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Title:
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Date:
2018-06-01

Citation:
Mitsios, J. P., Ekinci, E. I., Mitsios, G. P., Churilov, L. & Thijs, V. (2018). Relationship between glycated hemoglobin and stroke risk: A systematic review and meta-analysis. Journal of the American Heart Association, 7 (11), https://doi.org/10.1161/JAHA.117.007858.

Persistent Link:
https://hdl.handle.net/11343/256931

American Heart Association | American Stroke Association

Relationship Between Glycated Hemoglobin and Stroke Risk: A Systematic Review and Meta-Analysis

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Background—Diabetes mellitus is a major risk factor for ischemic stroke. Rising hemoglobin A_{1c} (HbA_{1c}) levels are associated with microvascular diabetes mellitus complication development; however, this relationship has not been established for stroke risk, a macrovascular complication.

Methods and Results—We conducted a systematic review and meta-analysis of observational cohort and nested case-control cohort studies assessing the association between rising HbA_{1c} levels and stroke risk in adults (≥18 years old) with and without type 1 or type 2 diabetes mellitus. Random-effects model meta-analyses were used to calculate pooled adjusted hazard ratios (HRs) and their precision. The systematic review yielded 36 articles, of which 29 articles (comprising n=532 779 participants) were included in our meta-analysis. Compared to non–diabetes mellitus range HbA_{1c} (<5.7%), diabetes mellitus range HbA_{1c} (≥6.5%) was associated with an increased risk of first-ever stroke with average HR (95% confidence interval) of 2.15 (1.76, 2.63), whereas pre–diabetes mellitus range HbA_{1c} (5.7–6.5%) was not (average HR [95% confidence interval], 1.19 [0.87, 1.62]). For every 1% HbA_{1c} increment (or equivalent), the average HR (95% confidence interval) for first-ever stroke was 1.12 (0.91, 1.39) in non–diabetes mellitus cohorts and 1.17 (1.09, 1.25) in diabetes mellitus cohorts. For every 1% HbA_{1c} increment, both non–diabetes mellitus and diabetes mellitus cohorts had a higher associated risk of first-ever ischemic stroke with average HR (95% confidence interval) of 1.49 (1.32, 1.69) and 1.24 (1.11, 1.39), respectively.

Conclusions—A rising HbA_{1c} level is associated with increased first-ever stroke risk in cohorts with a diabetes mellitus diagnosis and increased risk of first-ever ischemic stroke in non–diabetes mellitus cohorts. These findings suggest that more intensive HbA_{1c} glycemic control targets may be required for optimal ischemic stroke prevention. **(*J Am Heart Assoc*. 2018;7:e007858. DOI: 10.1161/JAHA.117.007858.)**

Key Words: cerebrovascular disease/stroke • diabetes mellitus • hemoglobin A_{1c} • meta-analysis • risk

Strokes represent a heterogeneous group of vascular pathologies that collectively act as a major global burden of mortality and lifelong morbidity. Diabetes mellitus is a major risk factor for the development of stroke, particularly ischemic stroke, with type 2 diabetes mellitus alone known to increase stroke risk 1.5 to 4 fold.[1] Macrovascular complications of diabetes mellitus (ischemic heart disease (IHD), stroke, and peripheral vascular disease) represent a major cause of diabetes mellitus related mortality and health-related expenditure.[2,3]

Glycated hemoglobin (HbA_{1c}) is a validated marker of 2 to 3 month glycemic control used within routine diabetes mellitus care. Current American Diabetes Association (ADA) diabetes mellitus management guidelines recommend a base target of HbA_{1c} <7.0% within routine diabetes mellitus care of non-pregnant adults.[4] This target is most validated for microvascular complication risk reduction and has unclear implications for optimal macrovascular risk reductions. Long-term follow-up studies of 2 randomized controlled trials (RCTs) have

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Accompanying Datas S1 through S4, Tables S1 through S6, and Figures S1 through S23 are available at http://jaha.ahajournals.org/content/7/11/e007858/DC1/embed/inline-supplementary-material-1.pdf

The abstract of this work was presented as an oral presentation at the Stroke Society of Australasia Conference, August 23 to 25, 2017, in Queenstown, New Zealand, and as a poster presentation at the Australian Diabetes Society Conference, August 30 to September 1, 2017, in Perth, Australia.

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Received October 14, 2017; accepted March 2, 2018.

Clinical Perspective

What Is New?

- Using a meta-analytical approach, we found that higher glycated hemoglobin levels were associated with an increased risk of first-ever ischemic stroke in both non–diabetes mellitus and diabetes mellitus cohorts.
- In people with established diabetes mellitus, higher glycated hemoglobin levels were associated with an increased risk of first-ever stroke.

What Are the Clinical Implications?

- Further interventional studies are needed to examine the effectiveness of more intensive glycemic control targets as part of primary and secondary stroke prevention, in pre–diabetes mellitus and diabetes mellitus cohorts.

demonstrated beneficial effects on long-term macrovascular outcomes with more intensive glycemic control, thereby suggesting a metabolic memory effect for hyperglycemia.[5,6]

Up to one half of all patients presenting with acute stroke have previously unknown abnormalities of glucose tolerance, with 20% to 40% of patients presenting with hyperglycemia at hospital admission.[7] Chronic hyperglycemia has been linked with several stroke risk factors including accelerated atherosclerosis, increased carotid intima media thickness (CIMT), cardiomyocyte dysfunction, atrial fibrillation (AF), and ischemic heart disease.[8–11] In non–diabetes mellitus patients with insulin resistance and recent ischemic stroke or transient ischemic attack, long-term treatment with pioglitazone reduced the risk of adverse cardiovascular outcomes.[12] The outcomes of this trial suggested that in the ischemic stroke subgroup, anti-hyperglycemic medication may need to start at lower HbA_{1c} thresholds than currently accepted levels.[12]

No systematic review and meta-analysis has generated consensus regarding the specific relationship between rising HbA_{1c} level and stroke risk.[13,14] We therefore aimed to fill this knowledge gap by conducting a systematic review and meta-analysis of observational studies to examine and determine a quantifiable risk relationship for the association between rising HbA_{1c} level and stroke risk, stratified by diabetes mellitus status, stroke temporality, and stroke subtype.

Methods

Study Design and Registration

We systematically reviewed cohort and nested case-control cohort studies that assessed the association between varying HbA_{1c} level and stroke risk. The protocol implemented as part of this systematic review and meta-analysis was constructed using the combined recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA),[15] Meta-analysis of Observational Studies in Epidemiology (MOOSE) group,[16] and the Cochrane Handbook for Systematic Reviews.[17] This study is registered with PROSPERO (CRD42017056706). The data, analytic methods, and study materials will be/have been made available to other researchers for purposes of reproducing the results or replicating the procedure. These are available within this manuscript and the associated online data supplement.

Literature Search Strategy

A systematic search of 5 literary databases (MEDLINE, Embase, PubMed, Web of Science, and the Cochrane Library) was performed between February 7, 2017, and March 5, 2017. Medical Subject Headings (MeSH) terms selected were synonymous with the following text words used: *glycosylated h(a)emoglobin, HbA_{1c}, glycated h(a)emoglobin, stroke, cerebral infarction, cerebral h(a)emorrhage,* and *transient isch(a)emic attack*." MeSH terms were "exploded" to maximise coverage.

Search results were restricted to human (≥18 years old) and English only articles. No publication filters were applied within any database. Search results were managed and duplicate entries removed using EndNote X7.7.1. A manual search of study references was performed for completeness. A complete list of MeSH and text words with Boolean operators applied within MEDLINE are provided in Figure S1.

Inclusion and Exclusion Criteria

Studies were considered for inclusion within meta-analyses and sensitivity analyses performed if they met the following criteria: (1) presented adjusted hazard ratios (HRs) or risk ratios (RRs, relative risk) for the association between varying HbA_{1c} level and stroke risk, defined by temporality (first-ever or recurrent) and subtype of event (ischemic, hemorrhagic, other); and (2) involved a minimum follow-up period of ≥12 months.

We excluded studies that met any of the following criteria: (1) failed the automatic exclusion criteria within the Scottish Intercollegiate Guidelines Network (SIGN)[18] quality tool (Data S1); (2) focused on specific subpopulations (including end-stage kidney disease (ESKD), dialysis, post-thrombolysis (tPA), post-myocardial infarction (AMI), and post-operative cohorts); (3) had insufficient or missing data for extrapolation and quality assessment; and (4) compared diabetes mellitus to non–diabetes mellitus cohorts.

In the source literature, effect sizes (HR or RR) were variably adjusted for covariates, with multiple effect sizes often reported. Consequently, we extracted the most extensively covariate-adjusted HR or RR data for use in the meta-analysis. However, if in the original source article adjustment

was performed for hypoglycemic medication use, we only included data that were not adjusted for hypoglycemic medication use, as the medication may have biased the association between the exposure and outcome. Data S2 provides a full description of inclusion and exclusion criteria applied during each phase of the search strategy.

Search Protocol Implementation and Data Extraction

Two reviewers (J.P.M., G.P.M.) independently screened all available articles by title and abstract using predefined inclusion and exclusion criteria. Following this, 2 reviewers (J.P.M., V.T.) performed a full-text review of articles identified through screening using predefined inclusion and exclusion criteria. Objective methodological study quality assessment was performed during full-text review using 2 critical appraisal checklists for cohort studies.[18,19] Any disagreements were resolved through discussion between reviewers. Narrative synthesis was performed for all studies deemed suitable for inclusion in the meta-analysis (n=36 studies). Data on key study parameters, including; author(s), year of publication, study location, sample size, participant demography, stroke outcome type, effect size data, and covariate adjustment performed, were extracted in duplicate and are detailed in Tables S1 through S6. Any discrepancies in data extracted were resolved through consultation between authors.

Statistical Analyses and Bias Assessment

The primary outcome measure of interest was the association between rising categorical or 1% increment (or equivalent) HbA_{1c} levels and stroke risk, stratified by diabetes mellitus status, stroke temporality, and stroke subtype. A random-effects model was used for all meta-analyses and sensitivity analyses. Meta-analyses were only performed on strata that contained a minimum of 3 studies ($n \geq 3$) to ensure adequate analytical power. RR data were treated as equivalent to HR data in all analyses.

The association between rising categorical HbA_{1c} levels and first-ever stroke risk was assessed through comparison of stroke risk between American Diabetes Association–defined non–diabetes mellitus range HbA_{1c} (<5.7%) (reference category) to pre–diabetes mellitus range HbA_{1c} (5.7%–6.5%) and diabetes mellitus range HbA_{1c} (≥6.5%) categories. Only studies that used a reference category within non–diabetes mellitus range HbA_{1c} and at least 1 comparator category within pre–diabetes mellitus range or diabetes mellitus range HbA_{1c} were included (Data S3, Figures S2 and S3).

The association between 1% increments (or equivalent) of HbA_{1c} and first-ever stroke risk was examined. Studies reporting 1 standard deviation (1sd) increment effect sizes were treated as equivalent to 1% HbA_{1c}, as the magnitude of these 1 standard deviation increments ≈ 1% increments (1±0.4%) and the effect sizes quoted approximated the estimated 1% increment equivalents (Tables S1– S6).

Many studies only reported categorical data. A linear regression model was used to estimate natural log-transformed 1% increment effect sizes and 95% confidence interval (CI) from this pool of categorical data using a method described by Greenland,[20] with statistical significance set at $P<0.05$. This estimated 1% data were then used within separate random-effects model meta-analyses performed. A detailed description of this method is provided in Data S4, Figures S4 and S5.

To avoid duplicate data use, whenever 2 studies reported on the same study population, we used the most recent study for the subgroup meta-analysis performed. Baseline and time-update mean values of HbA_{1c} were treated as equivalents. Time-updated HbA_{1c} values were selected in preference to single baseline values in studies that presented both. A random-effects model was used to generate overall effect sizes from effect size data that had been stratified by variables like sex or ethnicity.

Definitions used to classify stroke and diabetes mellitus status varied greatly within the source literature. Diabetes mellitus status was defined using reported diabetes mellitus status (medical history, clinician or patient reported) and/or glucose or HbA_{1c} measurement at study inclusion. Strokes were classified using *International Classification of Diseases, Ninth/Tenth Revision* (*ICD-9/10*) codes, World Health Organization criteria and/or study-defined stroke criteria. Stroke event occurrence was identified using hospital admission diagnosis, death certificate details, medical history details, clinician reports, and/or patient-reported status.

Given the heterogeneity in diabetes mellitus and stroke outcome classification and reporting, the decision was made to assign both diabetes mellitus and stroke outcome status based on each study's reported outcome status. Effect sizes adjusted for diabetes mellitus status were treated as representing non–diabetes mellitus data. Effect sizes adjusted for past stroke history were treated as representing first-ever stroke data.

Several sensitivity analyses were performed within this study, examining the; (1) effect of combining type 1 and type 2 diabetes mellitus cohorts, (2) importance of ischemic subtype stratification, (3) difference between estimated and quoted 1% HbA_{1c} increment data, and (4) effect of varying levels of covariate adjustment on results obtained. These sensitivity analyses are presented in Figures S6 through S10. The linear-regression estimated 1% HbA_{1c} meta-analyses are presented in Figure S11.

Based on the recommendations of the Cochrane Handbook,[17] we did not perform formal meta-regression because of insufficient study number (n<10 studies per subgroup). We assessed for statistical heterogeneity using the I^2 statistic. As per Higgins et al,[21] we assigned adjectives of "low," "moderate," and "high" for I^2 statistic values of 25%, 50% and 75%, respectively. I^2 statistic values below 25% were assigned the adjective of "low." The I^2 statistic describes the percentage of variation across studies that is attributable to heterogeneity rather than chance.[21] Consequently, the categories of I^2 statistic magnitude outlined do not refer to the absolute amount of observed heterogeneity.

Publication bias was assessed through construction of funnel plots and performing Egger's test for funnel plot asymmetry for each meta-analysis performed (Figures S12–S16). Statistical significance for publication bias assessment using Egger's test was set at $P<0.05$. Stata/IC 14.2 was used for all statistical analyses. Additional sensitivity analyses are presented in Figures S17 through S23.

Results

A total of 5831 articles were identified through the search strategy. Following duplicate removal (n=2279), a total of 3552 articles were screened by title and abstract. Of these, 310 articles were assessed by full-text review. A total of 56 studies were assessed for inclusion in meta-analyses performed, of which 20 were excluded for the following reasons: 7 studies did not provide HR or RR data; 3 studies provided only effect sizes adjusted for hypoglycemic medication use; 5 studies provided effect sizes which compared diabetes mellitus to non-diabetes mellitus participants; 1 study provided HR which compared intensively treated to non-intensively treated cohorts; 1 study had effect size covariate adjustment and stratification limitations; 1 study used a duplicate study population with incomplete HbA_{1c} strata use in effect size calculation; 1 study used a conditional HR that compared stroke and non-stroke patient cohorts; and 1 study used a pooled cardiovascular disease outcome without stratifying for a stroke outcome. A detailed overview of the study review process is presented in Figure 1.[22–41]

Of the 36 studies deemed suitable for meta-analysis, 7 reported recurrent stroke outcome data and were included only in narrative synthesis because of concerns regarding underpowering of meta-analyses following outcome stratification (Tables S1–S6). A total of 29 studies comprising 532 779 participants were used in meta-analyses and sensitivity analyses (Figure 1[22–41]). A narrative summary of baseline participant characteristics within all 36 articles identified for potential inclusion is provided in Tables S1 through S6.

First-Ever Stroke Risk in American Diabetes Association–Defined HbA_{1c} Ranges

Compared to non–diabetes mellitus range HbA_{1c} (<5.7%), pre–diabetes mellitus range HbA_{1c} (5.7%–6.5%) was not associated with a significant increased risk of first-ever stroke (average HR [95% CI], 1.19 [0.87, 1.62]). In contrast, diabetes mellitus range HbA_{1c} (≥6.5%) was associated with a significant increased risk of first-ever stroke when compared to non–diabetes mellitus range HbA_{1c} (average HR [95% CI], 2.15 [1.76, 2.63]).

We identified moderate and low I^2 statistic values (I^2=61.3% [P=0.051] and I^2=0% [P=0.460]) for the pre–diabetes mellitus and diabetes mellitus analyses, respectively. We did not find evidence of significant publication bias for either analysis (Figure S12).

Association Between Study-Quoted 1% HbA_{1c} Increments and First-Ever Stroke Risk

Figure 2[42–53] summarizes the meta-analyses assessing the association between study-quoted rising 1% HbA_{1c} increments and first-ever stroke risk, stratified by diabetes mellitus status and ischemic stroke subtype. For every 1% HbA_{1c} increment (or equivalent), the average HR (95% CI) for first-ever stroke risk was 1.12 (0.91, 1.39) in non–diabetes mellitus cohorts and 1.17 (1.09, 1.25) in diabetes mellitus cohorts. When restricted to studies only examining first-ever ischemic stroke, average HRs (95% CI) were 1.49 (1.32, 1.69) and 1.24 (1.11, 1.39) for non–diabetes mellitus and diabetes mellitus cohorts, respectively.

The I^2 statistic value was moderate for the analysis assessing first-ever stroke risk in patients with diabetes mellitus (I^2=59.0%, P=0.012). Sensitivity analysis identified studies with limited covariate adjustment as the likely source of this moderate I^2 statistic value (Figure S6). Exclusion of these studies reduced the I^2 statistic value from moderate to low (reduction from I^2=59.0% [P=0.012] to I^2=41.9% [P=0.111]) without inducing significant publication bias or altered pooled effect size significance (average HR [95% CI], 1.14 [1.07, 1.20] prior to exclusion and 1.17 [1.09, 1.25] following exclusion). We did not find evidence of significant publication bias in any subgroup analysis (Figures S13 and S14).

Association Between Linear Regression Estimated 1% HbA_{1c} Increments and First-Ever Stroke Risk

For every estimated 1% HbA_{1c} increment (or equivalent), the average HR (95% CI) for first-ever stroke was 1.17 (1.02, 1.34) and 1.17 (1.01, 1.36) for non–diabetes mellitus

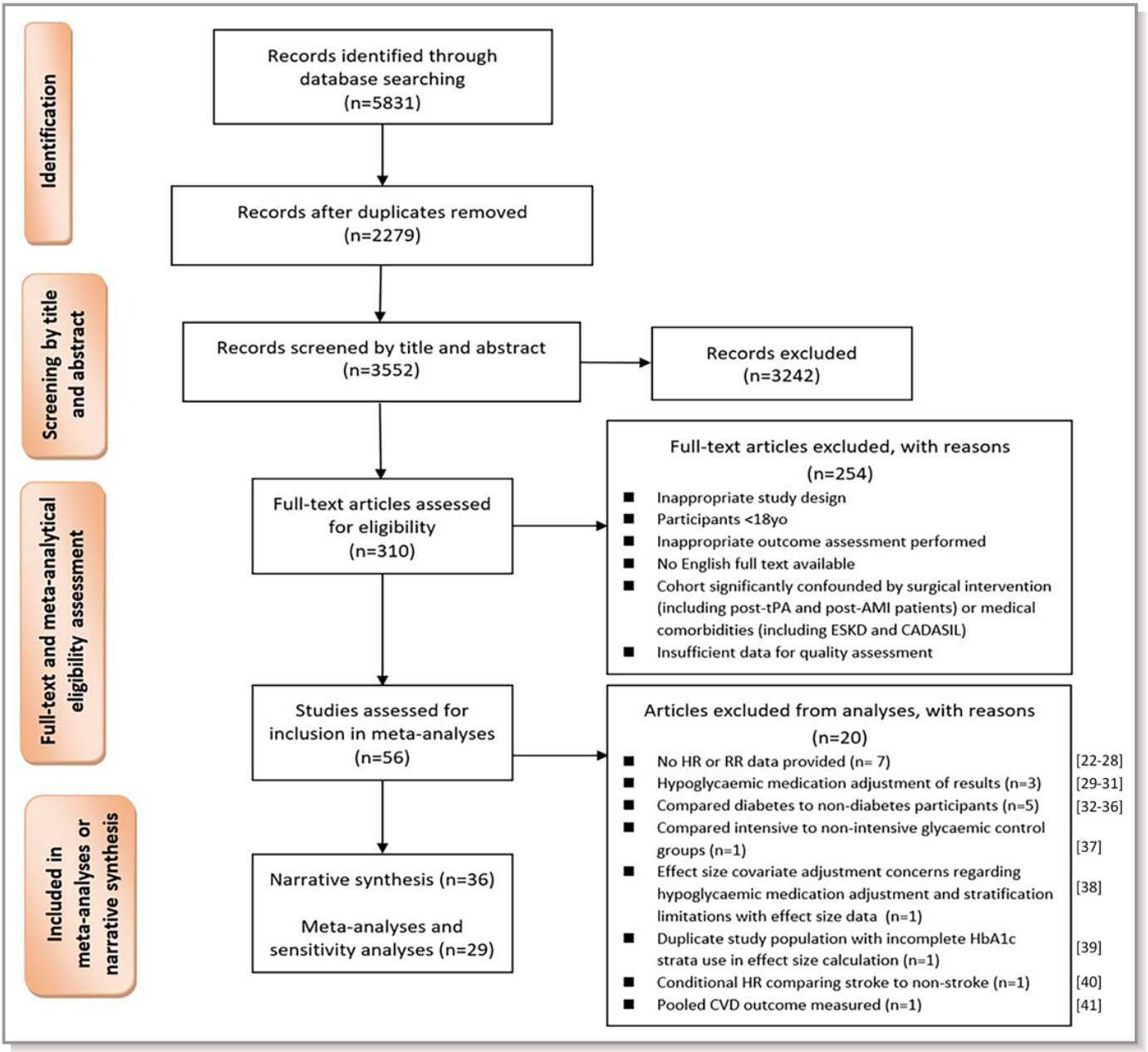

Figure 1. PRISMA flowchart outlining search strategy implementation and results at each stage. Results presented outline the number of articles identified during each stage of the search strategy. Duplicate removal was performed using the default duplicate removal function within EndNote X7.7.1. Screening by title and abstract was performed independently by 2 researchers using a defined set of inclusion criteria. Full-text review, including methodological quality assessment, was subsequently performed using defined inclusion criteria. Following this, articles were assessed for meta-analytical inclusion through consultation between 2 authors using a separate set of inclusion criteria. Articles deemed suitable for meta-analyses and sensitivity analyses were stratified based on cohort diabetes mellitus status and stroke outcome. Strata that lacked sufficient article number (n<3 articles) were presented within narrative synthesis only. A total of 29 articles were used in meta-analyses and sensitivity analyses conducted. The number of studies at each stage (n) is reflected in brackets. AMI indicates acute myocardial infarction; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); CVD, cardiovascular disease; ESKD, end-stage kidney disease; HR, hazard ratio; RR, risk ratio (relative risk); tPA, tissue plasminogen activator.

