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Glycated Hemoglobin and All-Cause and Cause-Specific Mortality in Singaporean Chinese Without Diagnosed Diabetes: The Singapore Chinese Health Study

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OBJECTIVE

Glycated hemoglobin (HbA1c) is a robust biomarker of the preceding 2 to 3 months average blood glucose level. The aim of this study was to examine the association between HbA1c and mortality in a cohort of Southeast Asians.

RESEARCH DESIGN AND METHODS

Analysis of 7,388 men and women, mean age 62 years, from the Singapore Chinese Health Study who provided a blood sample at the follow-up I visit (1999–2004) and reported no history of diabetes, previous adverse cardiovascular events, or cancer. A total of 888 deaths were identified through 31 December 2011 via registry linkage. Participants represented a random study sample of potential control subjects for a nested case-control genome-wide association study of type 2 diabetes in the population. Hazard ratios (HRs) for all-cause and cause-specific mortality by six categories of HbA1c were estimated with Cox regression models.

RESULTS

Relative to participants with an HbA1c of 5.4–5.6% (36–38 mmol/mol), participants with HbA1c ≥6.5% (≥48 mmol/mol) had an increased risk of all-cause, cardiovascular, and cancer mortality during an average of 10.1 years of follow-up; HRs (95% CIs) were 1.96 (1.56–2.46), 2.63 (1.77–3.90), and 1.51 (1.04–2.18), respectively. No level of HbA1c was associated with increased risk of respiratory mortality. Levels <6.5% HbA1c were not associated with mortality during follow-up. The results did not materially change after excluding observation of first 3 years post–blood draw.

CONCLUSIONS

HbA1c levels consistent with undiagnosed type 2 diabetes (≥6.5%) are associated with an increased risk of all-cause and cause-specific mortality in Chinese men and women.

Glycated hemoglobin (HbA1c) is a continuous marker of glycemia, and levels >5.7% (39 mmol/mol) are associated with increased risk for developing type 2 diabetes as well as micro- and macrovascular events (1). Tight glycemic control occurs naturally in healthy individuals, and HbA1c represents average glycemia for the prior 2 to 3 months (1). Recently, an International Expert Committee recommended HbA1c as a
test to diagnose type 2 diabetes mellitus, which has been recognized by the American Diabetes Association (1,2). With the establishment of these guidelines and a burgeoning research base, the examination of HbA1c with outcomes across populations will further the application and understanding of this biomarker.

Indeed, HbA1c has been shown to better assess risk of cardiovascular disease (CVD) or death from all causes compared with fasting plasma glucose, especially at glycemic levels deemed prediabetic (3). Previous studies have reported that elevated levels of HbA1c below the diabetes threshold (<6.5%) are associated with an increased risk for cardiovascular morbidity and mortality (3–12). Yet, this research base is not comprehensive, and data from Chinese populations are scant, especially in those without diabetes. This gap in the literature is important since Southeast Asian populations are experiencing epidemic rates of type 2 diabetes and related comorbidities with a substantial global health impact (13–16).

Overall, there are few cohort studies that have examined the etiologic association between HbA1c levels and all-cause and cause-specific mortality. There is even lesser insight on the nature of the relationship between HbA1c and significant clinical outcomes in Southeast Asian populations. Therefore, we examined the association between HbA1c and all-cause and cause-specific mortality in the Singapore Chinese Health Study (SCHS).

RESEARCH DESIGN AND METHODS
The design of the SCHS has been previously summarized (17). Briefly, the cohort was drawn from men and women, aged 45–74 years, who belonged to one of the major dialect groups (Hokkien or Cantonese) of Chinese in Singapore. Singapore is a unique population, due to its geographic location, independence, and industrialization over last 50 years, resulting in accelerated advances in medical care, disease prevention, and health promotion, leading to a high standard of living. Between April 1993 and December 1998, 63,257 individuals completed an in-person interview that included questions on usual diet, demographics, height and weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history including history of diabetes diagnosis by a physician, and family history of cancer. Informed subject consent was provided with completion of the baseline interview, and Institutional Review at the National University of Singapore, University of Pittsburgh, and the University of Minnesota granted approval of this study.

