eLife

RESEARCH ARTICLE

Figures and figure supplements

Weight loss, insulin resistance, and study design confound results in a meta-analysis of animal models of fatty liver

Harriet Hunter *et al*

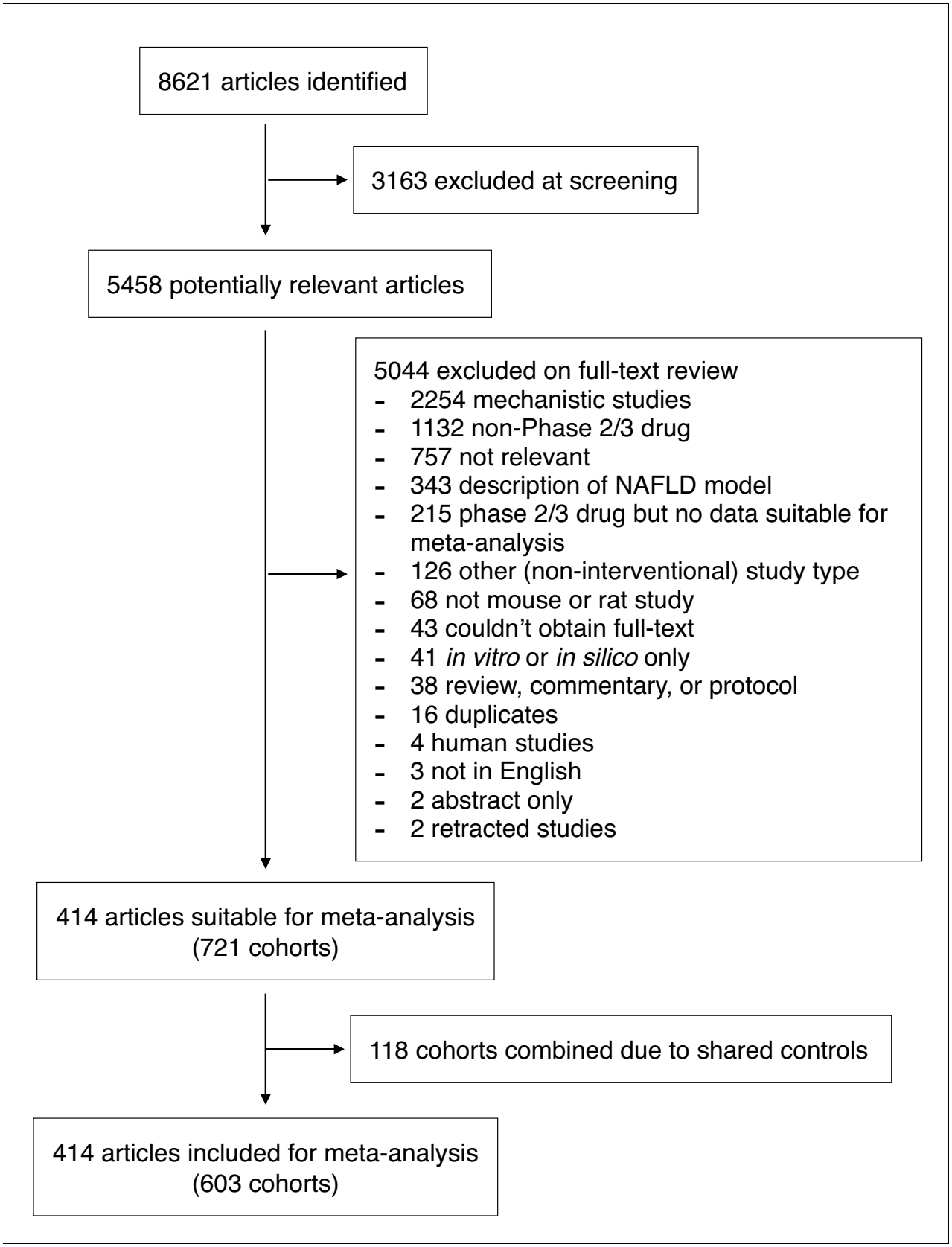

Figure 1. Study inclusion and exclusion flow chart.