and diabetes mellitus cohorts, respectively. When restricted to first-ever ischemic stroke, average HRs (95% CI) were 1.35 (0.91, 2.02) and 1.32 (1.23, 1.42) for non–diabetes mellitus and diabetes mellitus cohorts, respectively (Figure S11). Inclusion of studies with limited covariate adjustment resulted in a high I^2 statistic value, as shown in Figure S7. Exclusion of these studies resulted in a reduction of the I^2 statistic value from high to moderate (reduction from I^2=89.9% [P<0.001] to I^2=57.7% [P=0.051]) without inducing statistically significant publication bias

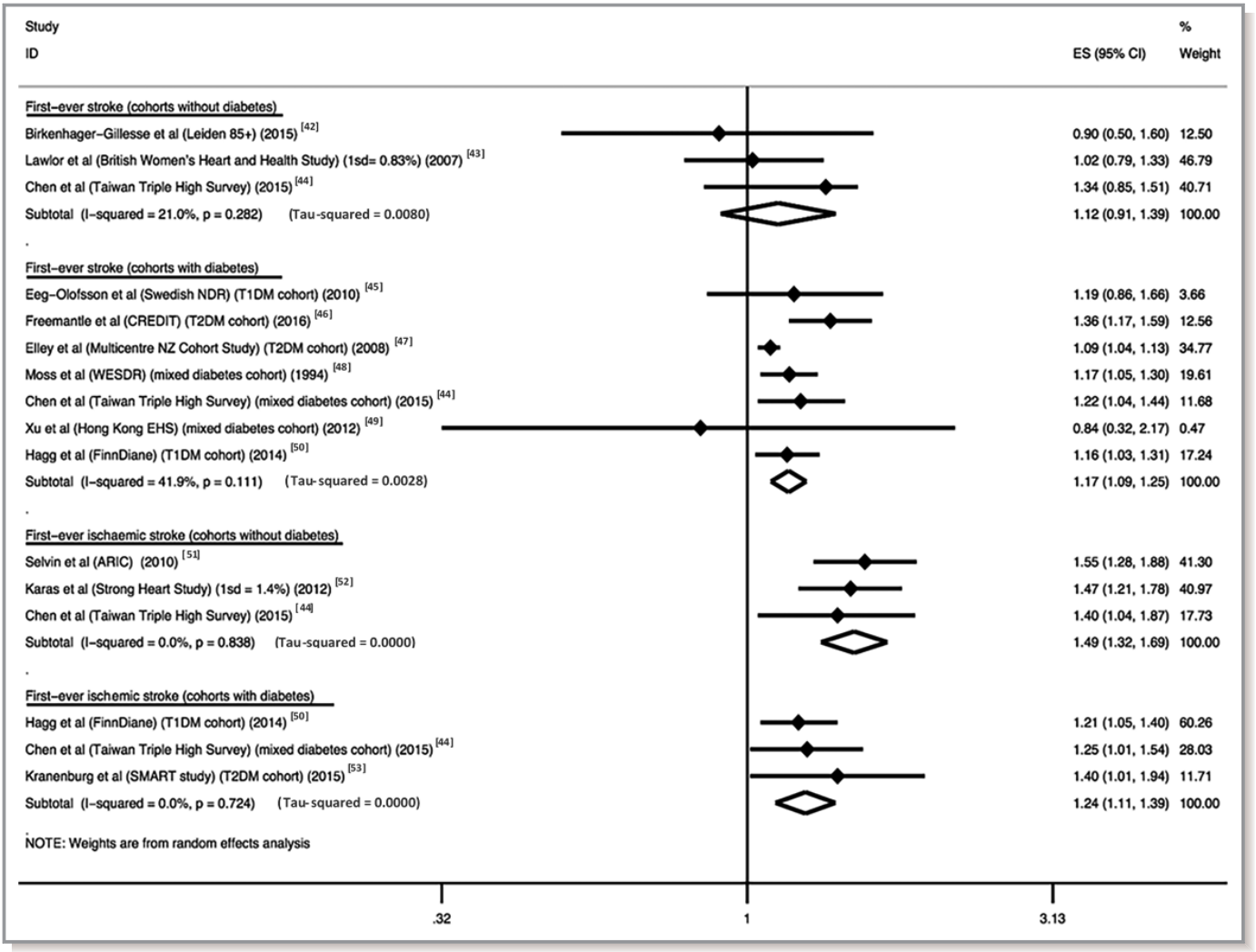

Figure 2. Association between study-quoted rising 1% HbA_{1c} increments and stratified first-ever stroke risk. Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA_{1c} increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data were treated as equivalent to HR data. Studies using 1 standard deviation (1 SD) HbA_{1c} increments for effect sizes quoted were treated as equivalent to 1% HbA_{1c} increment data. The corresponding HbA_{1c} increments for each standard deviation are as shown in brackets. Studies were stratified based on the diabetes mellitus status of their cohorts and their restriction of first-ever stroke to an ischemic stroke subtype. The outcome "first-ever stroke" reflects any stroke subtype. The outcome "first-ever ischemic stroke" included only studies that specifically restricted their stroke outcome to first-ever stroke of ischemic subtype. Diabetes cohorts included studies that measured type 1 diabetes mellitus (T1DM), type 2 diabetes (T2DM) or a combination of both (mixed diabetes mellitus cohort). Non–diabetes mellitus cohorts represented studies that used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes mellitus. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association.

(Figures S15 and S16) or altering the significance of the pooled effect sizes (average HR [95% CI], 1.21 [1.05, 1.40] prior to exclusion and 1.17 [1.01, 1.36] following exclusion).

Discussion

We demonstrated a significant association between rising 1% HbA_{1c} increments and first-ever stroke risk in cohorts with diabetes mellitus. In non–diabetes mellitus cohorts, analysis of estimated 1% HbA_{1c} data revealed a significant relationship with first-ever stroke, while study-quoted 1% HbA_{1c} data analyses were significant only for an association with first-ever ischemic stroke. Analysis of American Diabetes Association diabetes mellitus range HbA_{1c} (≥6.5%) revealed a significant 2.15-fold increased risk of first-ever stroke in diabetes mellitus range HbA_{1c} compared to non–diabetes mellitus range HbA_{1c} (<5.7%).

The absence of a clear association between pre–diabetes mellitus range HbA_{1c} and first-ever stroke identified is in keeping with the results of a previous meta-analysis by Huang et al.[54] This study identified a nonsignificant 5% increased risk of stroke associated with pre–diabetes mellitus range HbA_{1c} following meta-analysis of only 2 studies.[54]

Our study expands upon previous meta-analyses.[13,14] These studies demonstrated a significant association between rising 1% HbA_{1c} increments and stroke risk in patients with type 2 diabetes mellitus (where stroke represented any fatal or nonfatal stroke event) after combining study-quoted and estimated 1% HbA_{1c} data from a small number of included studies.

Our study addressed these limitations. Our study included 29 studies and studied ischemic stroke specifically. The use of separate meta-analyses for study-quoted and linear regression estimated 1% HbA_{1c} data within our meta-analysis avoids the inherent imputation bias associated with conversion of categorical data into a continuous data set.

Our study suggests the presence of an independent association between chronic hyperglycemia, even in the pre–diabetes mellitus range, and first-ever stroke risk. The strength of this association was enhanced when restricting stroke outcomes to first-ever ischemic stroke. This suggests that the inclusion of hemorrhagic and undefined stroke subtypes within the stroke outcome assessed may have blunted the statistical significance of the underlying relationship between hyperglycemia and ischemic stroke. This finding is in keeping with previous research that has suggested that diabetes mellitus is primarily a risk factor for ischemic stroke rather than hemorrhagic stroke,[7] and is supported by pathogenic data that links chronic hyperglycemia and ischemic stroke risk factors.[8–11]

The DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study) demonstrated a statistically significant risk reduction in macrovascular complication risk in participants managed initially with intensive glycemic control measures following 17 years of follow-up of a type 1 diabetes mellitus population.[5,55] Similarly, the UKPDS (United Kingdom Prospective Diabetes Study) follow-up study[6] demonstrated that intensive glycemic control in patients with type 2 diabetes mellitus led to fewer macrovascular complications after prolonged follow-up, suggesting a metabolic memory effect for earlier intensive control.

Despite this, several randomized controlled trials including VADT (Veterans Affairs Diabetes Trial),[56] ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation)[57] and ACCORD (Action to Control Cardiovascular Risk in Diabetes)[58] have refuted the presence of a statistically significant macrovascular complication risk reduction offered by intensified glycemic control, in the context of type 2 diabetes mellitus management. Common limitations within these randomized controlled trials that may explain the incongruence of their results with DCCT/EDIC and UKPDS include; the comparatively short follow-up intervals used, competing risk confounding associated with the older age of participants used, the inclusion of participants with poorly controlled diabetes mellitus, and, importantly, the inclusion of participants with preexisting cardiovascular disease (may be at heightened risk of hypoglycemia with insulin and sulfonylurea therapy). Newer agents reduce cardiovascular outcomes without major changes in HbA_{1c} or improved glycemic control, but these may act through other pathways and do not deter from the finding that pre–diabetes mellitus, as determined by HbA_{1c} level, appears associated with incident ischemic stroke.[59] This is evident within 2 recent glucagon-like peptide-1 trials that demonstrated significant reductions in a combined cardiovascular outcome of cardiovascular death, nonfatal acute myocardial infarction, or nonfatal stroke through their use in type 2 diabetes mellitus populations with high cardiovascular disease risk.[60,61]

Several measures were implemented within our study with the intention of reducing the magnitude of interstudy heterogeneity. We attempted to reduce heterogeneity by implementing an extensive set of inclusion and exclusion criteria that were designed to reduce common sources of heterogeneity and bias, including but not limited to; variability in study design, variability in effect measures used, insufficient follow-up time, and insufficient covariate adjustment. Given the implicit heterogeneity of observational study designs, a random-effects model was used in all analyses performed. The use of subgroup meta-analyses, stratified for key outcome parameters including stroke subtype (first-ever ischemic stroke versus first-ever stroke) and cohort diabetes mellitus status (diabetes mellitus versus non–diabetes mellitus cohorts), further aimed to reduce outcome measure related heterogeneity.

Of the subgroup meta-analyses focusing on the association between rising 1% HbA_{1c} increments and first-ever stroke risk, only 2 demonstrated I^2 values exceeding 25%, thereby indicating a very good level of heterogeneity control through our study design. Sensitivity analyses performed in Figures S6 and S7 demonstrated reductions in the magnitude of heterogeneity detected from moderate to low and high to moderate, respectively, following exclusion of studies with limited covariate adjustment. Given this result, it is a reasonable assertion that differences in the types and number of covariates adjusted for within individual studies is a likely major contributor to the statistical heterogeneity measured. This is not surprising when considering that many of these variables, including; age, sex, hypertension, smoking status, cholesterol level, and history of cardiovascular disease, are independent risk factors for the development of vascular disease including stroke.

A further potential reason for the statistical heterogeneity measured relates to the unavoidable differences in study definitions for key parameters of diabetes mellitus status and stroke. Decisions made relating to the treatment of studies whose results were statistically adjusted for past history of diabetes mellitus and stroke, and the acceptance of study-quoted diabetes mellitus and stroke outcome descriptors may also have contributed to the level of statistical heterogeneity detected but were unavoidable given the inherent variability in outcome definitions present within observational study designs.

Our study has limitations. We restricted our studies to those reporting only RR and HR data. The lack of a common, standardized definition for diabetes mellitus across all the studies could result in assessment bias. Likewise, the inclusion of studies with different stroke outcome classification systems is suboptimal given the inherent differences within the classification systems used. The use of a linear regression model to ≈1% HbA_{1c} effect size data from categorical HbA_{1c} data can provide only an approximation of this relationship and could not be combined with quoted data. The variability in covariate adjustment performed (types and number of covariates adjusted for) within the source studies included in our analyses imposed limitations on our ability to examine the independent effects of individual covariate adjustment on the statistical heterogeneity calculated using the I^2 statistic. Likewise, the limited number of studies ($n<10$) within each subgroup meta-analysis performed precluded the implementation of meta-regression techniques.

Although a comprehensive search strategy assessing multiple literary databases was performed, we may not have identified all relevant literature on this topic. We also did not include studies addressing this topic in languages other than English. We did not have access to individual patient data that would have permitted more detailed analyses. Our data are, however, in line with an individual patient data meta-analysis that assessed the risk of a composite outcome of stroke and myocardial infarction with varying levels of HbA_{1c}.[62] That study did not report on stroke outcomes separately but was able to identify an increased risk of acute myocardial infarction/stroke in patients with low levels of HbA_{1c}.[62] Our methodology was not able to identify such a J-shaped relationship. The limited number of articles within each subgroup analysis prevented use of formal meta-regression and analysis of HbA_{1c} as a risk factor for recurrent stroke.

Conclusions

In summary, our study suggests that both continuous and categorical elevations in HbA_{1c} are associated with increased first-ever ischemic stroke risk, irrespective of diabetes mellitus status. Prevention of macrovascular complications like stroke may need to start at lower HbA_{1c} thresholds. Further interventional studies are needed to explore the effectiveness of more intensive glycemic management within primary and secondary stroke prevention, in pre–diabetes mellitus and diabetes mellitus cohorts.

Acknowledgments

Special thanks to Ms Helen Baxter (Clinical Librarian, Austin Health Services Library, Austin Health) for her advice regarding selection of search terms, literature databases and Boolean operators during search strategy development. The Florey Institute of Neuroscience and Mental Health acknowledges the strong support from the Victorian Government and in particular the funding from the Operational Infrastructure Support Grant.

Sources of Funding

E.I.E. was supported by a Viertel Clinical Investigatorship, RACP Fellowship, and Sir Edward Weary Dunlop Medical Research Foundation research grant and a Stroke Foundation grant.

Disclosures

V.T. reports receiving consulting fees from Medtronic. V.T. is on the steering committee of the DIAGNOSE AF and REACT AF clinical trials sponsored by Medtronic. V.T. reports speaker and consulting fees and travel support by Boehringer Ingelheim, Pfizer/BMS, Daichi-Sankyo, and Bayer. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Data S1:

Scottish Intercollegiate Guidelines Network (SIGN) methodological quality assessment tool [1] automatic exclusion criteria:

Criterion 1.7:

"The outcomes are clearly defined."

Criterion 1.11:

"Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable."

Criterion 1.13:

"The main potential confounders are identified and taken into account in the design and analysis."

Data S2:

Inclusion and exclusion criteria for each phase of the search strategy:

Screening by title and abstract:

- Adults aged ≥18 yo
- Abstract available for assessment
- Human only studies
- Observational studies restricted to cohort and nested case-control cohort study designs
- Primary literature only (exclude reviews, systematic reviews and meta-analyses)
- Must include quantitative analysis of the association between HbA1c and one or more of the following:
    - Stroke; defined by fatality of event (fatal/non-fatal), temporality of event (first-ever or recurrent) and/or subtype of stroke (ischaemic, haemorrhagic, other)
    - Cardiovascular disease (CVD); only if there is inferred or explicit reference to quantitative analysis involving a stroke outcome within the study's definition of CVD
    - Post-acute stroke event mortality; only if there is inferred or explicit reference to recurrent stroke events being included as one of the potential causes of mortality measured by the study

Full-text review:

- Adults aged ≥18 yo
- English full-text available for assessment
- Human only studies
- Observational studies restricted to cohort and nested case-control cohort study designs
- Minimum follow-up of ≥12 months
- Must include quantitative analysis of the association between HbA1c level and stroke risk using one of the following relative measures; odds ratio (OR), risk ratio (RR, relative risk) or hazard ratio (HR)
- **Exclude if:**
    - Confounded by significant baseline morbidity (i.e. CADASIL patients, ESKD/dialysis patients and outcome measurement in post-operative patients (including post-AMI and post-tPA patients))- assessed on a case-by-case basis
    - Do not meet the automatic exclusion criteria within the Scottish Intercollegiate Guidelines Network (SIGN)- criteria: 1.7, 1.11, 1.13.[1]
    - Had insufficient data for methodological quality assessment and effect size extrapolation

Meta-analytical inclusion:

Must present hazard ratio or risk ratio (relative risk) data which assessed the association between rising HbA1c level and stroke risk (first-ever or recurrent stroke), **and** have met the following criteria:

- Clearly defined diabetes status of the sample cohort used in HR or RR calculation, either non-diabetes or diabetes cohort (comparing non-diabetes to non-diabetes and diabetes to diabetes patients)- excluded studies with HR or RR data comparing diabetes to non-diabetes cohorts
- HR or RR data for the association between 1% HbA1c increments (or equivalent) **or** inter-categorical HbA1c elevations (with a defined reference category), and stroke risk.
- HR or RR data must **not** be adjusted for hypoglycaemic medication (diabetes medication) use

Data S3:

Association between ADA defined pre-diabetes and diabetes range HbA1c and first-ever stroke risk

Studies presenting categorical HbA1c effect size data for a first-ever stroke outcome (not restricted to ischaemic stroke subtype) were considered for inclusion in the ADA HbA1c range inter-categorical meta-analyses performed if they met the following criteria:

- Reference category of HbA1c used was within the range of HbA1c included within the ADA-defined non-diabetes range HbA1c (<5.7%)
- At least one comparator category of HbA1c within the range of either a) ADA pre-diabetes range HbA1c (5.7%-6.5%) or b) ADA diabetes range HbA1c (≥6.5%)

Separate meta-analyses were performed to assess the association between ADA pre-diabetes and diabetes HbA1c, and first-ever stroke risk. Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio data for analyses performed. Random-effects model meta-analyses were conducted to calculate the risk of first-ever stroke in pre-diabetes range HbA1c levels and diabetes-range HbA1c levels, using non-diabetes range HbA1c as the reference category (effect size= 1.0).

Data S4:

Linear regression analysis method for estimating continuous (1% HbA1c increment) effect size data from categorical effect size data

Continuous (1% HbA1c increment) effect size data was generated from studies presenting inter-categorical effect size data, using linear regression analysis. The linear regression method used is based upon the method described in Greenland [2], and used within Selvin [3] and Zhang [4].

The dataset was stratified into 4 subgroups based on a) ischaemic stroke subtype restriction and b) cohort diabetes status. Effect size data (HR or RR) extracted from the source studies corresponded to set categorical ranges of HbA1c within each source study. The categories of HbA1c presented within each study were assigned point values of HbA1c in order to facilitate their conversion into a continuous dataset. The point values of HbA1c assigned were selected in the following order; (1) study-quoted categorical **mean HbA1c value**, (2) study-quoted categorical **median value**, (3) normal distribution estimated categorical value.

Point measures of HbA1c assigned to each category of HbA1c within each study were then paired with the corresponding **log-transformed** effect size for their category of HbA1c, thereby creating a set of (x,y) co-ordinates for each study (where x= HbA1c point measure and y= log-transformed effect size).

Linear regression analyses were then performed using all available (x,y) datasets for each of the four dataset subgroups in order to test the validity of a linearity assumption (significance set at $p<0.05$). Only 1 of the subgroup analyses failed to achieve statistical significance for a linear fit. Following two-way graph examination of this data set and given the statistical significance for linearity achieved in the remaining 3 dataset subgroups a linearity assumption was deemed appropriate for the overall association.

Separate linear regression analyses were conducted for each study's (x,y)=(HbA1c, log-effect size) data points in order to generate values for the linear coefficient ('a') and its 95% CI, where $y=ax+c$.

The linear coefficient ‘a’ represented the **log-transformed** 1% HbA1c increment effect size whilst its 95% CI represented the **log-transformed** 1% HbA1c increment effect size 95% CI.

Four studies [5-8] presented dichotomised HbA1c categorical data. As a result, linear regression analyses for these studies only provided a **log-transformed** 1% HbA1c increment effect size value but no 95% CI. The corresponding log-transformed 95% CI were estimated using the comparator (x,y) co-ordinate’s 95% CI as an estimate of overall statistical certainty, in lieu of linear regression calculated 95% CI.

