

## Supplemental Online Content

Seminer A, Mulihamo A, O'Brien C, et al. Cardioprotective glucose-lowering agents and dementia risk: a systematic review and meta-analysis. *JAMA Neurol*. Published online April 7, 2025. doi:10.1001/jamaneurol.2025.0360

**eMethods.** Search strategy

**eFigure 1.** PRISMA flow

**eFigure 2.** Risk of bias

**eFigure 3.** Funnel plot

**eFigure 4.** Association of glucose-lowering therapy with all dementia, meta-regression by proportion of female participants enrolled

**eFigure 5.** Association of glucose-lowering therapy with Lewy body Dementia

**eFigure 6.** Subgroup analysis above and below median follow-up

This supplemental material has been provided by the authors to give readers additional information about their work.

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## eMethods – Search strategy

SGLT-2 OR sodium-glucose cotransporter-2 inhibitor OR sglt-2 inhibitor OR empagliflozin OR

canagliflozin OR luseogliflozin OR dapagliflozin OR ertugliflozin OR tofogliflozin OR sergliflozin

OR remogliflozin OR ipragliflozin

OR

Glp-1 OR glucagon-like peptide-1 receptor OR glucagon-like peptide-1 receptor agonist OR

lixisenatide OR liraglutide OR semaglutide OR albiglutide OR dulaglutide OR exanatide

