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

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

Glycated hemoglobin (HbA_{1c}) 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 HbA_{1c} 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 HbA_{1c} were estimated with Cox regression models.

RESULTS

Relative to participants with an HbA_{1c} of 5.4–5.6% (36–38 mmol/mol), participants with HbA_{1c} ≥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 HbA_{1c} was associated with increased risk of respiratory mortality. Levels <6.5% HbA_{1c} 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

HbA_{1c} 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 (HbA_{1c}) 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 HbA_{1c} represents average glycemia for the prior 2 to 3 months (1). Recently, an International Expert Committee recommended HbA_{1c} as a

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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 HbA_{1c} with outcomes across populations will further the application and understanding of this biomarker.

Indeed, HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels and all-cause and cause-specific mortality. There is even lesser insight on the nature of the relationship between HbA_{1c} and significant clinical outcomes in Southeast Asian populations. Therefore, we examined the association between HbA_{1c} 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 include self-reported hypertensive status (yes/no) as diagnosed by a physician and BMI, calculated with self-reported height (m) and weight (kg) as kg/m^2. 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 ($\pm$2 years), time of blood draw, sex, and dialect. All participants with blood samples drawn and analyzed for HbA_{1c} were included in this analysis regardless of HbA_{1c} 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 HbA_{1c} 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 Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, CA). Using the standards developed in the National Glycohemoglobin Standardization Program, this method of percentage of HbA_{1c} 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, HbA_{1c} 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 HbA_{1c} category (≥6.5% [≥48 mmol/mol]) into four groups to determine if the highest HbA_{1c} 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 HbA_{1c} level. Crude and adjusted HRs and 95% CIs were estimated with Cox proportional hazards models. The HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} were performed by assigning participants the median of their HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}-specific age category contributed to the overall study person-years at risk total (standardized weight). These rates were summed for each HbA_{1c} 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 χ^2 *P* values. To investigate if HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} and age, BMI, and prevalence of self-reported hypertension, while an inverse association was observed between educational attainment and HbA_{1c}. There was a U-shaped association between HbA_{1c} and smoking status and male sex.

Fully adjusted HRs and 95% CIs for HbA_{1c} 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 HbA_{1c} level. The CHD and cancer mortality rates were higher for HbA_{1c} ≥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 HbA_{1c} categories corresponding to the highest rates. In the Cox regression analysis, HbA_{1c} levels ≥6.5% (≥48 mmol/mol) were strongly associated with all-cause, overall CVD,

Table 1—Participant characteristics according to category of HbA_{1c} percentage: the SCHS

	HbA_{1c} (%) category [mmol/mol]						
Characteristics	<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)	
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 (%)							<0.001
Less than primary school	19.3	21.0	20.1	22.9	24.3	24.1	
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/m^2	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.

as well as CHD and cerebrovascular mortality, and cancer mortality compared with the reference HbA_{1c} 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 HbA_{1c} ≥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 first 5 years post–blood draw were excluded, the association between elevated HbA_{1c} (HbA_{1c} ≥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 HbA_{1c} and respiratory causes of death. No other category of HbA_{1c} 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 HbA_{1c} 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 $P \geq 0.10$) aligning with the presented results. Formal tests of interaction by age and BMI were also not significant for any of the outcomes (all outcomes $P \geq 0.10$).

CONCLUSIONS

Chinese men and women with no history of cancer, reported diabetes, or CVD with an HbA_{1c} level ≥6.5% (≥48 mmol/mol) were at a significant increased risk of mortality during follow-up relative to their peers with an HbA_{1c} of 5.4–5.6% (36–38 mmol/mol). No other range of HbA_{1c} was significantly associated with risk of mortality during follow-up, and in secondary analyses, when the HbA_{1c} 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 HbA_{1c} and mortality in this population. These results are consistent with previous prospective cohort studies identifying chronically high HbA_{1c}, 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 HbA_{1c} levels between normal and <6.5%. Increased risk for all-cause mortality was found in three unique U.S. populations for individuals with HbA_{1c} at or below the prediabetic threshold (HbA_{1c} <5.7%) compared with a lower reference value (3,5,8). Two studies of European populations observed increased risk at HbA_{1c} >5.5%. and increased risk per each 1-percentage point increase in HbA_{1c} concentration (7,11). Moderately elevated HbA_{1c} (HbA_{1c} >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 HbA_{1c} (3,5,8). However, the lack of an association in the far left tail of HbA_{1c} 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 HbA_{1c} <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

Table 2—Age- and sex-standardized mortality rates, HRs, and 95% CIs of all-cause and cause-specific mortality according to HbA_{1c} percentage: the SCHS