The estimated 1% HbA1c increment log-transformed effect sizes (95% CI) within each of the four subgroups were then meta-analysed using a random-effects model in order to generate pooled effect sizes (95% CI) for each subgroup, as shown in **Supplementary Figure S11.**

Examples of linear regression assumption testing and linear regression log-transformed effect size (95% CI) method are shown in **Supplementary Figures S4-S5.**

Supplementary Table S1: The association between rising HbA1c levels and stroke risk in adults without diabetes mellitus

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Selvin [9] USA (2010)	ARIC Total=11092	45-64 yo (ARIC)	42.30%	14 yrs (median)	'White'= 77.6% 'Black'= 22.4%	First-ever **ischaemic** stroke	**Hazard ratios (95%CI)** Categorical HbA1c 5.0 to <5.5%= reference <5.0%= 1.09 (0.68,1.77) 5.5 to <6.0%= 1.16 (0.89,1.53) 6.0 to <6.5%= 2.19 (1.58,3.05)* ≥6.5%= 2.96 (1.87, 4.67)* 1% HbA1c increments = 1.55 (1.28,1.88)*	Age, sex, hypertension, HDL, LDL, log transformed TG, smoking status, BMI, WHR, ethnicity, family Hx DM, education status, alcohol consumption, physical activity, baseline FBG levels
Selvin [10] USA (2015)	ARIC Total= 11104 Diabetes= 762 Non-diabetes=10342	45-64 yo (ARIC)	Total= 41.4%	Total= 20 yrs	Total: 'White'= 76.6% 'Black'= 23.4%	First-ever **ischaemic** stroke	**Hazard ratios (95%CI)** Categorical HbA1c 5.7 to 6.4%= reference <5.7%= 0.74 (0.61,0.91)* >6.4%= 1.79 (1.31, 2.45)*	Age, sex, systolic BP, HDL, LDL, TG, smoking status, BMI, WHR, ethnicity, anti-hypertensive medications, parental Hx of DM, education status, alcohol consumption, physical activity
Selvin [11] USA (2013)	ARIC Total= 11077	45-64 yo (ARIC)	'White'= 44.3% 'Black'= 35.5%	Total= 18 yrs	'White'=77.58% 'Black'= 22.42%	First-ever stroke	**Hazard ratios (95%CI)** Categorical HbA1c <5.7%= reference 5.7% to <6.5%= 1.58 (1.23,2.03)*- 'white' 5.7% to <6.5%= 1.42 (1.02,1.97)*- 'black' ≥6.5%= 2.16 (1.38,3.37)*- 'white' ≥6.5%= 2.77 (1.81,4.23)*- 'black'	Age, sex, hypertension, HDL, LDL, log transformed TG, smoking status, BMI, WHR, family Hx DM, education status, alcohol use, physical activity
Karas [5] USA (2012)	Strong Heart Study Total= 2391	45-74 yo	Stroke patients = 43.3% Non-stroke patients = 45.5%	12 yrs (mean)	American Indians	First-ever **ischaemic** stroke	**Hazard ratios (95%CI)** Categorical HbA1c <6.5%= reference ≥6.5%= 1.50 (0.90, 2.51) 1 SD HbA1c increments =1.47 (1.21,1.78)* {1 SD= 1.4%}	Age, sex, systolic BP, HDL, LDL, smoking status, BMI, anti-hypertensive medications, diabetes status, serum creatinine, UACR, LA diameter, mitral annular calcification, HbA1c
Wang [12] USA (2011)	Strong Heart Study Total= 3850 Diabetes= 1386 Non-diabetes= 2464	45-74 yo	40%	15 yrs (median)	American Indians	First-ever stroke	**Hazard ratios (95%CI)** Categorical HbA1c <5.0%= reference 5.0 to <5.5%= 1.09 (0.68,1.74) 5.5 to <6.0%= 1.60 (1.00,2.57) 6.0 to <6.5%= 1.24 (0.61,2.53) ≥6.5%= 1.93 (1.06, 3.52)*	Age, sex, hypertension, systolic BP, HDL, LDL, smoking status, log urinary albumin:creatinine ratio, baseline FBG levels
Birkenhager-Gillesse [13] Netherlands (2015)	Leiden 85+ Study Total= 445	85-95 yo	35%	Total for fatal events= 10 yrs Total for non-fatal events = 5 yrs	Inhabitants of Leiden, Netherlands	First-ever stroke	**Hazard ratios (95%CI)** Categorical HbA1c 5.0 to 5.7%= reference <5.0%= 1.0 (0.4,2.8) 5.7 to 6.5%= 0.9 (0.4,2.0) HbA1c ~1% increments = 0.9 (0.5, 1.6)	Sex, systolic BP, total cholesterol, smoking status, BMI, AMI, stroke, cardiovascular disease at baseline (cardiac surgery, AMI, stroke), education status, living conditions, income, creatinine clearance, c-reactive protein, alcohol consumption

Supplementary Table S1 (continued)…

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Lawlor [14] UK (2007)	The British Women's Heart and Health Total= 3246	60-79 yo	0%	4.6 yrs (median)	British women, >99% 'white'	First-ever stroke	**Hazard ratios (95% CI)** 1 SD HbA1c increments = 1.02 (0.79,1.33) {1 SD= 0.83%}	Age, systolic BP, HDL, TG, LDL, smoking status, BMI, WHR, physical acitivity, socioeconomic status
Chen [15] Taiwan (2015)	Taiwan's Triple High Survey Total= 5277 Non-diabetes=4915 Diabetes= 362	≥18 yo	Non-diabetes patients = 46.5%	Total= 9.7 yrs (9.6-9.74) (median [IQR])	Taiwanese residents	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.34 (0.85,1.51)	Age, sex, systolic BP, TG, HDL, waist circumference, anti-hypertensives, lipid-lowering agents, anti-platelet drugs, anti-acid agents, family history of stroke, uric acid, creatinine
Goto [16] Japan (2015)	Japan Public Healthcare Study Total=29059 Non-diabetes=27279	40-69 yo	Stratified by HbA1c: <5.0%= 43.2% 5.0 to 5.4%= 36.3% 5.5 to 5.9%= 34.5% 6.0 to 6.4%= 39.5% ≥6.5%= 47.6%	9.4 yrs (median)	Japanese residents	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c 5.0 to 5.4%= reference <5.0%= 1.55 (1.17,2.05)* 5.5 to 5.9%= 0.99 (0.82,1.20) 6.0 to 6.4%= 0.97 (0.74, 1.26) ≥6.5%= 1.80 (1.30,2.50)*	Age, sex, systolic BP, non-HDL, HDL, smoking status, BMI, public health centre area, physical acitivity, alcohol consumption
Chonchol [17] USA (2010)	Cardiovascular Health Study Total=810	≥65 yo	41%	14.2 yrs (median)	'Black' participants by HbA1c %: ≤5.6%= 4% 5.61-6.20%= 6% ≥6.21%= 9%	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≤5.6%= reference 5.61 to 6.20%= 0.87 (0.54, 1.39) ≥6.21%= 1.08 (0.69, 1.70)	Age, gender, hypertension, LDL, smoking status, BMI, ethnicity, chronic kidney disease
Ikeda [18] Japan (2013)	Hisayama study Diabetes= 237 Non-diabetes=2614 Total= 2851	40-79 yo	Stratified by HbA1c: ≤5.0%= 46% 5.1 to 5.4%= 38.1% 5.5 to 6.4%= 41.9%	Total= 7 yrs	Japanese residents	First-ever **ischaemic** stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≤5.0%= reference 5.1 to 5.4%= 2.57 (0.91,7.29) 5.5 to 6.4%= 3.57 (1.27,10.0)*	Age, sex, hypertension, total cholesterol, HDL, smoking status, BMI, alcohol consumption, physical activity, ECG abnormalities
Myint [19] UK (2007)	EPIC-Norfolk Total= 10489	40-79 yo	Stratified by HbA1c: <5%= 42% 5 to 5.4%= 45% 5.5 to 6.9%= 46% ≥7.0%= 56%	8.5 yrs (mean)	British 99.6% 'white'	First-ever stroke	**Relative risk (95% CI)** Categorical HbA1c <5.0%= reference 5.0 to 5.4%= 0.78 (0.50, 1.22) 5.5 to 6.9%= 0.83 (0.54,1.27) ≥7.0%= 2.83 (1.40, 5.74)*	Age, sex, systolic BP, total cholesterol, TG, smoking status, BMI, AMI at baseline, alcohol consumption
Wu [20] China (2013)	ACROSS-China Total= 2186 Subgroup used =1540	Adults (mean age +/- SD = 64 +/- 11 yo in recurrent stroke patients, 61 +/- 12 yo in non stroke patients) **at 1 year**	Stroke patients = 54.2% Non-stroke patients = 62.3% **at 1 year**	Total= 1 yr	Chinese cohort	Recurrent stroke	**Hazard ratios (95% CI)** Categorical HbA1c <5.5%= reference 5.5 to <6.1%= 1.06 (0.35,3.23) 6.1 to <7.2%= 3.08 (1.10,8.64)* ≥7.2%= 3.31 (1.35,8.14)*	Age, gender, systolic and diastolic BP, HDL, LDL, TG, cholesterol, smoking status, BMI, waist circumference,coronary heart disease, hypertension, family Hx stroke, history of DM, ischemic stroke subtypes, OCSP subtypes, HOMA, antithrombotic agents, antihypertensive medications, lipid lowering medications, medication adherence, educational status, alcohol consumption, uric acid, homocysteine, creatinine, FBG

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants without diabetes mellitus within the source study. Covariates listed are those used in adjustment of results quoted. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *. Continuous results described as '1 SD' represent 1 standard deviation increment elevations in HbA1c. The SD value is shown in brackets provided. The descriptor 'stroke temporality' refers to the type of stroke outcome measured in the results presented for each study. DM= diabetes mellitus, CVD= cardiovascular disease, BP= blood pressure, LDL= low density lipoprotein, HDL= high density lipoprotein, TG= triglyceride, BMI= body mass index, WHR= waist-hip ratio, UACR= urinary albumin-creatinine ratio, FBG= fasting blood glucose, AMI= acute myocardial infarction, OCSP= Oxfordshire Community Stroke Project, HOMA= Homeostasis Model Assessment, LA= left atrium, ECG= electrocardiograph, Hx= history, yo= years old, IQR= interquartile range, yrs= years.

Supplementary Table S2: The association between rising HbA1c levels and stroke risk in adults with T1DM

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Stahl [21] Sweden (2016)	Swedish NDR Total= 33453	≥18 yo	55% in T1DM cohort	7.9 +/- 4.3 yrs (mean +/- SD)	Swedish diabetes patients	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≤6.9%= reference 7.0 to 7.8%= 1.30 (0.96,1.76) 7.9 to 8.7%= 1.96 (1.47,2.63)* 8.8 to 9.6%= 2.25 (1.64,3.08)* ≥9.7%= 3.61 (2.56,5.08)*	Age, sex, duration of DM, systolic BP, smoking status, BMI, atrial fibrillation, coronary heart disease, education status
Eeg-Olofsson [22] Sweden (2010)	Swedish NDR Total= 7454	20-65 yo	55.80%	4.95 yrs (mean)	Swedish diabetes patients	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c 5.0 to 7.9%= reference 8.0 to 11.9%= 1.40 (0.70,2.79) 1% HbA1c increments = 1.19 (0.86,1.66)	Age, sex, duration of DM, systolic BP, smoking status, BMI, total cholesterol, LDL, TG, history of CVD, albuminuria (>20 microg/min)
Hagg [23] Finland (2014)	FinnDiane Total= 4083	Adult mean age +/- SD = 37.4 +/- 11.8 yo	51.00%	9.0 +/- 2.7 yrs (mean +/- SD)	FinnDiane participants	First-ever stroke	**Hazard ratios (95% CI)** ~1% HbA1c increments = 1.16 (1.03,1.31)*	Sex, duration of DM, systolic and diastolic BP, TG, LDL, HDL, smoking status, waist circumference, coronary heart disease, diabetic nephropathy, severe diabetic retinopathy, anti-hypertensive medications, lipid lowering medications, aspirin

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants with T1DM within the source study. Covariates listed are those used in adjustment of results quoted. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *. The descriptor 'stroke temporality' refers to the type of stroke outcome measured in the results presented for each study. T1DM= type 1 diabetes mellitus, CVD= cardiovascular disease, BP= blood pressure, BMI= body mass index, WHR= waist-hip ratio, TG= triglyceride, HDL= high density lipoprotein, LDL= low density lipoprotein, DM= diabetes mellitus, yo= years old, SD= standard deviation, yrs= years.

Supplementary Table S3: The association between rising HbA1c levels and stroke risk in adults with T2DM

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Adler [24] UK (1999)	UKPDS 47 Total= 5102 For stroke analysis= 3670	25-65 yo	59%	10.3 yrs (median)	White caucasian= 83% Asian/Indian= 10% Afro-caribbean= 8%	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≤6.3%= reference >6.3 to ≤7.6 %= 1.2 (0.8,1.7) >7.6%= 1.1 (0.7,1.6)	Age, sex, diastolic BP only, total cholesterol, TG, HDL, smoking status, BMI, ethnicity, stroke history, physical acitivity, social class
Skriver [6] Denmark (2012)	Aarhus County Public data files Total=17760 For stroke analysis= 11747	Adult Median (IQR) age by HbA1c level: 67 (57-77) yo= <7% 65 (56-74) yo= ≥7%	Stratified by HbA1c: <7%= 50.4% ≥7%= 53.9%	2 yrs (median)	Danish residents	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c <7.0%= reference ≥7.0%= 1.00 (0.78,1.27)	Age, sex, duration of DM, prior hospital admission for CVD- (myocardial infarction, congestive heart failure, peripheral vascular disease and cerebrovascular disease represented prior cardiovascular disease) Non-cardiovascular diseases including; dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, hemiplegia,moderate to severe renal disease, diabetes with end-organ damage, any tumour, leukaemia, lymphoma, moderate or severe liver disease, metastatic solid tumour and AIDS
Kontopantelis [25] UK (2014)	UK CPRD Total= 246544	≥18 yo	Stratified based on year of inclusion in the study	Total= 6 yrs	English, Northern Irish, Welsh and Scottish participants	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≥6.25 to ≤6.75%= reference <6.25%= 1.169 (0.979,1.396) >6.75 to ≤7.25%= 1.084 (0.892,1.318) >7.25 to ≤7.75%= 1.205 (0.976,1.487) >7.75 to ≤8.25%= 1.366 (1.079,1.730)* >8.25%= 1.314 (1.072,1.611)*	Age, sex, systolic and diastolic BP, cholesterol, smoking status, BMI, history of macrovascular complications- (PVD, AMI, stroke, amputation), history of microvascular complications- (retinopathy, neuropathy, nephropathy, foot ulcer, CKD stage 4-5, foot ulcer), practice characteristics (diabetes prevalence, list size, region, area deprivation)
Freemantle [26] Multinational (EU, North America, Asia) (2016)	CREDIT Total=2999	>40 yo	51.20%	4.2 (3.5 - 4.4) yrs (median [IQR])	Median % from region: 24.5% North America 21.6% Eastern Europe 15.3% Southern Europe 17.0% France 8.4% Northern Europe 13.1% Japan	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.363 (1.168,1.591)*	Age, hypertension, history or presence of macrovascular disease
Kranenburg [27] Netherlands (2015)	SMART study Total= 1687 Hx CVD= 1156 No Hx CVD= 531	18-80 yo	No vascular disease group = 59.0%	6.1 (3.1 - 9.5) yrs (median [IQR])	Patients referred to the medical centre Utrecht	First-ever **ischaemic** stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.40 (1.01,1.94)*	Age, sex, duration of DM, systolic BP, smoking status, non-HDL level, modification of diet in renal disease
Lin [28] Taiwan (2014)	National Diabetes Care Management Program Total= 28354	≥30 yo	Stratified by HbA1c: <7.0%= 52.31% ≥7.0%= 45.22%	7.5 yrs (mean)	Ethnically Chinese participants	First-ever **ischaemic** stroke	**Hazard ratios (95% CI)** Categorical HbA1c <7.0%= reference 7.0 to 8.0%= 1.27 (1.13,1.43)* 8.0 to 9.0%= 1.55 (1.37,1.75)* ≥9.0%= 2.06 (1.85,2.31)*	Age and gender only

Supplementary Table S3 (continued)…

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Kong [7] China (2007)	Prince of Wales Hospital (Hong Kong) Total= 6386	Adult median (IQR) age =56 (46-67) yo	Stratified by number of treatment goals achieved	5.7 yrs (median)	Patients attending the Prince of Wales Hospital (Hong Kong)	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c ≥7.0%= reference <7.0%= 0.76 (0.58,0.99)*	Age and sex only
Zhao [29] USA (2014)	LSU Health Care Services Division Total=30154 Male= 9783 Female= 17422	Adult Mean +/- SD age by gender: male= 50.9 +/- 10.1 yo female= 51.48 +/- 10.1 yo	36.07%	6.7 yrs (mean)	African American (total): - Males= 56.1% - Females= 59.3%	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c 6.0 to 6.9%= reference <6.0%: male= 1.05 (0.88,1.26), female= 1.06 (0.93,1.21) 7.0 to 7.9%: male= 1.12 (0.94,1.33), female= 1.11 (0.97,1.27) 8.0 to 8.9%: male= 1.20 (0.98,1.46), female= 1.30 (1.12,1.52)* 9.0 to 9.9%: male= 1.23 (0.98,1.54), female= 1.41 (1.19,1.68)* ≥10.0%: male= 1.08 (0.86,1.36), female= 1.33 (1.11,1.59)* 1% HbA1c increments (male participants) = 1.02 (0.98,1.05) 1% HbA1c increments (female participants) = 1.06 (1.03,1.09)*	Age only
Cederholm [8] Sweden (2009)	Swedish NDR Total= 4753	30-70 yo	Stratified by BP and HbA1c groups	5.7 yrs (mean)	Swedish diabetes patients	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c 7.5 to 9.0% (BP:141-190/91-110)= reference <7.5% (BP ≤140/90)= 0.47 (0.36,0.63)*	Age and sex only
Giorda [30] Italy (2007)	DAI study Total= 14432 For stroke analysis = 11644	40-97 yo	48.20%	Total= 4 yrs	Italian cohort	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments Male participants= 1.27 (1.11,1.46)* Female participants= 1.07 (0.92,1.26)	Age only
Elley [31] New Zealand (2008)	Multicentre New Zealand cohort Total= 48444	Adult median age = 60 yo	49%	2.4 yrs (median)	49% European ethnicity	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.09 (1.04,1.13)*	Age, gender, duration of DM, systolic BP, total cholesterol:HDL ratio, smoking status, BMI, ethnicity, socio-economic status, urine albumin:creatinine ratio
Camafort [32] Spain (2011)	FRENA study Total= 974	Adult mean +/- SD age = 69 +/- 9 yo	59% (in stroke positive patients)	1.17 yrs (mean)	Patients attending FRENA study hospitals	**Ischaemic stroke** (first-ever and recurrent events)	**Relative risk (95% CI)** Categorical HbA1c ≥7.0%= reference <7.0%= 0.9 (0.4,1.9)	Age, gender, systolic BP, use of drugs, creatinine clearance levels, clinical presentation
Bots [33] Netherlands (2016)	SMART study Total= 1096	18-79 yo	76%	Total= 6.9 yrs for mortality and 6.4 yrs for vascular events	Patients referred to the medical centre Utrecht	**Ischaemic stroke** (first-ever and recurrent events)	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.09 (0.84,1.41)	Age, sex, duration of DM, systolic BP, non-HDL cholesterol, smoking status, eGFR (MDRD)
Hayashi [34] Japan (2013)	JCDM Total= 4014	Adult mean +/- SD age = 67.9 +/- 2.0 yo	Mean= 51.2%	Total= 5.5 yrs	Japanese participants	Stroke (first-ever and recurrent events)	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.001 (0.790,1.214)	Age, gender, duration of DM, systolic + diastolic BP, TG, LDL, HDL, FBG level

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants with T2DM within the source study. Covariates listed are those used in adjustment of results quoted. Results adjusted for hypoglycemic medication use were not selected. In these instances, the next most adjusted result(s) were selected. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *. The descriptor 'stroke temporality' refers to the type of stroke outcome measured in the results presented for each study.
T2DM= type 2 diabetes mellitus, CVD= cardiovascular disease, BP= blood pressure, LDL= low density lipoprotein, HDL= high density lipoprotein, TG= triglyceride, BMI= body mass index, WHR= waist-hip ratio, AIDS= Autoimmune Deficiency Syndrome, PVD= peripheral vascular disease, AMI= acute myocardial infarction, CKD= chronic kidney disease, eGFR (MDRD)= MDRD derived eGFR, FBG= fasting blood glucose, SD= standard deviation, IQR= interquartile range, yo= years old, yrs= years, Hx= history.

