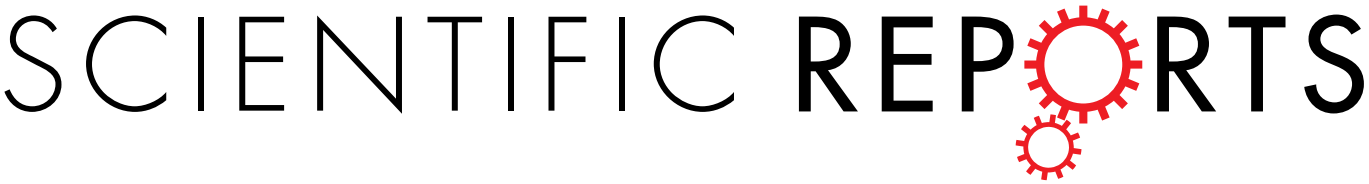

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Received: 07 September 2015
Accepted: 18 March 2016
Published: 05 April 2016

HbA_{1c} and Risks of All-Cause and Cause-Specific Death in Subjects without Known Diabetes: A Dose-Response Meta-Analysis of Prospective Cohort Studies

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Whether HbA_{1c} levels are associated with mortality in subjects without known diabetes remains controversial. Moreover, the shape of the dose–response relationship on this topic is unclear. Therefore, a dose–response meta-analysis was conducted. PubMed and EMBASE were searched. Summary hazard ratios (HRs) were calculated using a random-effects model. Twelve studies were included. The summary HR per 1% increase in HbA_{1c} level was 1.03 [95% confidence interval (CI) = 1.01–1.04] for all-cause mortality, 1.05 [95% CI = 1.02–1.07) for cardiovascular disease (CVD) mortality, and 1.02 (95% CI = 0.99–1.07) for cancer mortality. After excluding subjects with undiagnosed diabetes, the aforementioned associations remained significant for CVD mortality only. After further excluding subjects with prediabetes, all aforementioned associations presented non-significance. Evidence of a non-linear association between HbA_{1c} and mortality from all causes, CVD and cancer was found (all $P_{non\text{-}linearity} < 0.05$). The dose–response curves were relatively flat for HbA_{1c} less than around 5.7%, and rose steeply thereafter. In conclusion, higher HbA_{1c} level is associated with increased mortality from all causes and CVD among subjects without known diabetes. However, this association is driven by those with undiagnosed diabetes or prediabetes. The results regarding cancer mortality should be treated with caution due to limited studies.

HbA_{1c}, a major component of hemoglobin-glucose adducts[1], reflects the average blood glucose level within the prior 2 to 3 months[2], and is a well accepted biomarker for glycemic management in diabetic patients over the past several decades. HbA_{1c} has been consistently recommended as a diagnostic biomarker for diabetes by several societies[3–5]. At present, in clinical practice, a variety of diagnostic assays, including ion-exchange chromatography, electrophoresis, immunoassay, are available to measure HbA_{1c} levels[6,7]. Nonetheless, mounting evidence shows that electrochemical HbA_{1c} sensors (e.g., amperometric nonenzymatic sensors)[8] and optical HbA_{1c} sensors (e.g., vibrational spectroscopy)[6,9] possibly provide more convenient and cheaper assays for determining HbA_{1c} levels.

Previous studies in diabetic patients demonstrated a significant association between HbA_{1c} levels and all-cause mortality[10], which presented a J-shaped pattern[11]. However, whether these findings can extend into subjects without known diabetes is largely unknown. To fill this gap, some epidemiological studies were conducted but presented inconsistent results. Several studies observed that high HbA_{1c} levels ($\geq$6.5%, 48 mmol/mol) were significantly associated with increased all-cause mortality[2,12,13], whereas others failed to find any significant associations with all-cause mortality across the whole HbA_{1c} range[14,15]. In addition, for the shape of the dose–response relationship between HbA_{1c} levels and mortality, previous studies have suggested a J-shaped pattern[12,15], a U-shaped pattern[2], and a linear pattern[13]. Although a 2011 meta-analysis[16], including 5 studies, investigated the association

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of HbA_{1c} levels with mortality from cardiovascular disease (CVD) in non-diabetic population, substantial heterogeneity ($I^2 = 98.5\%$) and combination data from cross-sectional study[17] with those from prospective studies[18–21] raised concerns for the reliability of its findings.

With more attention to HbA_{1c} currently, investigation of the dose–response relationship between HbA_{1c} and mortality is critical for a better understanding of this biomarker, and can extend its' application into a broader field. However, to the best of our knowledge, a comprehensive dose–response meta-analysis on the HbA_{1c}-mortality association is not available to date. Therefore, the objectives of our study were to clarify the associations between HbA_{1c} levels and risks of death from all causes, CVD, or cancer in subjects without known diabetes, and to further investigate the exact shape of these associations.

Methods

Search strategy. We conducted this study and reported corresponding results in adherence to the PRISMA statement[22]. A comprehensive electronic search of PubMed and EMBASE was conducted up to January 2015. Detailed search strategy is presented in the Supplementary List S1. For including additional citations, we performed a manual search of the reference lists of included articles and pertinent reviews. We contacted the original authors to obtain extra information if necessary.