OR

biguanide OR metformin

OR

pioglitazone

AND

Usual care OR placebo

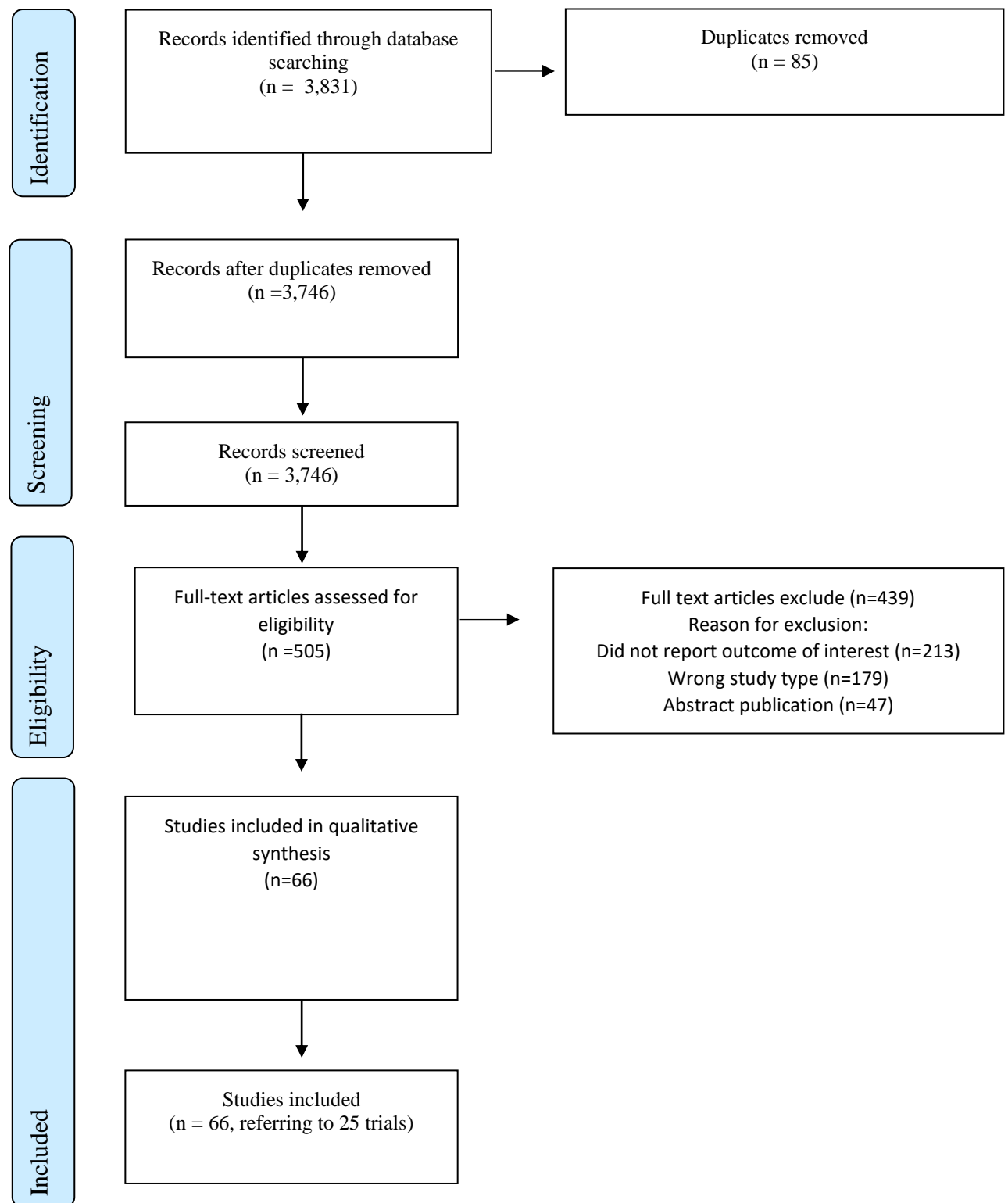
AND

RCT sensitive search strategy

*Note – dementia/cognitive impairment terms are intentionally omitted as they are unlikely to be included in study abstracts.*