Supplementary Table S4: The association between rising HbA1c levels and stroke risk in mixed diabetes cohorts

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Stroke temporality	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Xu [35] China (2012)	Hong Kong EHS Total= 2137	≥65 yo	Gender by HbA1c % level: <6.5%= 40% 6.5 to 7.4%= 32.9% 7.5 to 8.4%= 32.7% >8.5%= 37.3%	7.9 yrs (mean)	Hong Kong residents involved in the EHS	First-ever stroke	**Hazard ratios (95% CI)** Categorical HbA1c 7.5 to 8.4%= reference <6.5%= 2.12 (0.85,5.31) 6.5 to 7.4%= 1.49 (0.64,3.49) ≥8.5%= 2.43 (1.06,5.55)* **1% HbA1c increments:** 4.4 to 6.4% HbA1c: 0.49 (0.26,0.95)* 6.5 to 15.5% HbA1c: 1.30 (1.01,1.68)*	Age, sex, mean arterial pressure, total cholesterol, smoking status, BMI, history of CVD- (defined as self-reported physician-diagnosed ischaemic heart disease, circulatory disease or peripheral vascular disease), alcohol consumption, exercise, educational status
Moss [36] USA (1994)	WESDR Total= 2366 Cohort for outcomes assessed= 1265	≥30 yo	45.6% (in cohort of interest)	8.3 yrs (median) (in cohort of interest)	98.6% 'white'	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.17 (1.05,1.30)*	Age, sex, hypertension, history of CVD
Chen [15] Taiwan (2015)	Taiwan's Triple High Survey Total= 5277 Non-diabetes= 4915 Diabetes= 362	≥18 yo	Diabetes patients = 50.8%	9.7 yrs (9.6-9.74) (median [IQR])	Taiwanese residents	First-ever stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.22 (1.04,1.44)*	Age, sex, systolic BP, TG, HDL, waist circumference, family history of stroke, uric acid, creatinine
Selvin [37] USA (2005)	ARIC Total= 2482 Diabetes= 1635	45-64 yo	Not detailed	9 yrs (mean)	Not detailed	First-ever **ischaemic** stroke	**Relative risk (95% CI)** Categorical HbA1c Cat.1 (median=5.0%)= reference Cat. 2(median=6.0%)= 1.17 (0.62,2.19) Cat. 3(median= 9.0%)= 2.33 (1.29,4.21)*	Age, sex, systolic and diastolic BP,HDL, LDL, smoking status, BMI, WHR, ethnicity, anti-hypertensive medication,educational status
Alter [38] USA (1997)	Lehigh Valley Stroke Cohort Total= 621 Non-diabetes= 423 Diabetes= 198	Adult diabetes mean +/- SD= 70 +/- 10.8 yo	47.5% in diabetes subgroup, 51.4% overall	2 yrs (mean)	95%= 'white' 1.7%= 'black' 3.3%= 'hispanic'	Recurrent stroke	**Hazard ratios (95% CI)** 1% HbA1c increments = 0.87 (0.623,1.219)	Age, sex, hypertension, AMI, cardiac arrythmia, TIA
Ashburner [39] USA (2016)	ATRIA Total= 2101 people with diabetes	≥18 yo	Stratified by HbA1c: <7%= 63.2% 7.0 to 8.9%= 60.4% ≥9.0%= 57.5%	2.48 +/- 2.23 yrs (mean +/- SD)	**<7%:** White=86.5%, Black=3.5%, Other=0.7%, Asian/Pacific Islander=6.2%, Hispanic=3.1% **7.0-8.9%:** White=85.7%,Black=5.1%, Other=0.6% Asian/Pacific Islander=6.4%, Hispanic=2.2% **≥9.0%:** White=78.6%, Black=7.8%, Other=0.8% Asian/Pacific Islander=9.2%, Hispanic=3.9%	**Ischaemic stroke** (first-ever and recurrent events)	**Hazard ratios (95% CI)** Categorical HbA1c <7.0%= reference 7.0 to 8.9%= 1.09 (0.75,1.60) >9.0%= 1.10 (0.70,1.72)	**Unadjusted result** used as adjusted result includes adjustment for insulin use
Hirai [40] USA (2008)	WESDR Total= 1370 Subgroup used = 1007	≥30 yo	44.90%	Total= 16 yrs	Wisconsin residents	Stroke (first-ever and recurrent events)	**Hazard ratios (95% CI)** 1% HbA1c increments = 1.08 (0.98,1.18)	Age and sex only

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants with diabetes mellitus (T1DM, T2DM or unspecified type) in the source study. Mixed diabetes participants include T1DM, T2DM and/or unspecified diabetes type. Covariates listed are those used in adjustment of results quoted. Results adjusted for hypoglycemic medication use were not selected. In these instances, the next most adjusted result(s) were selected. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *.The descriptor 'stroke temporality' refers to the type of stroke outcome measured in the results presented for each study. T1DM= type 1 diabetes mellitus, T2DM= type 2 diabetes mellitus, CVD= cardiovascular disease, BMI= body mass index, BP= blood pressure, TG= triglyceride, LDL= low density lipoprotein, HDL= high density lipoprotein, WHR= waist-hip ratio, TIA= transient ischaemic attack, AMI= acute myocardial infarction, SD= standard deviation, IQR= interquartile range, yo= years old, yrs= years.

Supplementary Table S5: Association between rising HbA1c levels and ischaemic stroke risk, in adults without diabetes mellitus

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Diabetes status of participants assessed	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Selvin [9] USA (2010)	ARIC Total=11092	45-64 yo (ARIC)	42.30%	14 yrs (median)	'White'= 77.6% 'Black'= 22.4%	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c 5.0 to <5.5%= reference <5.0%= 1.09 (0.68,1.77) 5.5 to <6.0%= 1.16 (0.89,1.53) 6.0 to <6.5%= 2.19 (1.58,3.05)* ≥6.5%= 2.96 (1.87, 4.67)* 1% HbA1c increments = 1.55 (1.28,1.88)*	Age, sex, hypertension, HDL, LDL, log transformed TG, smoking status, BMI, WHR, ethnicity, family Hx DM, education status, alcohol consumption, physical activity, baseline FBG levels
Selvin [10] USA (2015)	ARIC Total= 11104 Diabetes= 762 Non-diabetes=10342	45-64 yo (ARIC)	41.40%	Total= 20 yrs	'White'= 76.6% 'Black'= 23.4%	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c 5.7 to 6.4%= reference <5.7%= 0.74 (0.61,0.91)* >6.4%= 1.79 (1.31, 2.45)*	Age, sex, systolic BP, HDL, LDL, TG, smoking status, BMI, WHR, ethnicity, anti-hypertensive medications, parental Hx of DM, education status, alcohol consumption, physical activity
Selvin [11] USA (2013)	ARIC Total= 11077	45-64 yo (ARIC)	'White'= 44.3% 'Black'= 35.5%	Total= 18 yrs	'White'=77.58% 'Black'= 22.42%	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c <5.7%= reference 5.7% to <6.5%= 1.50 (1.14,1.97)*- 'white' 5.7% to <6.5%= 1.38 (0.97,1.96)- 'black' ≥6.5%= 2.13 (1.34,3.41)*- 'white' ≥6.5%= 2.80 (1.79,4.38)*- 'black'	Age, sex, hypertension, HDL, LDL, log transformed TG, smoking status, BMI, WHR, family Hx DM, education status, alcohol use, physical activity
Karas [5] USA (2012)	Strong Heart Study Total= 2391	45-74 yo	Stroke patients = 43.3% Non-stroke patients = 45.5%	12 yrs (mean)	American Indians	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c <6.5%= reference ≥6.5%= 1.50 (0.90, 2.51) 1 SD HbA1c increments =1.47 (1.21,1.78)* {1 SD= 1.4%}	Age, sex, systolic BP, HDL, LDL, smoking status, BMI, anti-hypertensive medications, diabetes status, serum creatinine, UACR, LA diameter, mitral annular calcification, HbA1c
Chen [15] Taiwan (2015)	Taiwan's Triple High Survey Total= 5277 Non-diabetes=4915 Diabetes= 362	≥18 yo	Non-diabetes = 46.5%	Total (median [IQR]) =9.7 yrs (9.6-9.74)	Taiwanese residents	Non-diabetes	**Hazard ratios (95% CI)** 1% HbA1c increments =1.40 (1.04,1.87)*	Age, sex, systolic BP, TG, HDL, waist circumference, anti-hypertensives, lipid-lowering agents, anti-platelet drugs, anti-acid agents, family history of stroke, uric acid, creatinine
Goto [16] Japan (2015)	Japan Public Healthcare Study Total=29059 Non-diabetes =27279	40-69 yo	Stratified by HbA1c: <5.0%= 43.2% 5 to 5.4%= 36.3% 5.5 to 5.9%= 34.5% 6.0 to 6.4%= 39.5% ≥6.5%= 47.6%	9.4 yrs (median)	Japanese residents	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c 5.0 to 5.4%= reference <5.0%= 1.47 (0.996,2.15) 5.5 to 5.9%= 1.00 (0.78,1.29) 6.0 to 6.4%= 1.06 (0.75,1.51) ≥6.5%= 2.29 (1.53,3.42)*	Age, sex, systolic BP, non-HDL, HDL, smoking status, BMI, public health centre area, physical acitivity, alcohol consumption
Ikeda [18] Japan (2013)	Hisayama study Diabetes= 237 Non-diabetes=2614 Total= 2851	40-79 yo	Stratified by HbA1c: ≤5.0%= 46% 5.1 to 5.4%= 38.1% 5.5 to 6.4%= 41.9% ≤6.5%= 47.1%	Total= 7 yrs	Japanese residents	Non-diabetes	**Hazard ratios (95% CI)** Categorical HbA1c ≤5.0%= reference 5.1 to 5.4%= 2.57 (0.91,7.29) 5.5 to 6.4%= 3.57 (1.27,10.0)*	Age, sex, hypertension, total cholesterol, HDL, smoking status, BMI, alcohol consumption, physical activity, ECG abnormalities

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants without diabetes mellitus within the source study. Covariates listed are those used in adjustment of results quoted. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *. Continuous results described as '1 SD' represent 1 standard deviation increment elevations in HbA1c. The SD value is shown in brackets provided. HDL= high density lipoprotein, LDL= low density lipoprotein, TG= triglyceride, BMI= body mass index, WHR= waist-hip ratio, DM= diabetes mellitus, FBG= fasting blood glucose, UACR= urinary albumin creatinine ratio, LA= left atrial, ECG= electrocardiograph, IQR= interquartile range, yrs= years, yo= years old, Hx= history.

Supplementary Table S6: Association between rising HbA1c levels and ischaemic stroke risk, in adults with diabetes mellitus

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Diabetes status of participants assessed	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Hagg [23] Finland (2014)	FinnDiane Total= 4083	Adult mean age +/- SD = 37.4 +/- 11.8 yo	51.00%	9.0 +/- 2.7 yrs (mean +/- SD)	FinnDiane participants	T1DM	**Hazard ratios (95%CI)** ~1% HbA1c increments = 1.21 (1.05,1.40)*	Sex, duration of DM, systolic and diastolic BP, TG, LDL, HDL, smoking status, waist circumference, coronary heart disease, diabetic nephropathy, severe diabetic retinopathy, anti-hypertensive medications, lipid lowering medications, aspirin
Chen [15] Taiwan (2015)	Taiwan's Triple High Survey Total= 5277 Non-diabetes= 4915 Diabetes= 362	≥18 yo	Diabetes patients = 50.8%	9.7 yrs (9.6-9.74) (median [IQR])	Taiwanese residents	Mixed diabetes cohort	**Hazard ratios (95%CI)** 1% HbA1c increments = 1.25 (1.01,1.54)*	Age, sex, systolic BP, TG, HDL, waist circumference, family history of stroke, uric acid, creatinine
Selvin [37] USA (2005)	ARIC Total= 2482 Diabetes= 1635	45-64 yo	Not detailed	9 yrs (mean)	Not detailed	Mixed diabetes cohort	**Relative risk (95%CI)** Categorical HbA1c Category 1 (median=5.0%)= reference Category 2 (median=6.0%) = 1.17 (0.62,2.19) Category 3 (median= 9.0%) = 2.33 (1.29,4.21)*	Age, sex, systolic and diastolic BP, HDL, LDL, smoking status, BMI, WHR, ethnicity, anti-hypertensive medication, educational status
Stahl [21] Sweden (2016)	Swedish NDR Total= 33453	≥18 yo	55% in T1DM cohort	7.9 +/- 4.3 yrs (mean +/- SD)	Swedish diabetes patients	T1DM	**Hazard ratios (95%CI)** Categorical HbA1c ≤6.9% = reference 7.0 to 7.8%= 1.20 (0.87,1.66) 7.9 to 8.7%= 1.92 (1.41,2.60)* 8.8 to 9.6%= 2.09 (1.50,2.92)* ≥9.7%= 3.27 (2.27,4.71)*	Age, sex, duration of DM, systolic BP, smoking status, BMI, atrial fibrillation, coronary heart disease, education status
Bots [33] Netherlands (2016)	SMART study Total= 1096	18-79 yo	76%	Total= 6.9 yrs for mortality and 6.4 yrs for vascular events	Patients referred to the medical centre Utrecht	T2DM	**Hazard ratios (95%CI)** 1% HbA1c increments = 1.09 (0.84,1.41)	Age, sex, duration of DM, systolic BP, non-HDL cholesterol, smoking status. eGFR (MDRD)
Kranenburg [27] Netherlands (2015)	SMART study Total= 1687 Hx CVD= 1156 No Hx CVD= 531	18-80 yo	No vascular disease group = 59.0%	6.1 (3.1 - 9.5) yrs (median [IQR])	Patients referred to the medical centre Utrecht	T2DM	**Hazard ratios (95%CI)** 1% HbA1c increments = 1.40 (1.01,1.94)*	Age, sex, duration of DM, systolic BP, smoking status, non-HDL level, modification of diet in renal disease

Supplementary Table S6 (continued)…

Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Diabetes status of participants assessed	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) presented
Camafort [32] Spain (2011)	FRENA study Total= 974	Adult mean +/- SD age = 69 +/- 9 yo	59% (in stroke patients)	1.17 yrs (mean)	Patients attending FRENA study hospitals	T2DM	**Relative risk (95% CI)** Categorical HbA1c ≥7.0%= reference <7.0%= 0.9 (0.4,1.9)	Age, gender, systolic BP, use of drugs, creatinine clearance levels, clinical presentation
Lin [28] Taiwan (2014)	National Diabetes Care Management Program Total= 28354	≥30 yo	Stratified by HbA1c: <7.0%= 52.31% ≥7.0%= 45.22%	7.5 yrs (mean)	Ethnically Chinese participants	T2DM	**Hazard ratios (95% CI)** Categorical HbA1c <7.0%= reference 7.0 to 8.0%= 1.27 (1.13,1.43)* 8.0 to 9.0%= 1.55 (1.37,1.75)* ≥9.0%= 2.06 (1.85,2.31)*	Age and gender only
Ashburner [39] USA (2016)	ATRIA Total= 2101 people with diabetes	≥18 yo	Stratified by HbA1c: <7%= 63.2% 7.0 to 8.9%= 60.4% ≥9.0%= 57.5%	2.48 +/- 2.23 yrs (mean +/- SD)	**<7%:** White=86.5%, Black=3.5%, Other=0.7%, Asian/Pacific Islander=6.2%, Hispanic=3.1% **7.0-8.9%:** White=85.7%,Black=5.1%, Other=0.6% Asian/Pacific Islander=6.4%, Hispanic=2.2% **≥9.0%:** White=78.6%, Black=7.8%, Other=0.8% Asian/Pacific Islander=9.2%, Hispanic=3.9%	Mixed diabetes cohort	**Hazard ratios (95% CI)** Categorical HbA1c <7.0%= reference 7.0 to 8.9%= 1.09 (0.75,1.60) >9.0%= 1.10 (0.70,1.72)	**Unadjusted result** used as adjusted result includes adjustment for insulin use

Results presented represent the most adjusted hazard ratios (HR) or risk ratios (RR, relative risk) available in the source literature. Results presented only apply to participants with diabetes mellitus (T1DM, T2DM or unspecified type) in the source study. Mixed diabetes cohorts include T1DM, T2DM and/or unspecified diabetes type. Covariates listed are those used in adjustment of results quoted. Results adjusted for hypoglycaemic medication use were not selected. In these instances, the next most adjusted result(s) were selected. Where available, both continuous and categorical HR or RR data was included for each study. Statistically significant results are identified with *. T1DM= type 1 diabetes mellitus, T2DM= type 2 diabetes mellitus, BP= blood pressure, TG= triglyceride, LDL= low density lipoprotein, HDL= high density lipoprotein, BMI= body mass index, WHR= waist-hip ratio, eGFR= estimated glomerular filtration rate, Hx= history, yo= years old, yrs= years, SD= standard deviation, IQR= interquartile range.

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☐	6	cerebral hemorrhage.tw.	3617	Advanced	Display Results | More ▾	🗨
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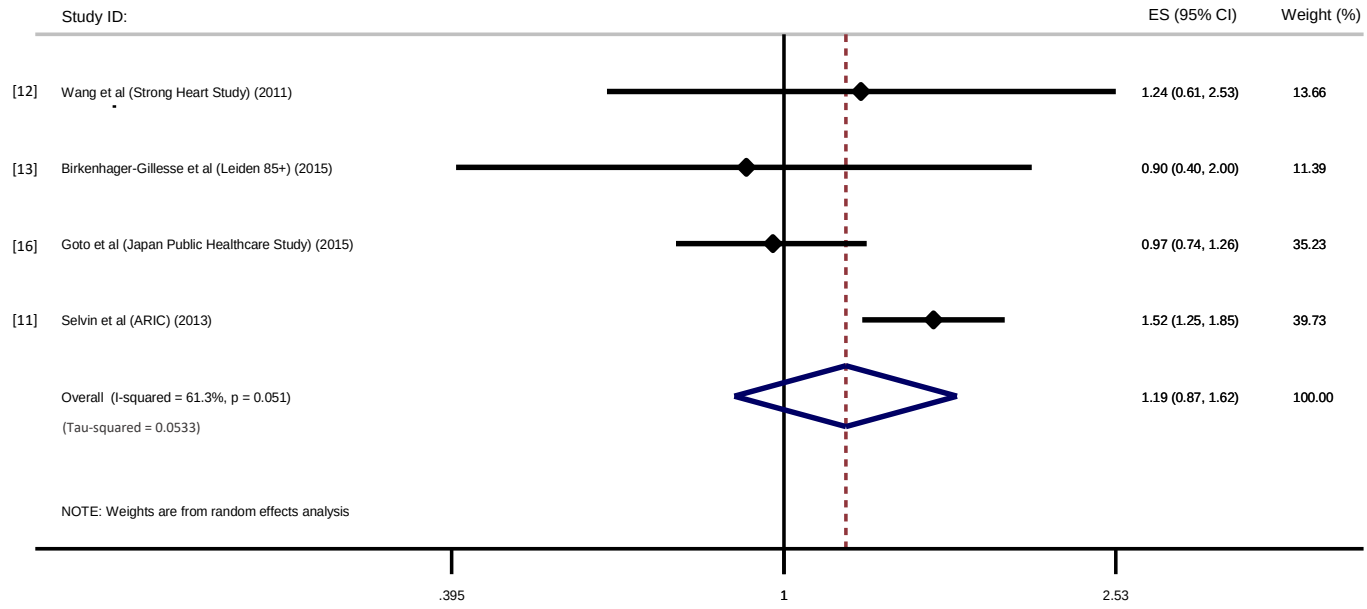
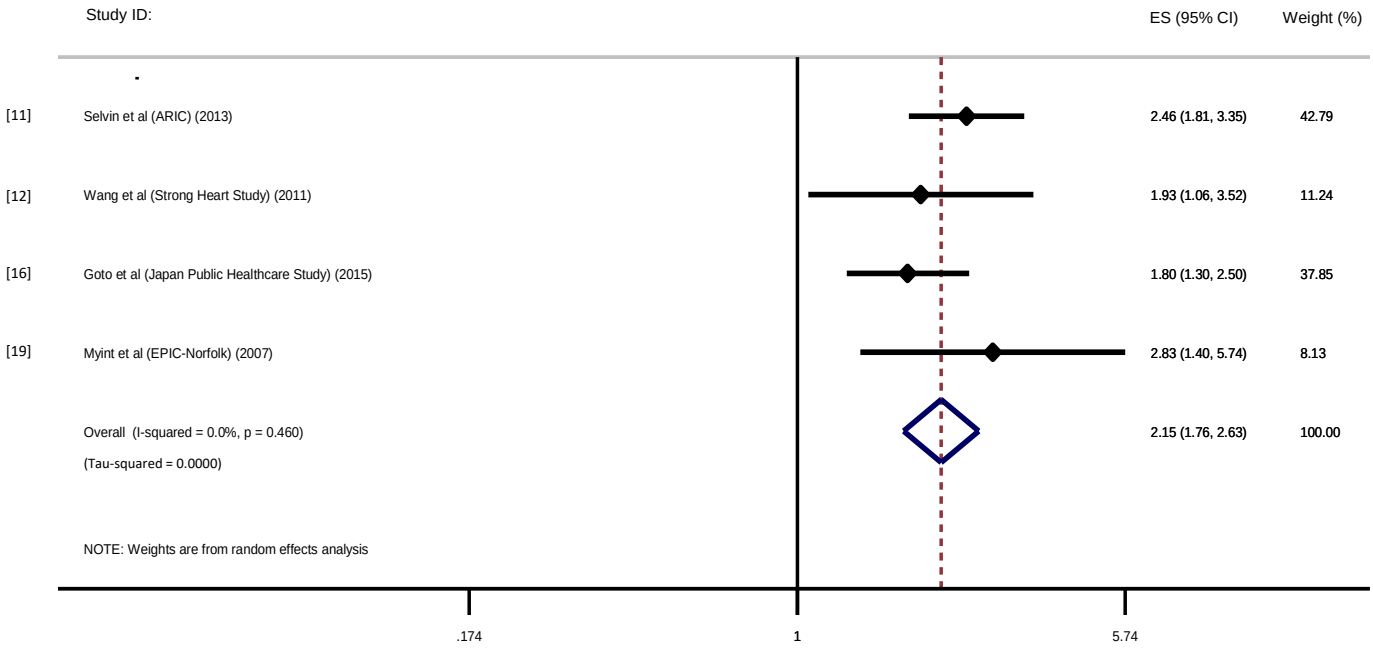
Supplementary Figure S1: Summary of search terms and Boolean operators used within the search strategy in MEDLINE

Search terms including MeSH and text-word terms together with Boolean operators, 'explosion' functions and filters applied are described. After filtering for human only studies a total of 1,123 results were obtained from the MEDLINE search. Search results depicted reflect the most recent (repeat) search performed on 5th Mar 2017. Synonymous searches were performed in the remaining four databases. Two searches using the same search strategy (as depicted above) were performed across all five databases, on 7th Feb 2017 and 5th Mar 2017, for completeness.