Study selection. Studies were eligible for inclusion if they met the following criteria: (1) participants: subjects without known diabetes; (2) exposure: HbA_{1c} levels measured by methods standardized by the National Glycohemoglobin Standardization Program or International Federation of Clinical Chemistry[23]; (3) outcome: adjusted risk estimates for at least three quantitative HbA_{1c} categories on the associations of HbA_{1c} levels with risks of death from all causes, CVD, or cancer; (4) study design: prospective cohort study. We excluded studies in which subjects were free of diabetes but suffered from other conditions (e.g., acute coronary syndrome).

Data extraction. Two investigators (G.C.Z. and J.H.C.) independently performed study screening through a two-stage method. At the first stage, we scrutinized titles and abstracts to exclude apparently irrelevant studies. At the second stage, we read carefully the full text to further exclude unrelated studies. Two investigators discussed together until consensus was reached when any discrepancy regarding the eligibility of studies occurred.

One investigator (G.C.Z.) performed data extraction, and then another investigator (J.H.C.) checked the results for accuracy. We re-checked data and discussed together to deal with any inconsistent results. Following information was extracted: first author, publication year, study location, mean age at baseline, sample size, mean follow-up duration, assessments of non-diabetic statuses and outcomes, methods of measuring HbA_{1c}, deaths and person-years for each HbA_{1c} level, categories of HbA_{1c}, maximally adjusted risk estimates and corresponding 95% confidence intervals (CIs), and adjustment factors. We extracted information from the publication with the longest follow-up duration when multiple publications derived from the same cohort.

Data synthesis and analysis. In this meta-analysis, hazard ratio (HR) for every 1% increase in HbA_{1c} level was used to assess the HbA_{1c}-mortality association. To support the International Federation of Clinical Chemistry HbA_{1c} system[23], we also calculated HR for a 10 mmol/mol increase in HbA_{1c} level. For one study[24], relative risk was treated as equivalent to HR. For another study[25] whose authors reported risk estimates for men and women separately, we pooled these data to yield an overall estimate using a random-effects model. The Hedges Q statistic was employed to qualitatively assess heterogeneity across studies, with $P < 0.10$ indicating statistically significant heterogeneity. The I^2 statistic was employed to quantify heterogeneity[26], with $I^2 > 50\%$ representing substantial heterogeneity, $30\% \leq I^2 \leq 50\%$ representing moderate heterogeneity, and $I^2 < 30\%$ representing low heterogeneity[27].

We performed a two-stage dose–response meta-analysis to identify whether higher HbA_{1c} level was significantly associated with increased mortality. First, for the purpose of pooling risk estimates from included studies using different HbA_{1c} categorization, we employed the generalized least square regression described by Orsini and colleagues[28] to calculate study-specific slopes (linear trends) and 95% CIs for every 1% increase in HbA_{1c} level within each study from the natural logs of maximally adjusted HRs and CIs across categories of HbA_{1c}. Then, we pooled them using a random-effects model to obtain the summary risk estimates. This method is based on specific HbA_{1c} level, distribution of deaths and person-years, and adjusted risk estimates and 95% CIs. Since all included studies reported HbA_{1c} level as range, we designated the midpoint of lower and upper limits as the assigned level. When the highest range was open-ended, we calculated the assigned level by adding the width of the adjacent range to the highest value specified. When the lowest range was open-ended, we calculated the assigned level by subtracting half of the width of the adjacent range from the lowest value specified[29]. The method described by Hamling and colleagues[30] was employed to convert risk estimates if the reference group reported in the original study was not the lowest group. For 4 studies[15,19,31,32] whose authors did not report person-years for each HbA_{1c} category, we approximately estimated these data from mean follow-up duration and number of subjects. For studies that provided risk estimates with more than one level of adjustment, we calculated study-specific slopes and 95% CIs with minimally adjusted data to examine whether the observed associations were largely explained by confounding. To determine whether increased mortality was due to inclusion of subjects with undiagnosed diabetes ($HbA_{1c} \geq 6.5\%$, 48 mmol/mol), we repeated our meta-analyses by excluding these subjects. To investigate whether HbA_{1c} was still associated with mortality in subjects with normal HbA_{1c} level ($HbA_{1c} < 5.7\%$, 39 mmol/mol), we repeated our meta-analyses by further excluding subjects with prediabetes ($5.7\% \leq HbA_{1c} \leq 6.4\%$, 39 mmol/mol $\leq HbA_{1c} \leq 46$ mmol/mol).

We explored a potential non-linear dose–response relationship between HbA_{1c} levels and mortality using restricted cubic spline function with 3 knots at the 10th, 50th, and 90th percentiles[33,34]. A $P_{\text{non-linearity}}$ was obtained by testing the null hypothesis that the estimated value of the second spline equals zero[34].

