Development of diabetes in trials of statins

An example of a systematic review and meta-analysis

Sattar N *et al.* Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; **375**: 735-742.

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Search strategy and selection criteria

Large placebo and standard-care-controlled endpoint trials of statins.

Excluded:

- trials comparing statins or statin doses,
- unstable individuals, organ transplants, haemodialysis.
- only patients with diabetes,
- trials assessing change in surrogate markers of CVD,
- 1000 or fewer participants,
- mean follow-up of 1 year or less.

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Search strategy and selection criteria

Trials needed to follow up patients in both treatment groups identically to avoid systematic error and resultant bias in diagnosis of incident diabetes.

Searched: Medline, Embase, and the Cochrane Central Register of Controlled Trials, from 1994 to 2009

Searched for randomised placebo and standard care-controlled endpoint trials of statins with the term “statin” as a title word and keyword, and with names of individual statins to identify reports of trials of adult patients.

Reports that were published in English between 1994 and 2009.

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Search strategy and selection criteria

Identified 2841 reports.

Reviewed by two independent readers, with a third reviewer to settle any discrepancies.

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Data sources

Contacted investigators from nine trials about unpublished data for incident diabetes.

Received data from six of these trials.

Final: 13 trials, for which six had previously published data for incident diabetes and seven had not.

Because the effect estimates for incident diabetes were directly reported as hazard ratios (HRs) in only three of the six published trials, we adopted a standard approach across all trials, in which we calculated odds ratios (ORs) and their 95% CIs from the abstracted data for the number of patients who did not have diabetes at baseline and those developing incident diabetes.

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Statistical analysis

Overall OR with a random-effects model meta-analysis, which assumes that the true underlying effect varies between trials.

Assessed statistical heterogeneity between trials with I^2 statistic (with 95% CIs), which provides a measure of the proportion of overall variation that is attributable to between-trial heterogeneity.

Used risk estimates obtained with random-effects meta-analysis instead of fixed-effects models, because this approach provides a more conservative assessment (ie, wide CIs) of the average effect size.

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Statistical analysis

Used meta-regression analyses to investigate potential sources of heterogeneity between trials.

Factors investigated were baseline age, baseline BMI, and percentage change in LDL-cholesterol concentrations, and these factors were decided before the meta-analysis was undertaken.

We analysed data with Stata version 10.1.

To test for publication bias, we formed a funnel plot and undertook the Egger test..

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Trials	Statin and control
ASCOT-LLA	Atorvastatin 10 mg or placebo
HPS	Simvastatin 40 mg or placebo
JUPITER	Rosuvastatin 20 mg or placebo
WOSCOPS	Pravastatin 40 mg or placebo
LIPID	Pravastatin 40 mg or placebo
CORONA	Rosuvastatin 20 mg or placebo
PROSPER	Pravastatin 40 mg or placebo
MEGA	Pravastatin 10–20 mg or no treatment
AFCAPS TexCAPS	Lovastatin 20–40 mg or placebo
4S	Simvastatin 20–40 mg or placebo
ALLHAT-LLT	Pravastatin 40 mg or no treatment
GISSI HF	Rosuvastatin 10 mg or placebo
GISSI PREVENZIONE	Pravastatin 20 mg or no treatment

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Trials	Participant population
ASCOT-LLA	Hypertension, CVD risk factors, no CHD
HPS	History of CVD
JUPITER	No CVD
WOSCOPS	No MI, raised cholesterol
LIPID	MI or unstable angina in previous 3 years
CORONA	Systolic heart failure (NYHA II-IV)
PROSPER	Elderly people with CVD or at high risk
MEGA	No CVD, raised cholesterol, Japanese
AFCAPS TexCAPS	No CVD
4S	Previous MI or angina
ALLHAT-LLT	CHD or CHD risk factors
GISSI HF	Chronic heart failure (NYHA II–IV)
GISSI PREVENZIONE	MI within past 6 months