## Figures

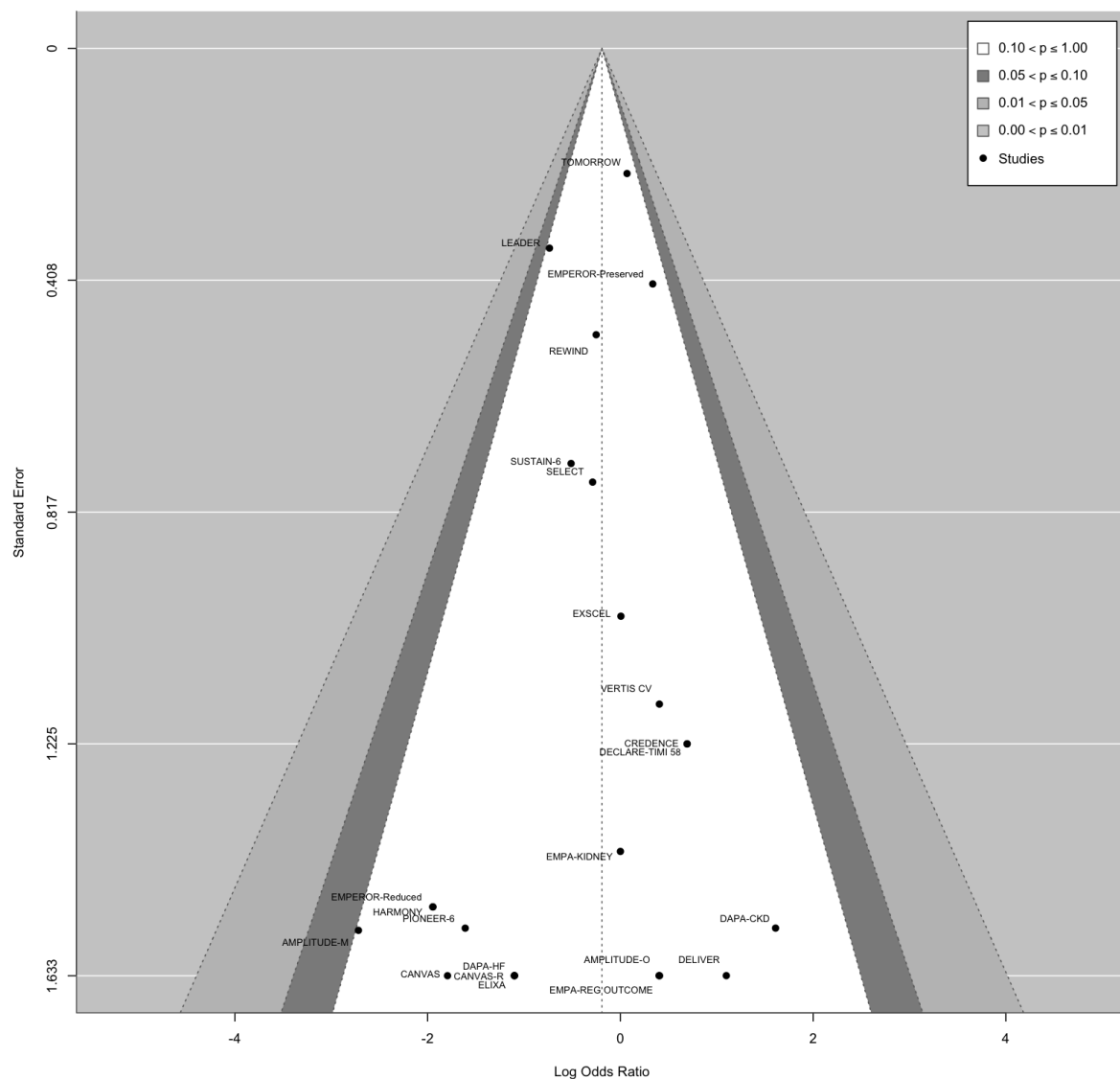
eFigure 1 – PRISMA flow



eFigure 2 – Risk of bias

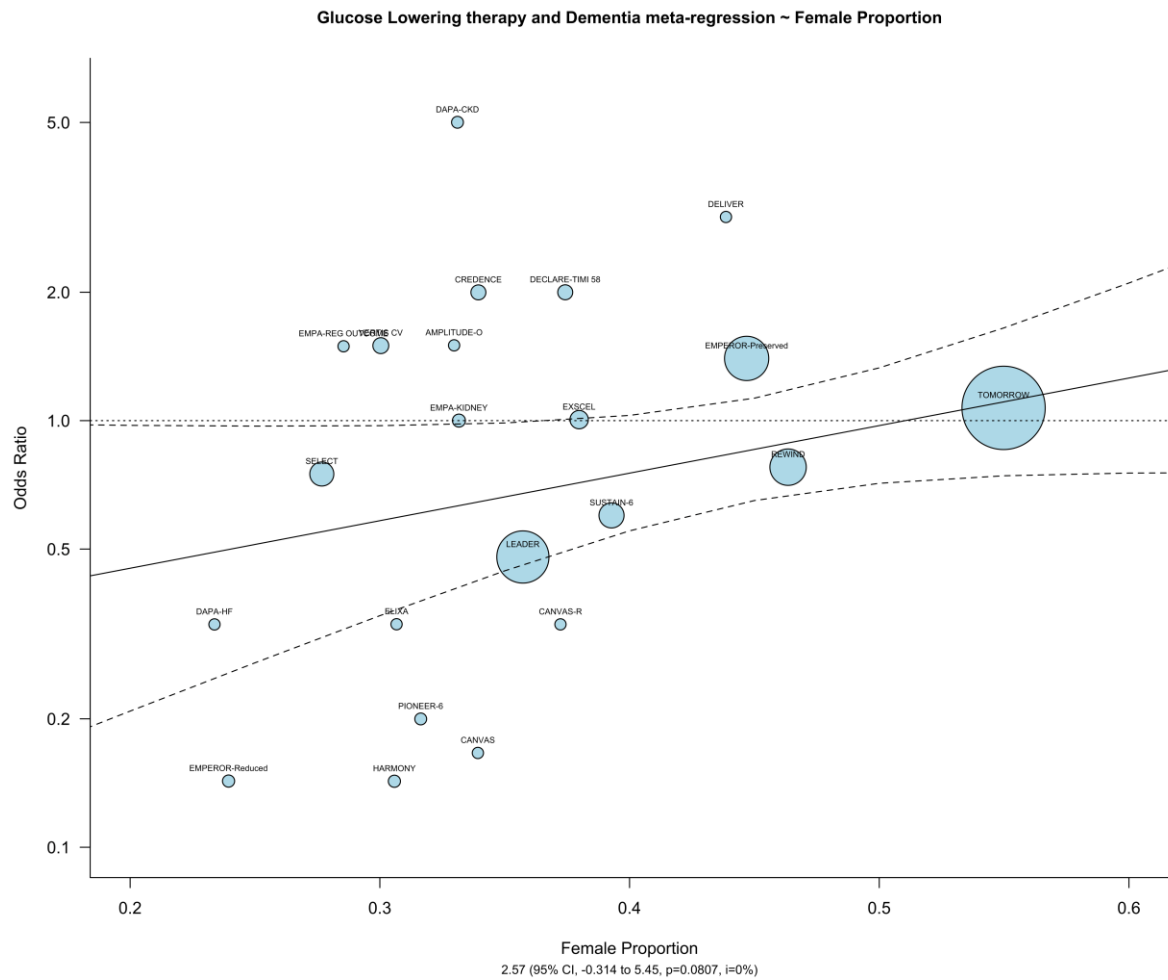
Unique ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall	
EMPA-REG OUTC	Empagliflozin	Placebo	+	+	+	+	+	+	+ Low risk ! Some concerns - High risk
CANVAS-R	Canagliflozin	Placebo	+	+	+	+	+	+	
CREDENCE	Canagliflozin	Placebo	+	+	+	+	+	+	
DAPA-HP	Dapagliflozin	Placebo	+	+	+	+	+	+	D1 Randomisation process D2 Deviations from the intended interventions D3 Missing outcome data D4 Measurement of the outcome D5 Selection of the reported result
DECLARE-TIMI 5	Dapagliflozin	Placebo	+	+	+	+	+	+	
DAPA-CKD	Dapagliflozin	Placebo	+	+	+	+	+	+	
EMPEROR-Reduc	Empagliflozin	Placebo	+	+	+	+	+	+	
VERTIS CV	Ertugliflozin	Placebo	+	+	+	+	+	+	
EMPEROR-Prese	Empagliflozin	Placebo	+	+	+	+	+	+	
CANVAS	Canagliflozin	Placebo	+	+	+	+	+	+	
DELIVER	Dapagliflozin	Placebo	+	+	+	+	+	+	
EMPA-KIDNEY	Empagliflozin	Placebo	+	+	+	+	+	+	
ELIXA	Lixisenatide	Placebo	+	+	+	+	+	+	
LEADER	Liraglutide	Placebo	+	+	+	+	+	+	
EXSCEL	Exenatide	Placebo	+	+	+	+	+	+	
HARMONY	Albiglutide	Placebo	+	+	+	+	+	+	
REWIND	Dulaglutide	Placebo	+	+	+	+	+	+	
PIONEER-6	Semaglutide	Placebo	+	+	+	+	+	+	
AMPLITUDE-O	Efpeglenatide	Placebo	+	+	+	+	+	+	
AMPLITUDE-M	Efpeglenatide	Placebo	+	+	+	+	+	+	
SUSTAIN	Semaglutide	Placebo	+	+	+	+	+	+	
TOMORROW	Pioglitazone	Placebo	+	+	+	+	+	+	
SELECT	Semaglutide	Placebo	+	+	+	+	+	+	