Evaluation of Participant Characteristics
At the follow-up interview (F1), which occurred in 1999–2004, subjects were asked to update their baseline interview information. All participant characteristics in this analysis reflect the F1 interview. Consistent in both interviews was inquiry on smoking habits/status (age started/quit, amount, frequency, and type) and typical consumption of alcoholic beverages (beer, wine, Western hard liquor, and Chinese hard liquor). Participants were asked to choose from eight frequency categories and four portion sizes, and levels of alcohol intake were expressed in units of drinks per week to facilitate comparison with Western populations. One drink was defined as 375 mL of beer (13.6 g of ethanol), 118 mL of wine (11.7 g of ethanol), and 30 mL of Western or Chinese hard liquor (10.9 g of ethanol). Other risk factors assessed included self-reported hypertension status (yes/no) as diagnosed by a physician and BMI, calculated with self-reported height (m) and weight (kg) as kg/m². Self-report of body weight has been shown to be highly valid across many populations, as well as specifically in Asians (18).

Type 2 Diabetes and CVD Assessment
Diabetes status was assessed by the following question: “Have you been told by a doctor that you have diabetes (high blood sugar)?” If yes: “Please also tell me the age at which you were first diagnosed?” A validation study of the self-report of diabetes mellitus cases used two different methods and was previously reported (19,20). Similarly, prevalent CVD was assessed by the following questions: “Have you been told by a doctor that you have had a heart attack or angina (chest pain or exertion that is relieved by medication)?” and “Have you been told by a doctor that you have had a stroke?” If yes: “Please tell me the age you were first diagnosed?”

Analysis Cohort Formation and Blood Collection
The study population derived from 28,346 participants of the total 54,243 who were alive and participated at F1, who provided consent at F1 to collect subsequent blood samples (a consent rate of ~65%). The participants for this study were a random selection of individuals from the full study population who did not report a history of diabetes or CVD at the baseline or follow-up interview and reported no history of cancer. This nondiabetic group was established to serve in future SCHS analyses as a comparison group to incident cases of type 2 diabetes from the full study population (excluded from this analysis) occurring between baseline and the follow-up interview, frequency matched on age (±2 years), time of blood draw, sex, and dialect. All participants with blood samples drawn and analyzed for HbA1c were included in this analysis regardless of HbA1c status for a total N = 7,388. Compared with individuals participating at F1 who did not report diabetes, CVD, or cancer, this analytic sample is slightly younger, more male, and reported more smoking, but was similar in respect to dialect, alcohol consumption, education, and BMI. Red blood cells were isolated from whole blood and frozen until analysis that was performed at University of Minnesota. Percentage of HbA1c was analyzed in a Clinical Laboratory Improvement Amendments–certified laboratory using an automated high-performance liquid chromatography method in which whole blood samples are treated with EDTA on a Tosoh G7 HPLC Glycated Hemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA). Using the standards developed in the National Glycohemoglobin Standardization Program, this method of percentage of HbA1c assessment was calibrated to the reference range of 4.3–6.0% (23–42 mmol/mol) and a laboratory coefficient of variation range 1.4–1.9% (21).

Mortality Assessment
Information on date and cause of death was obtained through linkage with the nationwide registry of birth and death in Singapore. Up to six different ICD-9 codes were recorded in the registry.
Primary cause of death was used for analysis. Vital status for cohort participants was updated through 31 December 2011. Only 27 persons were lost to follow-up due to migration out of Singapore, suggesting that emigration of the cohort participants was negligible and that vital statistics follow-up was virtually complete. The end points in the analyses in addition to all-cause mortality were: deaths from CVD (ICD-9 codes 394.0–459.0), ischemic coronary heart disease (CHD) (410.0–414.9, 427.5), cerebrovascular disease (430.0–438.0), respiratory diseases (480.0–496.0), and all cancers (140.0–195.8 and 199–208.9).

