but do not report previous diabetes diagnosed. However, this attempt of using both measured and diagnosed diabetes has little been used in mortality research.

There are several potential ways in which measured diabetes status at baseline and a prior diagnosis of diabetes jointly affect mortality. For one, people diagnosed with diabetes are expected to have had the disease longer than those without diagnosed diabetes at the same baseline HbA1c category. As a result, people with diagnosed diabetes are likely to have been exposed to long-term complications of diabetes and hyperglycemia status which contributes to increased risk of dying. However, it is also the case that these are encouraged to change their risky health behaviors and conduct intensive weight control that may lower a probability of premature death. It is also possible that only either diagnosed diabetes or measured diabetes at baseline dose matter regardless one another. For instance, only baseline HbA1c could predicts mortality disparities while a previous diagnosis of diabetes does not affect mortality, or vice versa.

Little information is available on associations among measured and diagnosed diabetes and mortality. Almost all prior knowledge with regard to diabetes and excess death is either the relative risk of

death associated with diabetes as an exposure at baseline diagnosed by self-reports or biomarkers in a prospective cohort study design (Palta et al., 2017; S. Saydah et al., 2009) and relative mortality rate in individuals with diabetes compared to those without diabetes based on longitudinal study design (An et al., 2015). Using a national representative sample of US adults this study examines the relative risk of death associated with diabetes in which diabetes is defined by both measured and diagnosed diabetes, net of potential mediating factors. To examine the mechanisms of linkage among diagnosed diabetes, baseline HbA1c and mortality, health behaviors and complications that have been shown to be associated with diabetes are included in statistical model.

Methods

Data were obtained from the Third National Health and Nutrition Examination Survey (NHANES) III, 1988-1994) and NHANES Continuous surveys 1999-2010. The survey includes national representative noninstitutionalized U.S. population using a multistage stratified probability sampling. A detailed explanation of the NHANES is available somewhere else (National Center for Health Statistics, Center for Disease Control and Prevention, 2010). NHANES participants were interviewed in their home and randomly selected participants subsequently received a physical and laboratory examination in a mobile examination center. NHANES participants who were eligible for matching were linked to the National Death Index (NDI) based on a 14-item identification scheme. The NHANES participants who were eligible for the linkage with NDI were followed up mortality status from the survey date through December 31, 2011. In the current study, mortality follow-up is limited to five years beyond the month at the examination to reduce potential bias derived from the possibility that participants had development of diabetes during the follow-up period. Thus, participants were censored if the participants died during the follow-up years, or reached five years after baseline or December 31, 2011.

This study includes sample of adults ages 40 through 84 at baseline and who were both interviewed and received examination. Respondents aged 85 or older are excluded to reduce bias induced by mortality selection and the open-ended coding of 85+ in the continuous NHANES. In addition, individuals with missing information on model covariates (n=5,910) or who died in the same month in which they were interviewed (n=7) were excluded from the analysis. Furthermore, I exclude individuals with a HbA1c level below 5.0% (n=1,780) in which there were few observations and deaths and an inversed relationship between HbA1c and mortality is often observed. The final sample size is 20,935.

