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)…

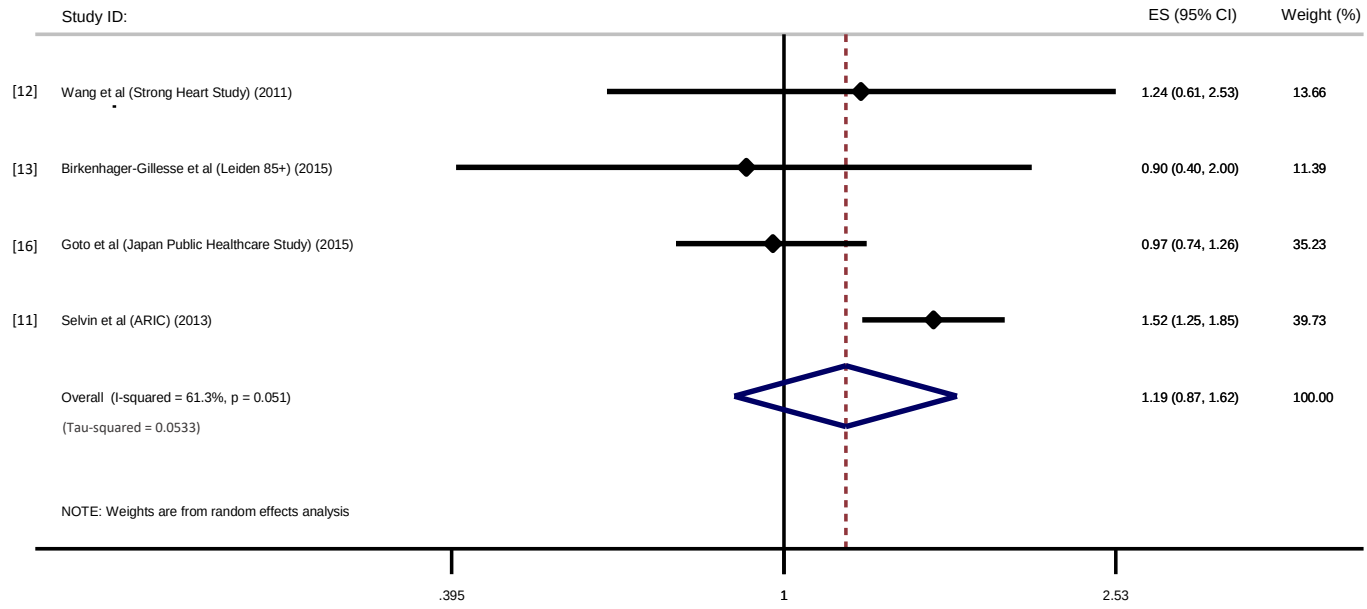
Author (citation) Country of origin (Year published)	Study cohort Sample size ('n' participants)	Age (in years)	Sex (% male)	Follow-up (in years)	Ethnicity description	Diabetes status of participants assessed	Adjusted effect sizes (95% CI)	Covariates used in adjustment of adjusted effect sizes (95% CI) 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.

☐	1	exp Hemoglobin A, Glycosylated/	28365	Advanced	Display Results | More ▾	🗨
☐	2	hba1c.tw.	23369	Advanced	Display Results | More ▾	🗨
☐	3	glycated hemoglobin.tw.	5354	Advanced	Display Results | More ▾	🗨
☐	4	glycated haemoglobin.tw.	2559	Advanced	Display Results | More ▾	🗨
☐	5	cerebral infarction.tw.	11375	Advanced	Display Results | More ▾	🗨
☐	6	cerebral hemorrhage.tw.	3617	Advanced	Display Results | More ▾	🗨
☐	7	cerebral haemorrhage.tw.	955	Advanced	Display Results | More ▾	🗨
☐	8	stroke.tw.	186643	Advanced	Display Results | More ▾	🗨
☐	9	transient ischemic attack.tw.	6472	Advanced	Display Results | More ▾	🗨
☐	10	transient ischaemic attack.tw.	1481	Advanced	Display Results | More ▾	🗨
☐	11	glycosylated hemoglobin.tw.	6312	Advanced	Display Results | More ▾	🗨
☐	12	glycosylated haemoglobin.tw.	2149	Advanced	Display Results | More ▾	🗨
☐	13	exp cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebral small vessel diseases/ or exp cerebrovascular trauma/ or exp dementia, vascular/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp stroke/ or exp vasculitis, central nervous system/ or exp vasospasm, intracranial/	315666	Advanced	Display Results | More ▾	🗨
☐	14	5 or 6 or 7 or 8 or 9 or 10 or 13	407020	Advanced	Display Results | More ▾	🗨
☐	15	1 or 2 or 3 or 4 or 11 or 12	46824	Advanced	Display Results | More ▾	🗨
☐	16	14 and 15	1141	Advanced	Display Results | More ▾	🗨
☐	17	1 and 13	351	Advanced	Display Results | More ▾	🗨
☐	18	limit 16 to animals	18	Advanced	Display Results | More ▾	🗨
☐	19	16 not 18	1123	Advanced	Display Results | More ▾	🗨

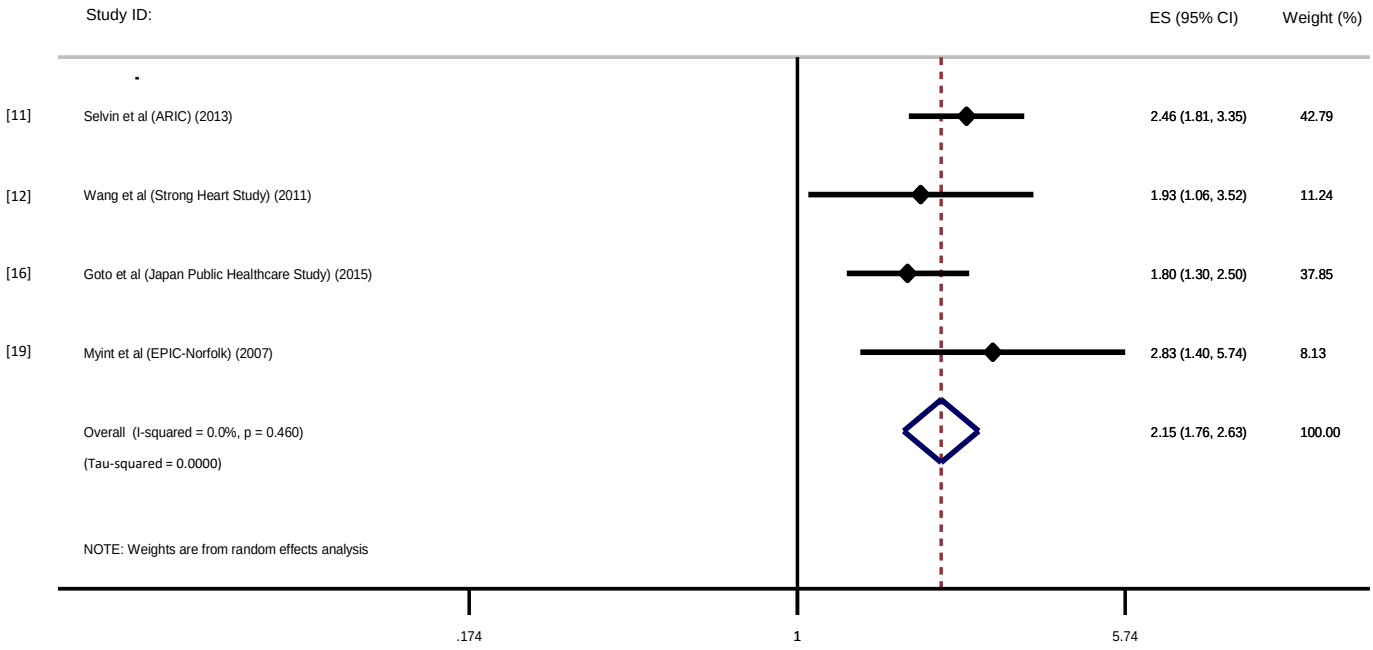
Supplementary Figure S1: Summary of search terms and Boolean operators used within the search strategy in MEDLINE

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.



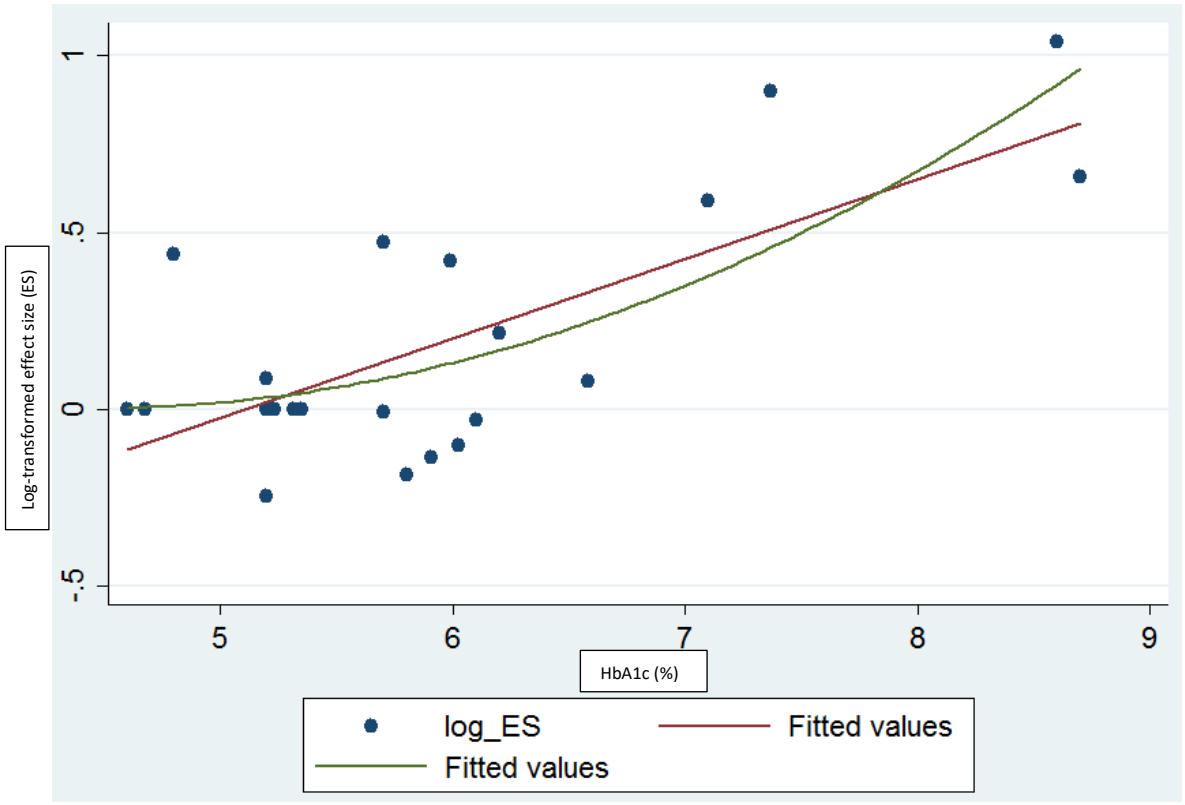
Supplementary Figure S2: Association between ADA-defined pre-diabetes range HbA1c (5.7%-6.5%) and first-ever stroke risk