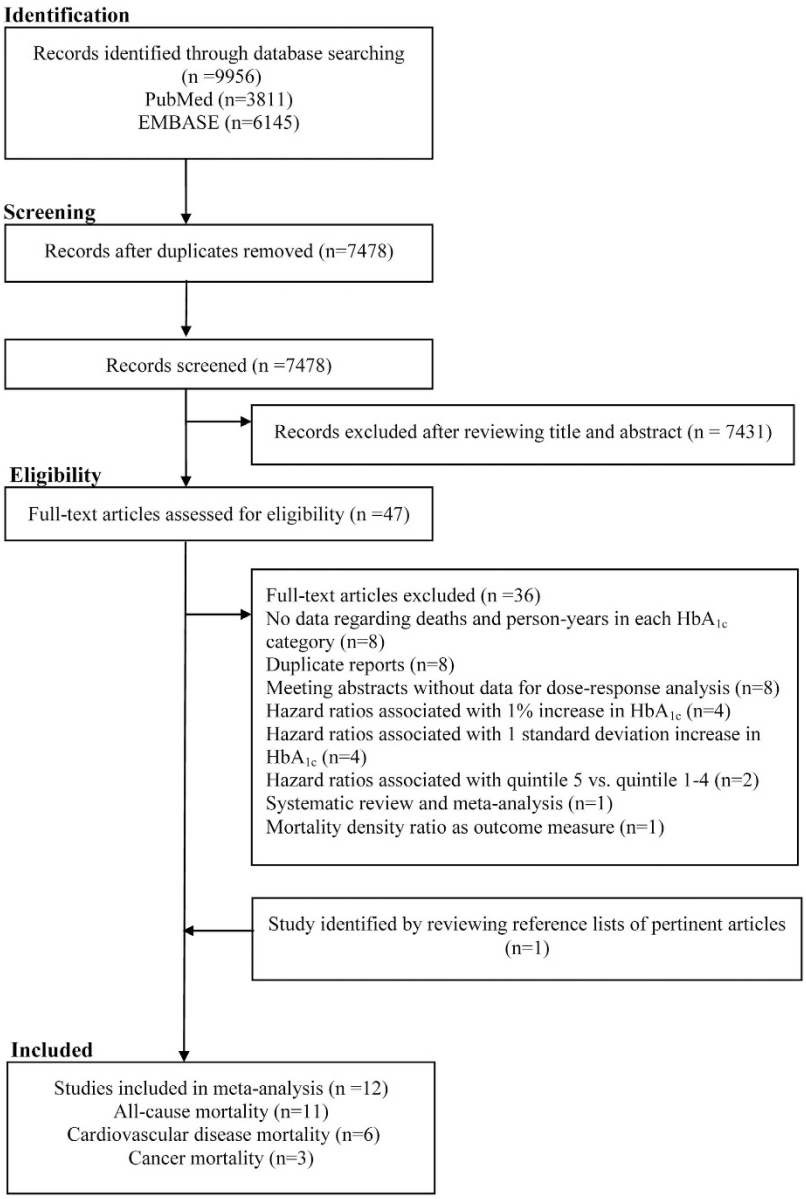

Figure 1. The flowchart of identifying relevant studies.

To determine the stability of summary results, we performed sensitivity analyses for all-cause and CVD mortality through three techniques, namely ignoring a single study in turn, repeating meta-analyses by a fixed-effects model, and applying various eligibility criteria. To identify whether the association of HbA_{1c} levels with mortality was modified by age, follow-up duration, sample size, and study location, we conducted subgroup analyses stratified by these study-level characteristics. A $P_{interaction}$ between subgroups was calculated by meta-regression. Considering limited studies for CVD and cancer mortality, subgroup analyses were performed only for all-cause mortality.

Begg rank correlation test[35] and Egger linear regression test[36] were employed to test publication bias, with $P < 0.1$ indicating publication bias. We conducted all data analyses through STATA software (version12.0, StataCorp, College Station, TX). Statistical significance level was set at $P < 0.05$ under two-sided test unless otherwise specified.

Results

Study identification and selection. Our comprehensive retrieval identified 3,811 and 6,145 records from PubMed and EMBASE, respectively. After removing duplicates and excluding obviously unrelated records, there were remaining 47 records that were potentially relevant. After checking the full text, 36 were further excluded (detailed reasons for exclusion are shown in Fig. 1). We included two studies[25,37] derived from the same cohort, because they reported different outcomes (one reported all-cause mortality[37], another reported cancer

mortality)[25]. In addition, we added one study[15] through the handsearch. Thus, 12 studies (11 cohorts) were eligible for inclusion (Fig. 1).

Study characteristics. The characteristics of included studies are summarized in Supplementary Table S1. The HbA_{1c} level ranged from 3.5% (15 mmol/mol)[24] to 10.4% (90 mmol/mol)[24] across studies. Of included studies, ten provided data necessary to calculate proportions of subjects in three clinical HbA_{1c} ranges (i.e., normal, prediabetes, and undiagnosed). Specifically, proportions of subjects with normal HbA_{1c} level, prediabetes, and undiagnosed diabetes were 85.90%, 11.33%, and 2.77%, respectively. The included studies were published between 2005[32] and 2015[2]. Four studies were conducted in Europe[2,19,31,38], 5 in the USA[14,15,24,25,37], and remaining 3 in Asia[12,13,32]. The mean age of participants at baseline varied from 44.7 years[2] to 78.7 years[19] across studies. The sample size of included study ranged from 810[14] to 26,549[24]. Our study included a total of 114,102 subjects, consisting of 41,616 men (36.5%) and 72,486 women (63.5%). The mean follow-up duration changed from 5.0 years[19] to 14.2 years[14], and during 1,161,714 person-years of follow-up, there were a total of 11,301 deaths. Most studies relied on self-reports of participants for the ascertainment of non-diabetic status, and only 2 studies[14,38] confirmed it through diagnostic test or use of anti-diabetic medications. Of included studies, the information regarding vital status and causes of death was obtained from diverse sources, including death certificate[19,25,31,32,37] and death registry[2,12,38]. Ten studies used high performance liquid chromatography method to measure HbA_{1c} level, and remaining 2 studies adopted affinity column method[14] or turbidimetric immunoinhibition assay method[24].