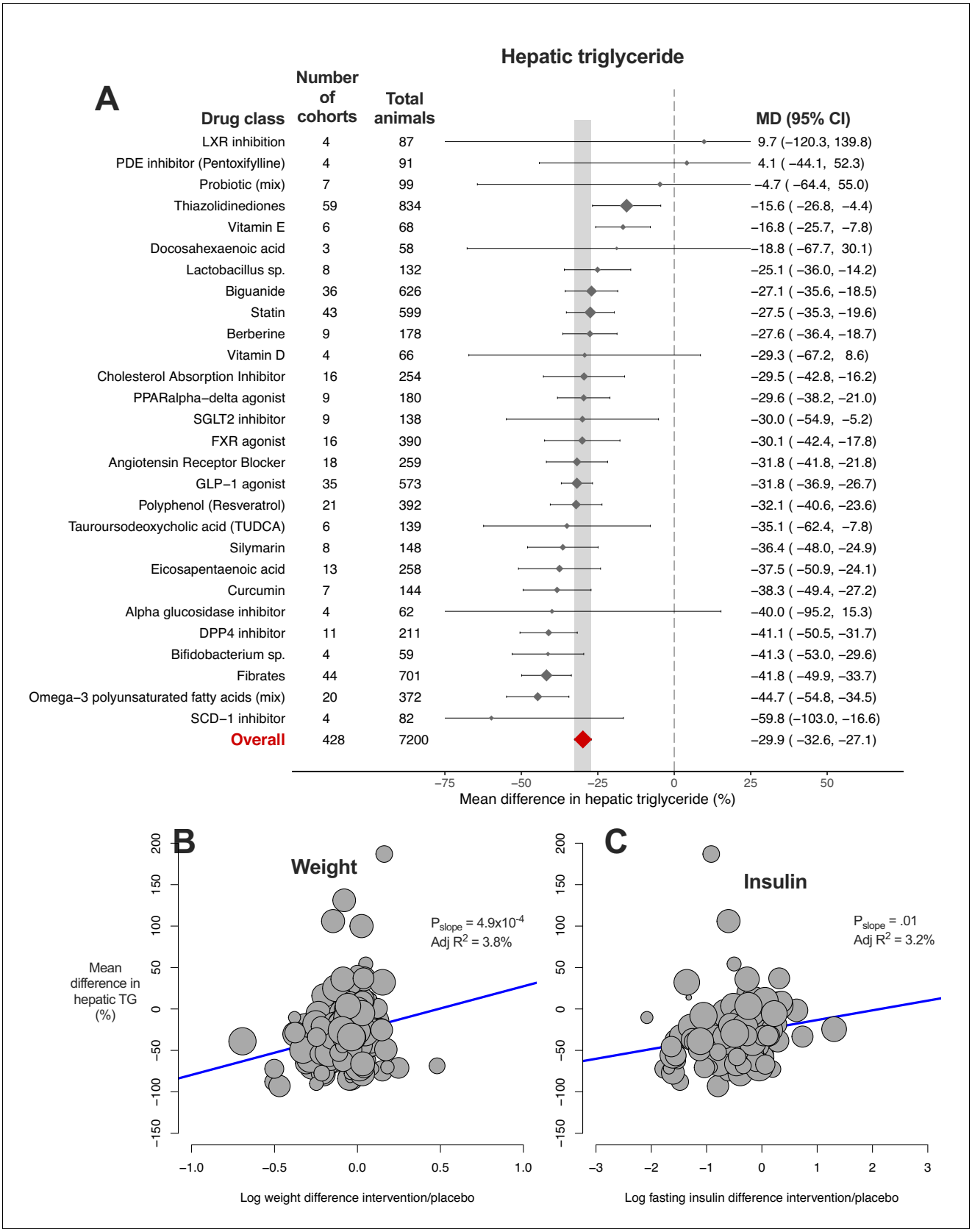

Figure 2. Meta-analysis of hepatic triglyceride content in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. Results are expressed as a percentage difference relative to control (/placebo). The

Figure 2 continued on next page

Figure 2 continued

total number of animals per subgroup is calculated from the sum of control and interventional animals for each subgroup. CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference; LXR, Liver X receptor; PDE, Phosphodiesterase; PPAR, Peroxisome proliferator-activated receptor; SCD-1, Stearoyl–CoA desaturase-1; SGLT2, Sodium-glucose co-transporter-2; TUDCA, Tauroursodeoxycholic acid. (**B**) Meta-regression bubble plot using (log) difference in weight between intervention and control animals, after removal of studies using models that induce weight loss. (**C**) Meta-regression bubble plot using (log) difference in fasting insulin between intervention and control animals, after removal of studies using models that induce weight loss.