The outcome is all-cause mortality occurred during the follow-up. Diabetes status is identified based on self-reported diagnosed diabetes and HbA1c levels. Self-reported diabetes is previously diagnosed diabetes constructed based on a question of whether the respondent had ever been told by a doctor or health professional that they have diabetes or sugar diabetes other than during pregnancy. If answered "yes" to the question, the respondents are considered as having been diagnosed with diabetes. Those who answered they had "borderline" diabetes are considered as non-diabetic. Among participants ages 20 and over, NHANES also collects laboratory-measured HbA1c levels during the examination that indicate the average glycemia attached to red blood cells for the past 2-3 months. Following treatment guidelines suggested by ADA, participants with a HbA1c value equals to or greater than 6.5% (48 mmol/mol) are classified as diabetic (ADA Diagnosis & Classification, 2009). Then the participants are categorized into four groups based on the HbA1c cutoff and self-reports of diabetes: (1) HbA1c < 6.5% and undiagnosed with diabetes (*<6.5% & Undiag*) (2) HbA1c < 6.5% and diagnosed with diabetes (*<6.5% & Diag*) (3) HbA1c ≥ 6.5% & undiagnosed with diabetes (*≥6.5% & Undiag*) and (4) HbA1c ≥ 6.5% & undiagnosed with diabetes (*≥6.5% & Diag*). Covariates are grouped into three categories: sociodemographic characteristics (age at time of survey, educational attainment, sex and race/ethnicity), health behaviors related factors (smoking, alcohol drinking, obesity and using health care service) and diabetes complications (hypertension, heart failure, heart attack, stroke and cancer). Age at baseline is centered at the age of 30. I categorize educational attainment as less than high school, high school, some

college and 4 years college graduate or higher. Race and ethnicity includes non-Hispanic whites, non-Hispanic blacks, Hispanics and other racial/ethnic groups. For drinking status, I categorize it as never drinker, former drinker (had less than 12 alcohol drinks in the last year) and current drinker (had at least 12 alcohol drinks in the last year). Smoking behavior is grouped as never smoker, former smoker and current smoker. Diabetes-related complications are all self-reports of diagnosis previously. Obesity is coded based on BMI, as less than 24.9 (normal weight), 25.0-29.9 (over-weight) and 35.0 or over (obese). All complications are self-reports, for instance, whether the participants have ever told by doctor that they have cancer.

Royston-Parmar survival models (Royston & Lambert 2011) were fitted to estimate hazard ratios and 95% CI for the diabetes group. Model 1 includes diabetes group defined above, race/ethnicity, age at baseline since 40, gender and education. Model 2 additionally includes health behavioral factors; smoking and drinking behaviors, BMI categories and not having access to health care. Model 3 adds the five self-reports of complications of diabetes. In descriptive statistics and mortality estimates are accounted for the NHANES survey weight using STATA 15 (StataCorp LP, College Station, Tx).

To assess the validity of the study, several sensitivity analyses were conducted. First of all, the use of HbA1c level of 6.5% as the cutoff value may over- or underestimate the impact of HbA1c on mortality, although the value of 6.5% is recommended by the American Diabetic Association. Thus, I estimate the same statistical model in which different cutoff values, 5.7% and 7.0% are used. Moreover, model without BMI categories was estimated to see how the reversal causal relationship between diabetes and obesity affect findings. In addition to the sensitivity analyses, the impact of diabetes duration (age at survey – age at diagnosis of diabetes, in years) is estimated net of continuous HbA1c level and other covariates in order to examine a potential mechanism linking diagnosed diabetes and mortality. In this analysis individuals who were diagnosed diabetes before 30 years prior to the survey are excluded.