eFigure 3 – Funnel plot

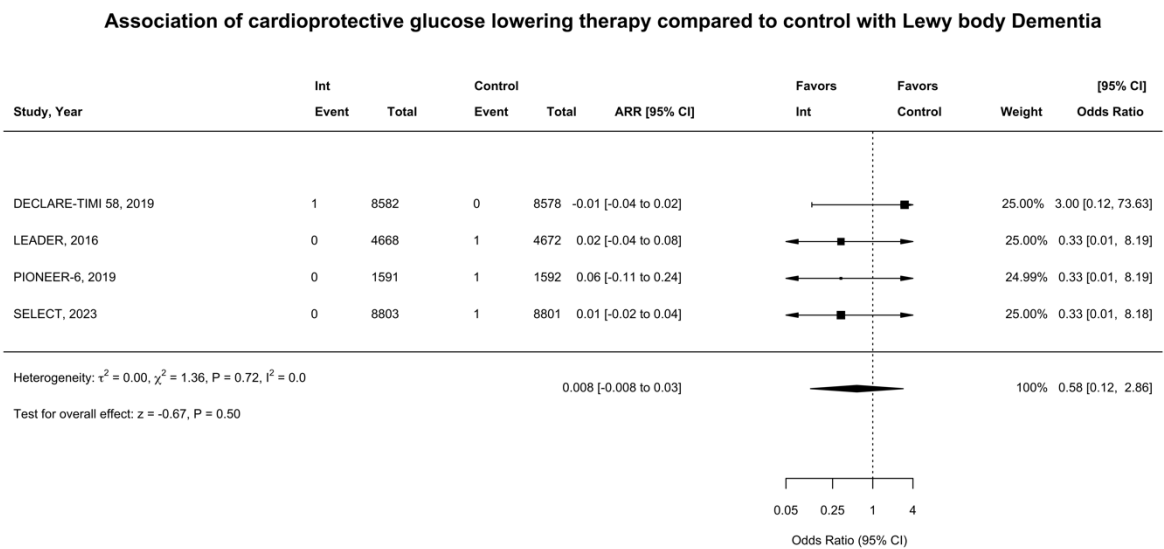


eFigure 3 – Contour enhanced funnel plot for included trials, primary outcome (dementia or cognitive impairment). Different levels of statistical significance for studies are indicated by the shaded regions, detailed within the figure. The grey vertical line represents the summary estimate. Each point is labelled to identify corresponding study/studies with label offset to the left of point.