	HbA_{1c} (%) category [mmol/mol]						
	<5.0 (*N* = 223) [<31]	5.0–5.3 (*N* = 847) [31–35]	5.4–5.6 (*N* = 2,131) [36–38]	5.7–6.0 (*N* = 2,754) [39–42]	6.1–6.4 (*N* = 923) [43–47]	≥6.5 (*N* = 510) [≥48]
Deaths/person-years	31/2,186.2	88/8,724.0	212/21,880.8	304/28,023.9	131/9,180.0	122/4,895.1
All-cause death# (*n*)	31	88	212	304	131	122
Mortality rate[a]	1,416	1,040	1,025	1,104	1,232	2,284
Final model[b]	1.38 (0.94, 2.01)	1.01 (0.79, 1.29)	1.00	0.99 (0.83, 1.18)	1.10 (0.88, 1.37)	1.96 (1.56, 2.46)
CVD death (*n*)	9	24	54	68	45	49
Mortality rate[a]	354	285	260	246	416	937
Final model[b]	1.56 (0.77, 3.16)	1.09 (0.67, 1.77)	1.00	0.84 (0.58, 1.20)	1.31 (0.88, 1.95)	2.63 (1.77, 3.90)
CHD death (*n*)	3	12	27	36	19	30
Mortality rate[a]	112	155	131	130	177	579
Final model[b]	1.02 (0.31, 3.36)	1.10 (0.56, 2.17)	1.00	0.87 (0.53, 1.44)	1.10 (0.61, 1.99)	3.22 (1.89, 5.47)
Cerebrovascular death (*n*)	3	8	19	18	12	14
Mortality rate[a]	139	88	91	67	109	265
Final model[b]	1.62 (0.48, 5.49)	1.02 (0.44, 2.33)	1.00	0.66 (0.34, 1.25)	1.04 (0.50, 2.16)	2.30 (1.14, 4.66)
Cancer death# (*n*)	10	38	101	142	56	41
Mortality rate[a]	483	440	484	514	540	767
Final model[c]	0.95 (0.50, 1.82)	0.93 (0.64, 1.35)	1.00	1.01 (0.78, 1.31)	1.07 (0.77, 1.49)	1.51 (1.04, 2.18)
Respiratory death# (*n*)	6	19	43	64	20	17
Mortality rate[a]	272	232	214	236	182	292
Final model[b]	1.24 (0.52, 2.93)	1.02 (0.59, 1.75)	1.00	0.99 (0.68, 1.46)	0.81 (0.47, 1.39)	1.43 (0.81, 2.52)

Test of linear trend of HR: $P < 0.001$ for all-cause, CVD, and CHD mortality; $P < 0.05$ for cancer mortality; $P > 0.05$ for cerebrovascular and respiratory. #BMI was modeled as quadratic opposed to linear. [a]Mortality rate is adjusted for age and per 100,000 person-years using the person-years and age distributions of the SCHS. [b]Adjusted for age, sex, dialect, interview year, education, smoking, alcohol, BMI, and hypertension status. [c]Adjusted for age, sex, dialect, interview year, education, smoking, alcohol, and BMI.

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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} level and respiratory disease mortality. Our results show no association between HbA_{1c} ≥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

for insulin but have shown increased lipid levels in association with increased HbA_{1c} levels; the individual impact of lipids on all-cause and cardiovascular mortality was not assessed (3,5,7–9,11). Collective adjustment for anthropometric, blood pressure, and lipid measures in these studies slightly attenuated the risk estimates, but did not impact the interpretation of results from previous models. While there is potentially residual confounding from unmeasured lipid values, the results from previous studies suggest this confounding would not significantly impact the interpretation of our results given the magnitude of the point estimates. HbA_{1c} is indicative of average glycemia of the prior 2 to 3 months; how representative this one-time measure is of an individual over longer time periods is less clear, but evaluation from a single measure is often used in the clinical setting. A limited sample of participants with HbA_{1c} <5.0% (<31 mmol/mol) reduced the power to detect a signal in the data in some disease-specific mortality categories. Due to the elevated tail for HR of the highest HbA_{1c} group, the *P* for trend statistic should be interpreted cautiously. Self-report of BMI and the lifestyle factors of smoking and alcohol intake leads to some misclassification and likely residual confounding in the models. We did not have other updated lifestyle factors from the baseline assessment (dietary intake and physical activity); however, adjustment for baseline levels of these factors did not alter the results. Strengths of the study also need to be considered. This large Asian population uniquely contributes to the literature on the topic. Other strengths include the high participant response rate, detailed collection of data through face-to-face interview, thorough adjustment for measured confounders, very low level of participants lost to follow-up, and nearly complete mortality assessment with objectively obtained records on time and cause of death.