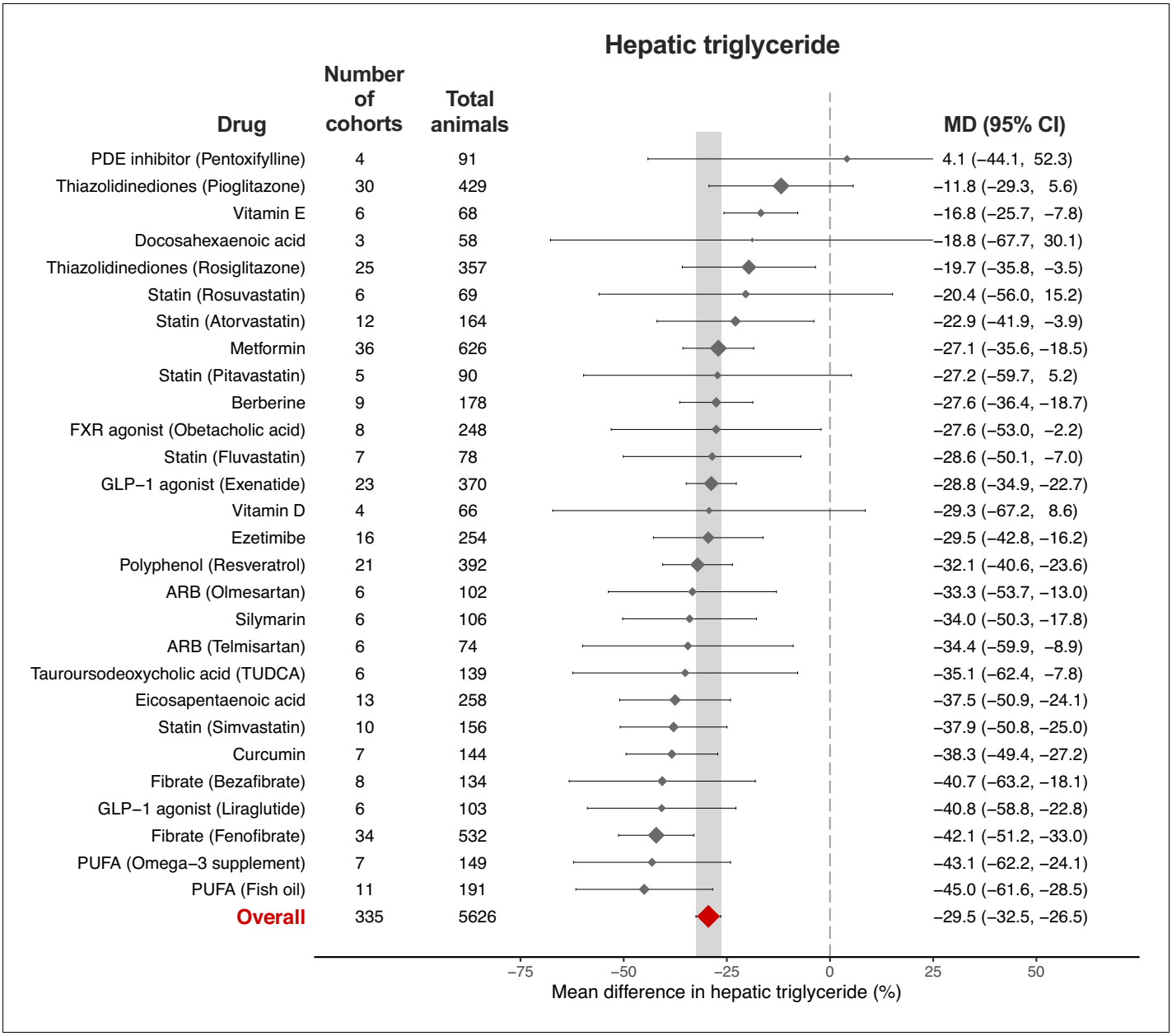

Figure 2—figure supplement 1. Meta-analysis of hepatic triglyceride content in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. Results are expressed as a percentage change relative to control (/placebo). Total animals is the sum of control and interventional animals for each subgroup. ARB, angiotensin receptor blocker; CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference; LXR, Liver X receptor; PDE, Phosphodiesterase; PPAR, Peroxisome proliferator-activated receptor; PUFA; omega-3 polyunsaturated fatty acid; SCD-1, Stearoyl–CoA desaturase-1; SGLT2, Sodium-glucose co-transporter-2; TUDCA, Tauroursodeoxycholic acid.