Association of HbA_{1c} levels with all-cause mortality. Eleven individual studies were eligible for the two-stage dose–response analysis of HbA_{1c} levels and all-cause mortality, involving a sum of 113,526 subjects and 11,301 deaths. The summary HR per 1% increase in HbA_{1c} level was 1.03 [95% CI = 1.01–1.04] (for every 10 mmol/mol increase, 1.03 [95% CI = 1.01–1.04]), with evidence of low heterogeneity ($I^2 = 28.9\%$, $P = 0.17$) (Fig. 2a). Parallel analysis with minimally adjusted data from 8 individual studies[2,13–15,24,31,32,37] produced an HR of 1.03 [95% CI = 1.02 –1.05]. However, the initial pooled result presented non-significance after excluding participants with undiagnosed diabetes [HR = 1.01, 95% CI = 0.99–1.03] (Fig. 2b)[2,12,13,19,24,31,32,37]. After further excluding subjects with prediabetes, a non-significant risk estimate was observed [HR = 1.01, 95% CI = 0.98–1.03] (Fig. 2c)[12,13,24,25].

Association of HbA_{1c} levels with CVD mortality. Six individual studies were eligible for the association between HbA_{1c} levels and CVD mortality, with a total of 36,695 participants and 1,713 deaths. The pooled HR per 1% increase in HbA_{1c} level was 1.05 [95% CI = 1.02–1.07] (for every 10 mmol/mol increase, 1.04 [95% CI = 1.02– 1.06]) (Fig. 3a), with evidence of low heterogeneity ($I^2 = 4.3\%$, $P = 0.39$). Meta-analysis of HRs with the least degree of adjustment[13,14,31,32] yielded an HR of 1.04 [95% CI = 1.01–1.07]. After excluding participants with undiagnosed diabetes[12,13,19,31,32], the result was attenuated slightly, but remained significant [HR = 1.04, 95% CI = 1.01–1.06] (Fig. 3b). However, after further excluding participants with prediabetes[12,13], higher HbA_{1c} level was not significantly associated with increased mortality from CVD [HR = 1.00, 95% CI = 0.87–1.15] (Fig. 3c).

Association of HbA_{1c} levels with cancer mortality. Only 3 studies were included in the two-stage dose–response analysis of HbA_{1c} levels and cancer mortality, involving a total of 36,252 individuals and 2,115 deaths. Random-effects meta-analysis revealed an HR of 1.03 [95% CI = 0.99–1.07] per 1% increase in HbA_{1c} level (for every 10 mmol/mol increase, 1.02 [95% CI = 0.98–1.06]) (Fig. 4a), with evidence of moderate heterogeneity ($I^2 = 41.2\%$, $P = 0.18$). With 2 studies[25,31] reporting minimally adjusted HRs, a pooled HR of 1.04 [95% CI = 1.01–1.06] was obtained. Our analysis produced a non-significant pooled risk estimate [HR = 1.02, 95% CI = 0.98–1.06] (Fig. 4b) after excluding participants with undiagnosed diabetes[12,25,31]. Further excluding participants with prediabetes[12] resulted in an HR of 1.01 [95% CI = 0.90–1.13] (Fig. 4c).

Non-linear dose–response analyses. Using restricted cubic spline function, we found the evidence of non-linear associations between HbA_{1c} levels and risks of death from all causes ($P_{\text{non-linearity}} < 0.0001$) (Fig. 5a), CVD ($P_{\text{non-linearity}} < 0.0001$) (Fig. 5b) and cancer ($P_{\text{non-linearity}} = 0.0001$) (Fig. 5c). The curves were relatively flat when HbA_{1c} levels were less than approximately 5.7% (39 mmol/mol), and rose steeply thereafter. The curvilinear slope reached the maximal value at HbA_{1c} level of around 6.5% (48 mmol/mol). Similar increasing patterns were observed for CVD and cancer mortality.

Subgroup and sensitivity analyses. The significant association between HbA_{1c} levels and all-cause mortality remained in all subgroups (see Supplementary Table S2). Pooled risk estimates from the random-effects model and fixed-effects model were virtually identical. Omitting a single study in turn did not significantly change the summary risk estimate of either all-cause or CVD mortality. Repeating meta-analyses according to various eligibility criteria did not change our pooled results, either (see Supplementary Table S3).

Publication bias. There was no evidence of publication bias for any association as revealed by Begg's test and Egger's test (all $P > 0.1$).

Discussion

The findings from the two-stage dose–response analyses suggested that in subjects without known diabetes, higher HbA_{1c} level is a predictor of increased all-cause and CVD mortality but not of cancer mortality. In subjects without diabetes, higher HbA_{1c} level is a predictor of increased CVD mortality only; in those with normal HbA_{1c} level, higher HbA_{1c} level is not a predictor of any studied mortality outcome.