To conclude, in this large cohort of Singaporean Chinese adults without diagnosed diabetes, we observed an increased risk for all-cause, CVD, and cancer mortality during follow-up in individuals with elevated HbA_{1c} levels (HbA_{1c} ≥6.5% [≥48 mmol/mol]). No other level of HbA_{1c} was associated

Table 3—HRs and 95% CIs for all-cause mortality, cardiovascular mortality, and cancer mortality according to category of HbA_{1c} percentage and stratified by sex, smoking status, and hypertensive status: the SCHS

	HbA_{1c} (%) category [mmol/mol]							
	<5.0 (*N* = 223) [<31]	5.0–5.3 (*N* = 847) [31–35]	5.4–5.6 (*N* = 2,131) [36–38]	5.7–6.0 (*N* = 2,754) [39–42]	6.1–6.4 (*N* = 923) [43–47]	≥6.5 (*N* = 510) [≥48]	*P* for trend
All-cause death#							
Males	1.31 (0.83, 2.05)	0.94 (0.69, 1.29)	1.00	0.99 (0.79, 1.23)	1.07 (0.81, 1.42)	1.66 (1.24, 2.23)	<0.01
Females	1.57 (0.78, 3.15)	1.12 (0.74, 1.69)	1.00	1.01 (0.76, 1.36)	1.14 (0.79, 1.64)	2.60 (1.81, 3.75)	<0.001
Ever smoke	1.44 (0.87, 2.37)	1.10 (0.79, 1.54)	1.00	1.03 (0.81, 1.31)	1.15 (0.86, 1.55)	1.76 (1.27, 2.44)	<0.05
Never smoke	1.32 (0.74, 2.36)	0.86 (0.59, 1.25)	1.00	0.98 (0.75, 1.27)	1.08 (0.77, 1.51)	2.24 (1.63, 3.08)	<0.001
Hypertensive	1.41 (0.77, 2.60)	0.99 (0.67, 1.46)	1.00	0.87 (0.66, 1.16)	0.97 (0.69, 1.37)	2.05 (1.48, 2.84)	<0.001
Nonhypertensive	1.35 (0.83, 2.19)	1.03 (0.74, 1.42)	1.00	1.08 (0.86, 1.35)	1.20 (0.90, 1.61)	1.81 (1.31, 2.50)	<0.01
CVD death							
Males	1.63 (0.76, 3.51)	1.01 (0.56, 1.82)	1.00	0.74 (0.47, 1.16)	1.11 (0.66, 1.85)	1.95 (1.18, 3.24)	0.06
Females	0.87 (0.11, 6.58)	1.26 (0.54, 2.94)	1.00	1.10 (0.59, 2.03)	1.85 (0.95, 3.61)	4.59 (2.38, 8.84)	<0.001
Ever smoke	1.34 (0.52, 3.48)	0.95 (0.49, 1.87)	1.00	0.69 (0.42, 1.12)	1.04 (0.59, 1.82)	2.14 (1.23, 3.72)	<0.05
Never smoke	1.68 (0.58, 4.89)	1.20 (0.60, 2.39)	1.00	1.02 (0.60, 1.74)	1.83 (1.03, 3.26)	3.42 (1.94, 6.03)	<0.001
Hypertensive	1.78 (0.68, 4.65)	1.52 (0.83, 2.78)	1.00	0.76 (0.45, 1.27)	1.44 (0.84, 2.45)	2.50 (1.46, 4.30)	<0.01
Nonhypertensive	1.34 (0.47, 3.83)	0.59 (0.24, 1.42)	1.00	0.95 (0.58, 1.55)	1.13 (0.60, 2.10)	2.81 (1.57, 5.03)	<0.001
Cancer death#							
Males	1.05 (0.48, 2.32)	0.99 (0.61, 1.61)	1.00	1.17 (0.83, 1.64)	1.29 (0.85, 1.97)	1.78 (1.12, 2.82)	<0.05
Females	0.87 (0.27, 2.81)	0.86 (0.48, 1.54)	1.00	0.83 (0.56, 1.23)	0.78 (0.45, 1.34)	1.17 (0.62, 2.19)	0.80
Ever smoke	1.18 (0.50, 2.78)	1.11 (0.66, 1.87)	1.00	1.25 (0.87, 1.79)	1.33 (0.85, 2.08)	1.64 (0.97, 2.78)	0.09
Never smoke	0.79 (0.28, 2.19)	0.75 (0.43, 1.28)	1.00	0.84 (0.58, 1.22)	0.86 (0.51, 1.42)	1.45 (0.86, 2.44)	0.13

When not 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 was modeled as quadratic opposed to linear.

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 HbA_{1c} percentage clinical cut points. Additional studies are warranted in order to describe the distribution of HbA_{1c} in Asian populations and to characterize the mortality risk associated with levels of HbA_{1c} below the threshold for diabetes.

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