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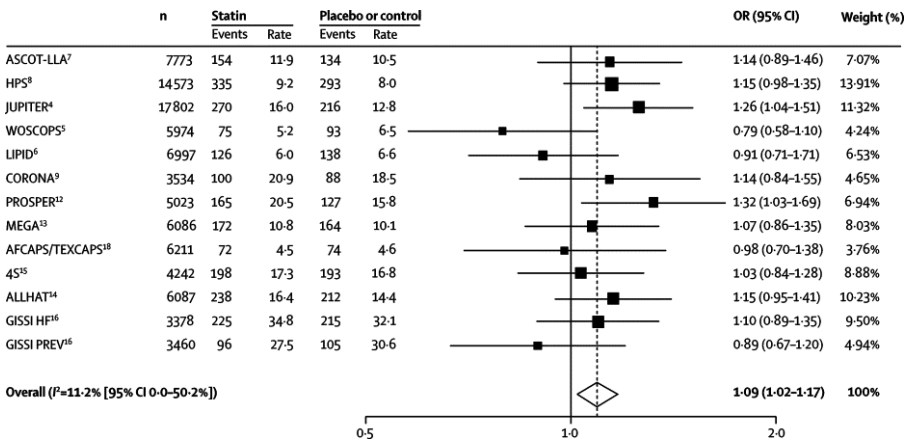

91,140 patients with no diabetes at baseline.

Rate = events per 1000 patient-years, random effects model.

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Meta-regression

On baseline age, baseline BMI, and on-treatment percentage reduction in LDL-cholesterol concentration

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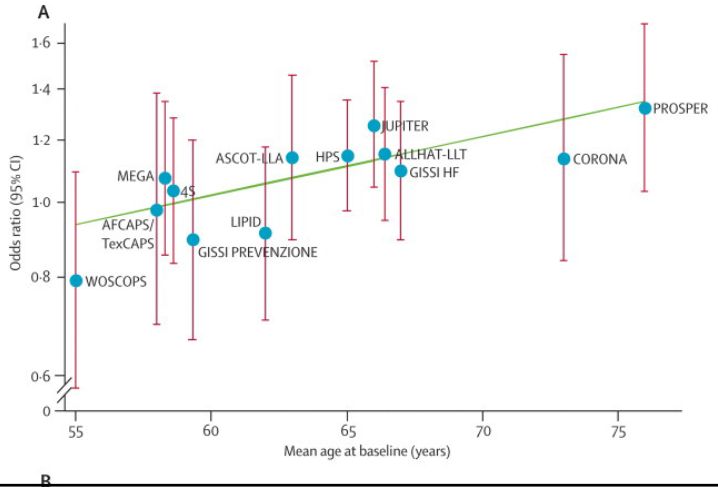

Age

p =0·019

(note log vertical scale)

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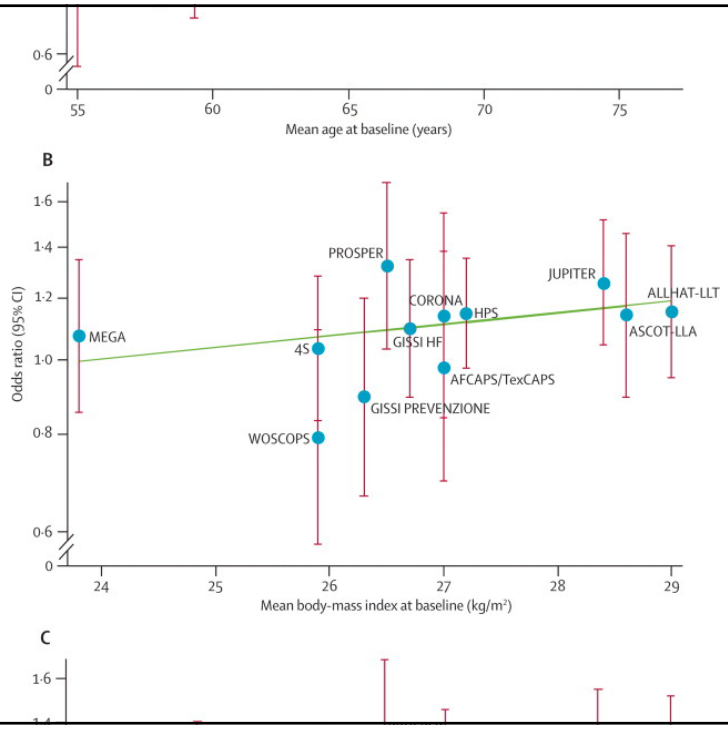
Meta-regression

On baseline age, baseline BMI, and on-treatment percentage reduction in LDL-cholesterol concentration