Results

Table 1 presents descriptive statistics of the four diabetes groups (n=20,935). Mean follow-up is 4.18 years with a total of 87,655.25 person-years. There were 1,658 adults identified as deceased during the 5-years follow-up. The large majority of sample are in *<6.5% & Undiag* (85.3%) and relatively small percentages of the sample are in *<6.5% & Diag* (4.3%), *≥ 6.5% & Undiag* (3.1%) and *≥ 6.5% & Diag* (7.2%). The percentage of diabetes is 10.3% (*≥ 6.5% & Undiag* + *≥ 6.5% & Diag*) and 11.5% (*≥ 6.5% & Undiag* + *≥ 6.5% & Diag*) when diabetes is diagnosed by HbA1c criteria and diagnosed diabetes, respectively. There is racial/ethnic differentials in diabetes status: non-Hispanic Blacks and Hispanics are disproportionately in the two diabetic groups (HbA1c≥ 6.5%) than in non-diabetic group (HbA1c < 6.5%), suggesting that diabetes prevalence is higher in Blacks and Hispanics compared to non-Hispanic Whites, which is consistent with a previous finding (Cowie et al., 2009). The mean age at baseline is younger in *<6.5% & Undiag* (56.1 years) than other groups. There is an inverse relationship between education and diabetes status, the proportion of 4 years of college is higher in the non-diabetic groups than the diabetic groups. With regard to smoking and drinking behaviors, there is a notable gap by diagnosed diabetes. The percentages of current smokers, moderate and heavy drinkers are higher in undiagnosed groups (*<6.5% & Undiag* and *≥ 6.5% & Undiag*) than diagnosed groups (*<6.5% & Diag* and *≥ 6.5% & Diag*). There is also a considerable difference in the distribution of five complications by a previous diagnosis of diabetes, rather than the HbA1c criteria. For instance, the weighted percentage of the sample with self-reported diagnosed stroke is 2.8% and 4.4% in *<6.5% & Undiag* and *≥ 6.5% & Undiag*, but 10.7% and 10.0% in *<6.5% & Diag* and *≥ 6.5% & Diag*, respectively.

Hazard ratios from the Royston-Parmar survival regression models are presented in Table 2. In all three models, hazard ratios for death among the two diagnosed groups (*<6.5% & Diag* and *≥ 6.5% & Diag*) are significantly higher than that of *<6.5% & Undiag*, which is the reference group. For example, hazard ratios in Model 1 for *<6.5% & Diag* and *≥ 6.5% & Diag* are 1.688 (95% CI:1.315 to 2.166) and 2.046 (95% CI:1.684 to 2.487), respectively. In Model 2, it is observed that hazard ratios and

corresponding significance for the two diagnosed groups are almost intact when factors related to health behaviors are additionally adjusted for. However, reduced hazard ratios for the two diagnosed groups are observed in Model 3 after controlling for the five complications, but the significance of hazard ratios remained. With regard to another undiagnosed group, *≥ 6.5% & Undiag*, on the other hand, there is no statistically difference between the two undiagnosed groups (*<6.5% & Undiag* and *≥ 6.5% & Undiag*) in all three models. Compared to Model 1, hazard ratio for the group appears to be lower than 1 in Model 2 and 3, but its 95% confidence interval ranges do not include 1, rainging approximately from 0.66 to 1.45 in these two models.

Along with estimating models presented in Table 2, several Wald statistical tests were conducted following each model in order to examine mortality differences between diabetes groups. In all three models, mortality risk for *≥ 6.5% & Undiag*, which is undiagnosed diabetes cases, is statistically lower than the two diagnosed groups. However, there is no statistical difference between the two diagnosed groups in all three models. In summary, the results in Table 2 suggest that once individuals were diagnosed with diabetes previously, they have excess risk of dying than those without diagnosed diabetes, irrespective of whether they were identified as diabetic based on the HbA1c cutoff.

These findings appeared to be robust to changes in cutoff values of HbA1c. Results from two sensitivity analyses (Table A1) reveal that the two diagnosed groups have significantly higher mortality than the reference when diabetes is defined as either HbA1c ≥ 5.7% and HbA1c ≥ 7.0%. One exception is that the risk ratio for *Diabetic & Undiag* in Model A1 is statistically significant (HR:1.279, 95% CI: 1.080-1.514), in which diabetes is defined as HbA1c ≥ 5.7%. This reflects the positive association between HbA1c and the excess risk of death in HbA1c values between 5.7% and 6.5%. Including individuals with HbA1c levels between 5.7% and 6.5% in *Diabetic & Undiag* results in increased relative risk of this group compared to *Non-Diabetic & Undiag*.

Cumulative survivorships over the follow-up period for the four groups are graphically presented in Figure 1. Each survivorship is calculated based on coefficients in Model 3 in Table 2. Over time during the follow-up, the slopes for the groups appear to be divided largely into two groups based on diagnosed diabetes status rather than HbA1c criteria. That is, the two undiagnosed groups show a relatively high survivorship than the two diagnosed groups and there is small difference within each group of diagnosis of diabetes.