Statistical Analysis
For the primary analyses, HbA1c was divided into six categories to align with the distribution of the population, clinical relevance, and cut points used in the literature. The categories were <5.0, 5.0–5.3, 5.4–5.6, 5.7–6.0, 6.1–6.4, and ≥6.5% (corresponding intervals are <31, 31–35, 36–38, 39–42, 43–47, and ≥48 mmol/mol). Secondary analyses aimed to clarify a threshold effect further divided the upper HbA1c category (≥6.5% [≥48 mmol/mol]) into four groups to determine if the highest HbA1c values would drive any observed association. These groups were 6.5–6.6, 6.7–7.0, 7.1–7.5, and >7.5% (corresponding mmol/mol intervals are 48–49, 50–52, 53–57, and >57). Smoking status was classified as “never smoked,” “former smoker,” and “current smoker.” Alcohol was characterized as routine practice of none (“no routine consumption”), light-moderate (“any up to seven drinks a week”), and heavy (“more than seven drinks a week”) for females. Male alcohol consumption categories were characterized according to none (“no routine consumption”), light-moderate (“any up to 14 drinks a week”), and heavy (“>14 drinks a week”). In this analysis, education was characterized into three groups: no formal education; primary schooling; and secondary school or beyond. Participant characteristics were calculated across categories. Means and SDs were derived for continuous variables, and proportions were calculated for categorical variables. All-cause mortality and cause-specific mortality hazard ratios (HRs) were calculated by HbA1c level. Crude and adjusted HRs and 95% CIs were estimated with Cox proportional hazards models. The HbA1c category of 5.4–5.6% was chosen as the reference category to provide a stable comparison, the alignment with previous studies, and so potential clinically relevant ranges above and below could be examined. The main effect crude model included only the HbA1c level. Adjusted models were constructed in this manner: Model 1 was adjusted for age, sex, dialect, and interview year. Model 2 was adjusted further for education, smoking status, and alcohol consumption. Model 3 was adjusted for all previous covariates plus BMI. Lastly, model 4 adjusted for the previous covariates of model 3 in addition to hypertension status, except for in the instance of cancer mortality. The authors determined hypertension not to hold the properties of a traditional confounder in the association between HbA1c and cancer incidence, refraining from adjustment. In the results table, we present the final model, as the strength and nature of the results did not materially change with covariate adjustment. Tests of linear trend across categories of HbA1c were performed by assigning participants the median of their HbA1c category and entering this new variable into a separate Cox proportional hazards regression model. BMI was modeled as a linear continuous variable for CVD, CHD, and cerebrovascular mortality but showed a quadratic association with all-cause, all-cancer, and respiratory mortality and was modeled accordingly. A quadratic model of continuous HbA1c values was also used to test for nonlinearity in the overall association. Person-years at risk for mortality (i.e., follow-up time scale) for each participant were calculated as the duration from blood draw to the date of mortality or through end of follow-up, 31 December 2011, whichever came first. Age- and sex-adjusted mortality rates were calculated for each HbA1c level by categorizing age into three groups, <60, 60–69 years old, and ≥70 years old, and calculating sex-specific crude mortality rates for each age group (events/person-years). These crude rates were then multiplied by the proportion of person-years each HbA1c-specific age category contributed to the overall study person-years at risk total (standardized weight). These rates were summed for each HbA1c level and multiplied by 100,000 to create an age- and sex-adjusted mortality rate. Distribution of time to event was left-skewed, log transformation increased skewness, and time was left untransformed. Using parameter estimates, we computed interaction HRs, 95% CI, and Wald $\chi^2$ $P$ values. To investigate if HbA1c levels differed across levels of sex, BMI, smoking, or age, separate multiplicative interactions were tested by adding product terms to the proportional hazards model. The proportional hazards assumption was assessed by HbA1c category, and no violations were detected. Sensitivity analysis was also performed for each mortality outcome, by excluding observation in the first 2 and 3 years post–blood draw for all 7,388 individuals, for purposes of accounting for possible subclinical disease or underlying poor health. All statistical analysis was performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS
During 74,890 person-years of follow-up, there were 888 total deaths, of which 249 were due to CVD, 388 were due to cancer, and 169 were recorded as respiratory mortality. Participant characteristics at baseline are reported in Table 1. There was a positive association between HbA1c and age, BMI, and prevalence of self-reported hypertension, while an inverse association was observed between educational attainment and HbA1c. There was a U-shaped association between HbA1c and smoking status and male sex.

Fully adjusted HRs and 95% CIs for HbA1c level are presented in Table 2 along with age- and sex-standardized mortality rates. The crude mortality rate was 1,186 deaths per 100,000 person-years. The age- and sex-standardized mortality rates for all-cause, CVD, and cerebrovascular each showed a J-shaped pattern according to HbA1c level. The CHD and cancer mortality rates were higher for HbA1c ≥6.5% (≥48 mmol/mol) and otherwise displayed no apparent pattern. The age- and sex-standardized mortality rate for respiratory diseases appeared U-shaped, with the lowest and highest HbA1c categories corresponding to the highest rates. In the Cox regression analysis, HbA1c levels ≥6.5% (≥48 mmol/mol) were strongly associated with all-cause, overall CVD, asthma, and chronic obstructive pulmonary disease (COPD) mortality.
as well as CHD and cerebrovascular mortality, and cancer mortality compared with the reference HbA1c, of 5.4–5.6% (36–38 mmol/mol). These results were not materially altered upon exclusion of observation of the first 2 or 3 years post–blood draw (results not shown). When HbA1c ≥6.5% (≥48 mmol/mol) was further divided into four groups, significantly increased hazard was observed for each of the four categories for both all-cause mortality and overall CVD mortality (results not shown). When the 5 years post–blood draw were excluded, the association between elevated HbA1c (HbA1c ≥6.5% [≥48 mmol/mol]) and increased risk for cerebrovascular mortality or cancer mortality was no longer significant for these two outcomes. There was no association between any level of HbA1c and respiratory causes of death. No other category of HbA1c was significantly associated with any outcome in this population.