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

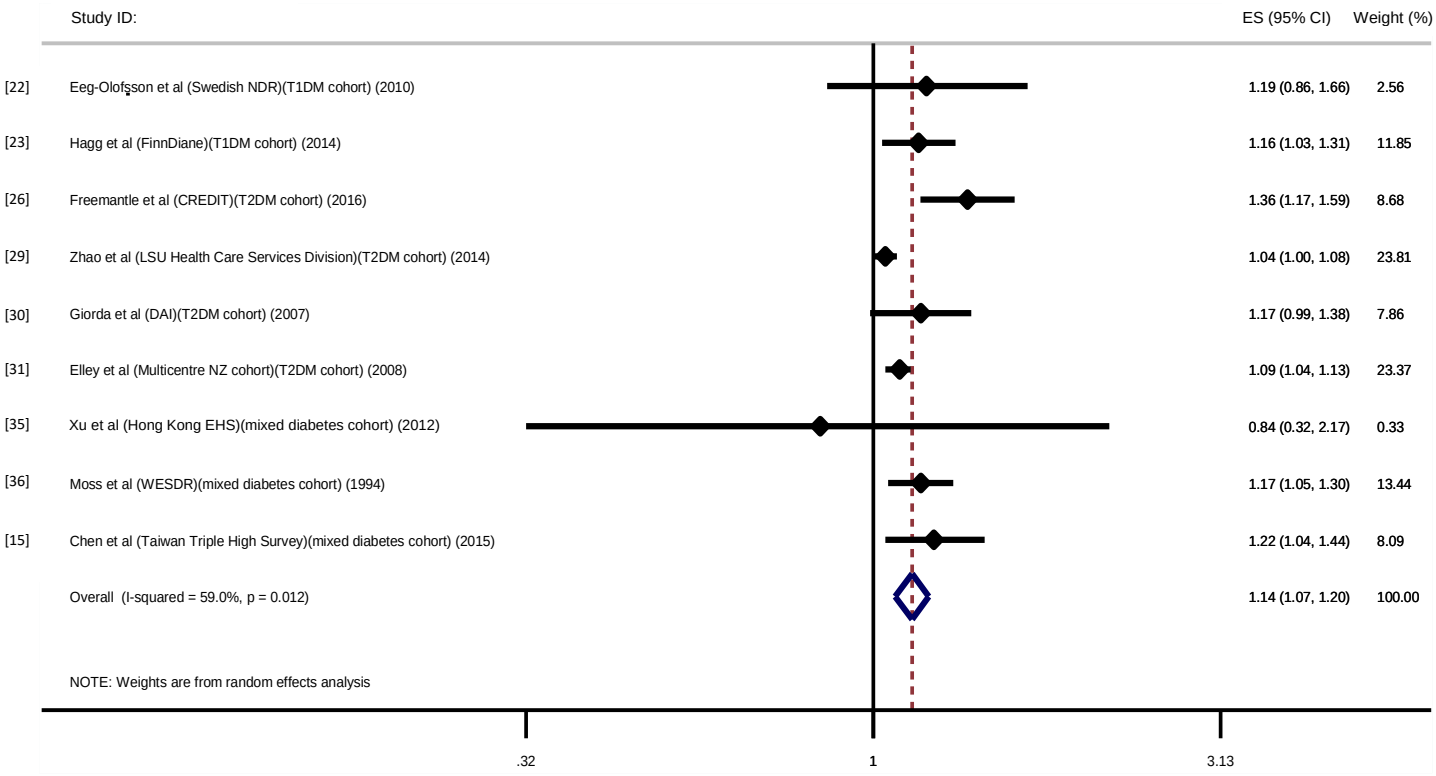
log_ES	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
HbA1c	.4251409	.0660964	6.43	0.098	-.4146938	1.264975
_cons	-2.206962	.4153153	-5.31	0.118	-7.484043	3.070119

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

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

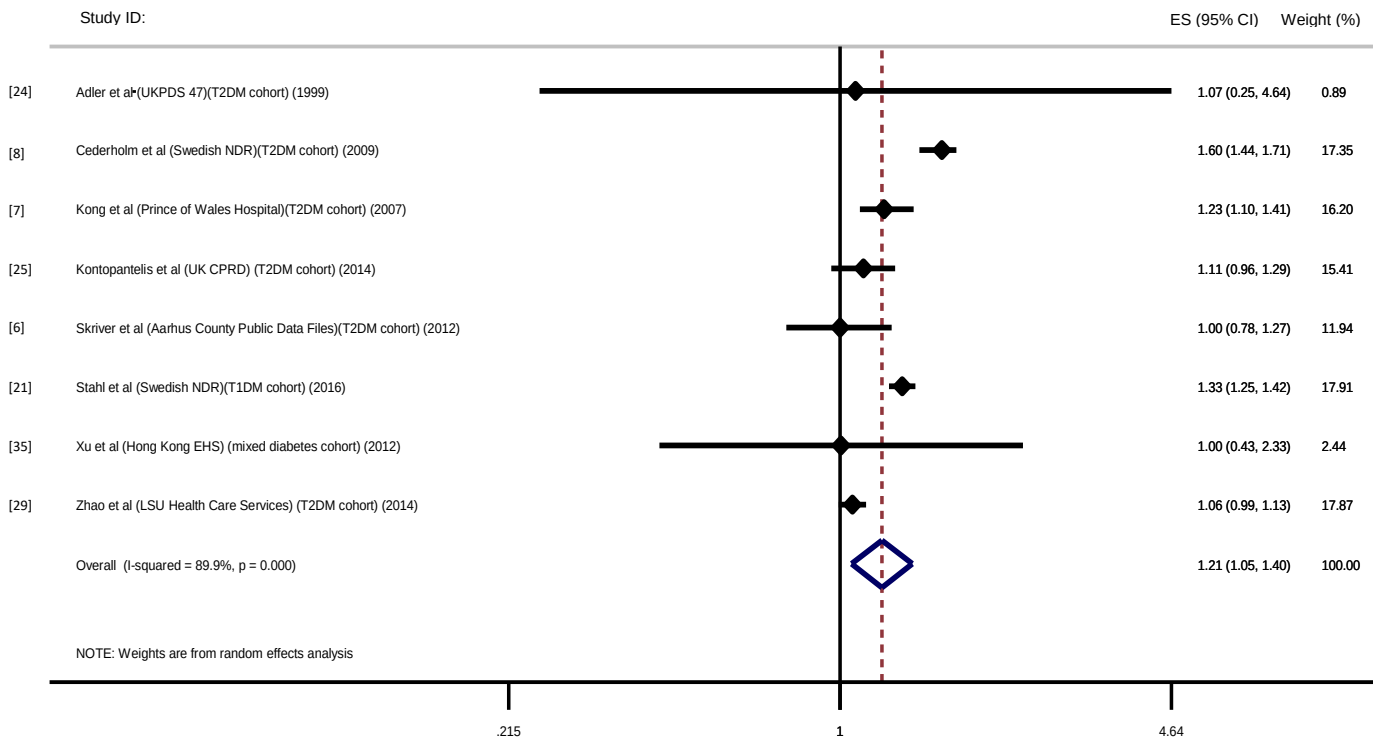
Supplementary Figure S5: 1% HbA1c increment effect size (95% CI) estimation method using the example of Selvin [11]

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).



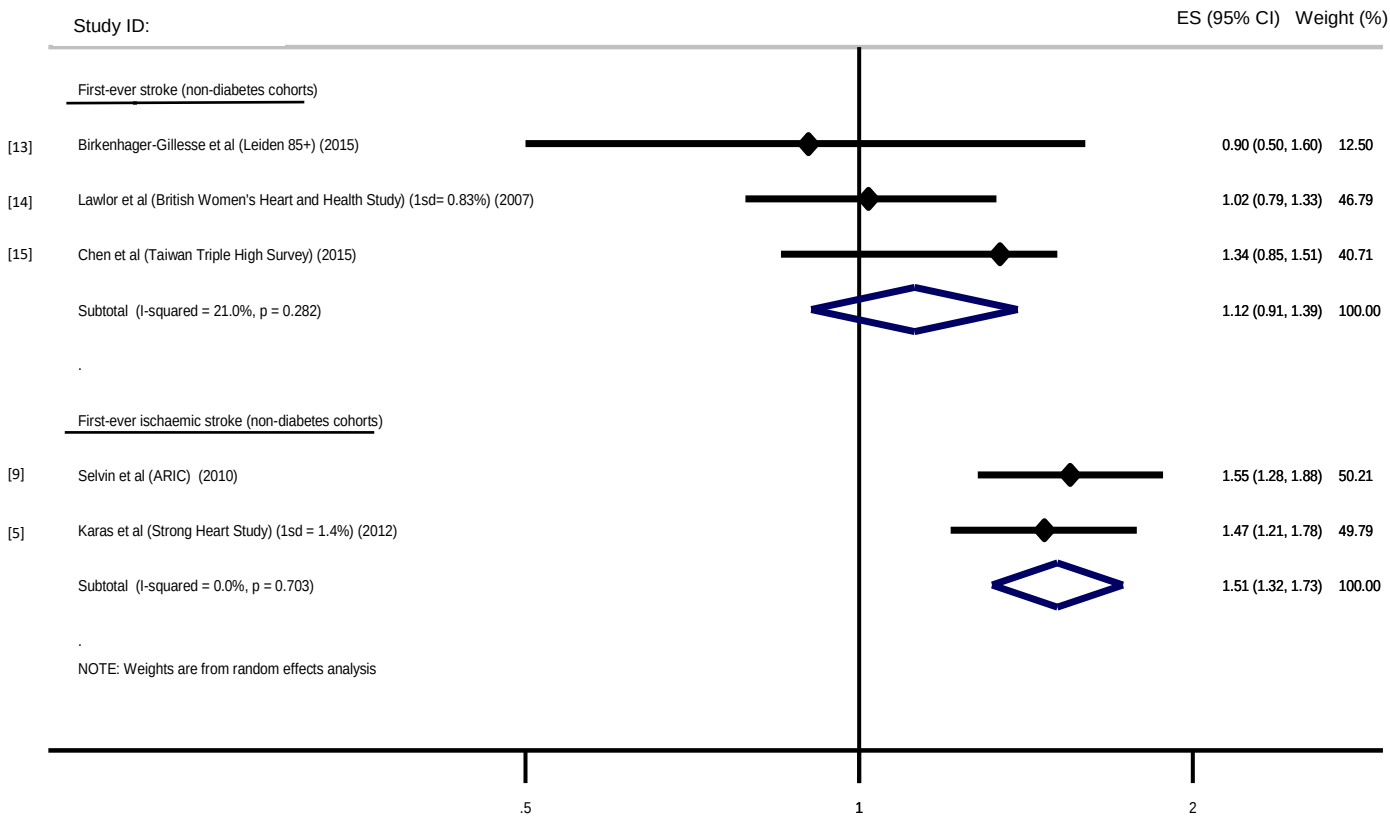
Supplementary Figure S6: Sensitivity analysis for inadequate covariate adjustment in study-quoted 1% HbA1c increment data

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.