Table 3 presents the effect of duration of diagnosed diabetes and continuous HbA1c with adjustment for covariates used in Model 2. These models only include individuals who were diagnosed with diagnosed diabetes. Also, the analysis is limited to those with duration <50 years, yielding the mean duration of diabetes is 9.5 ± 8.9 years. The mean HbA1c among the restricted sample is and 7.3 ± 1.7%, respectively. Results indicate that duration and continuous HbA1c levels are significantly associated with excess mortality when they are estimated both separately and simultaneously. In Model 6 in which diabetes duration and HbA1c are included together, one year increase in duration since the diagnosis of diabetes is associated with an increase in the risk of death by a factor of 1.015, controlling for HbA1c level at baseline.

Discussion

In traditional research on the impact of diabetes on death, diabetes has been identified by either self-reports or biochemical marker, but the unique properties of each measure have received little attention. In a clinical setting, one's diabetes status and subsequent treatment have been primarily determined based on baseline assessments of laboratory results. However, as risk factors involved in the onset and development of diabetes affect mortality in both directly and indirectly, considering whether individuals were diagnosed with diabetes as well as the current status of diabetes is also critical. Consistent with other studies, this study found a positive and significant impact of HbA1c ≥ 6.5% and diagnosed diabetes when

they are estimated in a separate statistical model (results not shown). When considered together, results are surprising that individuals with diabetes diagnosed show significantly higher mortality risk than those without diagnosed diabetes, regardless of diabetes diagnosed by the HbA1c cutoff of 6.5%.

There are two possible explanations for the observed strong effect of diagnosed diabetes. First, individuals with the pervious diagnosis of diabetes may have more severe case of diabetes and related complications than those without diagnosed diabetes even though they all have diabetes at baseline. Indeed, the prevalence of self-reported complications for the two diagnosed groups is much higher than the undiagnosed groups within the same HbA1c category (Table 1). Furthermore, an inclusion of these complications in Model 3 (Table 2) reduces relative risk of dying between diagnosed and undiagnosed groups. Although adding the complications does not remove a significant difference between diagnosed and undiagnosed groups, this could be because the model adds only cancer and vascular-related complications, while diabetes is also associated with non-vascular diseases including infectious disease, liver disease and other physical disabilities that may contribute to death (Chiu & Wray, 2011; Seshasai et al 2011). Also, all complications are self-reported and there might be a measurement error that may underestimate the mediate impacting of the complications. It is possible that under-reporting of diabetes makes the result less precise. However, given relatively low prevalence of undiagnosed diabetes in the US population, around 3% in 2011-2012, and substantial improvement of diabetes screening and awareness in recent years, it is hard to think that undiagnosed diabetes affects the conclusion (An et al., 2015; Menke, Casagrande, Geiss, & CC, 2015; Selvin & Ali, 2017). Second, individuals with diagnosed diabetes are expected to have the disease longer than those without diagnosed diabetes within the same HbA1c ladder. In this study, I found that the risk of death increases continuously with duration of diabetes, even after controlling for HbA1c level at baseline Table 3. The finding is consistent with other previous studies: these studies demonstrated that duration of diabetes is positively and significantly associated with mortality because people are at an increased risk of diverse vascular damages including

atherosclerosis, myocardial infraction and stroke with diabetes duration (Brun et al., 2000; Donaghue et al., 2003; Fox et al., 2004a; Valensi, Pariès, & Attali, 2003).