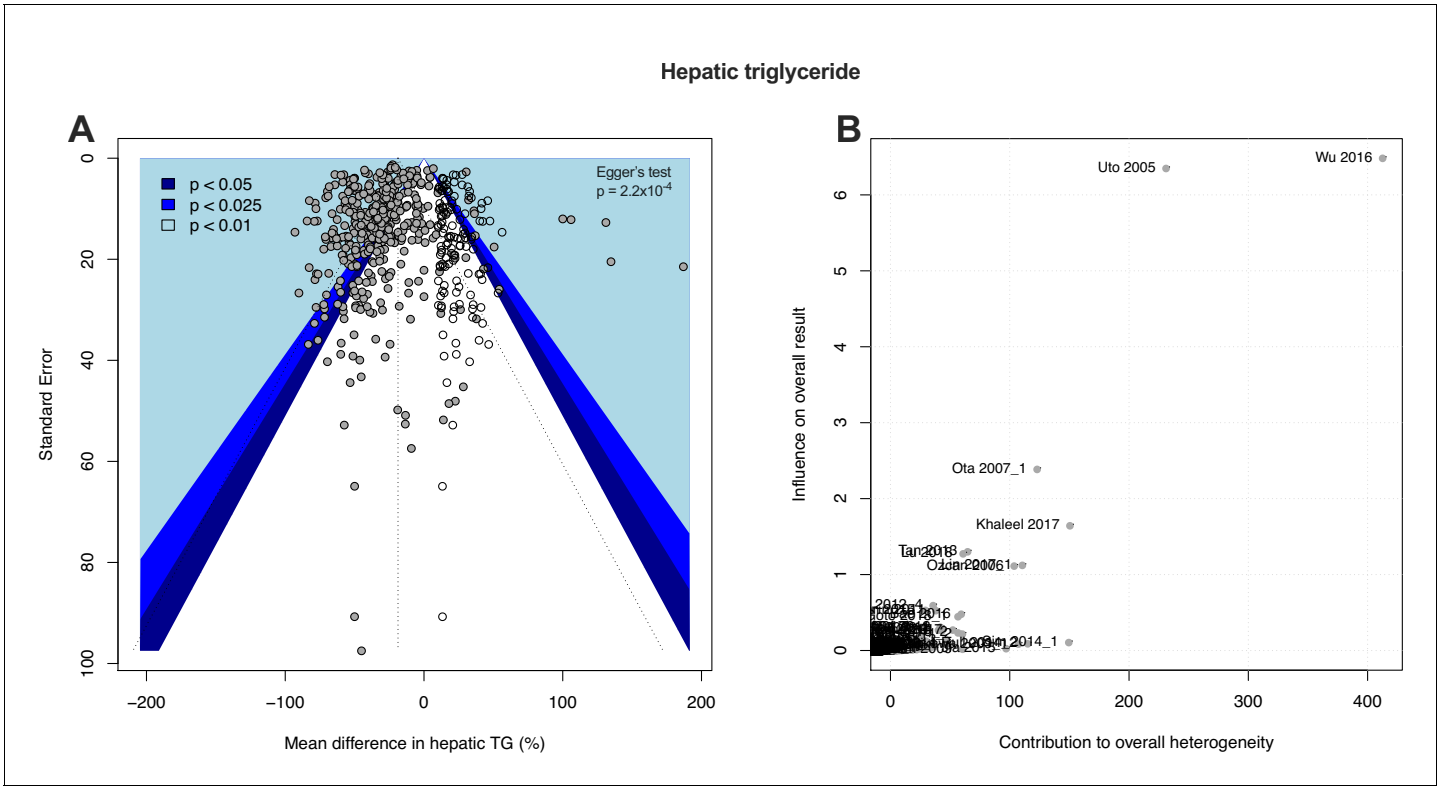

Figure 2—figure supplement 2. Funnel plot with trim-and-fill added studies and Baujat plot from meta-analysis of hepatic triglyceride content. (**A**) Funnel plot illustrating study distribution (publication) bias in 428 original studies (solid grey circles) with 125 added studies (from trim-and-fill). The statistical significance associated with each study is illustrated with the coloured background. Egger's test p-value indicates the likelihood that the original studies came from a symmetrical distribution. (**B**) Baujat plot showing individual study contributions to heterogeneity in the meta-analysis. The studies with highest contribution were excluded in a sensitivity analysis.

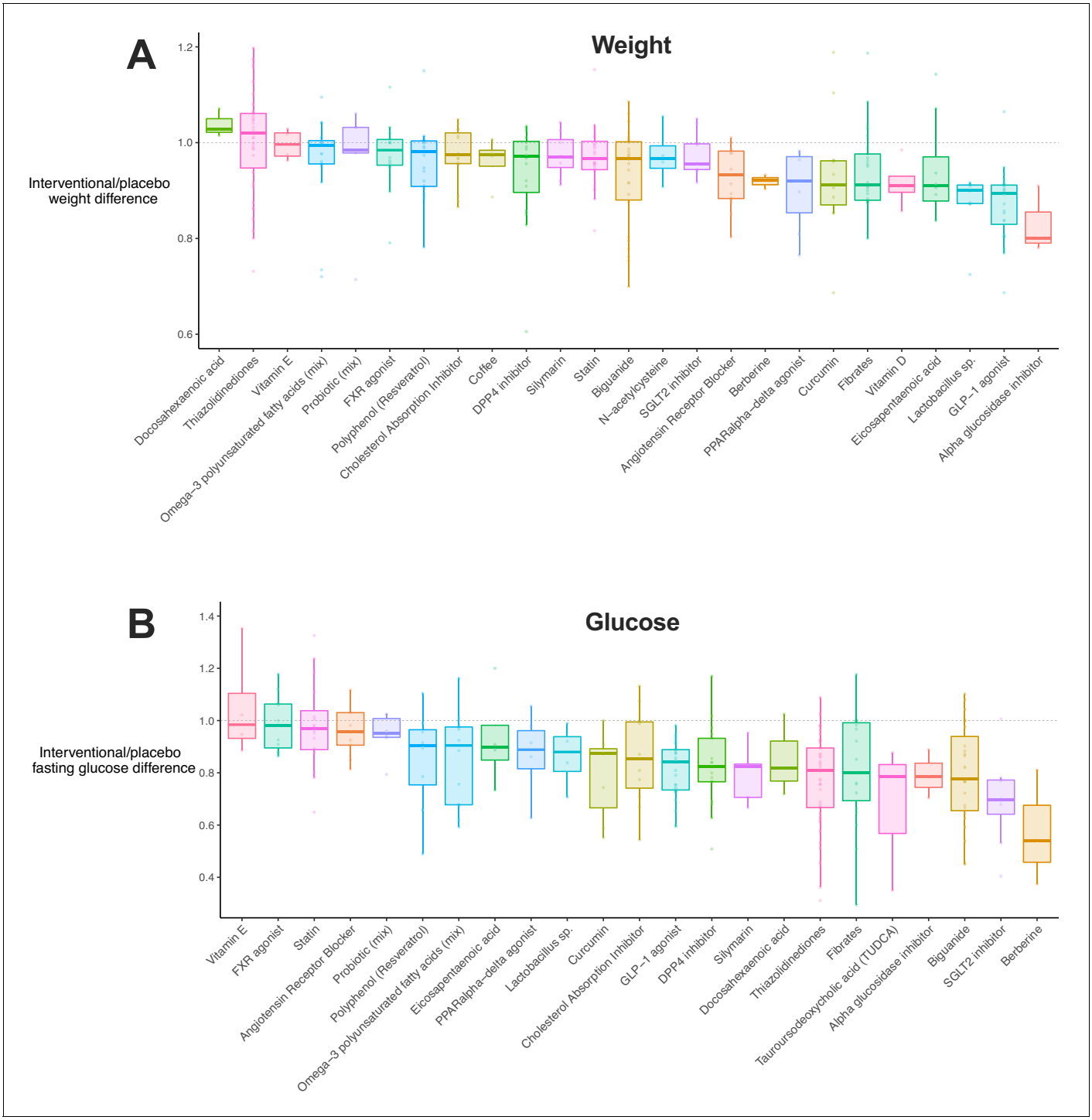

Figure 3. Weight and glucose difference associated with use of each drug class. (**A**) Box plot illustrating the difference in weight in interventional animals, expressed as a decimal of the weight of the control animals. Raw data points are plotted for each drug class. (**B**) Box plot for difference in fasting glucose in interventional animals, expressed as a decimal of the weight of the control animals. Raw data points are plotted for each drug class.