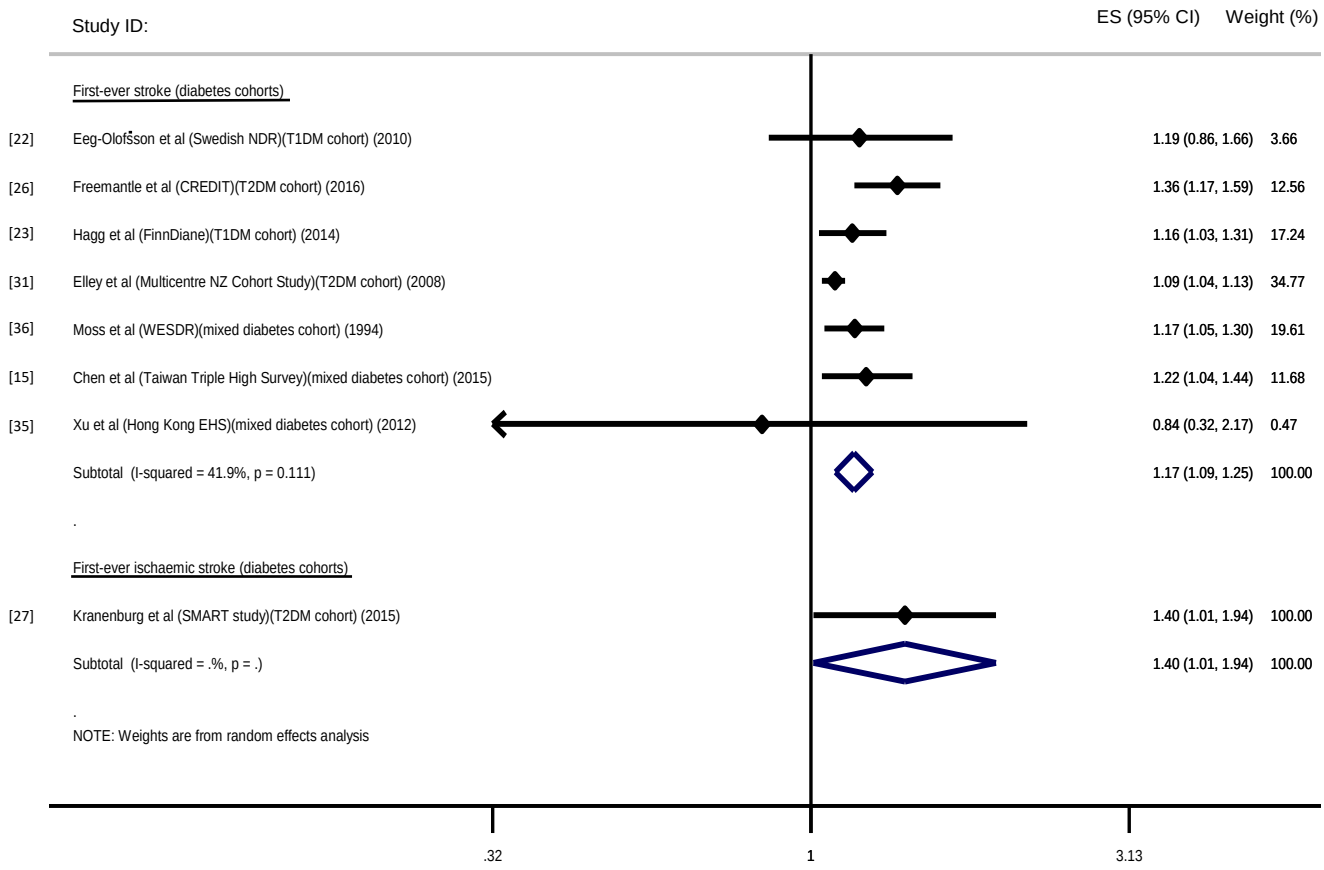
Supplementary Figure S7: Sensitivity analysis for inadequate covariate adjustment in estimated 1% HbA1c increment data

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.



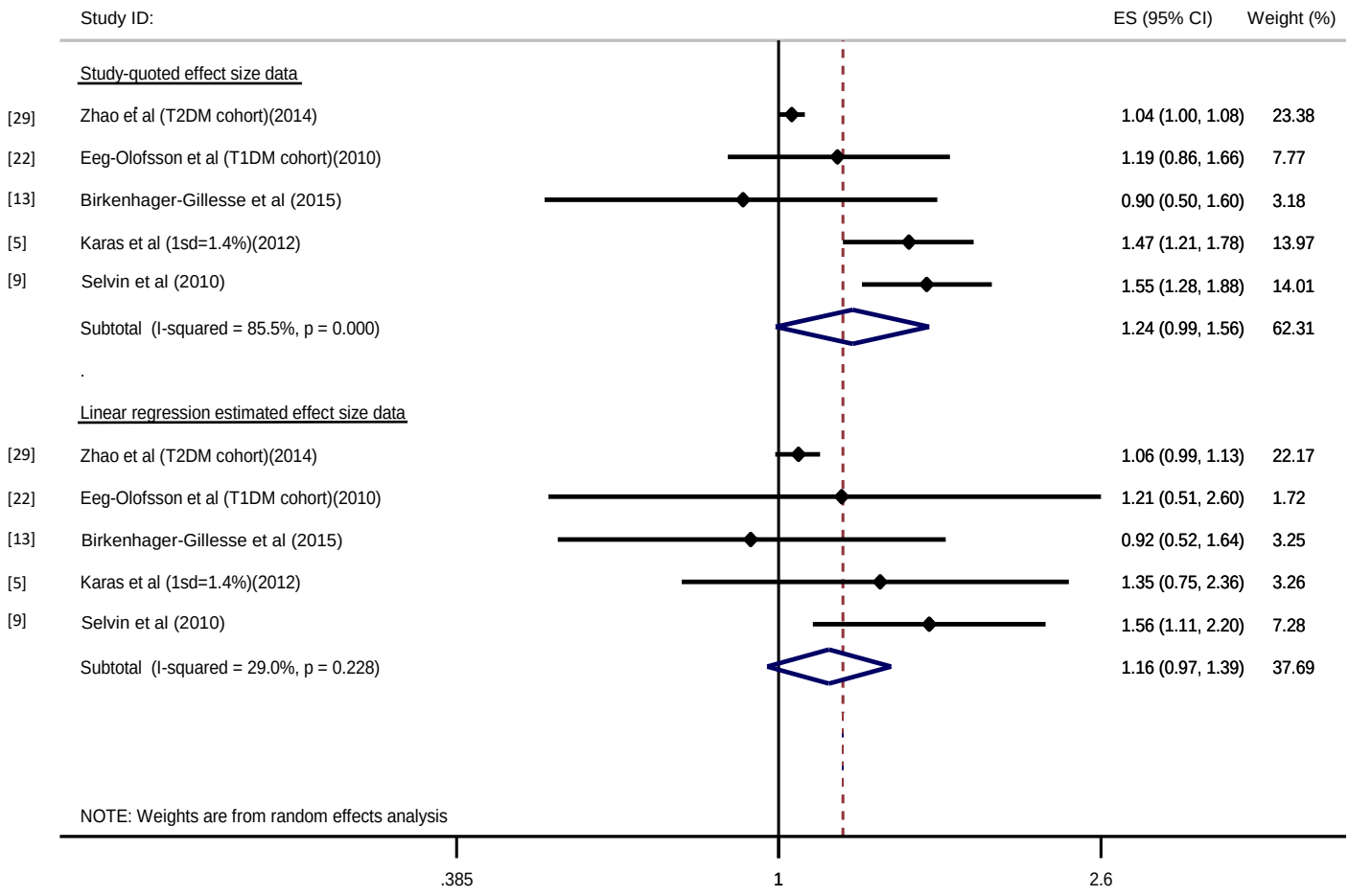
Supplementary Figure S8: Comparison of study-quoted 1% HbA1c increment first-ever stroke and first-ever ischaemic stroke effects sizes, in non-diabetes cohorts

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).



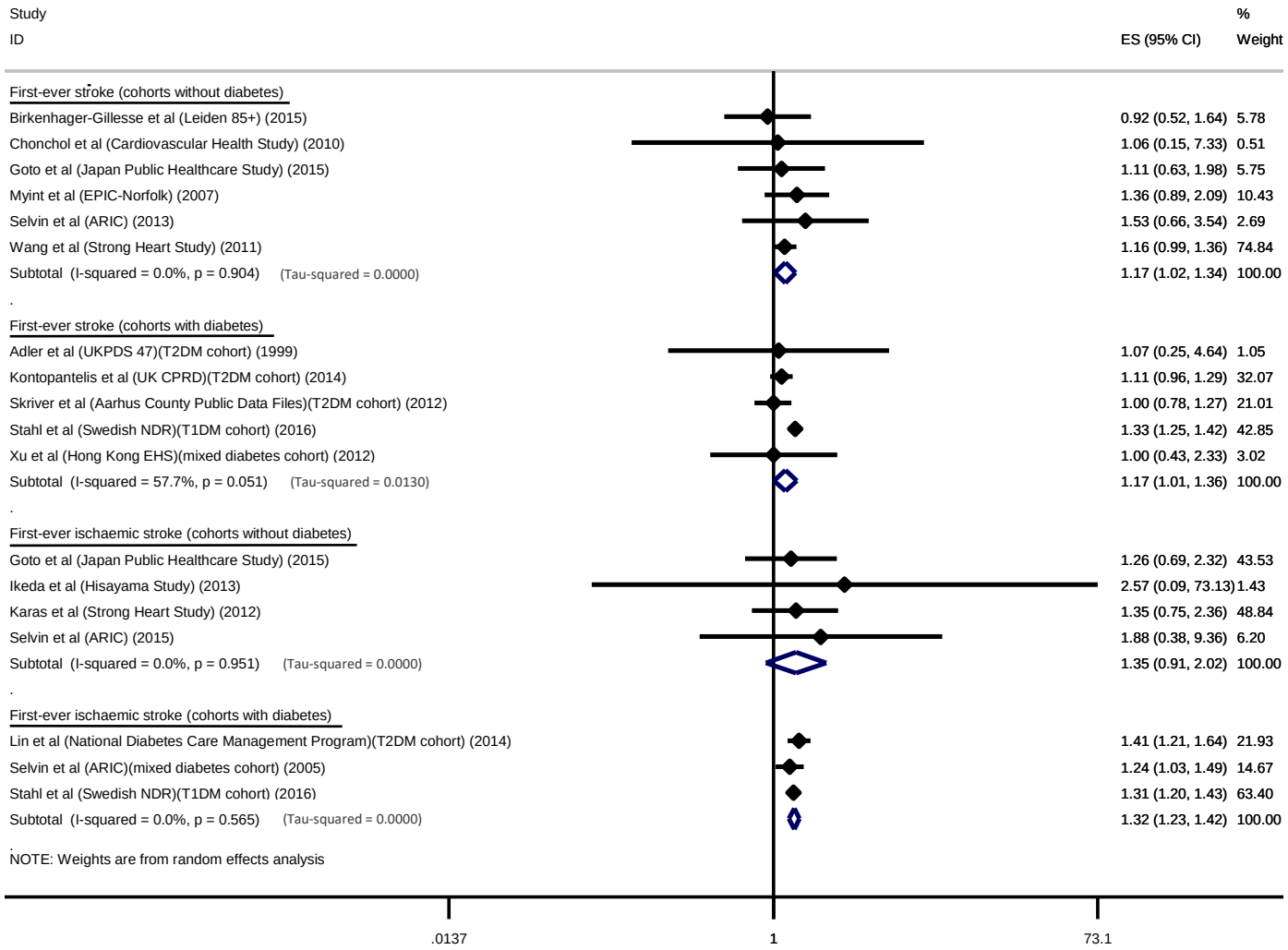
Supplementary Figure S9: Comparison of study-quoted 1% HbA1c increment first-ever stroke and first-ever ischaemic stroke effects sizes, in diabetes cohorts

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.