This study also demonstrated that individuals with undiagnosed diabetes (≥ *6.5% & Undiag*) have *lower* mortality risk than <*6.5% & Diag* as well as ≥ *6.5% & Diag*. Although some articles found a similar evidence that mortality in people with undiagnosed diabetes is as low as people with diagnosed diabetes, few researchers have explicitly analyzed the pattern (Stokes & Preston, 2017). The observed lower mortality among undiagnosed diabetes is somewhat different from a general understanding about undiagnosed diabetes because a number of researchers has warned the potential and critical health consequences of undiagnosed diabetes (Gregg et al., 2004). Furthermore, it is observed that people with an undiagnosed case are more likely to be racial minorities, have lower education and being obese (Selvin, Wang, Lee, Bergenstal, & Coresh, 2017) and these characteristics have been found to be associated with higher mortality. In this study, however, people with undiagnosed diabetes do have a lower mortality risk than those with diagnosed diabetes even though these people with diagnosed with diabetes are identified as non-diabetic at baseline. The result suggests that although individuals with undiagnosed diabetes may exposure to the further development of disease due to lack of timely intervention, the cumulative damage and risks of death from diabetes that these people have had are smaller than that of those with diabetes diagnosed in the past have.

This study highlights several qualifications to the previous evidence on diabetes biomarkers and mortality. As noted, there is a broad consistent evidence showing strong positive associations of biochemical indicators for diabetes and the risk of death. These results may actually reflect higher mortality rates among individuals with diagnosed diabetes who are exposed to diabetes-related risks for a long-term than those without diagnosed diabetes whose baseline HbA1c level is expected to be lower than the former group. Furthermore, the current study provides recommendations for jhealth professionals. Given a rapid increase in social burden due to deaths attributable to diabetes in recent decades, health providers should pay attention not only to blood test result of participants at enrollment, but also to

patients' diabetes history and the presence and development of its complications since first medical diagnosis of diabetes. Furthermore, more resources for health behavioral interventions and glycemia control need to be allocated to individuals with diabetes diagnosed previously, regardless of their current diabetes biochemical markers.

Despite the contributions of this study, several limitations should be acknowledged. First, due to the lack of information on a wide range of diabetes-related complications and exact time of the onset of diabetes, the mechanisms that link diagnosed and measured diabetes and mortality were only partially tested. Second, sample size and number of deaths in *<6.5% & Diag* and *≥ 6.5% & Undiag* are relatively small and estimates for these categories should be interpreted with caution.

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TABLES

Table 1. Sample Characteristics by HbA1c Criteria and Self-Diagnosed Diabetes. Adults Ages 40 – 84 at Baseline (n=20,935). NHANES III (1988-1994) and Continuous NHANES 1999-2010.

	Non-diabetic (Hba1c <6.5%)		Diabetic (Hba1c ≥ 6.5%)	
	Undiagnosed	Diagnosed	Undiagnosed	Diagnosed
	<6.5% & Undiag	*<6.5% & Diag*	*≥ 6.5% & Undiag*	*≥ 6.5% & Diag*
Unweighted N (%)	16,775	1,055	981	2,124
Weighted percentage	85.3	4.3	3.1	7.2
Person-years	70,921	4,176.75	4,108	8,449.5
Unweighted N of deaths	1,129	144	77	308
HbA1c level, mean (SD)	5.5	5.9	7.5	8.1
Race/ethnicity				
Non-Hispanic White	79.5	71.6	62.4	63.4
Non-Hispanic Black	8.4	12.7	17.2	16.6
Hispanic	7.6	10.1	13.4	13.9
Others	4.4	5.6	6.9	6.1
Male	47.2	46.7	56.1	50.5
Age at baseline (SD)	56.1	62.0	60.5	61.1
Educational attainment				
Less than high school	18.2	25.3	30.8	32.6
High school	26.5	26.4	28.0	25.8
< 4 years college	27.8	27.2	25.2	27.2
4 years college +	27.5	21.1	16.1	14.5
Smoking behavior				
Never	47.6	46.3	43.5	47.4
Current smoker	20.8	16.2	20.3	16.7
Former	31.6	37.4	36.2	35.9
Drinking status				
Never	11.2	17.5	17.4	18.1
Former drinker	18.8	26.9	24.3	23.8
Current drinker	70.0	55.6	58.2	58.1
BMI categories				
-24.9	30.1	13.2	8.4	14.1
25.0-34.9	57.9	55.2	58.0	54.8
35.0 -	11.9	31.6	33.6	31.1
Not having health care	10.0	1.7	12.3	2.8
Self-reported complications (Yes)				
Hypertension	35.9	72.6	55.9	66.1
Heart failure	2.3	10.0	5.9	11.6
Heart attack	4.3	12.2	8.6	12.7
Stroke	2.8	10.7	4.4	10.0
Cancer	12.6	18.3	14.7	15.0