eFigure 4 – Association of glucose-lowering therapy with all dementia, meta-regression by proportion of female participants enrolled



eFigure 5 – Association of glucose-lowering therapy with Lewy body Dementia

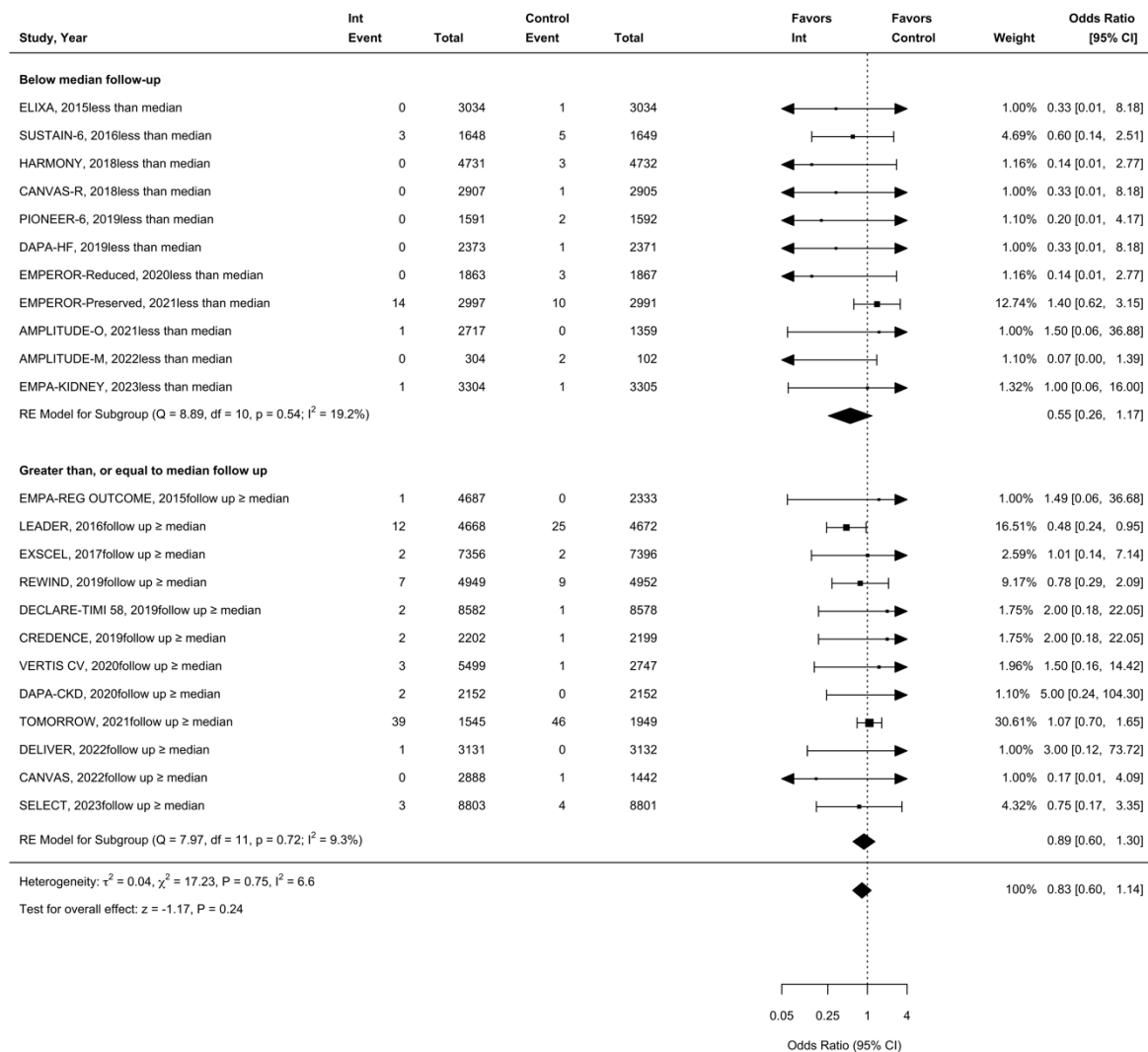


eFigure 5 – Forest plot demonstrating the association of glucose lowering therapy compared to control with Lewy body dementia. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.  
Int - Intervention, CI-Confidence Interval



eFigure 6 – Subgroup analysis above and below median follow-up

**Association of Glucose lowering therapy compared to control with Dementia or Cognitive Impairment**



eFigure 6 – Forest plot demonstrating the association of glucose lowering therapy compared to control with dementia or cognitive impairment by follow up duration. The squares and bars represent the mean values and 95% confidence intervals of the effect sizes, while the area of the squares reflects the weight of the studies. The combined effects appear as diamonds and the vertical dashed line represents the line of no effect.  
Int - Intervention, CI-Confidence Interval