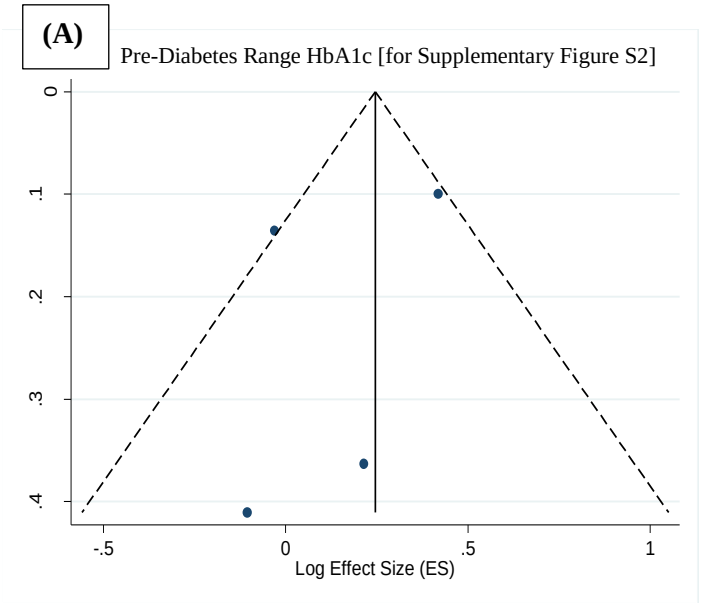
Supplementary Figure S10: Comparison of study-quoted and linear regression estimated 1% HbA1c effect size data

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.



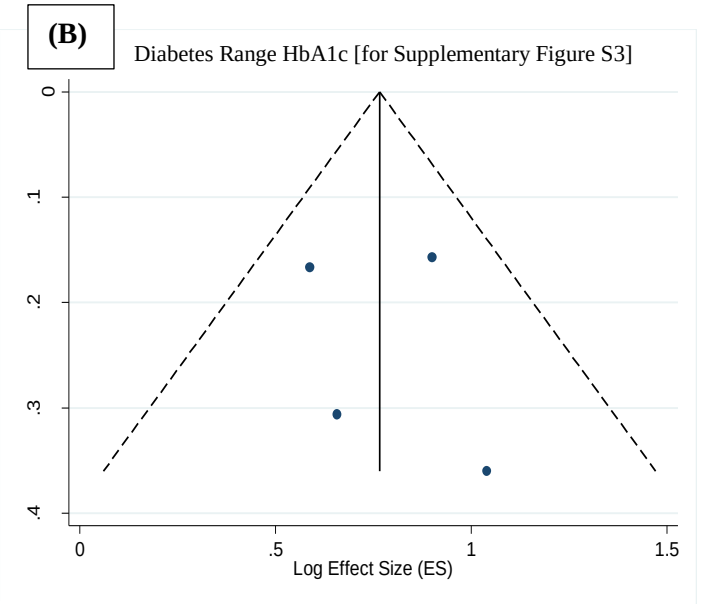
Supplementary Figure S11: Association between linear regression estimated rising 1% HbA1c increments and stratified first-ever stroke risk

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

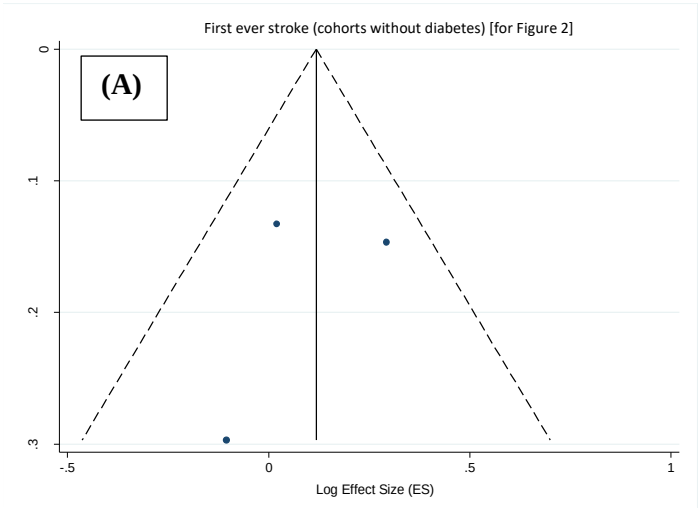


Egger's test

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

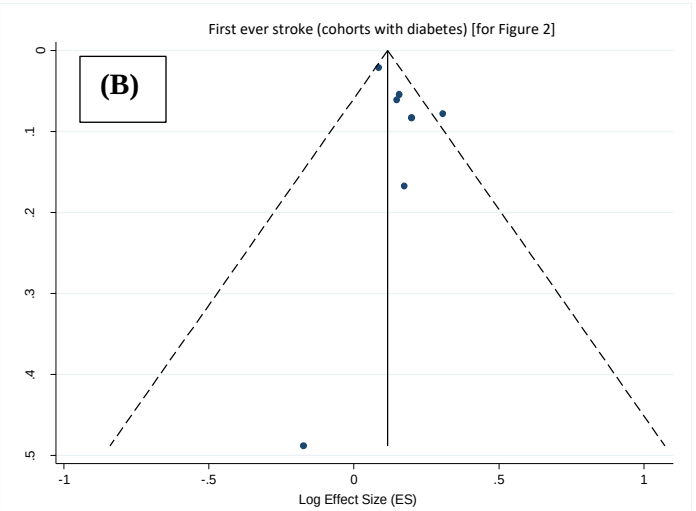
Supplementary Figure S12: Publication bias assessment for inter-categorical meta-analyses within Supplementary Figures S2-S3

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.



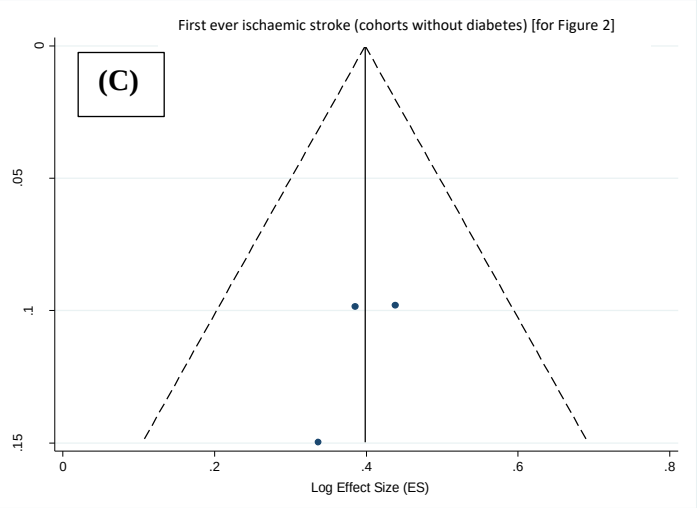
Egger's test

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



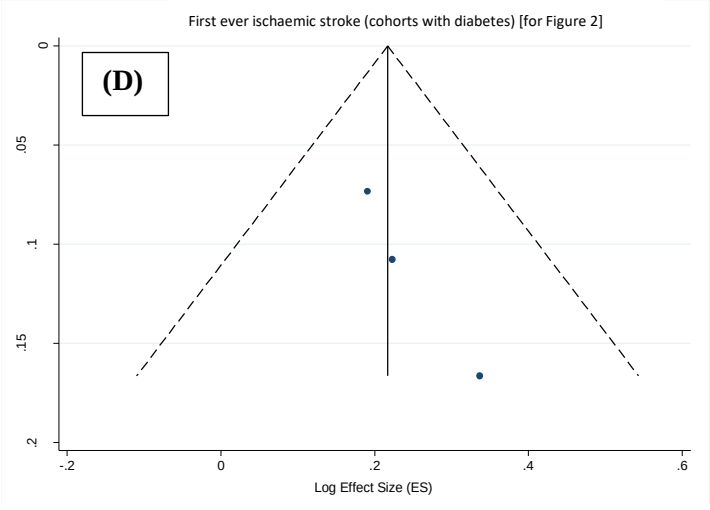
Egger's test

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

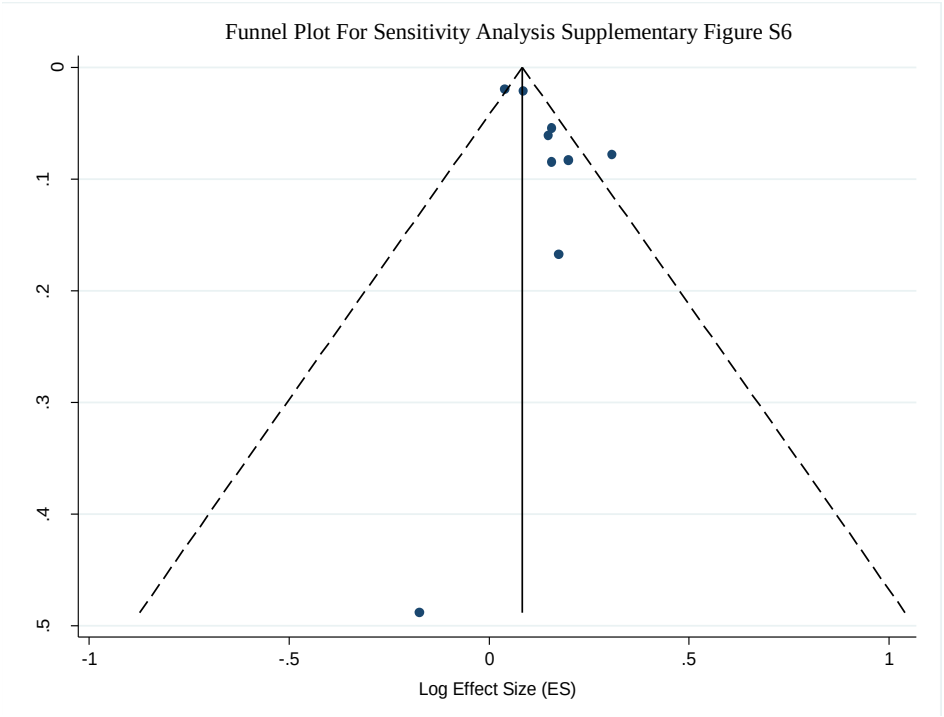


Egger's test

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.