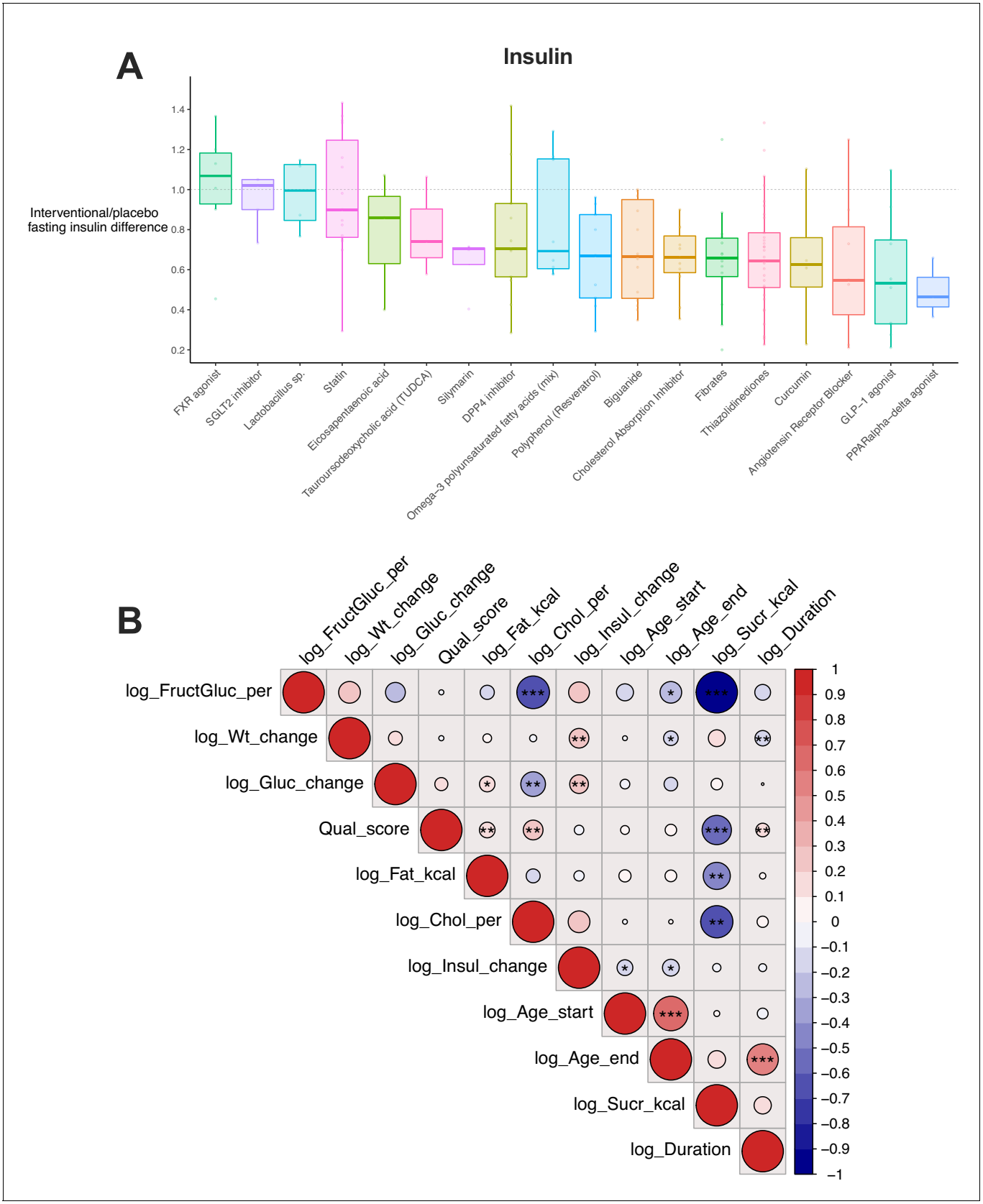

Figure 3—figure supplement 1. Insulin difference associated with use of each drug class and correlation plot of characteristics of studies. (**A**) Box plot illustrating the difference in fasting insulin in interventional animals, expressed as a decimal of the weight of the control animals. Raw data points are

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plotted for each drug class. (**B**) Plot of Pearson correlation co-efficients (encoded by colour, where red = 1, blue = −1) for continuous traits associated with each cohort. Traits have been log-transformed prior to analysis. Stars indicate p-value associated with each correlation: ***p<0.001, **p<0.01, *p<0.05.