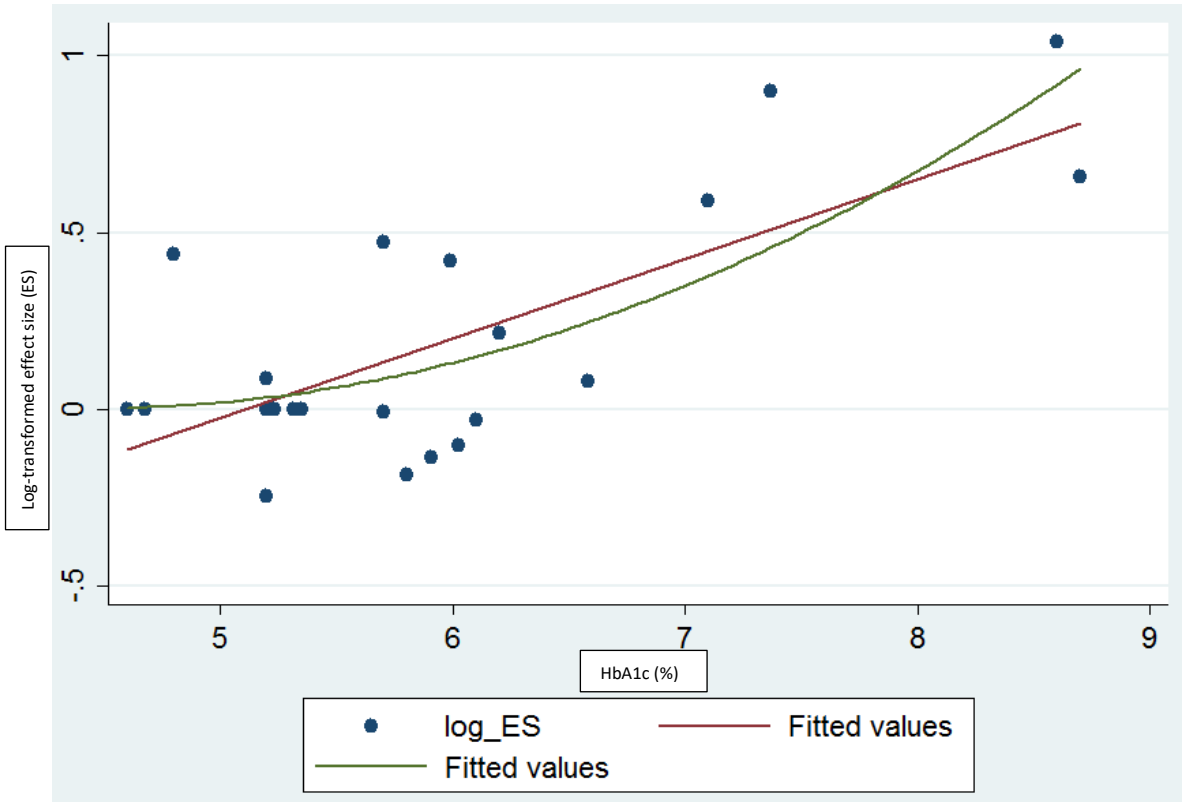
Supplementary Figure S2: Association between ADA-defined pre-diabetes range HbA1c (5.7%-6.5%) and first-ever stroke risk

Studies which used a reference category of HbA1c within the non-diabetes range (<5.7%) and a comparator range of HbA1c within pre-diabetes range HbA1c (5.7%-6.5%) were included within random-effects model meta-analysis performed. Pooled meta-analytical effect sizes (ES) (95% CI) presented reflect meta-analytical generated hazard ratios (HR) (95% CI). Risk ratio (RR, relative risk) data were treated as equivalent to hazard ratios (HR). Weights (%) used in the meta-analysis were generated using an inverse-variance method. The reference category used (ES=1.0) reflects non-diabetes range HbA1c (<5.7%).



Supplementary Figure S3: Association between ADA-defined diabetes range HbA1c (≥6.5%) and first-ever stroke risk

Studies which used a reference category of HbA1c within the non-diabetes range (<5.7%) and a comparator range of HbA1c within diabetes range HbA1c (≥6.5%) were included within random-effects model meta-analysis performed. Pooled meta-analytical effect sizes (ES) (95% CI) presented reflect meta-analytical generated hazard ratios (HR) (95% CI). Risk ratio (RR, relative risk) data were treated as equivalent to hazard ratios (HR). Weights (%) used in the meta-analysis were generated using an inverse-variance method. The reference category used (ES=1.0) reflects non-diabetes range HbA1c (<5.7%).




```
. regress log_ES HbA1c
```

Source	SS	df	MS	Number of obs	=	23
				F(1, 21)	=	23.69
Model	1.4259195	1	1.4259195	Prob > F	=	0.0001
Residual	1.26411504	21	.060195954	R-squared	=	0.5301
				Adj R-squared	=	0.5077
Total	2.69003454	22	.122274297	Root MSE	=	.24535

log_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
HbA1c	.225322	.0462956	4.87	0.000	.129045	.3215989
_cons	-1.150402	.2783665	-4.13	0.000	-1.729297	-.5715076

Supplementary Figure S4: Linear regression analysis used to confirm linear hypothesis used in estimation of 1% HbA1c data

Studies presenting data for the association between inter-categorical HbA1c(%) elevations and first-ever stroke risk, in non-diabetes cohorts, were used. Risk ratios (RR, relative risk) were treated as equivalent to hazard ratios (HR). A series of (x,y) co-ordinates (HbA1c point value, In(HR)) were generated and used within linear regression analysis demonstrated. Significance for linear fit was set at $p<0.05$. A two-way graph was constructed to visually assess the linear regression fit for the data set. log-transformed HR (95% CI) = natural logarithm (In) transformed HR (95% CI).

-> Study = Selvin et al 2013 (ARIC)

Source	SS	df	MS	Number of obs	=	3
				F(1, 1)	=	41.37
Model	.396617203	1	.396617203	Prob > F	=	0.0982
Residual	.009586536	1	.009586536	R-squared	=	0.9764
				Adj R-squared	=	0.9528
Total	.406203739	2	.20310187	Root MSE	=	.09791

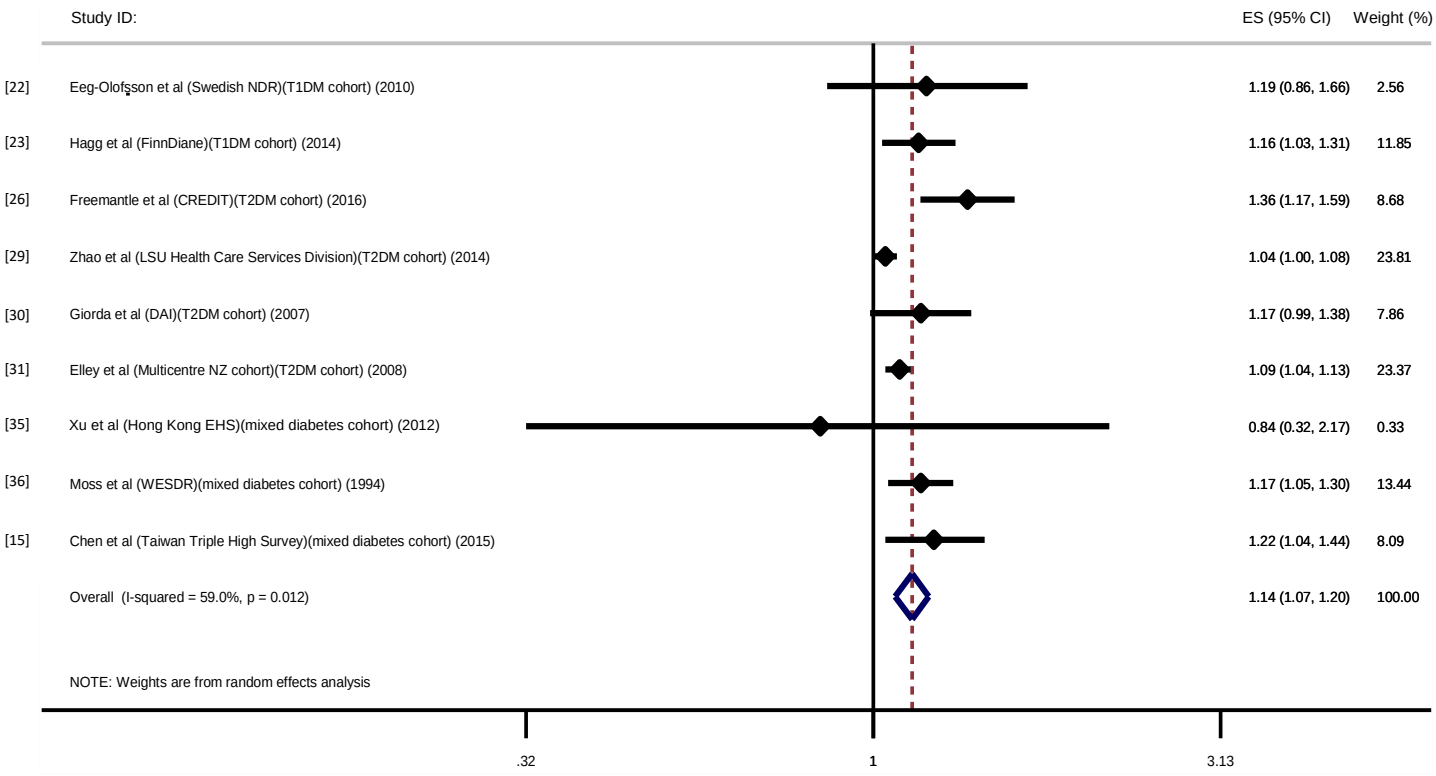
log_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
HbA1c	.4251409	.0660964	6.43	0.098	-.4146938	1.264975
_cons	-2.206962	.4153153	-5.31	0.118	-7.484043	3.070119

Log-transformed effect size (95% CI)= 0.425 (-0.415,1.265)

Exponentiated effect size (95% CI)= 1.53 (0.66,3.54)

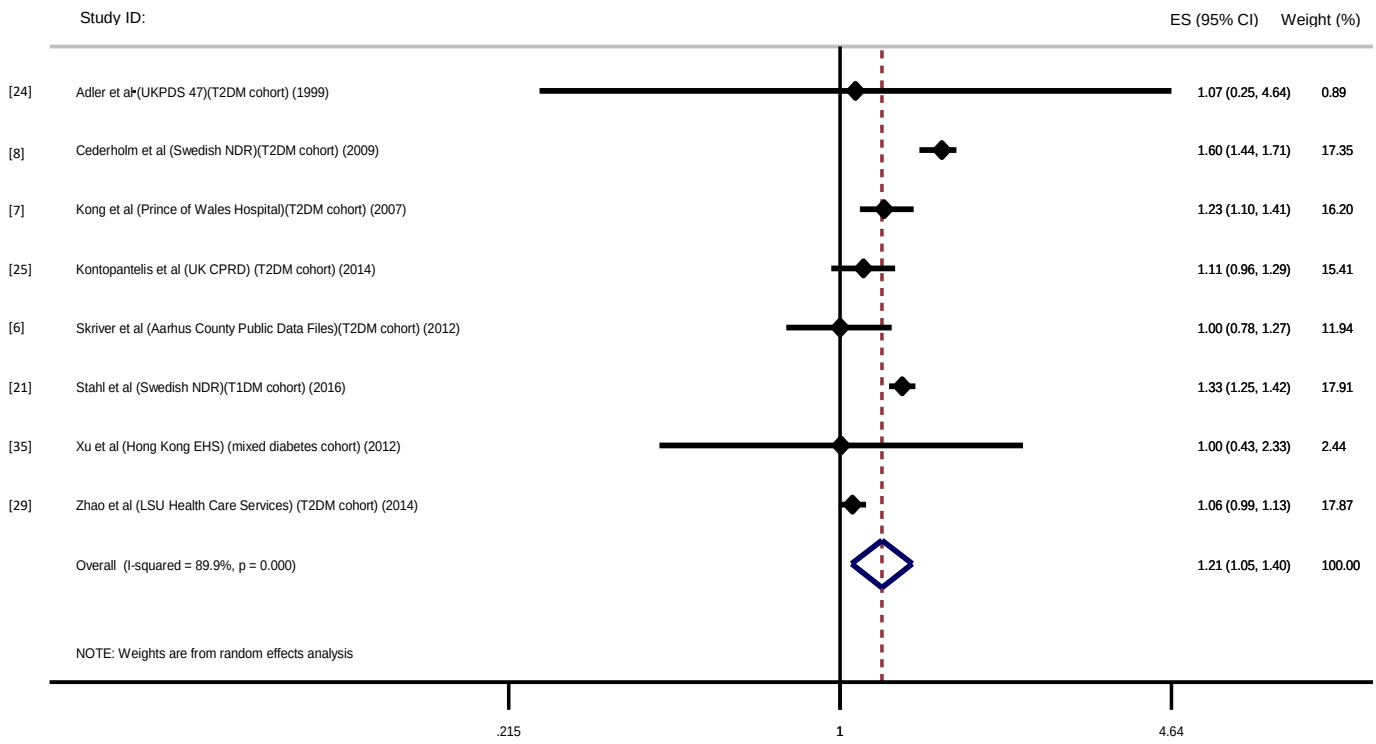
Supplementary Figure S5: 1% HbA1c increment effect size (95% CI) estimation method using the example of Selvin [11]

Inter-categorical HR (95% CI) data presented in Selvin [11] were extrapolated and used to create a series of (x,y) co-ordinates corresponding to (HbA1c point value, In(HR)). A linear regression model was used to calculate the natural logarithm values corresponding to estimated 1% HbA1c increment In(HR) and In(95% CI), as shown above. These values were then used in ensuing random-effects model meta-analyses and sensitivity analyses. log-transformed HR (95% CI)= natural logarithm (In) transformed HR (95% CI).



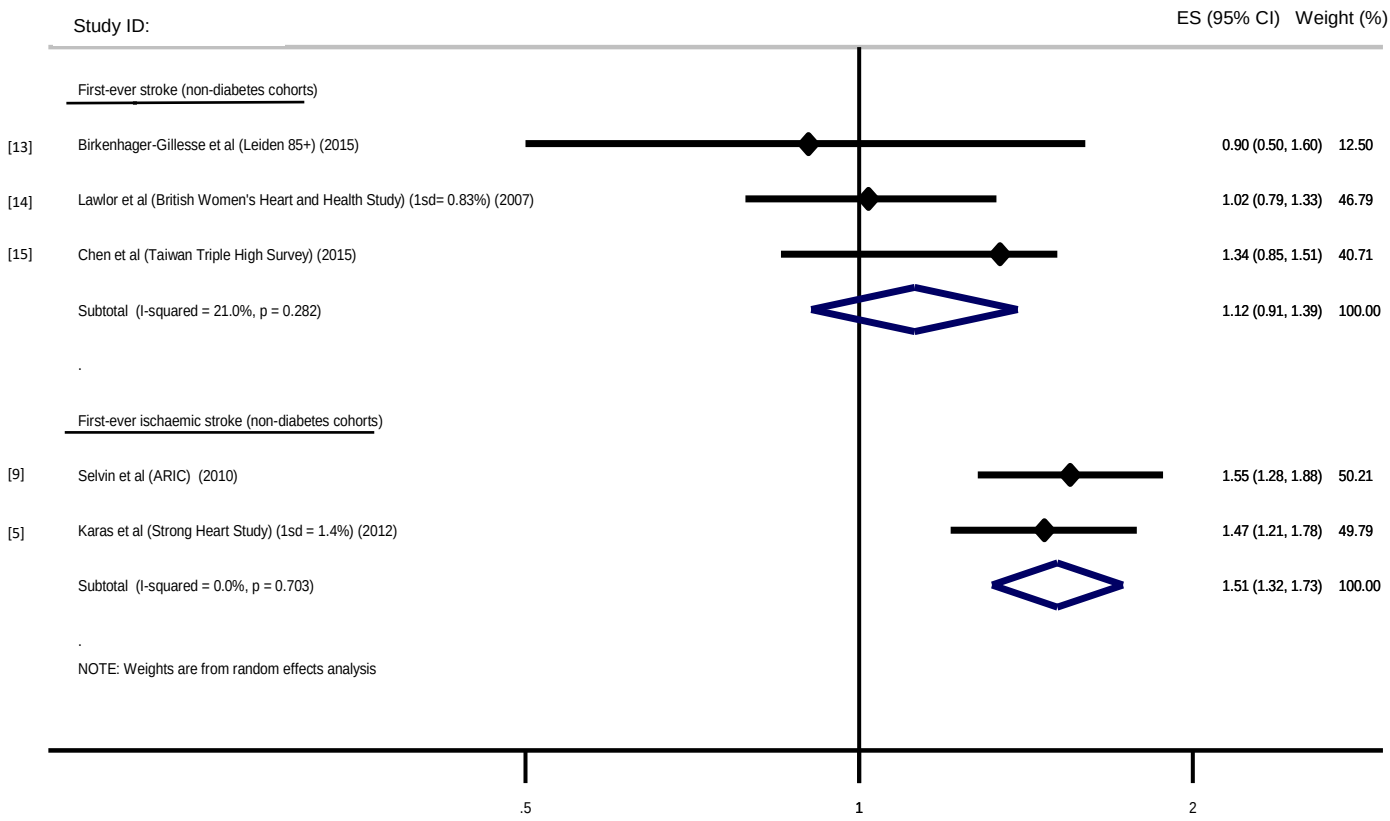
Supplementary Figure S6: Sensitivity analysis for inadequate covariate adjustment in study-quoted 1% HbA1c increment data

A moderate I^2 statistic was calculated when all available diabetes cohort studies examining a first-ever stroke outcome were included within random-effects meta-analysis, as shown (I^2=59.0%, p=0.012). Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio (HR) data. Weights (%) were calculated using the inverse-variance method. Exclusion of studies with very limited covariate adjustment use in covariate-adjusted effect size calculation (Zhao [29] and Giorda [30]) resulted in a reduction in I^2 statistic magnitude (from moderate to low) without significantly altering the meta-analytical effect sizes (ES[95% CI]= 1.17 [1.09,1.25], I^2=41.9% [p=0.111]). Effect sizes (ES) represent hazard ratios (HR). T1DM= type 1 diabetes, T2DM= type 2 diabetes, mixed diabetes= type 1 or type 2 diabetes.



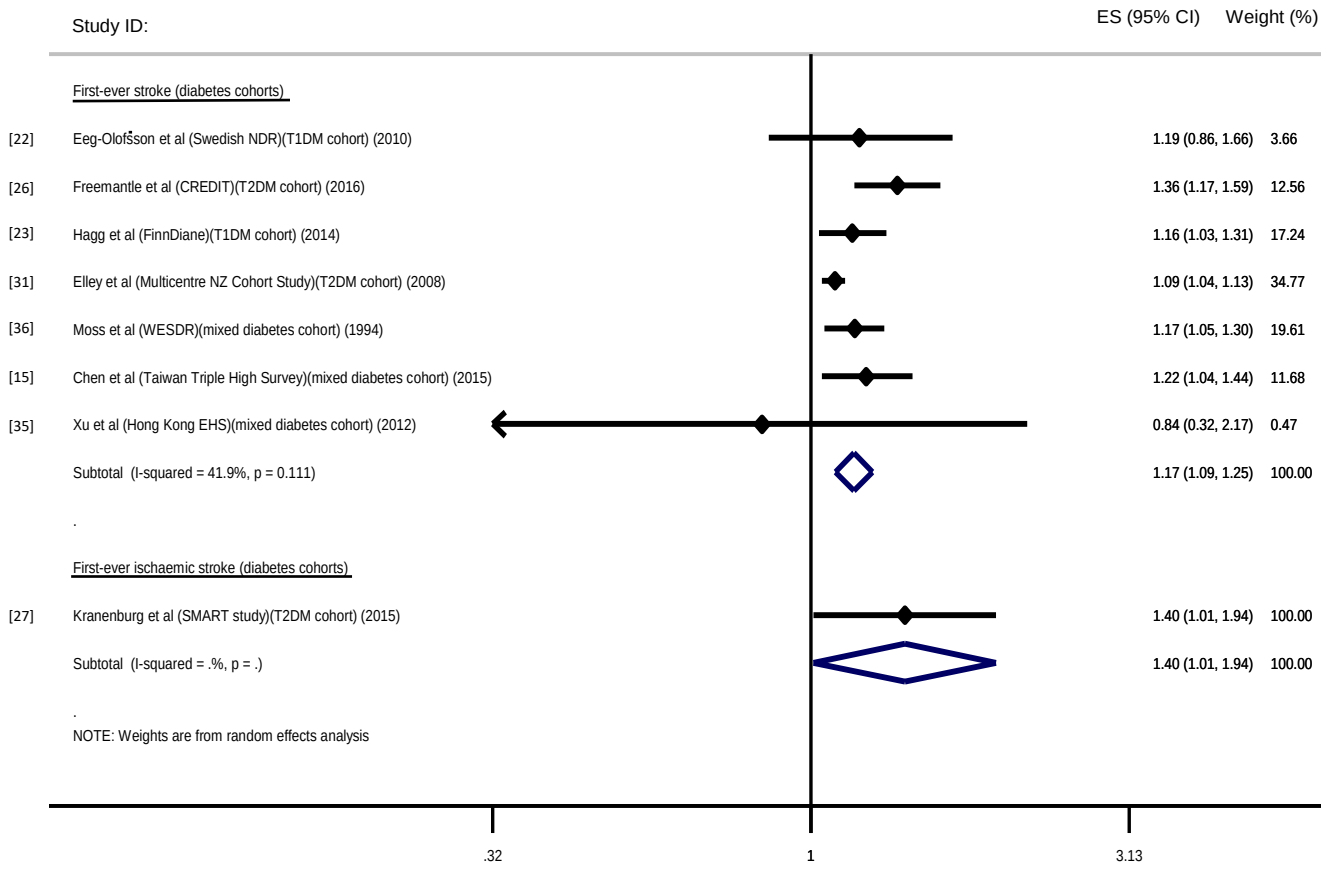
Supplementary Figure S7: Sensitivity analysis for inadequate covariate adjustment in estimated 1% HbA1c increment data

A high I^2 statistic value was present when all available diabetes cohort studies examining a first-ever stroke outcome were included within random-effects meta-analysis, as shown (I^2=89.9%, p<0.001). Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio (HR) data. Weights (%) were calculated using the inverse-variance method. Exclusion of studies with very limited covariate adjustment use in covariate-adjusted effect size calculation (Kong [7], Zhao [29], Cederholm [8]) resulted in a reduction in the I^2 statistic value (from high to moderate) without significantly altering the meta-analytical effect sizes (ES[95% CI]= 1.17 [1.01,1.36], I^2=57.7% [p=0.051]). Effect sizes (ES) represent hazard ratios (HR). T1DM= type 1 diabetes, T2DM= type 2 diabetes, mixed diabetes= type 1 or type 2 diabetes.