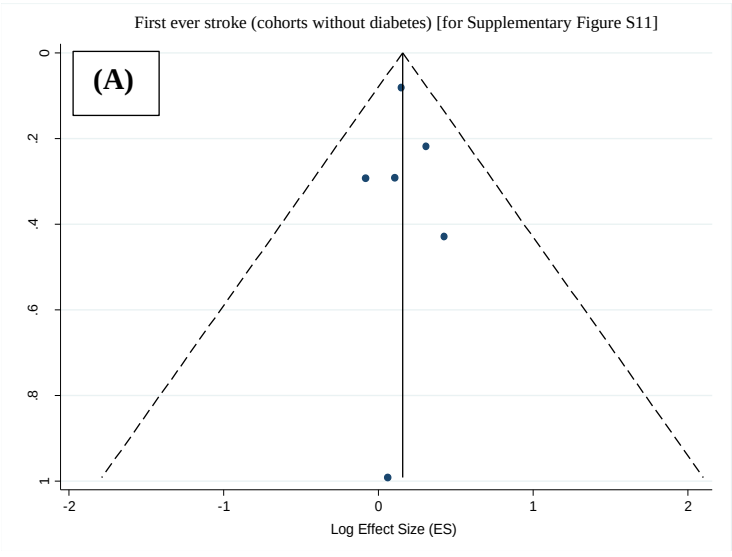


Egger's test

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

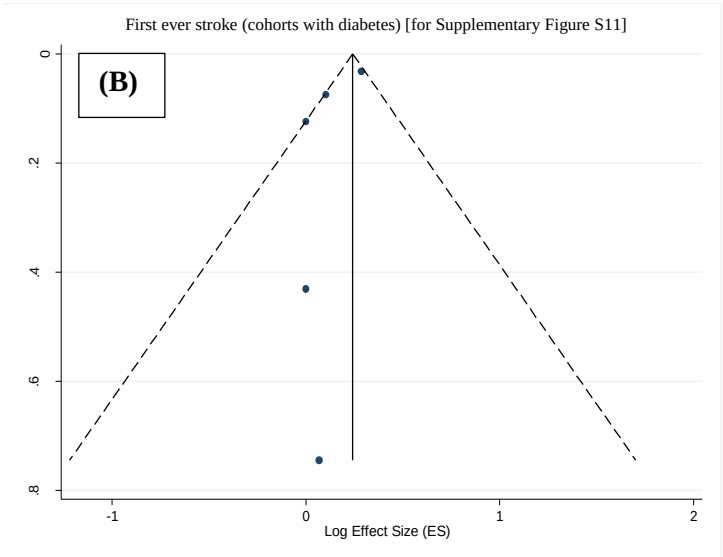
Supplementary Figure S14: Publication bias assessment for sensitivity analysis within Supplementary Figure S6

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.



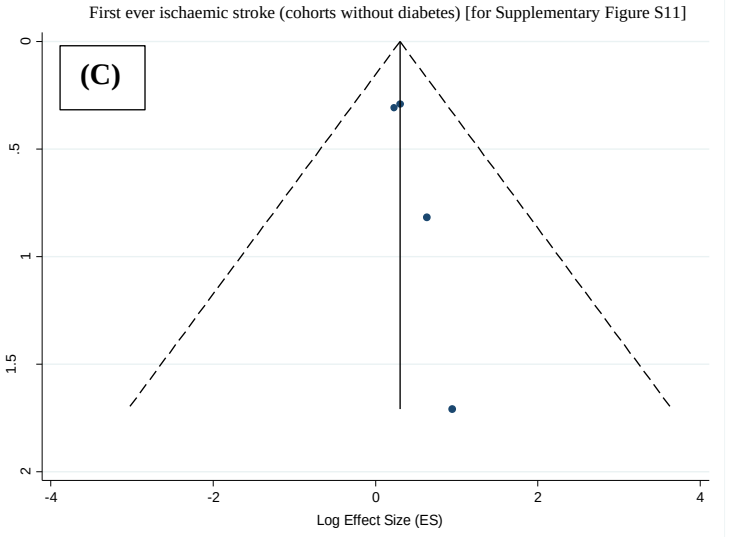
Egger's test

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



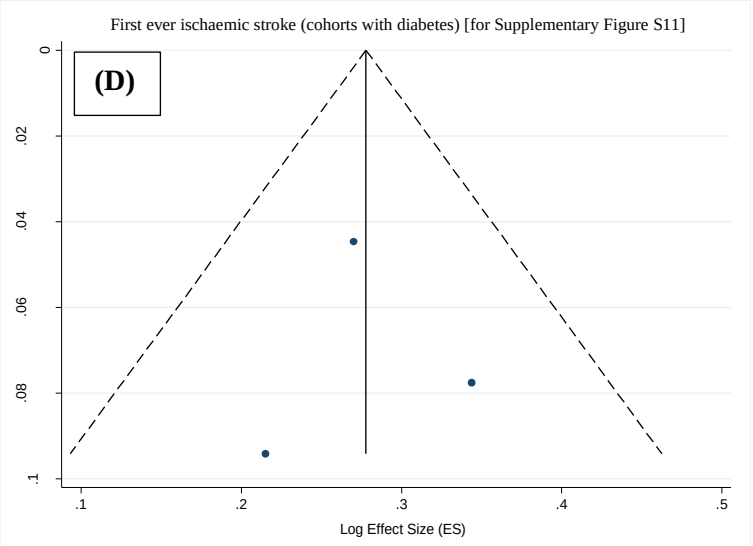
Egger's test

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

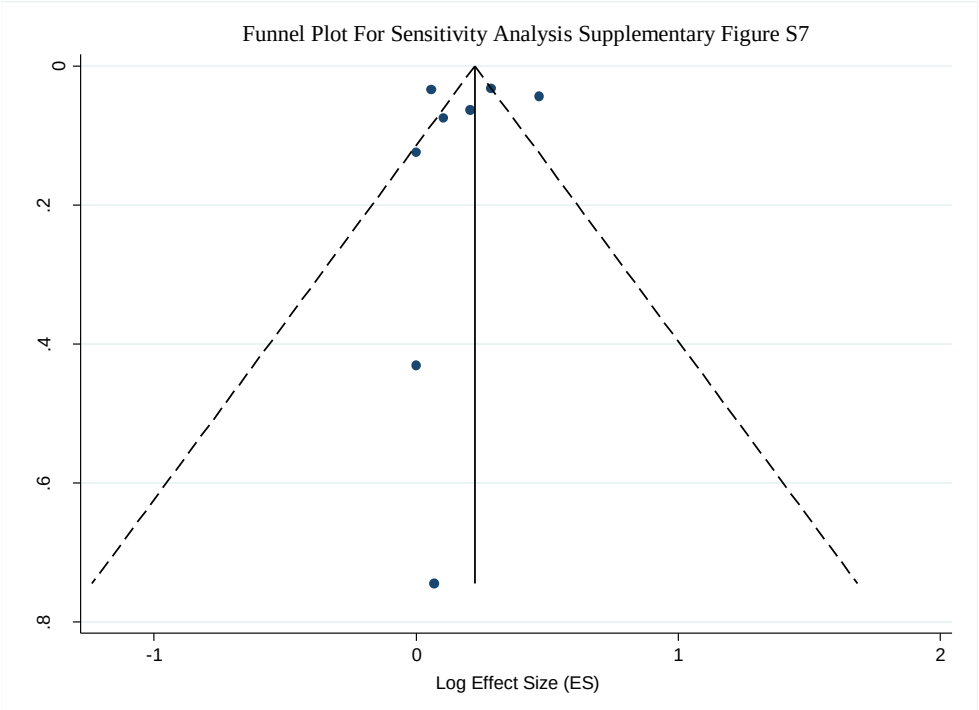


Egger's test

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.