Fully adjusted HRs and 95% CIs for total mortality, cardiovascular mortality, and cancer mortality are presented in Table 3 stratified by sex, smoking status (never/ever), and hypertensive status. Irrespective of the stratifying factor, we observe a J-shaped pattern for all-cause and CVD mortality, consistent with the results of the entire dataset. Akin to the nonstratified analysis, individuals with HbA1c levels ≥6.5% (≥48 mmol/mol) appear to be at a suggestive increase in hazard for cancer mortality, regardless of the stratifying factor. The formal tests of interaction were not significant for these groups (all outcomes P > 0.10) aligning with the presented results. Formal tests of interaction by age and BMI were also not significant for any of the outcomes (all outcomes P > 0.10).

**CONCLUSIONS**

Chinese men and women with no history of cancer, reported diabetes, or CVD with an HbA1c level ≥6.5% (≥48 mmol/mol) were at a significant increased risk of mortality during follow-up relative to their peers with an HbA1c of 5.4–5.6% (36–38 mmol/mol). No other range of HbA1c was significantly associated with risk of mortality during follow-up, and in secondary analyses, when the HbA1c level ≥6.5% (≥48 mmol/mol) was divided into four categories, this increased risk was observed in all four categories; thus, these data represent a clear threshold association between HbA1c and mortality in this population. These results are consistent with previous prospective cohort studies identifying chronically high HbA1c outside of diabetes, to be associated with increased risk for all-cause and CVD-related mortality (3–12,22).

However, these results are not entirely consistent with other populations, including Asian populations, as other studies have reported graduated risk in HbA1c levels between normal and <6.5%. Increased risk for all-cause mortality was found in three unique U.S. populations for individuals with HbA1c at or below the prediabetic threshold (HbA1c <5.7%) compared with a lower reference value (3.5,8). Two studies of European populations observed increased risk at HbA1c >5.5% and increased risk per each 1-percentage point increase in HbA1c concentration (7,11). Moderately elevated HbA1c (HbA1c >6.0%) was indicative of increased risk in an analysis of Japanese individuals without known diabetes (9). Some previous studies have also observed an increased risk with mortality in the lowest category of HbA1c (3.5,8). However, the lack of an association in the far left tail of HbA1c distribution is consistent across Asian population (9,10). We are also cautious in the interpretation of the cause-specific results in the SCHS population with HbA1c <5.0% due to the low numbers of accumulated outcomes.

Hyperglycemia is a known risk factor for CVD, not limited to individuals with diabetes. This may be in part due to the vascular damage caused by oxidative stress in periods of hypo- and

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**Table 1—Participant characteristics according to category of HbA1c percentage: the SCHS**

| Characteristics     | HbA1c (% category [mmol/mol]) |
|---------------------|-------------------------------|
|                     | <5.0 (≤31) | 5.0–5.3 (31–35) | 5.4–5.6 (36–38) | 5.7–6.0 (39–42) | 6.1–6.4 (43–47) | ≥6.5 (≥48) | P for trend |
| N (% of population) | 223 (3)    | 847 (11)     | 2,131 (29)     | 2,754 (37)     | 923 (13)       | 510 (7)   | <0.001     |
| Age, years          | 61.9 (7.3) | 61.6 (7.7)   | 61.5 (7.4)     | 62.4 (7.5)     | 64.0 (7.6)     | 63.9 (7.8) | <0.001     |
| Female (%)          | 39.9       | 50.8         | 52.5           | 53.4           | 51.7           | 47.1      | 0.6573     |
| Education (%)       |            |              |                |                |                |           |            |
| Less than primary school | 19.3       | 21.0         | 20.1           | 22.9           | 24.3           | 24.1      | <0.001     |
| Primary schooling   | 48.0       | 47.2         | 46.2           | 45.8           | 48.0           | 49.0      |           |
| Secondary school or beyond | 32.7       | 31.8         | 33.7           | 31.3           | 27.7           | 26.9      |           |
| Cantonese dialect (%) | 55.6       | 48.6         | 46.8           | 50.4           | 50.0           | 46.3      | 0.1783     |
| Smoke (%)           |            |              |                |                |                |           | <0.01      |
| Never               | 62.8       | 70.5         | 70.0           | 63.8           | 60.4           | 61.6      |           |
| Former              | 17.9       | 17.5         | 15.0           | 17.2           | 18.5           | 18.0      |           |
| Current             | 19.3       | 12.0         | 15.0           | 19.0           | 21.1           | 20.4      |           |
| Alcohol (%)         |            |              |                |                |                |           | <0.01      |
| None                | 71.3       | 81.6         | 80.3           | 79.7           | 82.7           | 82.8      |           |
| 0 to 1 drink/day    | 22.9       | 14.9         | 16.0           | 16.9           | 13.3           | 12.3      |           |
| >1 drink/day        | 5.8        | 3.5          | 3.7            | 3.4            | 4.0            | 4.9       |           |
| BMI, kg/m²          | 22.4 (3.1) | 22.1 (3.3)   | 22.5 (3.3)     | 23.0 (3.5)     | 23.8 (3.6)     | 24.4 (3.5) | <0.001     |
| Hypertensive (%)    | 31.4       | 30.3         | 28.9           | 34.2           | 41.5           | 47.3      | <0.001     |