NHANES survey weight is accounted for.

Table 2. Estimated Hazard Ratios. Adults Ages 40 – 84 at Baseline (n=20,935). NHANES III (1988-1994) and Continuous NHANES 1999-2010.

	Model 1	95% CI	Model 2	95% CI	Model 3	95% CI
Diabetes status						
Non-diabetic & Undiagnosed (*Ref*)	1.000		1.000		1.000	
Non-diabetic & Diagnosed	1.688	1.315,2.166	1.684	1.313,2.161	1.443	1.125,1.850
Diabetic & Undiagnosed	1.009	0.694,1.467	0.995	0.681,1.454	0.972	0.664,1.422
Diabetic & Diagnosed	2.046	1.684,2.487	2.085	1.710,2.543	1.760	1.437,2.156
Race/ethnicity						
Non-Hispanic White (*Ref*)	1.000		1.000		1.000	
Non-Hispanic Black	1.412	1.188,1.679	1.373	1.153,1.634	1.399	1.169,1.673
Hispanic	0.860	0.652,1.135	0.906	0.688,1.193	1.019	0.770,1.349
Others	0.592	0.368,0.951	0.564	0.350,0.911	0.542	0.332,0.883
Male	1.659	1.440,1.912	1.607	1.379,1.873	1.562	1.334,1.829
Age at baseline	1.090	1.082,1.098	1.098	1.089,1.107	1.088	1.079,1.098
Educational attainment						
Less than high school (*Ref*)	1.000		1.000		1.000	
High school	0.870	0.731,1.036	0.938	0.788,1.117	0.981	0.824,1.168
< 4 years college	0.707	0.576,0.868	0.772	0.629,0.948	0.789	0.642,0.970
4 years college +	0.523	0.413,0.661	0.636	0.502,0.805	0.674	0.530,0.856
Smoking behavior						
Never (*Ref*)			1.000		1.000	
Current smoker			2.971	2.430,3.632	2.782	2.271,3.408
Former			1.595	1.346,1.889	1.495	1.260,1.774
Drinking status						
Never (*Ref*)			1.000		1.000	
Former drinker			0.862	0.694,1.070	0.888	0.713,1.108
Current drinker			0.766	0.621,0.946	0.810	0.652,1.007
BMI categories						
-24.9 (*Ref*)			1.000		1.000	
25.0-34.9			0.741	0.634,0.865	0.691	0.591,0.809
35.0 -			1.044	0.813,1.342	0.892	0.692,1.149
Not having usual health care			1.165	0.840,1.615	1.061	0.763,1.476

Complications		
Hypertension	1.263	1.081,1.476
Heart failure	2.297	1.835,2.876
Heart attack	1.100	0.887,1.363
Stroke	1.391	1.123,1.724
Cancer	1.451	1.229,1.714

NHANES survey weight is accounted for.
*p<.05 **p<.01

Table 3. The Impact of Duration of Diagnosed Diabetes among Adults with Diagnosed Diabetes. NHNAES III (1988-1994) and Continuous NHANES 1999-2010.