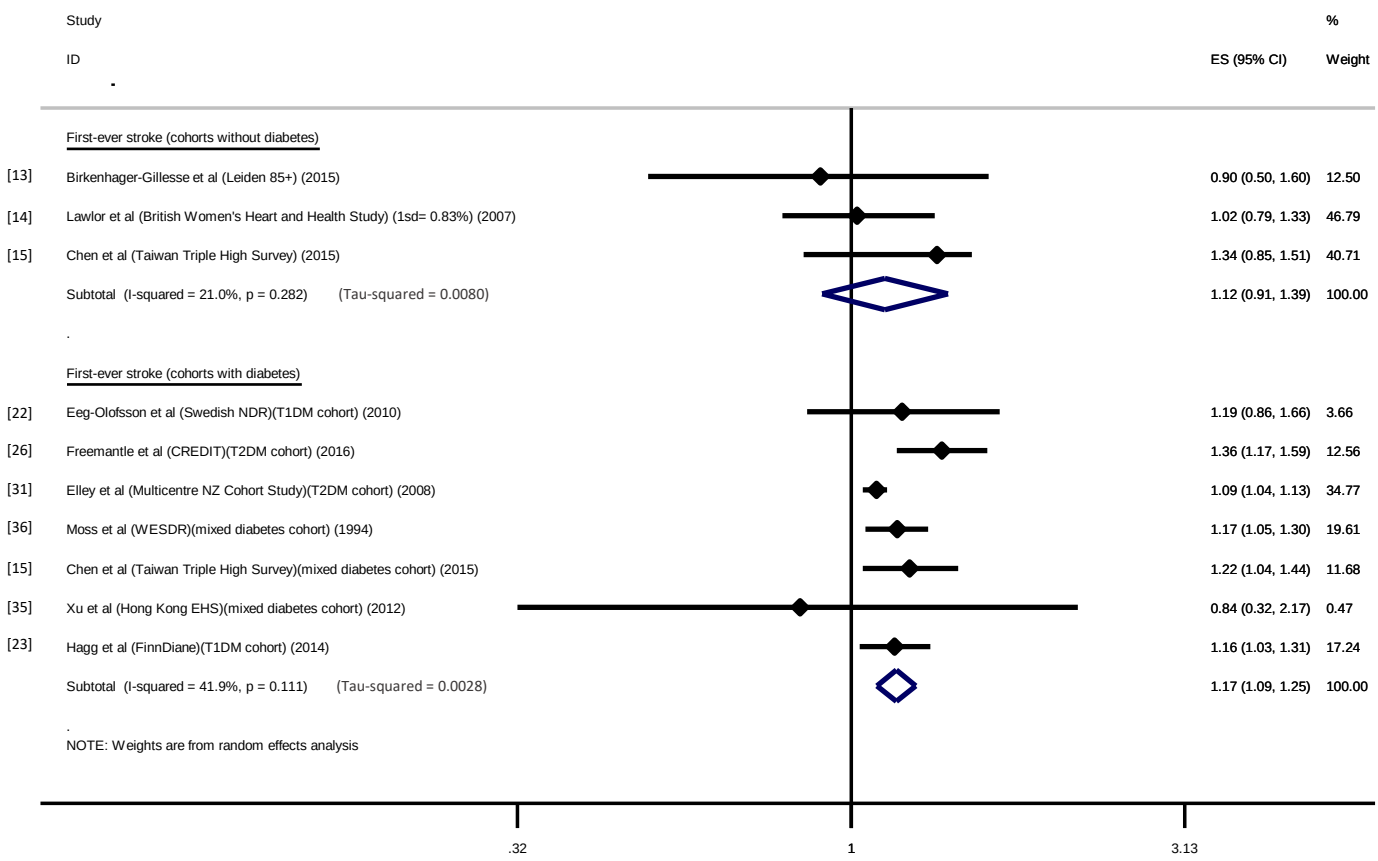


Egger's test

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

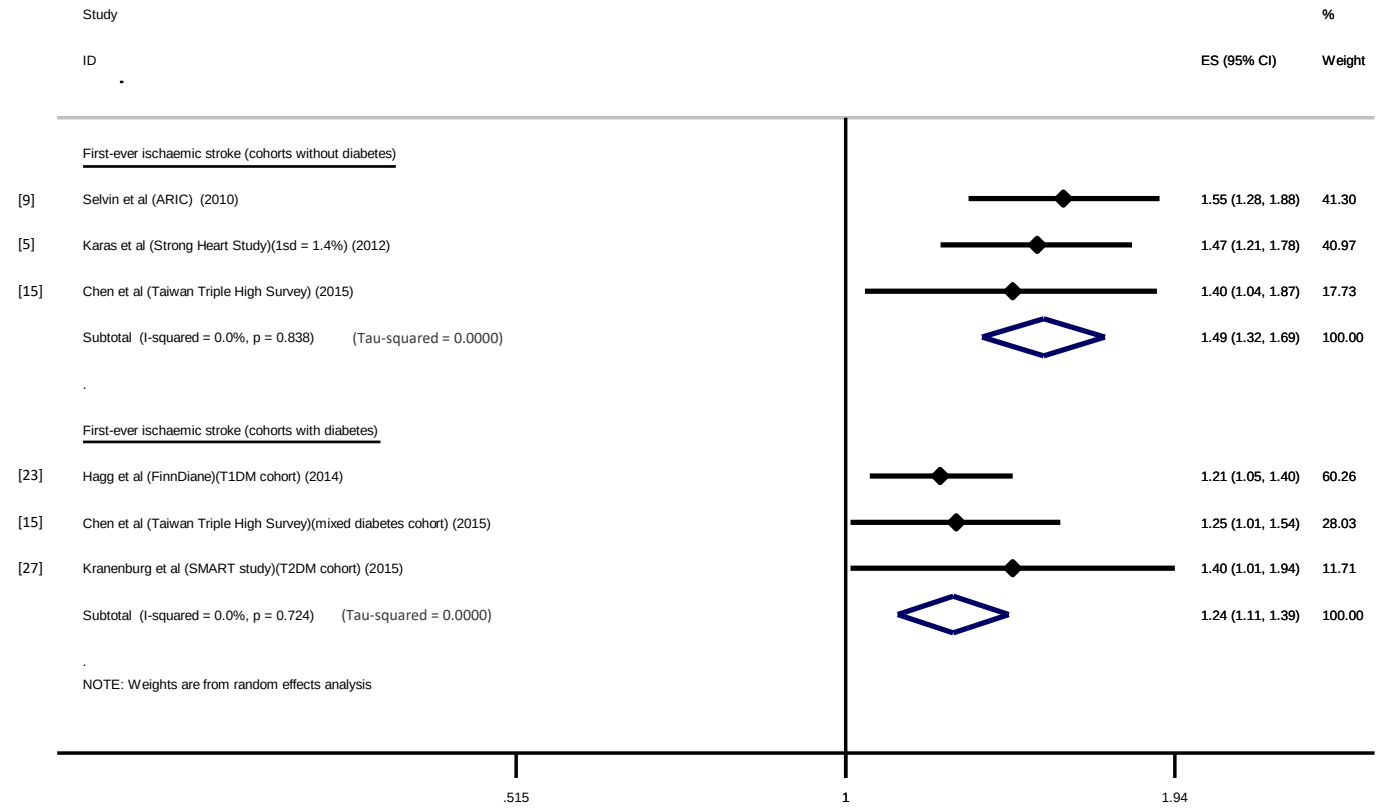
Supplementary Figure S16: Publication bias assessment for sensitivity analysis within Supplementary Figure S7

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.



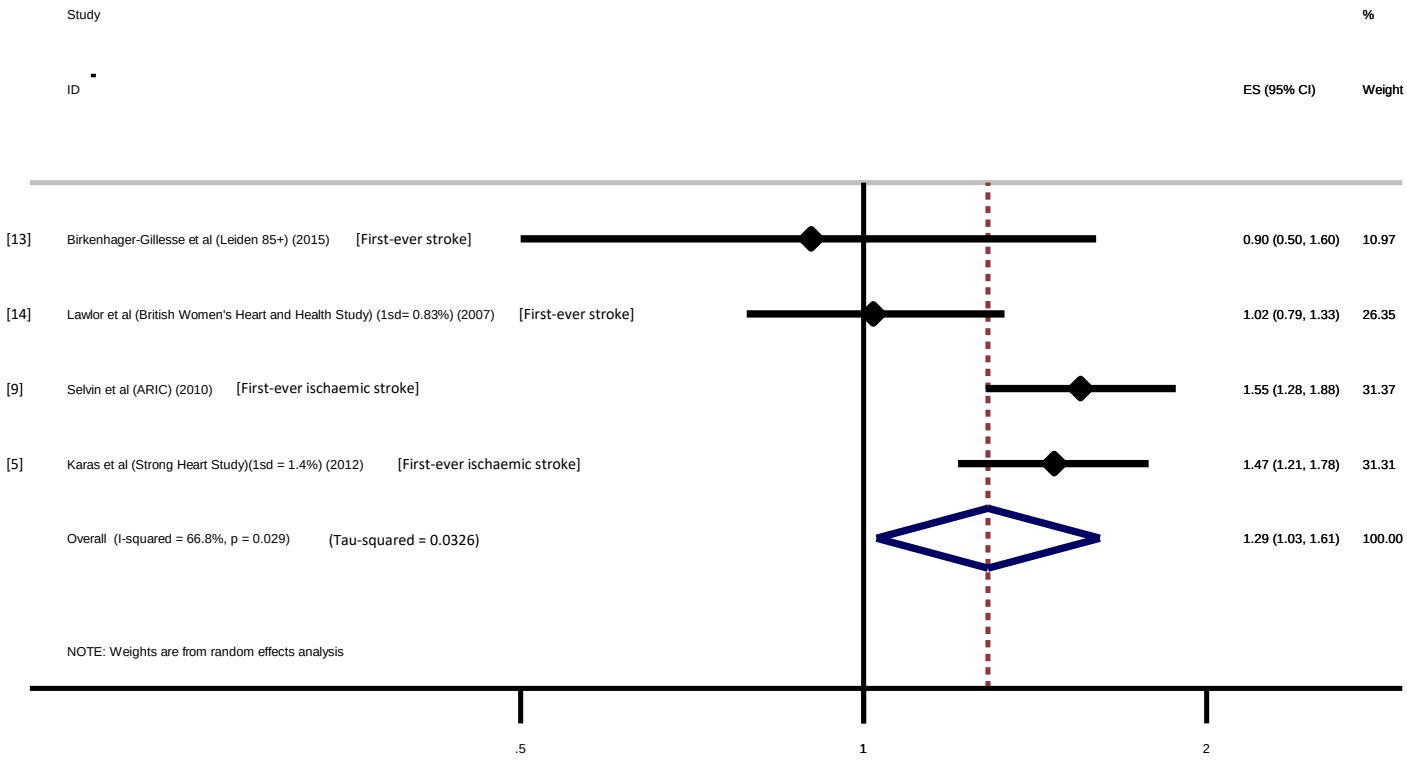
Supplementary Figure S17: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and first-ever stroke in non-diabetes and diabetes cohorts (as described in Figure 2)

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.



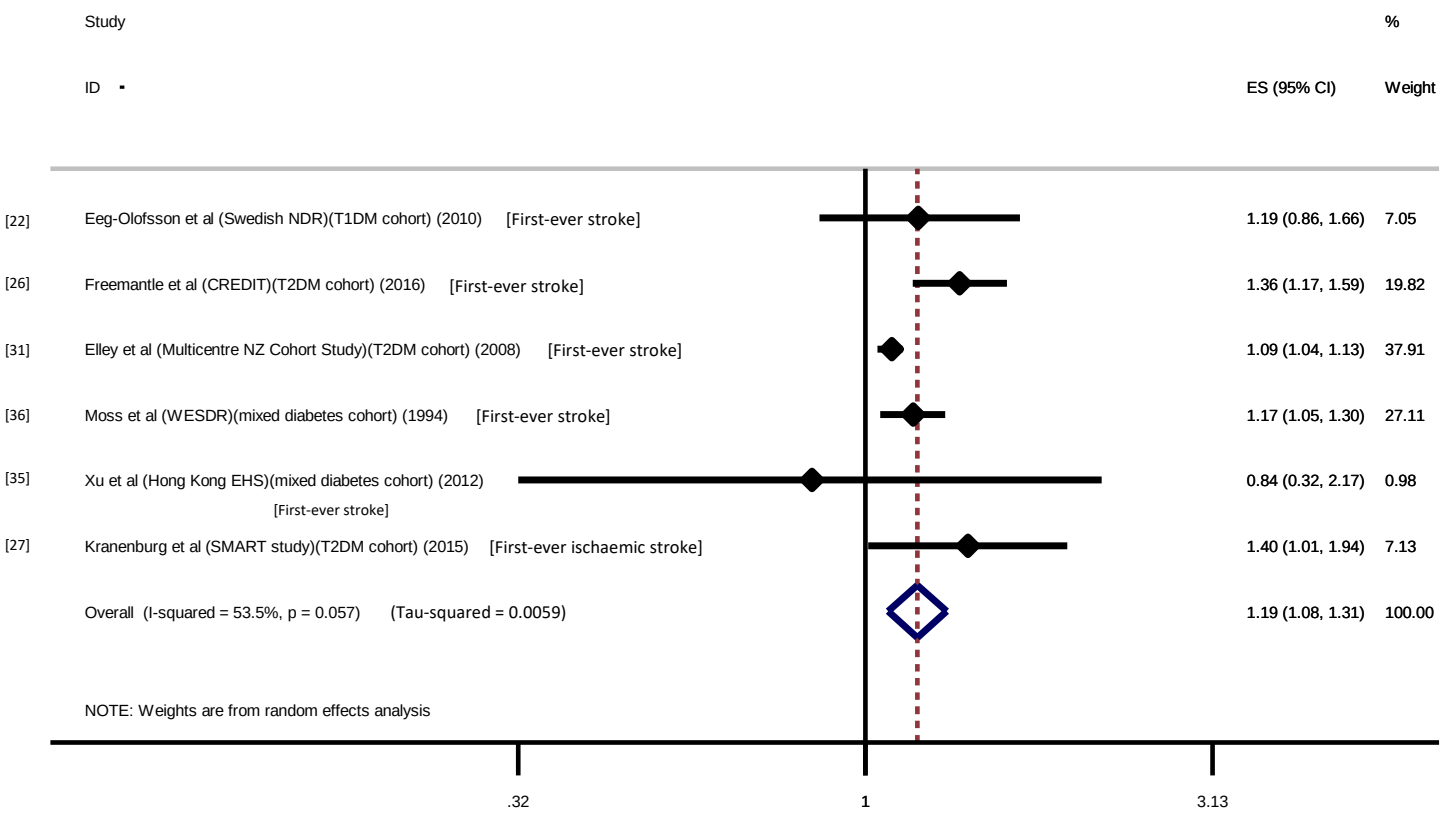
Supplementary Figure S18: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and first-ever ischaemic stroke in non-diabetes and diabetes cohorts (as described in Figure 2)

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.