For continuous variables, mean (SD) was calculated and is shown.
hyperglycemia (23, 24). For individuals with impaired fasting glucose and impaired glucose tolerance, increased oxidative stress and endothelial dysfunction are present before the onset of diabetes (25). The association between chronically high levels of HbA1c and development of and death from cancer is not as well defined (9, 26–30). Abnormal metabolism may play a role in cancer development and death. This is important, considering cancer is the leading cause of death in Singapore for adults 15–59 years of age (31). Increased risk for cancer mortality was found in individuals with impaired glucose tolerance (30). Nondiabetic women with elevated HbA1c were found to have increased risk for colorectal cancer (32). Oxidative stress was found to be associated with an increase in colorectal cancer risk in a prospective cohort population independent of diabetes status (33). Oxidative stress also induces DNA methylation, damage-promoting chronic inflammation, and cytokine signaling response promoting cell proliferation and creation of tumor mass (34–36). Lastly, hyperglycemia may be a surrogate measure for high insulin levels. Hyperinsulinemia and IGF-I are associated with increased cancer risk, possibly through mitogenic effects and tumor formation (27, 28, 37). This is the basis for the insulin-cancer hypothesis. Simply put, chronic levels of hyperinsulinemia reduce the production of IGF binding proteins 1 and 2. The absence of these proteins results in excess bioactive IGF-I, supporting tumor development (38). Chronic hyperglycemia, indicating high levels of insulin and IGF-I, may explain inhibition of cell apoptosis, increased cell proliferation, and increased cancer risk (39).

The results presented on respiratory mortality are novel. The authors found no previous studies looking at the association between HbA1c level and respiratory disease mortality. Our results show no association between HbA1c ≥6.5% (≥48 mmol/mol) and risk for death from respiratory causes during follow-up.

It is important to recognize the limitations of this study to give the results context. Other clinical measures such as lipids and insulin levels were not measured. Previous studies have not adjusted...
When stratified by one of the following, models were adjusted for age, sex, dialect, interview year, education, smoking, alcohol, BMI, and hypertension status (except for hypertension in cancer mortality).

| BMI category (kg/m²) | Cancer death | Cardiac death | CVD death | All-cause death |
|---------------------|--------------|---------------|-----------|----------------|
| Never smoke         |              |               |           |                |
| 0.00–0.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 0.50–0.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 1.00–1.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 1.50–1.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 2.00–2.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 2.50–2.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 3.00–3.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 3.50–3.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 4.00–4.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 4.50–4.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 5.00–5.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 5.50–5.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 6.00–6.49           | 1.00         | 1.00          | 1.00      | 1.00           |
| 6.50–6.99           | 1.00         | 1.00          | 1.00      | 1.00           |
| 7.00–7.49           | 1.00         | 1.00          | 1.00      | 1.00           |

For trend, $P<0.05$.
with risk of death during follow-up. These results were not materially different when sensitivity analyses were performed excluding observation of the first 2 and 3 years observation post-blood draw. Effect modification by age, sex, or smoking was not apparent in any mortality outcome. These findings contribute to the scientific body of knowledge by adding a large prospective study in an Asian population with clinically relevant HbA1c percentage clinical cut points. Additional studies are warranted in order to describe the distribution of HbA1c in Asian populations and to characterize the mortality risk associated with levels of HbA1c below the threshold for diabetes.

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Author Contributions. M.P.B. wrote the manuscript and researched the data. A.O.O. researched the data, contributed to the discussion, and edited and reviewed the manuscript. J.S.P. and W.-P.K. edited and reviewed the manuscript. M.G.D. oversaw HbA1c analysis. M.P.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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