We found evidence of a non-linear association between HbA_{1c} and mortality from all causes, CVD and cancer in this meta-analysis. The dose-response curves were relatively flat for HbA_{1c} less than around 5.7%, and rose

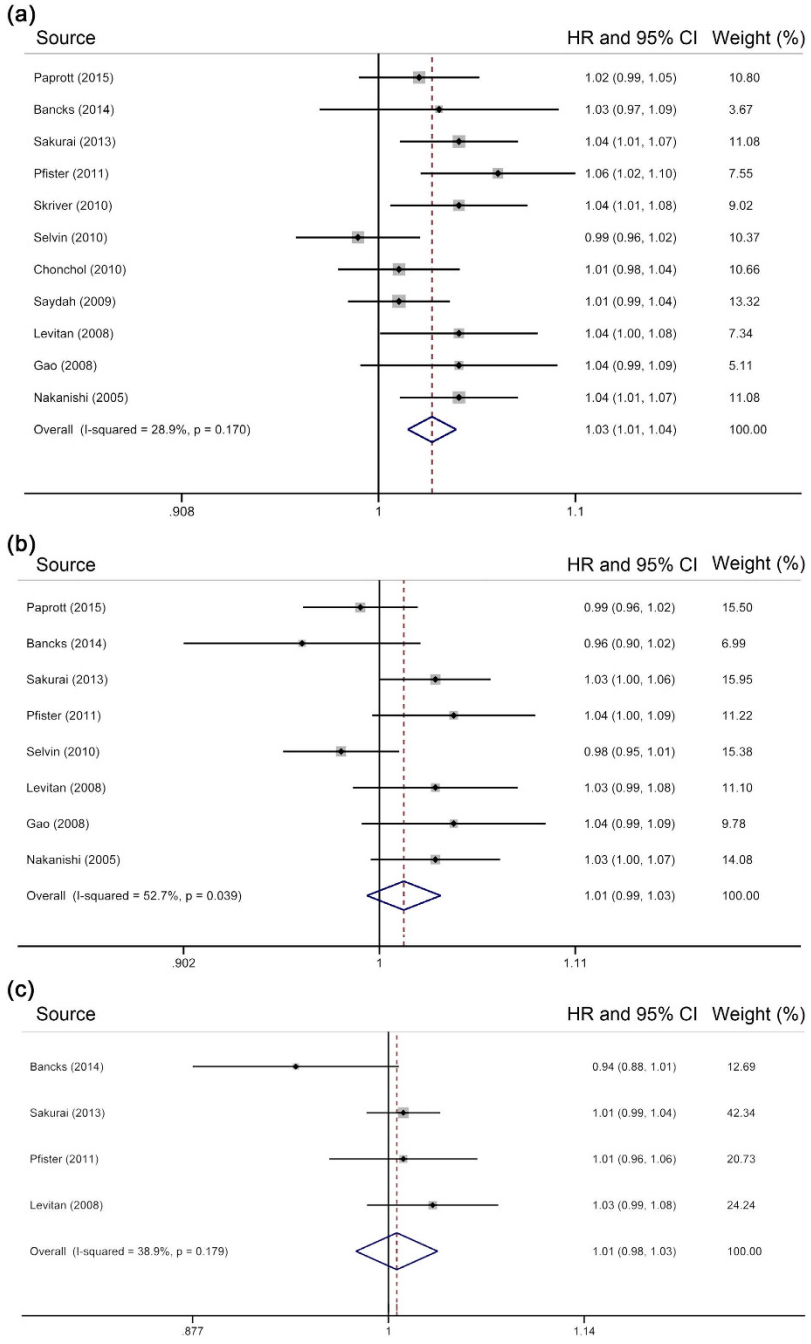

Figure 2. Meta-analysis on HbA_{1c} and all-cause mortality in (**a**) subjects without known diabetes, (**b**) those without diabetes, and (**c**) those with normal HbA_{1c} range. The squares represent the hazard ratio per 1% increase in HbA_{1c} level for each individual study, with the area reflecting the weight assigned to the study. The horizontal line across each square represents the 95% confidence interval. The diamond represents the summary hazard ratio per 1% increase in HbA_{1c} level, with width representing 95% confidence interval.

steeply thereafter. This fact reveals a clear threshold effect for the association of HbA_{1c} levels with mortality. In addition, from the perspective of mortality benefit and health care burden, it suggests that the most appropriate HbA_{1c} level of initiating intervention is approximately 5.7%. Considering the essential requirement for HbA_{1c} to maintain normal metabolism of our body, it is reasonable that normal HbA_{1c} levels are not significantly associated with increased mortality, which was also clearly shown in our two-stage dose–response analyses on HbA_{1c} levels and mortality. However, mounting evidence shows that people are at high risk of some health conditions that could significantly increase mortality risk when HbA_{1c} level increases abnormally. For example, hyperglycemia measured by HbA_{1c} has been found to be associated with increased risks of stroke[39], coronary heart disease[40], colorectal cancer[41], as well as hearing impairment[42] in people without a history of diabetes.