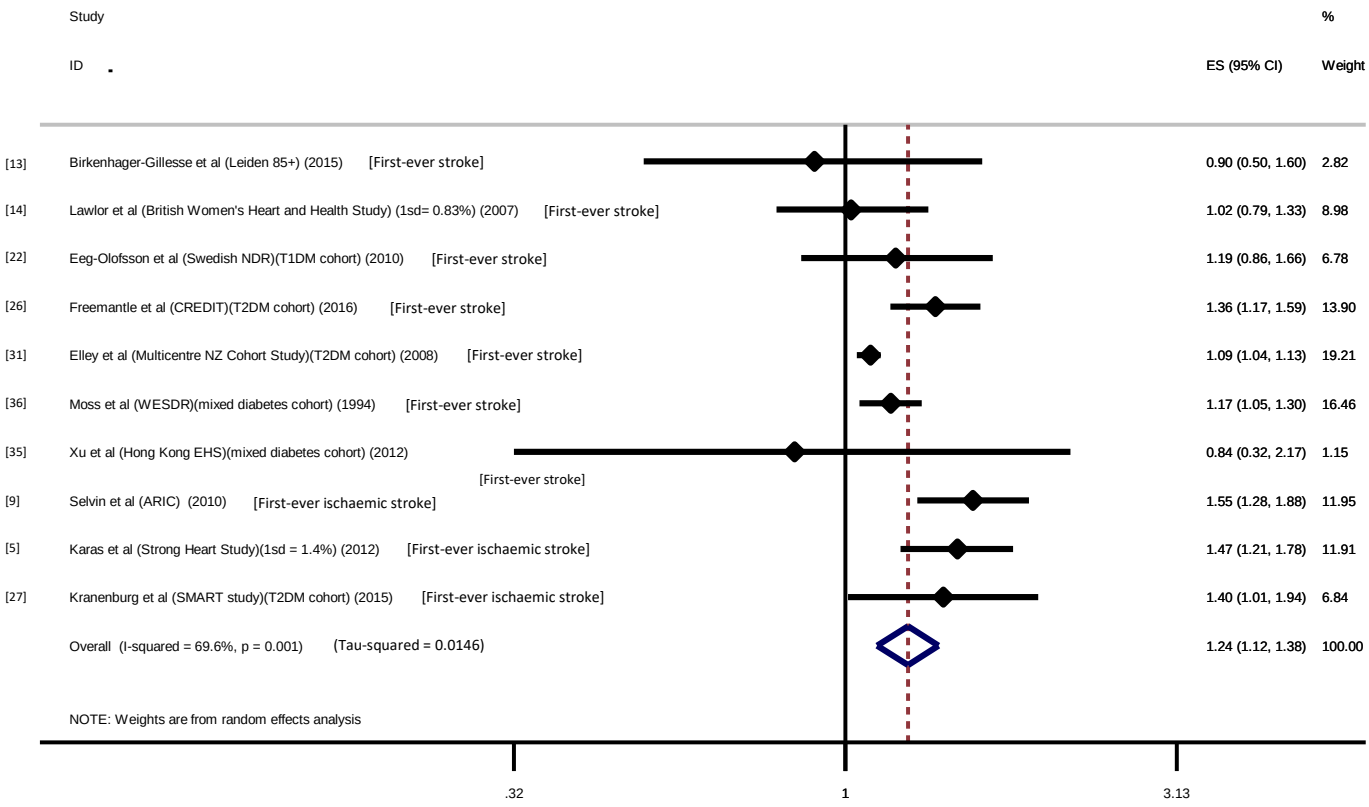
Supplementary Figure S19: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, in non-diabetes cohorts

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



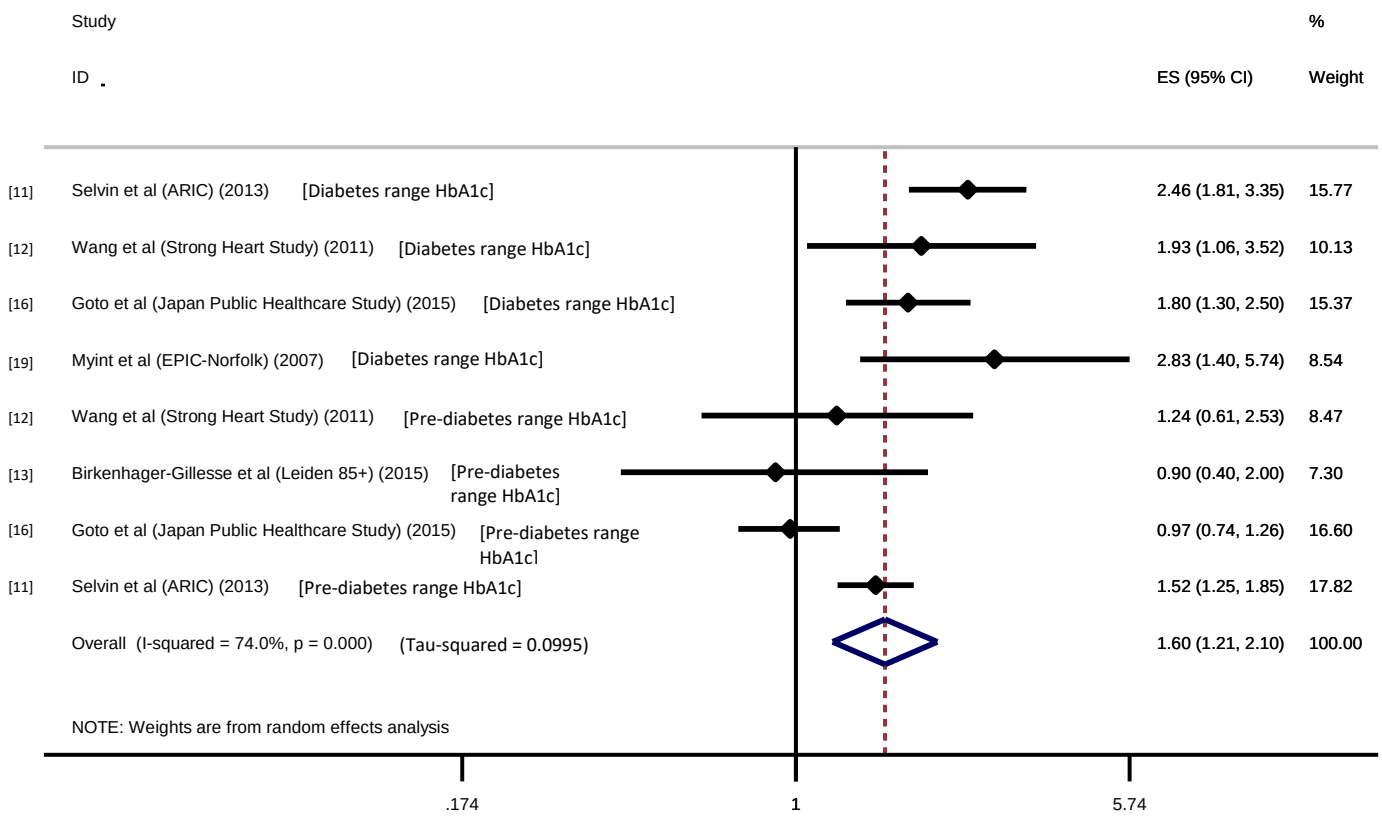
Supplementary Figure S20: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, in diabetes cohorts

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.



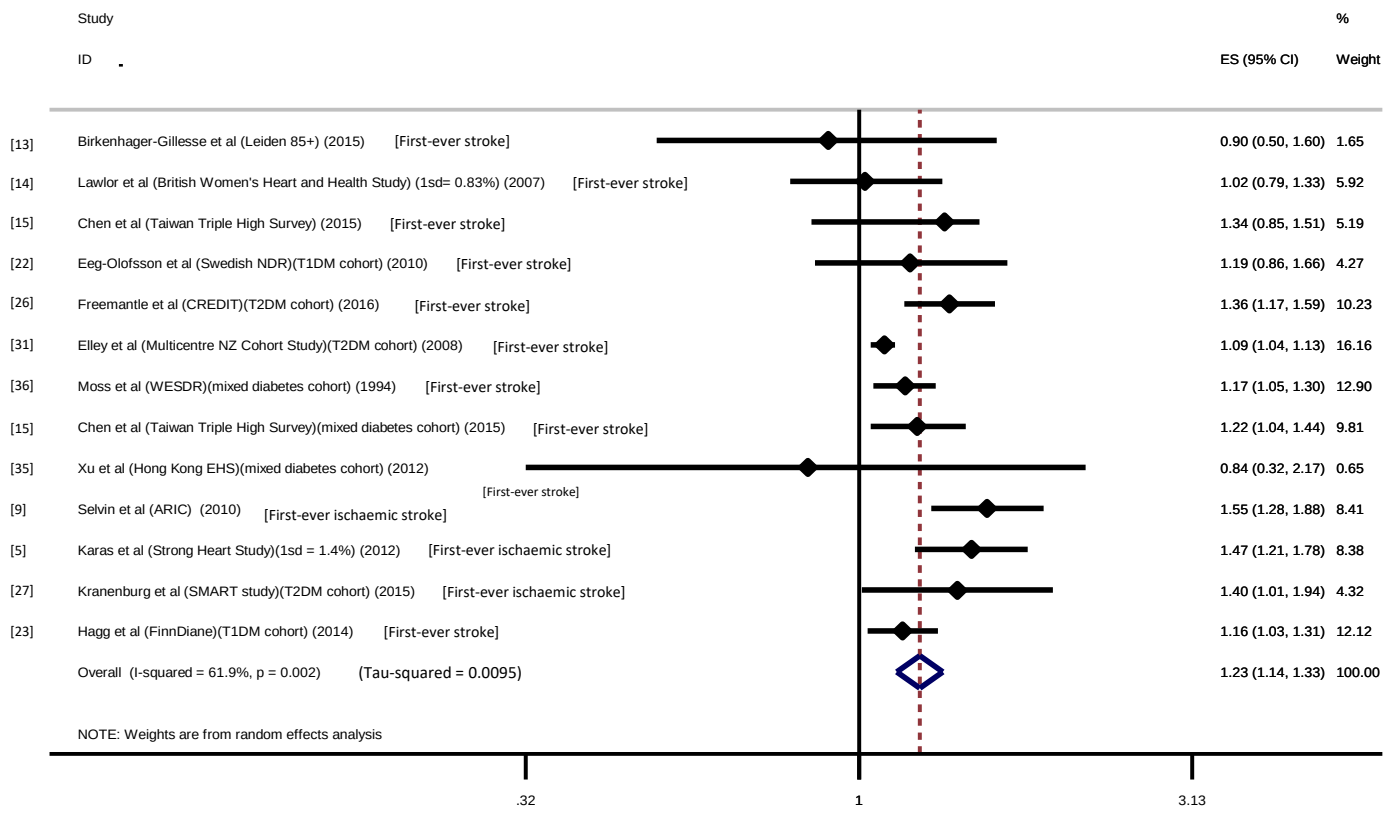
Supplementary Figure S21: Additional subgroup analysis: Association between study-quoted rising 1% HbA1c increments and the combined outcome of first-ever stroke and first-ever ischaemic stroke events, regardless of cohort diabetes status (combination of Supplementary Figures S19 and S20)

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.

Data supplement references:

1. SIGN Methodology Checklist 3: Cohort studies. Scotland: Scottish Intercollegiate Guideline Network; 2012. Available from: http://www.sign.ac.uk/assets/checklist_for_cohort_studies.rtf. Accessed 21 March, 2017.

2. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiologic Reviews. 1987;9:1-30.

3. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus. Ann Intern Med. 2004;141:421-431.