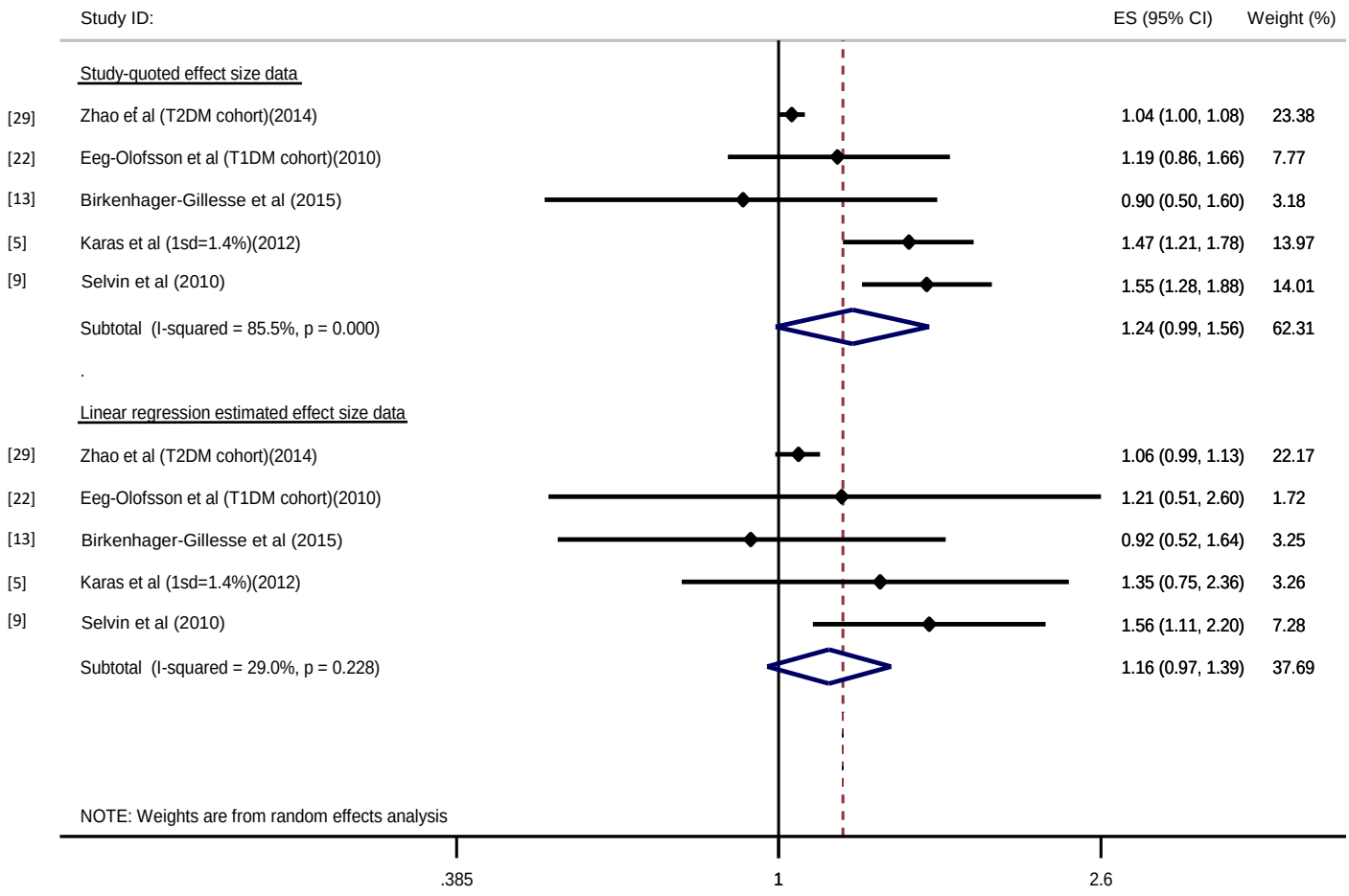
Supplementary Figure S8: Comparison of study-quoted 1% HbA1c increment first-ever stroke and first-ever ischaemic stroke effects sizes, in non-diabetes cohorts

Studies presenting 1% HbA1c increment data (or equivalent) for the association with first-ever stroke and first-ever ischaemic stroke outcomes, in non-diabetes cohorts, were used to assess the importance of ischaemic stroke subtype stratification on random-effects model meta-analytical outcomes derived. Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio (HR) data. 1 standard deviation data (1sd) was treated as equivalent to 1% HbA1c data. Effect sizes (ES) represent hazard ratios (HR).



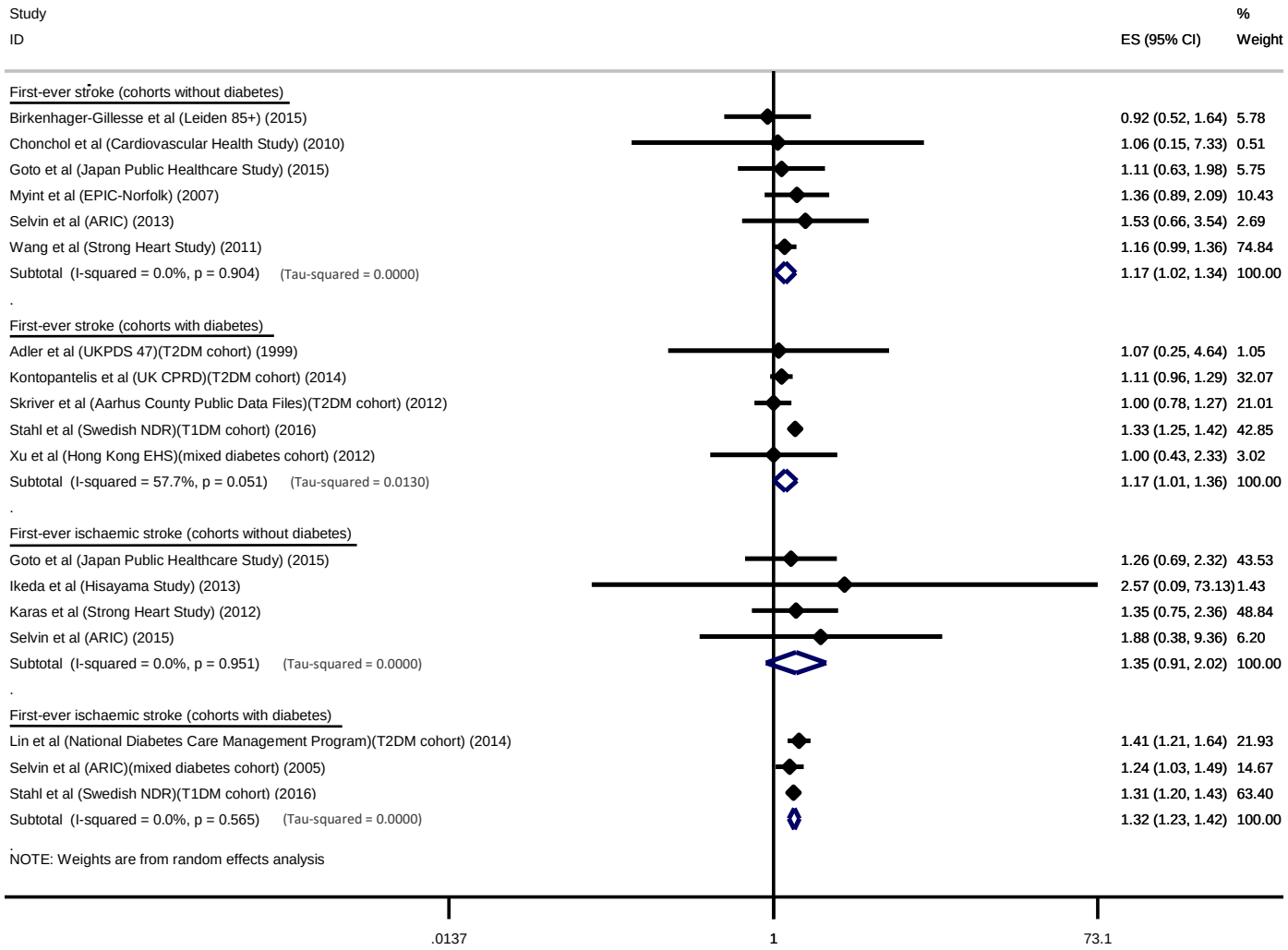
Supplementary Figure S9: Comparison of study-quoted 1% HbA1c increment first-ever stroke and first-ever ischaemic stroke effects sizes, in diabetes cohorts

Studies presenting 1% HbA1c increment data (or equivalent) for the association with first-ever stroke and first-ever ischaemic stroke outcomes, in diabetes cohorts, were used to assess the importance of ischaemic stroke subtype stratification on random-effects model meta-analytical outcomes derived. Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio (HR) data. Effect sizes (ES) represent hazard ratios (HR). T1DM= type 1 diabetes, T2DM= type 2 diabetes and mixed diabetes = T1DM or T2DM cohorts.



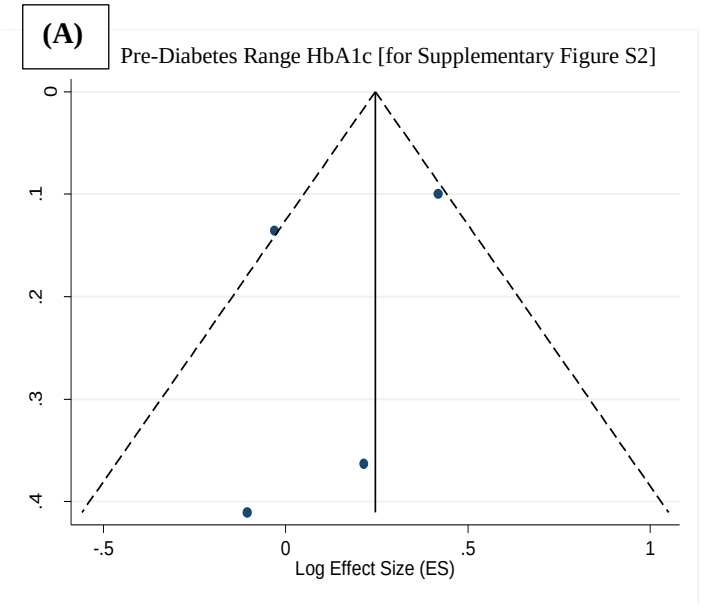
Supplementary Figure S10: Comparison of study-quoted and linear regression estimated 1% HbA1c effect size data

Studies presenting continuous (1% increment or equivalent) and categorical HbA1c(%) effect size data were used to assess the accuracy of the linear regression estimation method used in estimated 1% HbA1c increment meta-analysis for the association with first-ever stroke. Estimated 1% HbA1c increment effect sizes were calculated and compared to reported 1% HbA1c increment effect sizes, through independent random-effects model meta-analyses. Risk ratio (RR, relative risk) data was treated as hazard ratio (HR) data. 1 standard deviation (1sd) HbA1c increment data was treated as equivalent to 1% HbA1c increment data. Effect sizes (ES) represent hazard ratios (HR). T1DM= type 1 diabetes and T2DM= type 2 diabetes.



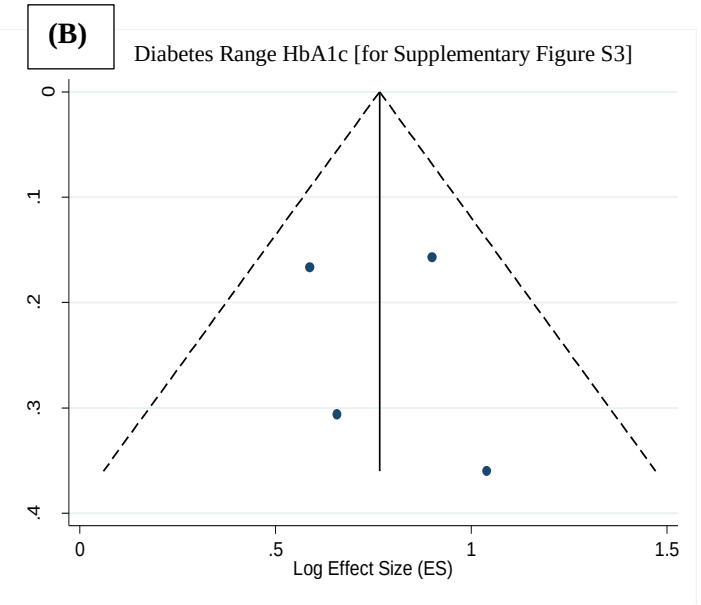
Supplementary Figure S11: Association between linear regression estimated rising 1% HbA1c increments and stratified first-ever stroke risk

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising categorical range HbA1c(%) and first-ever stroke risk were used in the estimation of rising 1% HbA1c increment effect sizes. Effect sizes (ES) (95% CI) derived from random-effects model meta-analysis within each subgroup analysis represent hazard ratios (HR) (95% CI). Using a linearity assumption for the continuous relationship between HbA1c(%) and first-ever stroke risk, linear regression analyses were performed using log-transformed effect size (95% CI) data, in order to calculate estimated 1% HbA1c increment effect size (95% CI) equivalents from inter-categorical HbA1c data. Studies were stratified based on the diabetes status of their cohorts and their restriction of first-ever stroke to an ischaemic stroke subtype. The outcome 'first-ever stroke' only included studies which did not restrict their stroke outcome to first-ever ischaemic stroke. The outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Diabetes cohorts included studies which measured type 1 diabetes, type 2 diabetes or a combination of both. Non-diabetes cohorts represented studies which either used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes. Pooled effect sizes (95% CI) are shown for each outcome subgroup. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled-effect sizes (ES) (95% CI) for each subgroup presented. ES=1.0 indicates no statistically significant association between rising 1% HbA1c increment in the subgroup analysis performed. Studies, identified through sensitivity analyses, which resulted in higher magnitude I^2 statistic values due to insufficient covariate adjustment [7,8,29] were excluded from the analyses presented. T1DM= type 1 diabetes mellitus, T2DM= type 2 diabetes mellitus, mixed diabetes cohort= cohort with type 1 and type 2 diabetes mellitus participants.



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.4185779	.2779831	1.51	0.271	-.7774867	1.614642
bias	-1.285685	1.800184	-0.71	0.549	-9.03125	6.459881

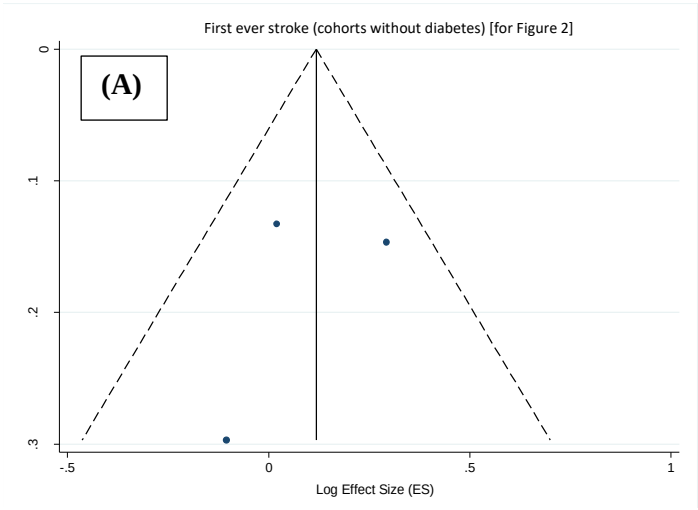


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.6778805	.3498638	1.94	0.192	-.8274619	2.183223
bias	.4538893	1.703781	0.27	0.815	-6.876889	7.784668

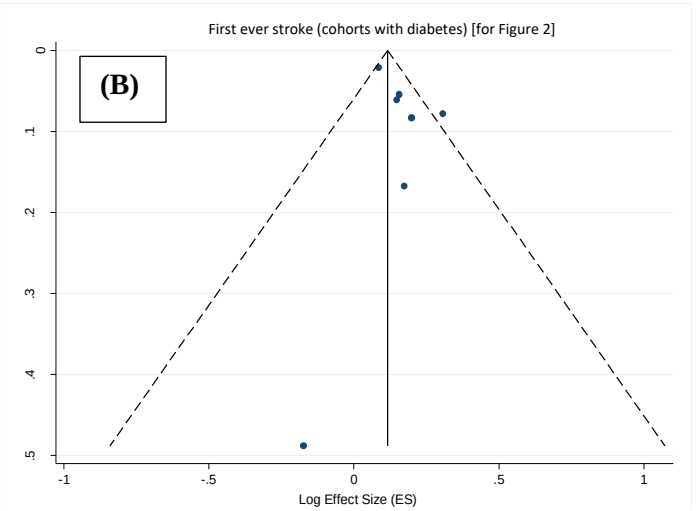
Supplementary Figure S12: Publication bias assessment for inter-categorical meta-analyses within Supplementary Figures S2-S3

Funnel plots with their corresponding Egger's results are presented for each of the inter-categorical ADA defined HbA1c meta-analyses within Supplementary Figures S2-S3. Funnel plot **(A)** and the corresponding Egger's test result corresponds to the inter-categorical analysis examining the risk of first-ever stroke when comparing pre-diabetes range HbA1c (5.7%-6.5%) to non-diabetes range HbA1c (<5.7%) (Supplementary Figure S2). Funnel plot **(B)** and the corresponding Egger's test result corresponds to the inter-categorical analysis examining the risk of first-ever stroke when comparing diabetes range HbA1c (≥6.5%) to non-diabetes range HbA1c (<5.7%) (Supplementary Figure S3). Significance for funnel plot asymmetry was set at $p<0.05$ for the Egger's bias result shown. Log Effect Size (ES)= natural logarithm of effect sizes.



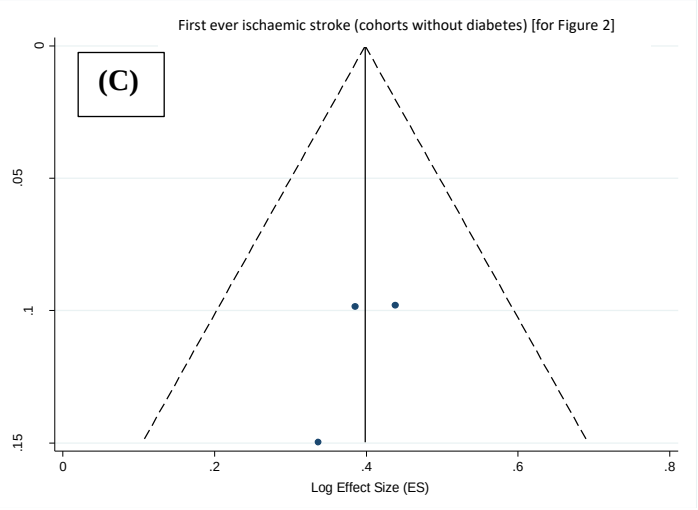
Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.3003079	.4687805	0.64	0.637	-5.656114	6.256729
bias	-1.176709	2.896373	-0.41	0.754	-37.97862	35.6252



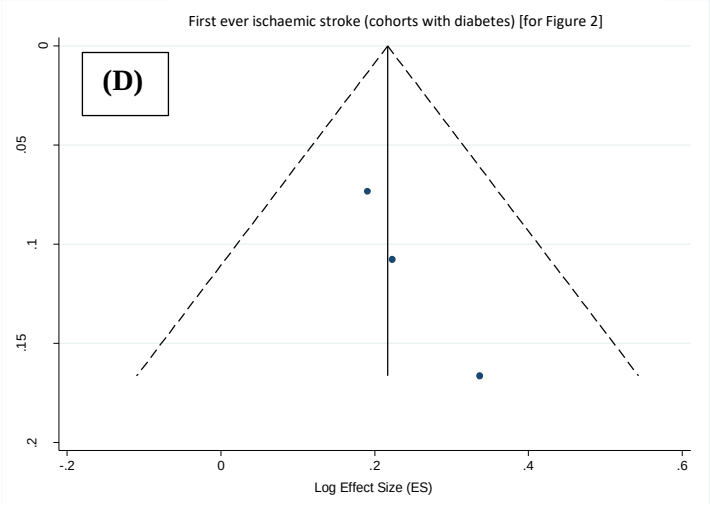
Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0773881	.0328034	2.36	0.065	-.0069356	.1617118
bias	1.071147	.6993229	1.53	0.186	-.7265197	2.868814



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.5571949	.1321119	4.22	0.148	-1.121447	2.235836
bias	-1.477859	1.210233	-1.22	0.437	-16.85533	13.89961

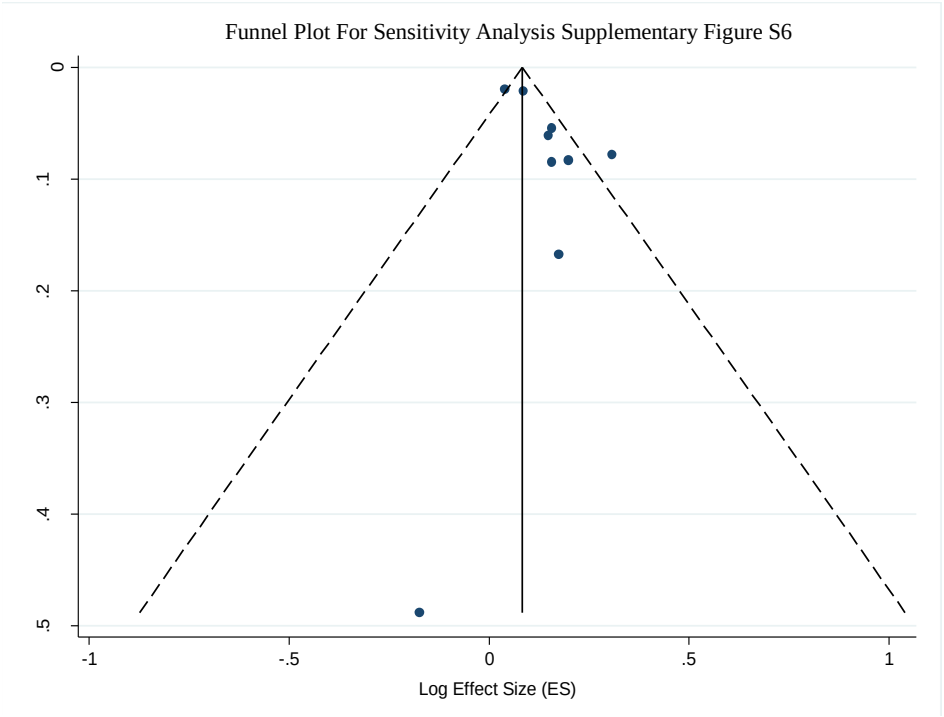


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0780188	.0294887	2.65	0.230	-.2966701	.4527077
bias	1.478332	.2988326	4.95	0.127	-2.318696	5.27536

Supplementary Figure S13: Publication bias assessment for subgroup meta-analyses within Figure 2

Funnel plots with their corresponding Egger's results are presented for each of the subgroup meta-analyses presented within Figure 2. Funnel plot **(A)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever stroke (cohorts without diabetes)'. Funnel plot **(B)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever stroke (cohorts with diabetes)'. Funnel plot **(C)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever ischaemic stroke (cohorts without diabetes)'. Funnel plot **(D)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever ischaemic stroke (cohorts with diabetes)'. Significance for funnel plot asymmetry was set at $p<0.05$ for the Egger's bias results shown. Log Effect Size (ES)= natural logarithm of effect sizes.