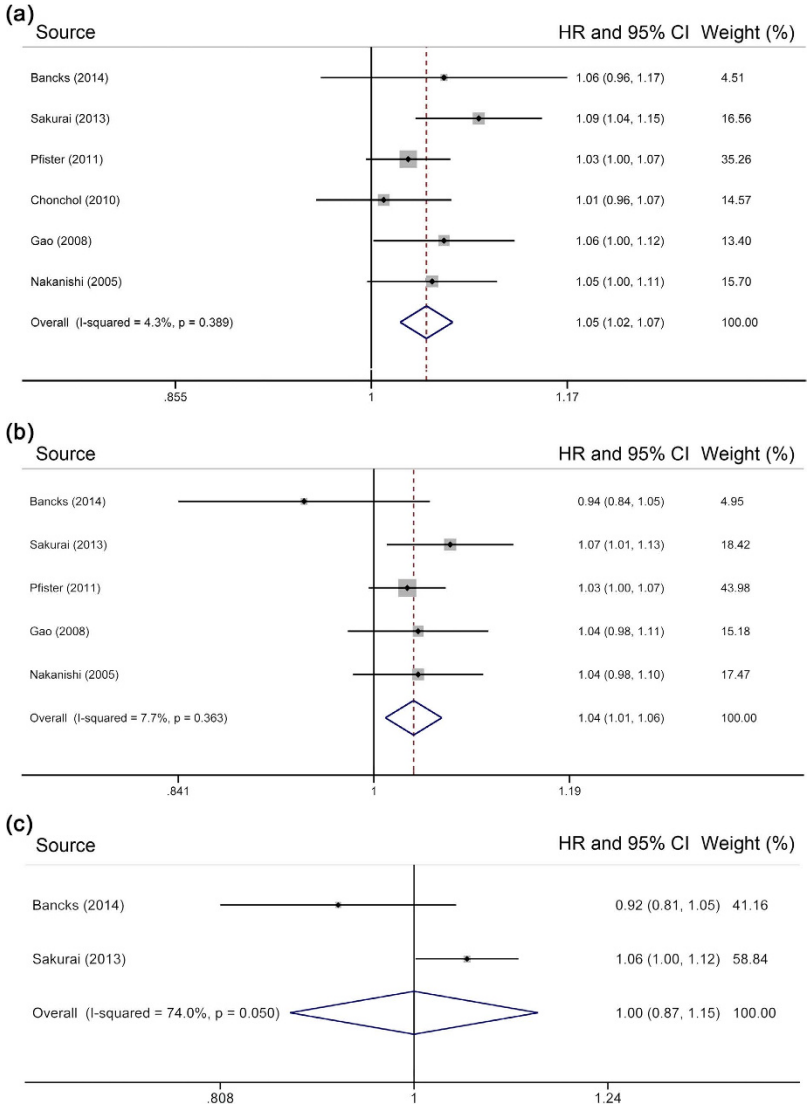

Figure 3. Meta-analysis on HbA_{1c} and cardiovascular disease mortality in (**a**) subjects without known diabetes, (**b**) those without diabetes, and (**c**) those with normal HbA_{1c} range. The squares represent the hazard ratio per 1% increase in HbA_{1c} level for each individual study, with the area reflecting the weight assigned to the study. The horizontal line across each square represents the 95% confidence interval. The diamond represents the summary hazard ratio per 1% increase in HbA_{1c} level, with width representing 95% confidence interval.

In this study, our two-stage dose–response analyses did not find any significant associations with cancer mortality in the whole studied population as well as in subjects with $HbA_{1c} < 6.5\%$. Considering limited studies and relatively wide CIs for risk estimates, the failure to detect significant associations was possibly caused by lack of power. In addition, if using a fixed-effects model to achieve data pooling, significant risk estimates could be obtained (for the whole studies population, HR = 1.03, 95% CI = 1.01–1.06, $P < 0.01$; for subjects with $HbA_{1c} < 6.5\%$, HR = 1.03, 95% CI = 1.00–1.05, $P = 0.03$). With those considerations above, the results for cancer mortality in these two groups should be treated with caution, and more studies on HbA_{1c} and cancer mortality are needed.

Previous studies found that hyperglycemia measured by HbA_{1c} was significantly related to increased all-cause mortality in diabetic subjects[10]. Our study extended this association into subjects without known diabetes. The deleterious effect of hyperglycemia on mortality is biologically plausible. Ample evidence shows that hyperglycemia can result in oxidative stress (OS)[43,44] through several potential mechanisms involving generation of reactive oxygen species, non-enzymatic glycation of proteins, and auto-oxidation of glucose[43]. OS then results in vascular endothelial dysfunction, which contributes to the presence of CVD[45]. OS can induce DNA damage[46], protein carbonylation[47], actions on signaling pathways[48], possibly resulting in gene mutation or cell proliferation[48]. Therefore, OS is also a candidate contributor for cancer development[49]. Taken together, hyperglycemia-induced OS plays a major role in the underlying mechanisms for the association of hyperglycemia with increased mortality.