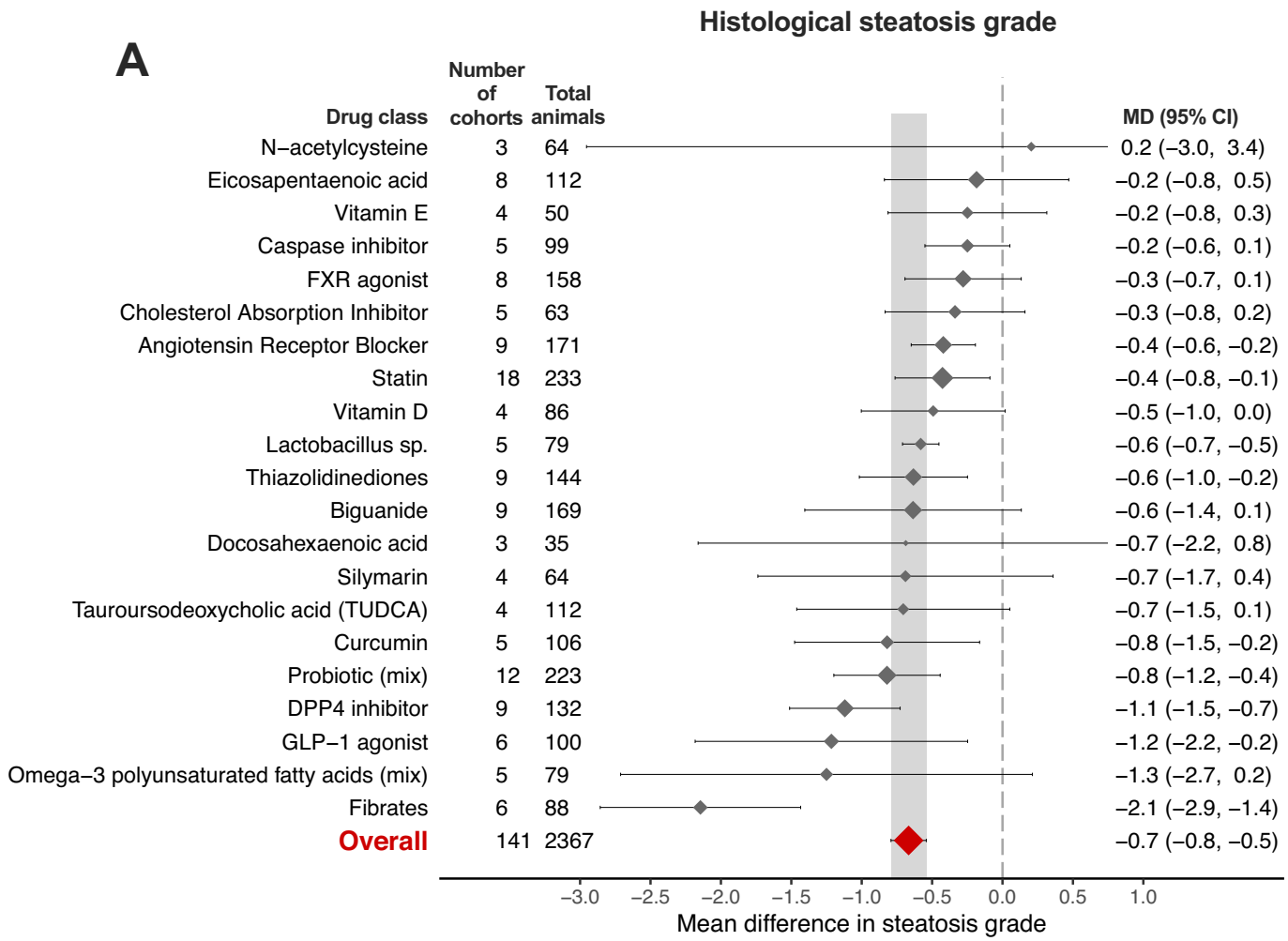

Figure 4. Meta-analysis of steatosis grade in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. The total number of animals is calculated from the sum of control and interventional animals for

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Figure 4 continued

each subgroup. CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference; TUDCA, Tauroursodeoxycholic acid. (**B**) Meta-regression bubble plot using (log) difference in fasting glucose between interventional and control animals, after removal of studies using models that induce weight loss. (**C**) Meta-regression bubble plot using (log) difference in fasting insulin between interventional and control animals, after removal of studies using models that induce weight loss.