4. Zhang Y, Hu G, Yuan Z, Chen L. Glycosylated Hemoglobin in Relationship to Cardiovascular Outcomes and Death in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. PLoS One. 2012;7:e42551.

5. Karas MG, Devereux RB, Wiebers DO, Whisnant JP, Best LG, Lee ET, Howard BV, Roman MJ, Umans JG, Kizer JR. Incremental Value of Biochemical and Echocardiographic Measures in Prediction of Ischemic Stroke: The Strong Heart Study. Stroke. 2012;43:720-726.

6. Skriver MV, Stovring H, Kristensen JK, Charles M, Sandbaek A. Short-term impact of HbA1c on morbidity and all-cause mortality in people with type 2 diabetes: a Danish population-based observational study. Diabetologia. 2012;55:2361-2370.

7. Kong APS, Yang X, Ko GTC, So WY, Chan WB, Ma RCW, Ng VWS, Chow CC, Cockram CS, Tong PCY, Wong V, Chan JCN. Effects of Treatment Targets on Subsequent Cardiovascular Events in Chinese Patients With Type 2 Diabetes. Diabetes Care. 2007;30:953-959.

8. Cederholm J, Zethelius B, Nilsson PM, Eeg-Olofsson K, Eliasson B, Gudbjornsdottir S, on behalf of the Swedish National Diabetes Register. Effect of tight control of HbA1c and blood pressure on cardiovascular diseases in type 2 diabetes: An observational study from the Swedish National Diabetes Register (NDR). Diabetes Research and Clinical Practice. 2009;86:74-81.

9. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL. Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults. NEJM. 2010;362:800-811.

10. Selvin E, Rawlings AM, Lutsey PL, Maruthur N, Pankow JS, Steffes M, Coresh J. Fructosamine and Glycated Albumin and the Risk of Cardiovascular Outcomes and Death. Circulation. 2015;132:269-277.

11. Selvin E, Rawlings AM, Bergenstal RM, Coresh J, Brancati FL. No Racial Differences in the Association of Glycated Hemoglobin With Kidney Disease and Cardiovascular Outcomes. Diabetes Care. 2013;36:2995-3001.

12. Wang H, Shara NM, Lee ET, Devereux R, Calhoun D, de Simone G, Umans JG, Howard BV. Hemoglobin A1c, Fasting Glucose, and Cardiovascular Risk in a Population With High Prevalence of Diabetes: The Strong Heart Study. Diabetes Care. 2011;34:1952-1958.

13. Birkenhager-Gillesse EG, den Elzen WPJ, Achterberg WP, Mooijaart SP, Gussekloo J, de Craen AJM. Association Between Glycosylated Hemoglobin and Cardiovascular Events and Mortality in Older Adults without Diabetes Mellitus in the General Population: The Leiden 85-Plus Study. Journal of the American Geriatrics Society. 2015;63:1059-1066.

14. Lawlor DA, Fraser A, Ebrahim S, Smith GD. Independent Associations of Fasting Insulin, Glucose and Glycated Haemoglobin with Stroke and Coronary Heart Disease in Older Women. PLoS Medicine. 2007;4:e263 .

15. Chen YY, Lin YJ, Chong E, Chen PC, Chao TF, Chen SA, Chien KL. The Impact of Diabetes Mellitus and Corresponding HbA1c Levels on the Future Risks of Cardiovascular Disease and Mortality: A Representative Cohort Study in Taiwan. PLoS One. 2015;10:e0123116.

16. Goto A, Noda M, Matsushita Y, Goto M, Kato M, Isogawa A,Takahashi Y, Kurotani K, Oba S, Nanri A, Mizoue T, Yamagishi K, Yatsuya H, Saito I, Kokubo Y, Sawada N, Inoue M, Iso H, Kadowaki T, Tsugane S, JPHC Study Group. Hemoglobin A1c Levels and the Risk of Cardiovascular Disease in People Without Known Diabetes: A Population-Based Cohort Study in Japan. Medicine. 2015;94:e785.

17. Chonchol M, Katz R, Fried LF, Sarnak MJ, Siscovick DS, Newman AB, Strotmeyer ES, Bertoni A, Shlipak MG. Glycosylated hemoglobin and the risk of death and cardiovascular mortality in the elderly. Nutrition, Metabolism and Cardiovascular Diseases. 2010;20:15-21.

18. Ikeda F, Doi Y, Ninomiya T, Hirakawa Y, Mukai N, Hata J, Shikata K, Yoshida D, Matsumoto T, Kitazono T, Kiyohara Y. Haemoglobin A1c even within non-diabetic level is a predictor of

cardiovascular disease in a general Japanese population: the Hisayama Study. Cardiovascular Diabetology. 2013;12:164.

19. Myint PK, Sinha S, Wareham NJ, Bingham SA, Luben RN, Welch AA, Khaw KT. Glycated Hemoglobin and Risk of Stroke in People Without Known Diabetes in the European Prospective Investigation Into Cancer (EPIC)-Norfolk Propsective Populaton Study: A Theshold Relationship?. Stroke. 2007;38:271-275.

20. Wu S, Shi Y, Wang C, Jia Q, Zhang N, Zhao X, Liu G, Wang Y, Liu L, Wang Y, On Behalf of the Investigators for the Survey on Abnormal Glucose Regulation in Patients With Acute Stroke Across China (ACROSS-China). Glycated Hemoglobin Independently Predicts Stroke Recurrence within One Year after Acute First-Ever Non-Cardioembolic Strokes Onset in A Chinese Cohort Study. PLoS One. 2013;8:e80690.

21. Stahl CH, Lind M, Svensson AM, Gudbjornsdottir S, Martensson A, Rosengren A. Glycaemic control and excess risk of ischaemic and haemorrhagic stroke in patients with type 1 diabetes: a cohort study of 33 453 patients. Journal of Internal Medicine. 2017;281:261-272.

22. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S, Eliasson B. Glycemic Control and Cardiovascular Disease in 7,454 Patients With Type 1 Diabetes: An observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33:1640-1646.

23. Hagg S, Thorn LM, Forsblom CM, Gordin D, Saraheimo M, Tolonen N, Waden J, Liebkind R, Putaala J, Tatlisumak T, Groop PH on behalf of the FinnDiane Study Group. Different Risk Factor Profiles for Ischemic and Hemorrhagic Stroke in Type 1 Diabetes Mellitus. Stroke. 2014;45:2558-2562.

24. Adler AI, Neil HAW, Manley SE, Holman RR, Turner RC for the UKPDS Study Group. Hyperglycemia and hyperinsulinemia at diagnosis of diabetes and their association with subsequent cardiovascular disease in the United Kingdom Prospective Diabetes Study (UKPDS 47). American Heart Journal. 1999;138:S353-S359.

25. Kontopantelis E, Springate DA, Reeves D, Ashcroft DM, Rutter M, Buchan I, Doran T. Glucose, blood pressure and cholesterol levels and their relationships to clinical outcomes in type 2 diabetes: a retropsective cohort study. Diabetologia. 2015;58:505-518.

26. Freemantle N, Danchin N, Calvi-Gries F, Vincent M, Home PD. Relationship of glycaemic control and hypoglycaemic episodes to 4-year cardiovascular outcomes in people with type 2 diabetes starting insulin. Diabetes, Obesity and Metabolism. 2016;18:152-158.

27. Kranenburg G, van der Graaf Y, van der Leeuw J, Nathoe HMW, de Borst GJ, Kappelle LJ, Visseren FLJ, Westerink J on behalf of the SMART Study Group. The Relation Between HbA1c and Cardiovascular Events in Patients With Type 2 Diabetes With and Without Vascular Disease. Diabetes Care. 2015;38:1930-1936.

28. Lin CC, Yang CP, Li CI, Liu CS, Chen CC, Lin WY, Hwang KL, Yang SY, Li TC. Visit-to-visit variability of fasting plasma glucose as predictor of ischemic stroke: competing risk analysis in a national cohort of Taiwan Diabetes Study. BMC Medicine. 2014;12:165.

29. Zhao W, Katzmarzyk PT, Horswell R, Wang Y, Johnson J, Hu G. Sex Differences in the Risk of Stroke and HbA1c among Diabetic Patients. Diabetologia. 2014;57:918-926.

30. Giorda CB, Avogaro A, Maggini M, Lombardo F, Mannucci E, Turco S, Alegiani SS, Raschetti R, Velussi M, Ferrannini E, The DAI Study Group. Incidence and Risk Factors for Stroke in Type 2 Diabetic Patients: The DAI Study. Stroke. 2007;38:1154-1160.

31. Elley CR, Kenealy T, Robinson E, Drury PL. Glycated haemoglobin and cardiovascular outcomes in people with Type 2 diabetes: a large prospective cohort study. Diabetic Medicine. 2008;25:1295-1301.

32. Camafort M, Alvarez-Rodriguez LR, Munoz-Torrero JFS, Sahuquillo JC, Lopez-Jimenez L, Coll R, Monreal M, the FRENA Investigators. Glucose control and outcome in patients with stable diabetes and previous coronary, cerebrovascular or peripheral artery disease. Findings from the FRENA Registry. Diabetic Medicine. 2011;28:73-80.

33. Bots SH, van der Graaf Y, Nathoe HMW, de Borst GJ, Kappelle JL, Visseren FLJ, Westerink J, on behalf of the SMART Study Group. The influence of baseline risk on the relation between HbA1c and risk for new cardiovascular events and mortality in patients with type 2 diabetes and symptomatic cardiovascular disease. Cardiovascular Diabetology. 2016;15:101.

34. Hayashi T, Araki A, Kawashima S, Sone H, Watanabe H, Ohrui T, Yokote K, Takemoto M, Kubota K, Noda M, Noto H, Ina K, Nomura H, Japan CDM group. Metabolic predictors of ischemic heart disease

and cerebrovascular attack in elderly diabetic individuals: difference in risk by age. Cardiovascular Diabetology. 2013;12:10.

35. Xu L, Chan WM, Hui YF, Lam TH. Association between HbA1c and cardiovascular disease mortality in older Hong Kong Chinese with diabetes. Diabetic Medicine. 2012;29:393-398.

36. Moss SE, Klein R, Klein BEK, Meuer SM. The Association of Glycemia and Cause-Specific Mortality in a Diabetic Population. Arch Intern Med. 1994;154:2473-2479.

37. Selvin E, Coresh J, Shahar E, Zhang L, Steffes M, Sharrett AR. Glycaemia (haemoglobin A1c) and incident ischaemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Lancet Neurology. 2005;4:821-826.

38. Alter M, Lai SM, Friday G, Singh V, Kumar VM, Sobel E. Stroke Recurrence in Diabetics: Does Control of Blood Glucose Reduce Risk?. Stroke. 1997;28:1153-1157.

39. Ashburner JM, Go AS, Chang Y, Fang MC, Fredman L, Applebaum KM, Singer DE. Effect of Diabetes and Glycemic Control on Ischemic Stroke Risk in AF Patients: ATRIA Study. Journal of the American College of Cardiology. 2016;67:239-247.

40. Hirai FE, Moss SE, Klein BEK, Klein R. Relationship of Glycemic Control, Exogenous Insulin, and C-Peptide Levels to Ischemic Heart Disease Mortality Over a 16-Year Period in People With Older-Onset Diabetes: The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). Diabetes Care. 2008;31:493-497.