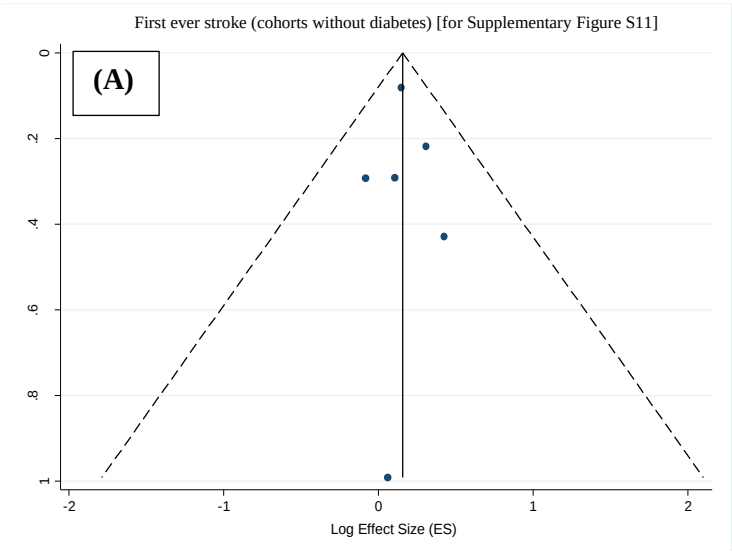


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.038861	.0259898	1.50	0.179	-.0225951	.1003172
bias	1.481164	.6662809	2.22	0.062	-.0943401	3.056668

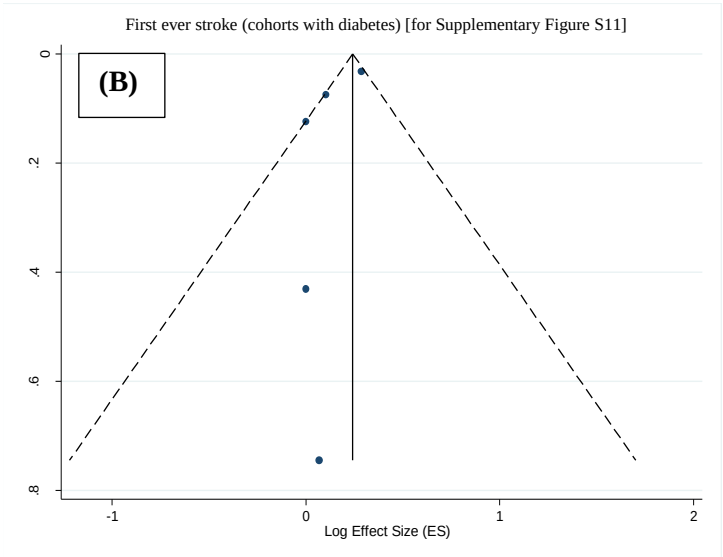
Supplementary Figure S14: Publication bias assessment for sensitivity analysis within Supplementary Figure S6

The funnel plot and its corresponding Egger's results are shown for the sensitivity analysis presented within Supplementary Figure S6. Significance for funnel plot asymmetry was set at $p<0.05$ for the Egger's bias result shown. Log Effect Size (ES)= natural logarithm of effect sizes.



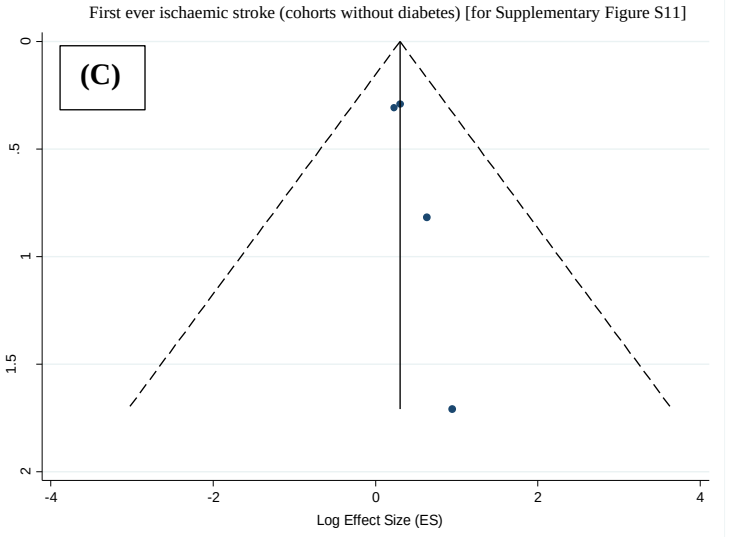
Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.1484285	.0701057	2.12	0.102	-.046216	.343073
bias	.0572481	.4080872	0.14	0.895	-1.075784	1.19028



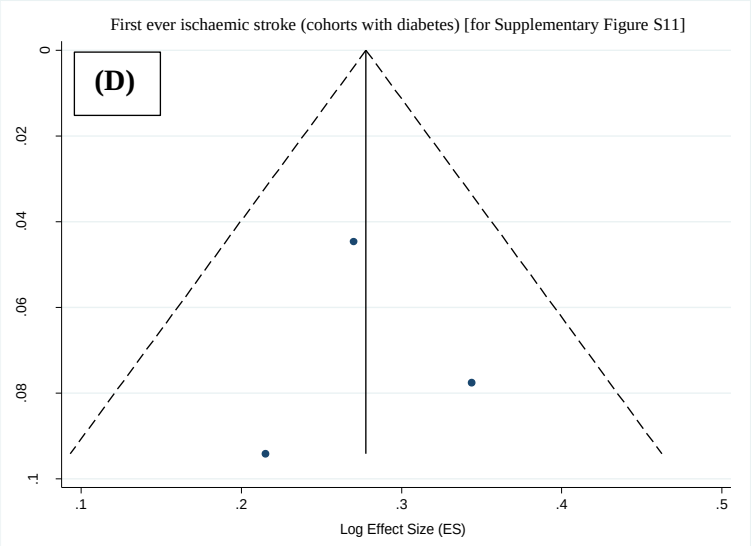
Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.3039004	.0537641	5.65	0.011	.1327991	.4750017
bias	-1.337711	.8304371	-1.61	0.206	-3.980532	1.305111



Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.105108	.0616582	1.70	0.230	-.1601858	.3704019
bias	.5521436	.1509735	3.66	0.067	-.097443	1.20173

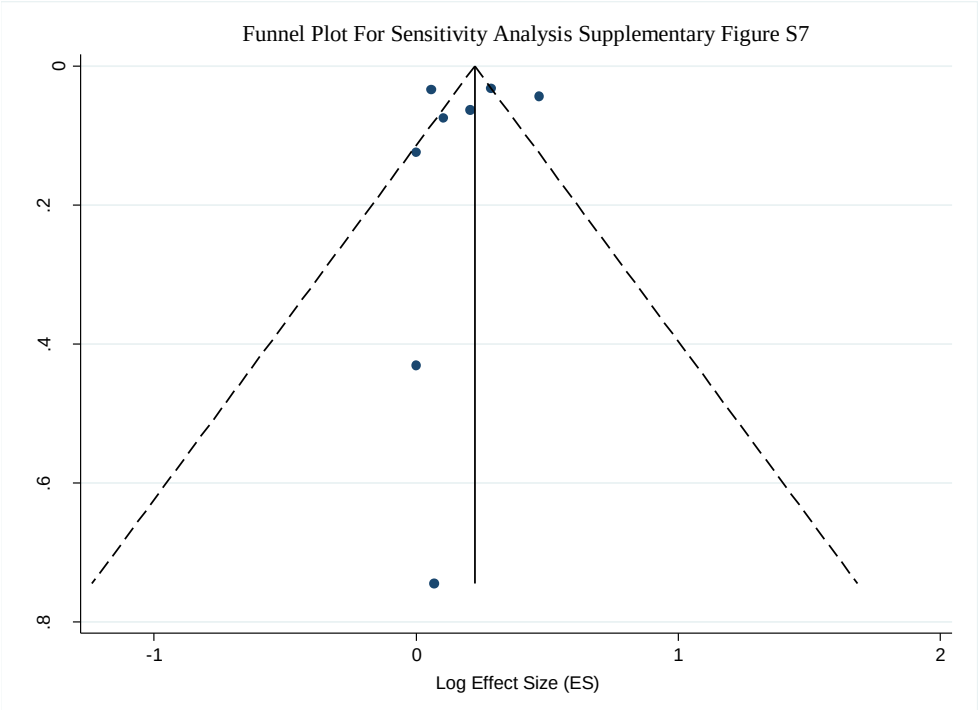


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2758432	.1240259	2.22	0.269	-1.300056	1.851742
bias	.0328475	1.998098	0.02	0.990	-25.35539	25.42108

Supplementary Figure S15: Publication bias assessment for subgroup meta-analyses within Supplementary Figure S11

Funnel plots with their corresponding Egger's results are presented for each of the subgroup meta-analyses presented within Supplementary Figure S11. Funnel plot **(A)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever stroke (cohorts without diabetes)'. Funnel plot **(B)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever stroke (cohorts with diabetes)'. Funnel plot **(C)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever ischaemic stroke (cohorts without diabetes)'. Funnel plot **(D)** and the corresponding Egger's test result corresponds to the subgroup analysis 'First-ever ischaemic stroke (cohorts with diabetes)'. Significance for funnel plot asymmetry was set at $p<0.05$ for the Egger's bias results shown. Log Effect Size (ES)= natural logarithm of effect sizes.

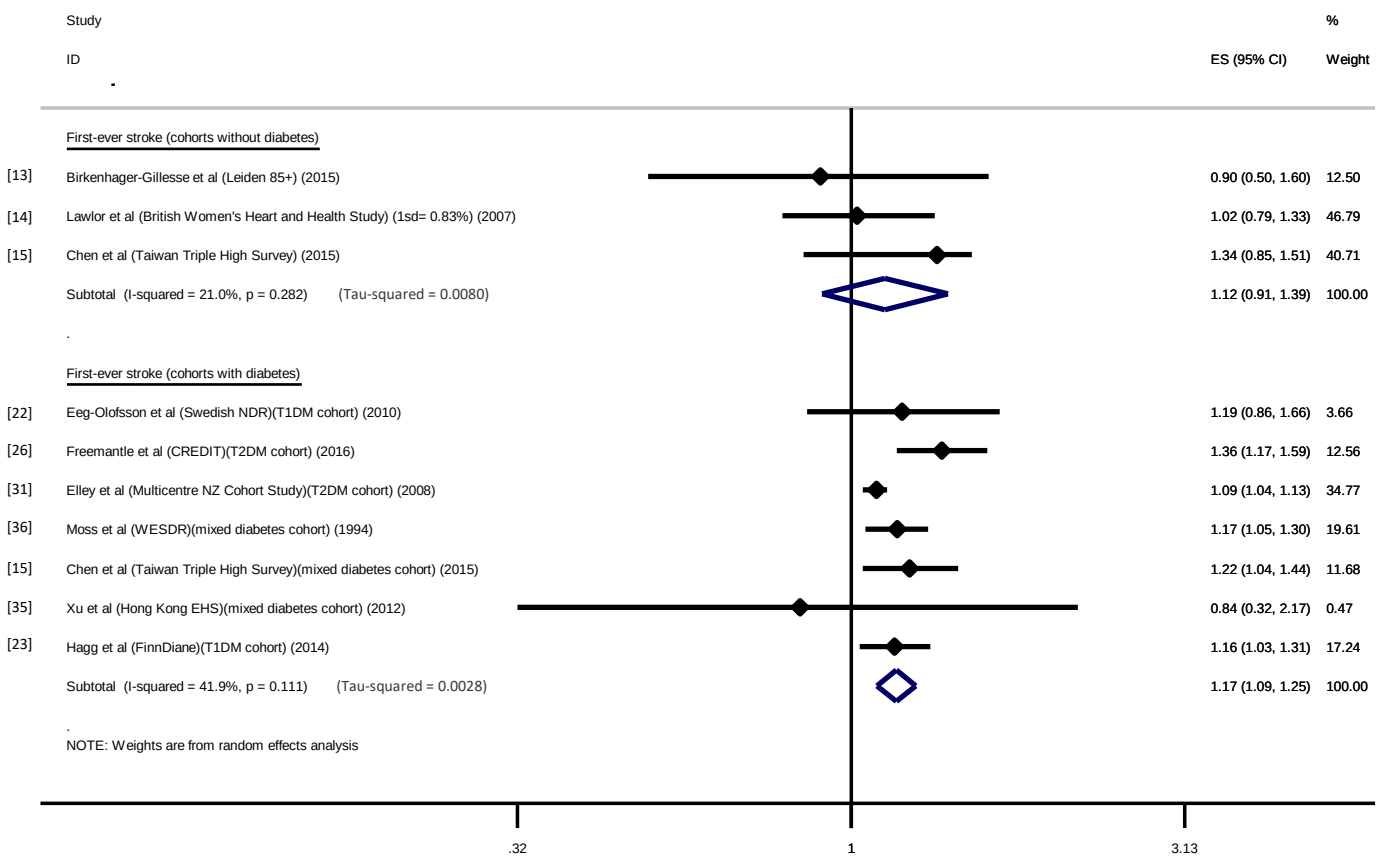


Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.2532916	.1077359	2.35	0.057	-.0103286	.5169117
bias	-.6795283	2.030174	-0.33	0.749	-5.647186	4.288129

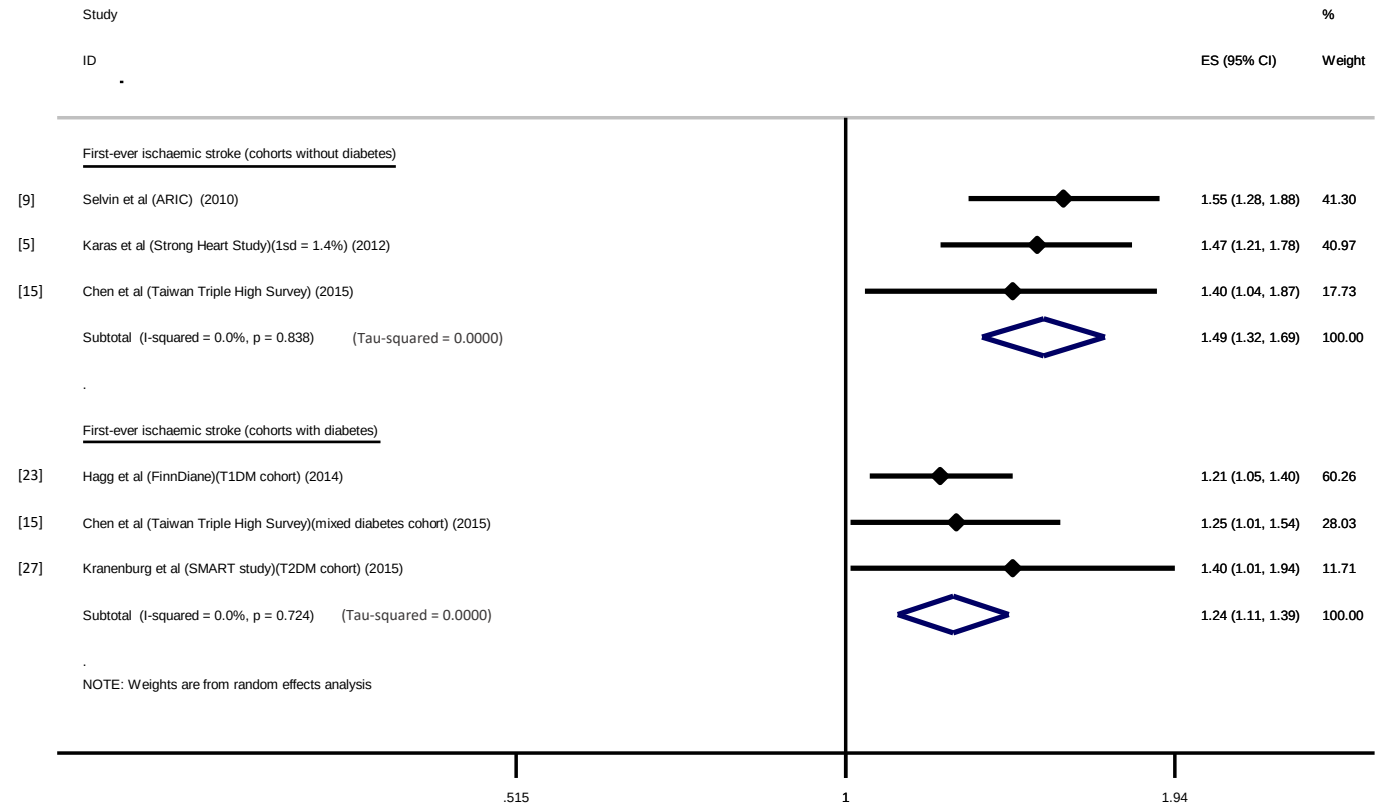
Supplementary Figure S16: Publication bias assessment for sensitivity analysis within Supplementary Figure S7

The funnel plot and its corresponding Egger's results are shown for the sensitivity analysis presented within Supplementary Figure S7. Significance for funnel plot asymmetry was set at $p<0.05$ for the Egger's bias result shown. Log Effect Size (ES)= natural logarithm of effect sizes.



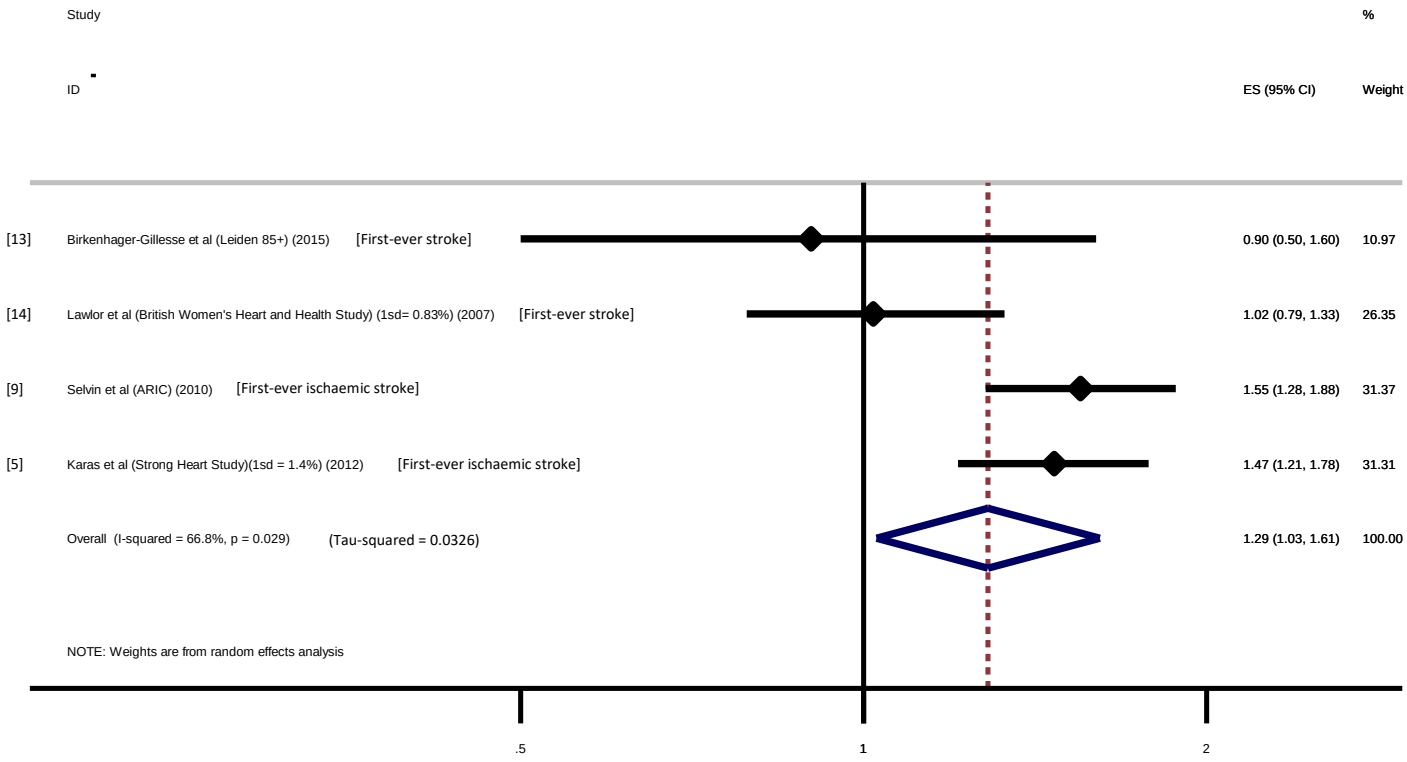
Supplementary Figure S17: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and first-ever stroke in non-diabetes and diabetes cohorts (as described in Figure 2)

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA1c increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data was treated as equivalent to HR data. Studies using 1 standard deviation (1sd) HbA1c increments for effect sizes quoted were treated as equivalent to 1% HbA1c increment data. The corresponding HbA1c increment for each standard deviation are as shown in brackets provided. Studies were stratified based on the diabetes status of their cohorts and their restriction of first-ever stroke to an ischaemic stroke subtype. The outcome 'first-ever stroke' reflects any stroke subtype. The outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Diabetes cohorts included studies which measured type 1 diabetes (T1DM), type 2 diabetes (T2DM) or a combination of both (mixed diabetes cohort). Non-diabetes cohorts represented studies which used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association.