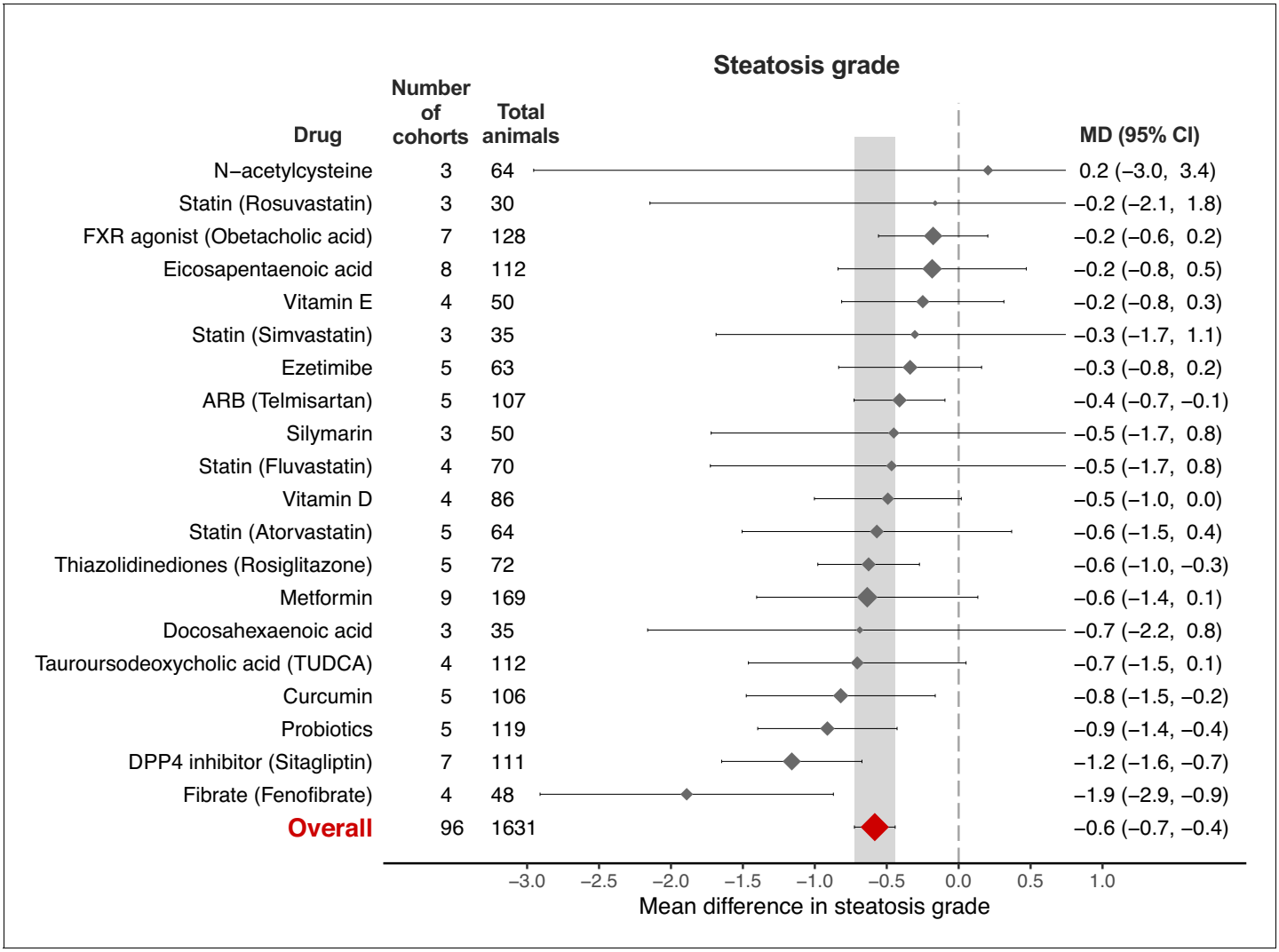

Figure 4—figure supplement 1. Meta-analysis of steatosis grade in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. Total animals is the sum of control and interventional animals for each subgroup. ARB, angiotensin receptor blocker; CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; MD, mean difference; TUDCA, tauroursodeoxycholic acid.