In the present meta-analysis, most of included studies ascertained non-diabetic status through self-reports. Consequently, our study population comprised a part of subjects with undiagnosed diabetes in the context of

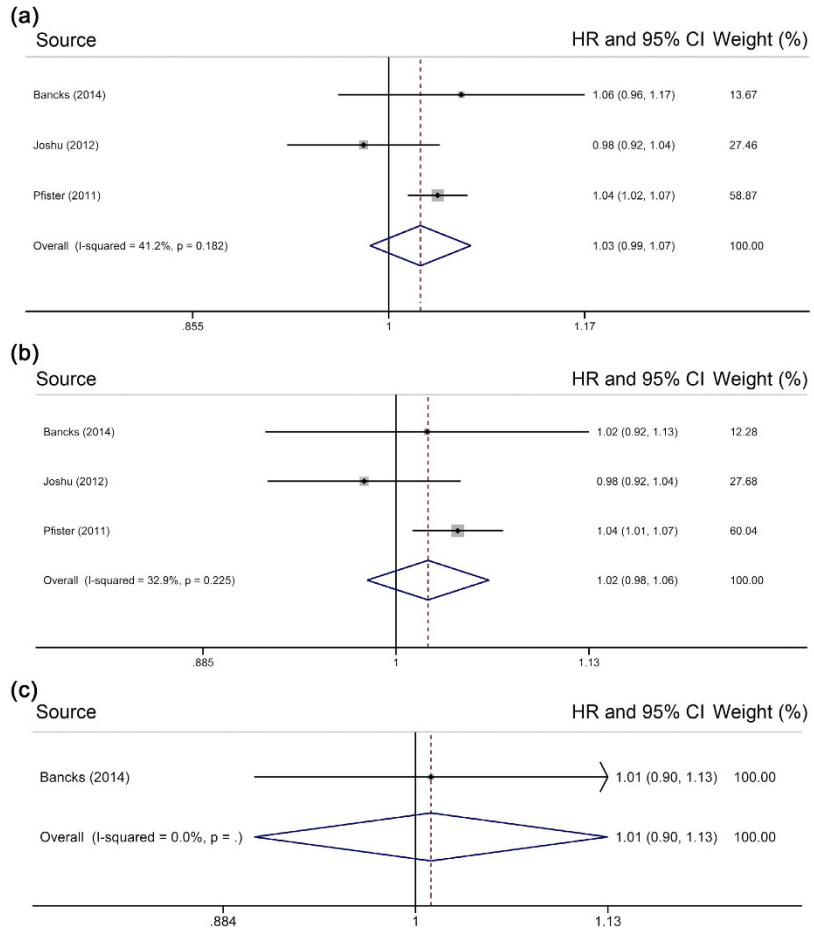

Figure 4. Meta-analysis on HbA_{1c} and cancer mortality in (**a**) subjects without known diabetes, (**b**) those without diabetes, and (**c**) those with normal HbA_{1c} range. The squares represent the hazard ratio per 1% increase in HbA_{1c} level for each individual study, with the area reflecting the weight assigned to the study. The horizontal line across each square represents the 95% confidence interval. The diamond represents the summary hazard ratio per 1% increase in HbA_{1c} level, with width representing 95% confidence interval.

a large proportion of diabetic cases being not captured by self-reports[50]. Several epidemiological studies have demonstrated increased mortality in subjects with undiagnosed diabetes[51,52]. Considering the aforementioned facts, the increased all-cause and CVD mortality observed in the two-stage dose–response analyses might be resulted from inclusion of those with undiagnosed diabetes. Therefore, whether higher HbA_{1c} level is still predictive of increased mortality among subjects with $HbA_{1c} < 6.5\%$ is unclear. For addressing this critical concern, we repeated our meta-analyses by excluding subjects with undiagnosed diabetes. Corresponding results showed that the positive association with higher HbA_{1c} level remained for CVD mortality only, suggesting that higher HbA_{1c} level is still a predictor of increased CVD mortality but not of all-cause mortality in subjects with $HbA_{1c} < 6.5\%$. The underlying reasons for the above phenomenon are unclear. A possible explanation is that the association between higher HbA_{1c} level and mortality from non-CVD is of extreme non-significance, making the contribution of CVD mortality to all-cause mortality insubstantial.

Several cross-sectional studies consistently indicate that HbA_{1c} levels increase with age in individuals without known diabetes[53–55]. Taking into account the above fact in combination with the dose–response patterns observed in our study, age is a possible effect modifier of the HbA_{1c}-mortality association. However, the result of our subgroup analysis stratified by age did not provide evidence to support this hypothesis. Another candidate effect modifier is sex, considering that a sex difference in HbA_{1c} levels has been reported despite inconclusive results[53,56]. Of included studies, only 3[12,13,25] investigated this potential effect modifier. Two of them[12,13] consistently revealed no modification effect by sex for all-cause and CVD mortality, whereas the remaining one[25] found that the significant positive association of HbA_{1c} levels with increased cancer mortality was only seen in women. Limited studies precluded our attempts to investigate this potential effect modifier through subgroup analysis[12,13,25]. Therefore, more studies are warranted to identify whether sex can modify the HbA_{1c}-mortality association.