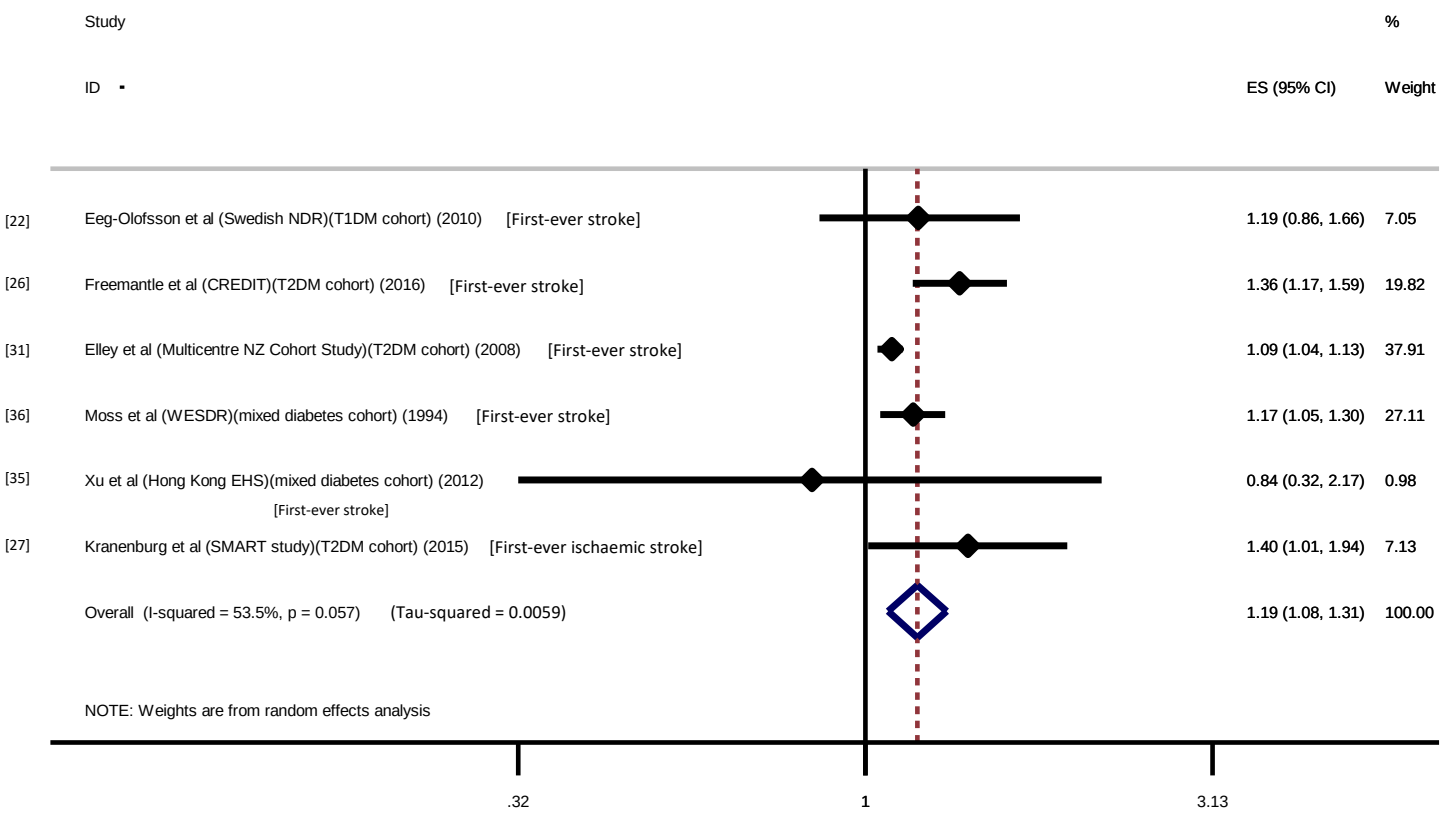
Supplementary Figure S18: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and first-ever ischaemic stroke in non-diabetes and diabetes cohorts (as described in Figure 2)

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA1c increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data was treated as equivalent to HR data. Studies using 1 standard deviation (1sd) HbA1c increments for effect sizes quoted were treated as equivalent to 1% HbA1c increment data. The corresponding HbA1c increment for each standard deviation are as shown in brackets provided. Studies were stratified based on the diabetes status of their cohorts and their restriction of first-ever stroke to an ischaemic stroke subtype. The outcome 'first-ever stroke' reflects any stroke subtype. The outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Diabetes cohorts included studies which measured type 1 diabetes (T1DM), type 2 diabetes (T2DM) or a combination of both (mixed diabetes cohort). Non-diabetes cohorts represented studies which used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association.



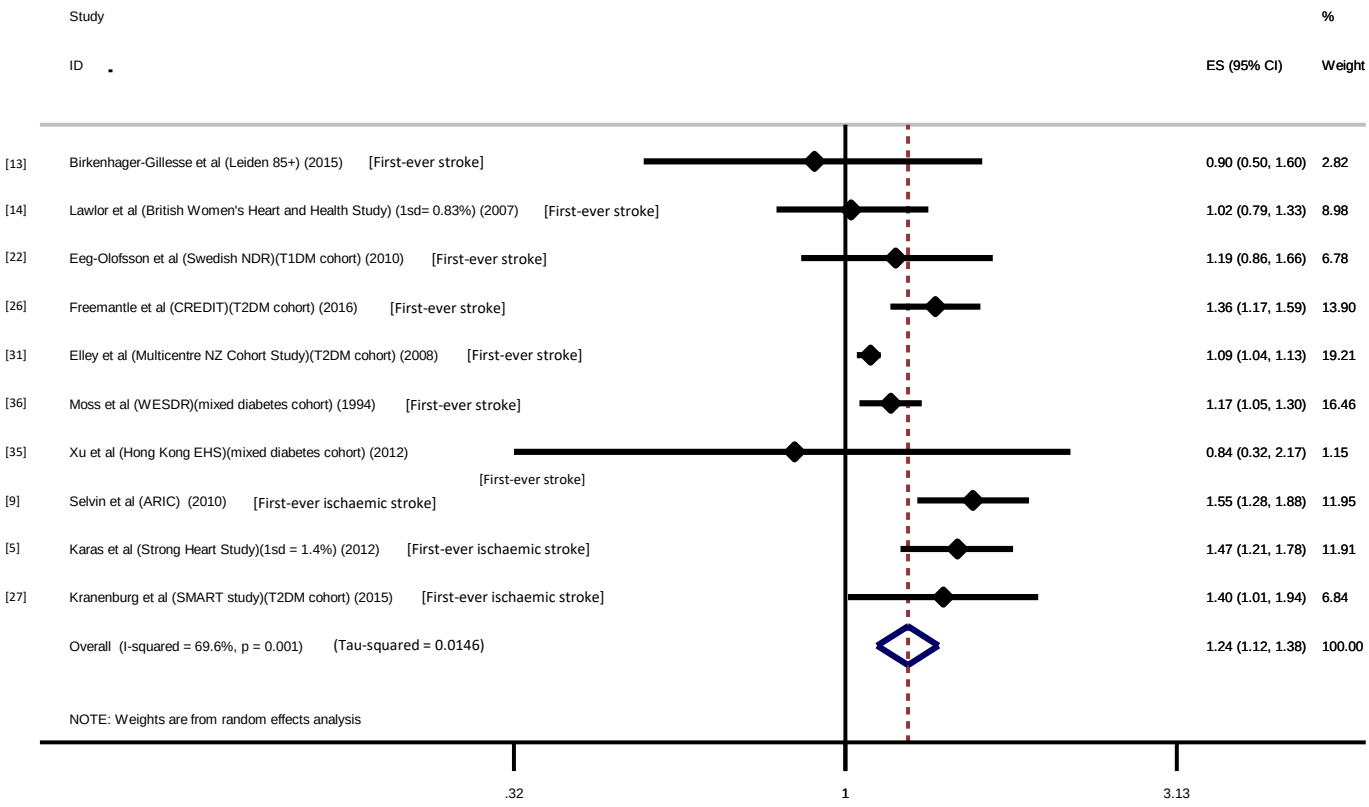
Supplementary Figure S19: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, in non-diabetes cohorts

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA1c increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data was treated as equivalent to HR data. Studies using 1 standard deviation (1sd) HbA1c increments for effect sizes quoted were treated as equivalent to 1% HbA1c increment data. The corresponding HbA1c increment for each standard deviation are as shown in brackets provided. The data presented depicts the association between rising 1% HbA1c increments and a combined outcome of first-ever stroke and first-ever ischaemic stroke strata (depicted in Figure 2), for studies using non-diabetes cohorts. The outcome 'first-ever stroke' reflects any stroke subtype and the outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Non-diabetes cohorts represented studies which used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association. Chen [15] was excluded from this analysis to avoid bias attributable to duplicate study cohort



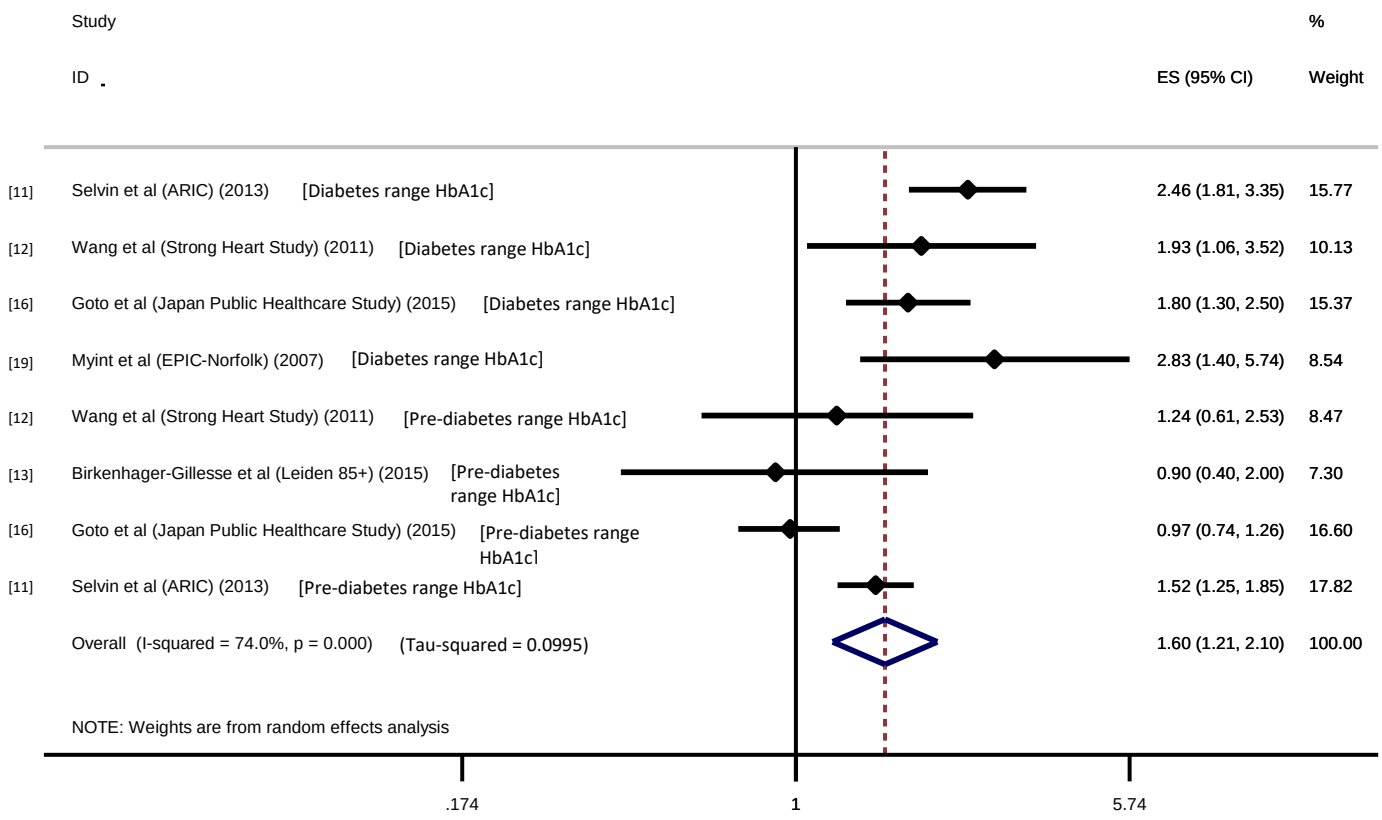
Supplementary Figure S20: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, in diabetes cohorts

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA1c increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data was treated as equivalent to HR data. Studies using 1 standard deviation (1sd) HbA1c increments for effect sizes quoted were treated as equivalent to 1% HbA1c increment data. The data presented depicts the association between rising 1% HbA1c increments and a combined outcome of first-ever stroke and first-ever ischaemic stroke strata (depicted in Figure 2), for studies using diabetes cohorts. The outcome 'first-ever stroke' reflects any stroke subtype and the outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Diabetes cohorts included studies which measured type 1 diabetes (T1DM), type 2 diabetes (T2DM) or a combination of both (mixed diabetes cohort). The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association. Hagg [23] and Chen [15] have been excluded from this analysis to avoid bias attributable to duplicate study cohort inclusion.



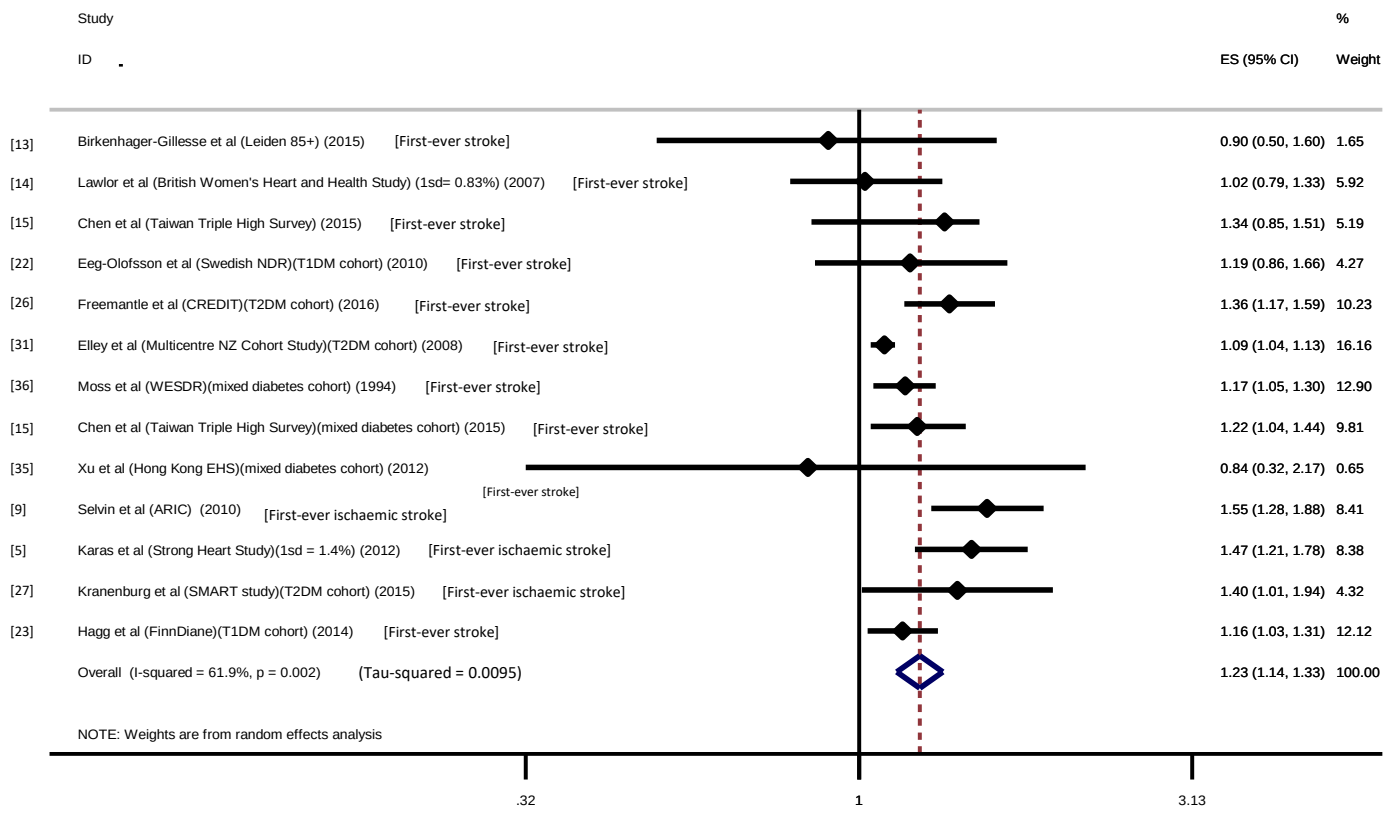
Supplementary Figure S21: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, regardless of cohort diabetes status (combination of Supplementary Figures S19 and S20)

Studies presenting hazard ratio (HR) or risk ratio (RR, relative risk) data assessing the association between rising 1% HbA1c increments and first-ever stroke risk were identified and used to calculate meta-analytical effect sizes (ES) (95% CI). RR data was treated as equivalent to HR data. Studies using 1 standard deviation (1sd) HbA1c increments for effect sizes quoted were treated as equivalent to 1% HbA1c increment data. The corresponding HbA1c increment for each standard deviation are as shown in brackets provided. The data presented depicts the association between rising 1% HbA1c increments and a combined outcome of first-ever stroke and first-ever ischaemic stroke strata (depicted in Figure 2), for studies using non-diabetes or diabetes cohorts. The outcome 'first-ever stroke' reflects any stroke subtype and the outcome 'first-ever ischaemic stroke' only included studies which specifically restricted their stroke outcome to first-ever stroke of ischaemic subtype. Diabetes cohorts included studies which measured type 1 diabetes (T1DM), type 2 diabetes (T2DM) or a combination of both (mixed diabetes cohort). Non-diabetes cohorts represented studies which used participants with no diabetes mellitus or whose effect size(s) were adjusted for diabetes. The I^2 statistic values for each subgroup analysis assessing the percentage of variation across studies that is due to heterogeneity, rather than chance, are presented below each subgroup analysis. A random-effects model using the inverse-variance method for weighting was used to generate pooled effect sizes for each subgroup. ES=1.0 indicates no statistically significant association. Hagg [23] and Chen [15] have been excluded from this analysis to avoid bias attributable to duplicate study cohort inclusion.



Supplementary Figure S22: Additional subgroup analysis: Association between first-ever stroke risk and combined ADA-defined pre-diabetes and diabetes range HbA1c (≥5.7%), compared to non-diabetes range HbA1c (<5.7%)

Studies which used a reference category of HbA1c within the non-diabetes range (<5.7%) and a comparator range of HbA1c within pre-diabetes range HbA1c (5.7%-6.5%) or diabetes range HbA1c (≥6.5%) were included within random-effects model meta-analysis performed. Pooled meta-analytical effect sizes (ES) (95% CI) presented reflect meta-analytical generated hazard ratios (HR) (95% CI). Risk ratio (RR, relative risk) data were treated as equivalent to hazard ratios (HR). Weights (%) used in the meta-analysis were generated using an inverse-variance method. The reference category used (ES=1.0) reflects non-diabetes range HbA1c (<5.7%).



Supplementary Figure S23: Additional subgroup analysis: Comparison of study-quoted 1% HbA1c increment first-ever stroke and first-ever ischaemic stroke effect sizes regardless of cohort diabetes status (combination of Supplementary Figures S8 and S9)

Studies presenting 1% HbA1c increment data (or equivalent) for the association with first-ever stroke and first-ever ischaemic stroke outcomes, in non-diabetes and diabetes cohorts, were used to assess the importance of ischaemic stroke subtype stratification on random-effects model meta-analytical outcomes derived in Supplementary Figures S8, S9, S19 and S20. Risk ratio (RR, relative risk) data was treated as equivalent to hazard ratio (HR) data. 1 standard deviation data (1sd) was treated as equivalent to 1% HbA1c data. Effect sizes (ES) represent hazard ratios (HR). The analysis presented within this Supplementary Figure (S23) presents the pooled effect size when the studies presented within Supplementary Figures S8 and S9 are pooled within the same meta-analysis.

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