		Model 4		Model 5		Model 6
	HR	95% CI	HR	95% CI	HR	95% CI
Duration (in years)			1.017	[1.004,1.029]	1.015	[1.002,1.028]
HbA1c (continuous)	1.078	[1.022,1.136]			1.112	[1.026,1.205]

Only participants with diagnosed diabetes within 30 years prior to the survey are included.
Covariates in Model 2 in Table 2 are controlled for in these models.

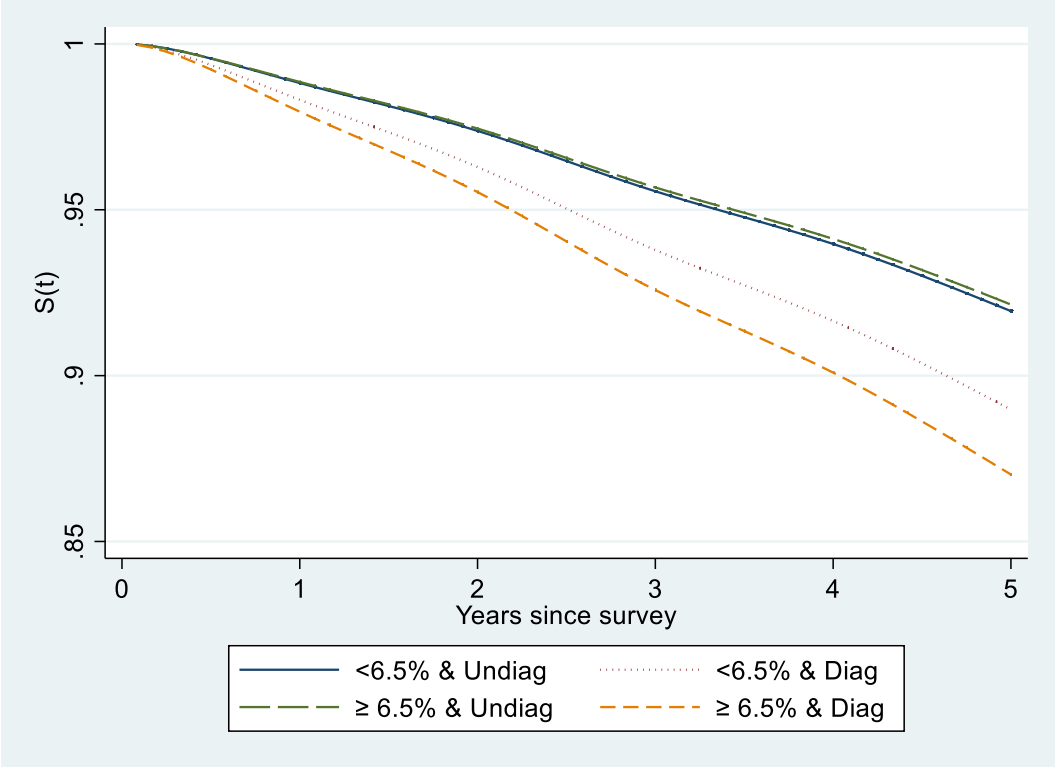

Figure 1. Survival Curves in Follow-up estimated by Royston-Parmar Models by Diabetes Status. Survivorships are calculated based on Model 3 in Table 2.

Appendix

Table A1. Estimated Hazard Ratios from Sensitivity Analyses.

	Model A1	95% CI	Model A2	95% CI
Non-Diabetic & Undiag	1.000		1.000	
Non-diabetic & Diag	1.939	[1.206,3.120]	1.785	[1.440,2.213]
Diabetic & Undiag	1.279	[1.080,1.514]	1.452	[0.850,2.481]
Non-diabetic & Diag	2.185	[1.799,2.653]	2.168	[1.739,2.702]

Model A1: *Non-Diabetic* is defined as HbA1c $\geq$ 5.7%
Model A2: *Non-Diabetic* is defined as HbA1c $\geq$ 7.0%
Undig: Not diagnosed with diabetes previously
Diag: Diagnosed with diabetes previously
Covariates in Model 2 in Table 2 are controlled for in these models.