Our study has several limitations. First, all included studies measured HbA_{1c} level on a single occasion at baseline. Considering the within-subject variation of HbA_{1c} level and measurement error, our results might be subject to regression dilution bias[57], indicating an underestimated effect size for the association of HbA_{1c} levels with mortality. Nonetheless, within-subject variation of HbA_{1c} in the healthy population has been found to be

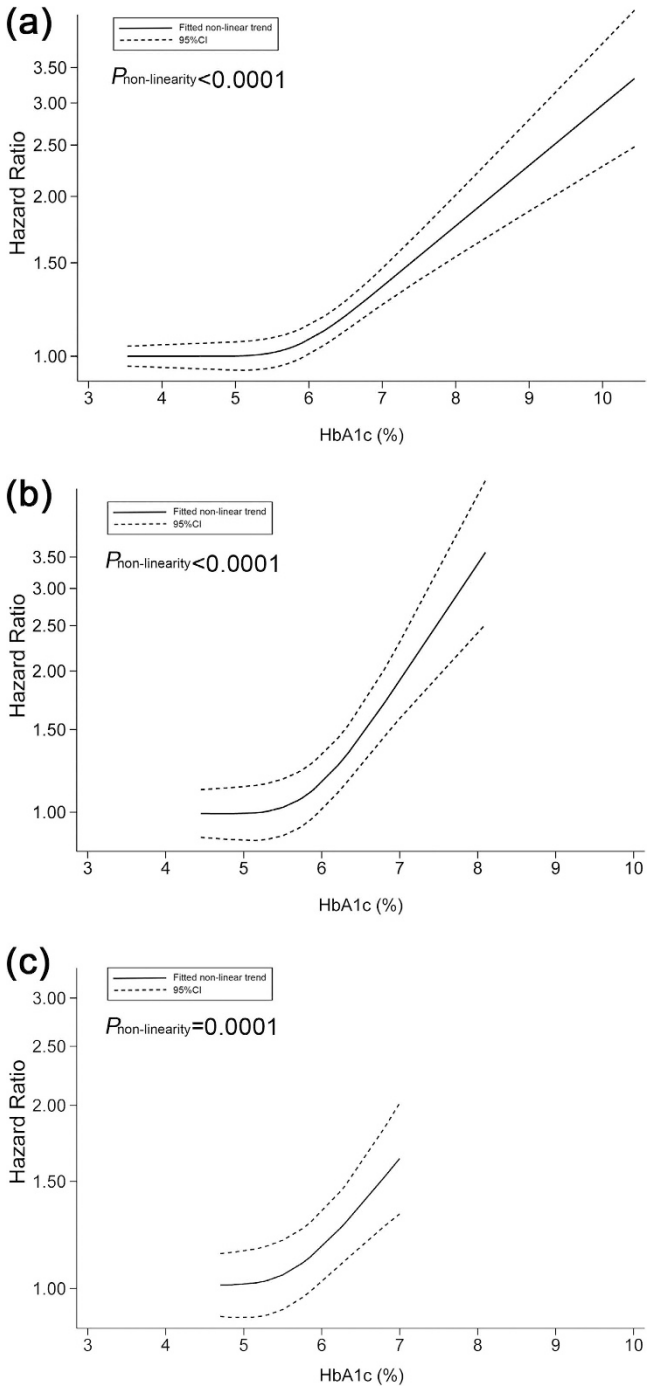

Figure 5. Non-linear dose–response analyses on the association of HbA_{1c} level with mortality from (**a**) all causes, (**b**) cardiovascular disease, and (**c**) cancer.

minimal[58]. Second, several included studies used death certificate to ascertain the causes of death[14,19,25,31,32]. Information from death certificate is inaccurate in some conditions[59]. Therefore, misclassification bias possibly affected our results on the associations between HbA_{1c} levels and risks of death from CVD and cancer. Third, although we extracted the most fully adjusted risk estimates, our results might be still biased by residual confounding. Nevertheless, the pooled results of maximally and minimally adjusted risk estimates are similar, indicating that the observed associations in our study cannot be explained predominantly by confounding. Fourth, we cannot calculate summary risk estimates for groups with undiagnosed diabetes as well as those with prediabetes because of diverse categorization across studies, although these data are important for medical practitioners. Fifth, our results may be influenced by language bias, because we restricted our search to studies published in English or Chinese. Nevertheless, it has been found that the effect of language restriction on the results of systematic reviews is non-significant[60]. Finally, although not indicated by both Begg's test and Egger's test, our results

may be still driven by publication bias because above two tests have insufficient power when including limited studies. Moreover, exclusion of several studies where necessary data for dose–response analysis were not reported possibly results in publication bias.

In conclusion, higher HbA_{1c} level is associated with increased mortality from all causes, CVD, and cancer among subjects without known diabetes. However, this association is influenced by those with undiagnosed diabetes or prediabetes. Because of limited studies, the results in relation to cancer mortality should be treated with caution, and more studies are therefore warranted to investigate whether higher HbA_{1c} level is associated with increased cancer mortality.

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Acknowledgements

No funding or financial support was received for this study. The authors thank Dr. Elizabeth Selvin (Johns Hopkins Bloomberg School of Public Health) for providing original data.

Author Contributions

G.C.Z. and J.P.G. conceived the study idea. G.C.Z. and J.H.C. performed literature search, study selection, and data extraction. M.X.Y. and Y.Z. performed statistical analyses and interpretation of corresponding results. G.C.Z. drafted the initial manuscript. J.P.G. had primarily responsibility for final content. All authors made critical comment for the initial manuscript.

Additional Information

Supplementary information accompanies this paper at http://www.nature.com/srep

Competing financial interests: The authors declare no competing financial interests.

How to cite this article: Zhong, G.-C. *et al.* HbA_{1c} and Risks of All-Cause and Cause-Specific Death in Subjects without Known Diabetes: A Dose-Response Meta-Analysis of Prospective Cohort Studies. *Sci. Rep.* **6**, 24071; doi: 10.1038/srep24071 (2016).