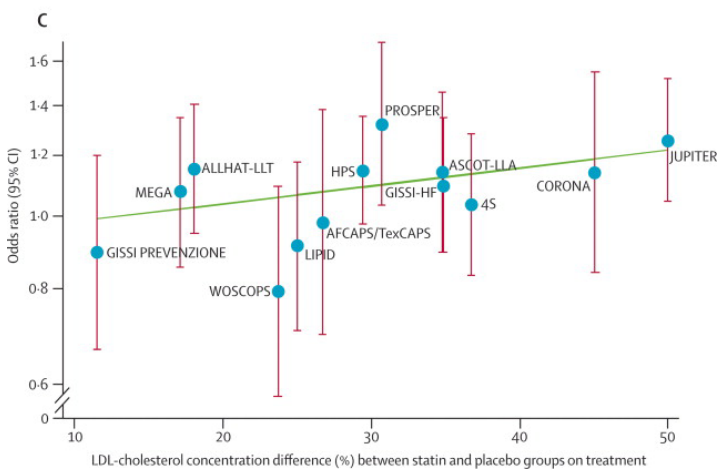
The older the person is, the greater the increase is in the risk of diabetes when taking statins.

For younger people, aged 55 to 60, no increased risk, OR ≈ 1.00.



BMI

p=0·177



LDL-cholesterol difference

p=0·102

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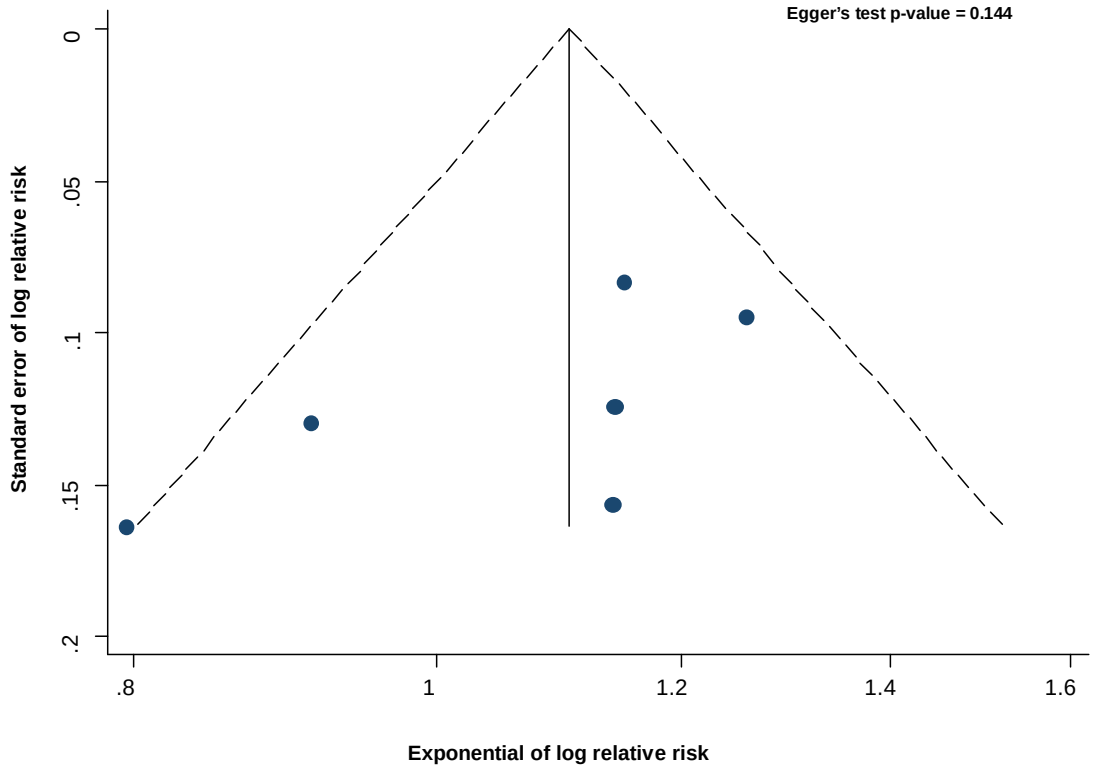
Publication bias

Go to PDF file for funnel plot of the trials with published diabetes incidence data.

Funnel plot of the six statin trials which published data on incident diabetes with 95% confidence limits



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Publication bias

There is nothing to suggest publication bias in the funnel plot or Eggar test.

Combined estimates:

- all trials OR = 1.09
- published trials OR = 1.10

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