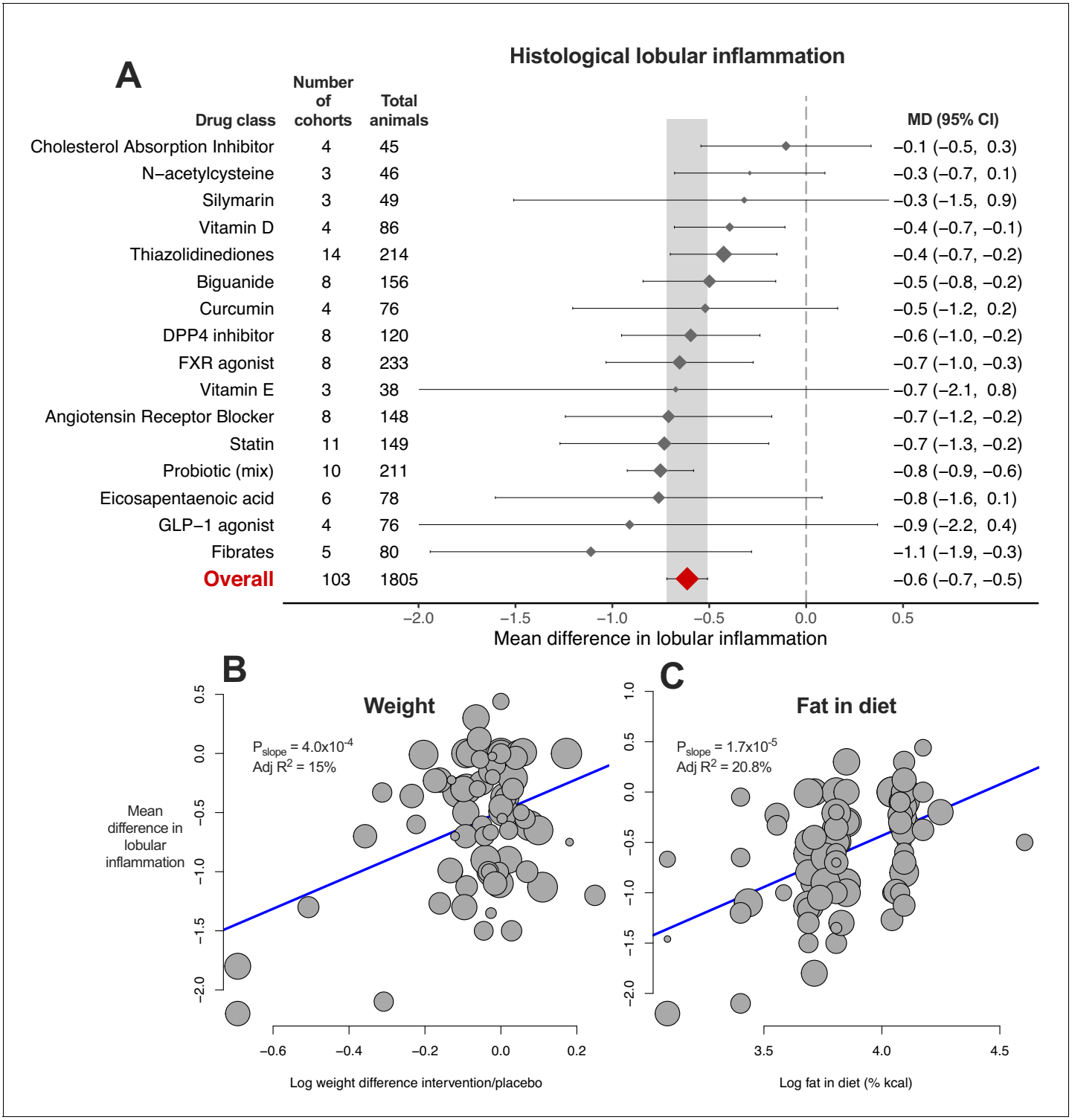

Figure 5. Meta-analysis of lobular inflammation in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. The total number of animals is calculated from the sum of control and interventional animals for each subgroup. CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference. (**B**) Meta-regression bubble plot using (log) difference in weight between interventional and control animals, after removal of studies using models that induce weight loss. (**C**) Meta-regression bubble plot using (log) fat (%kcal) in diet for each cohort.

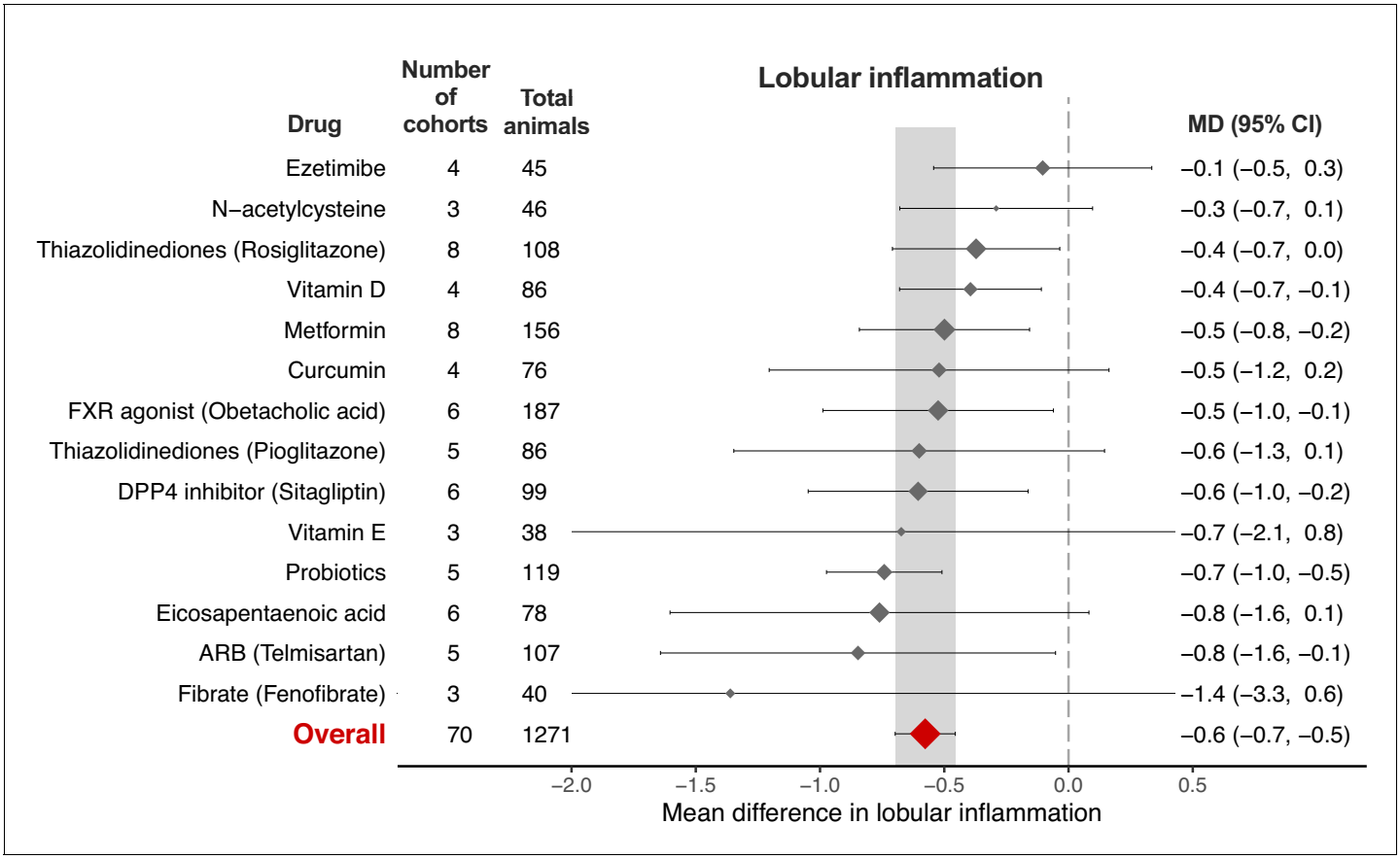

Figure 5—figure supplement 1. Meta-analysis of lobular inflammation in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. Total animals is the sum of control and interventional animals for each subgroup. ARB, angiotensin receptor blocker; CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; MD, mean difference.

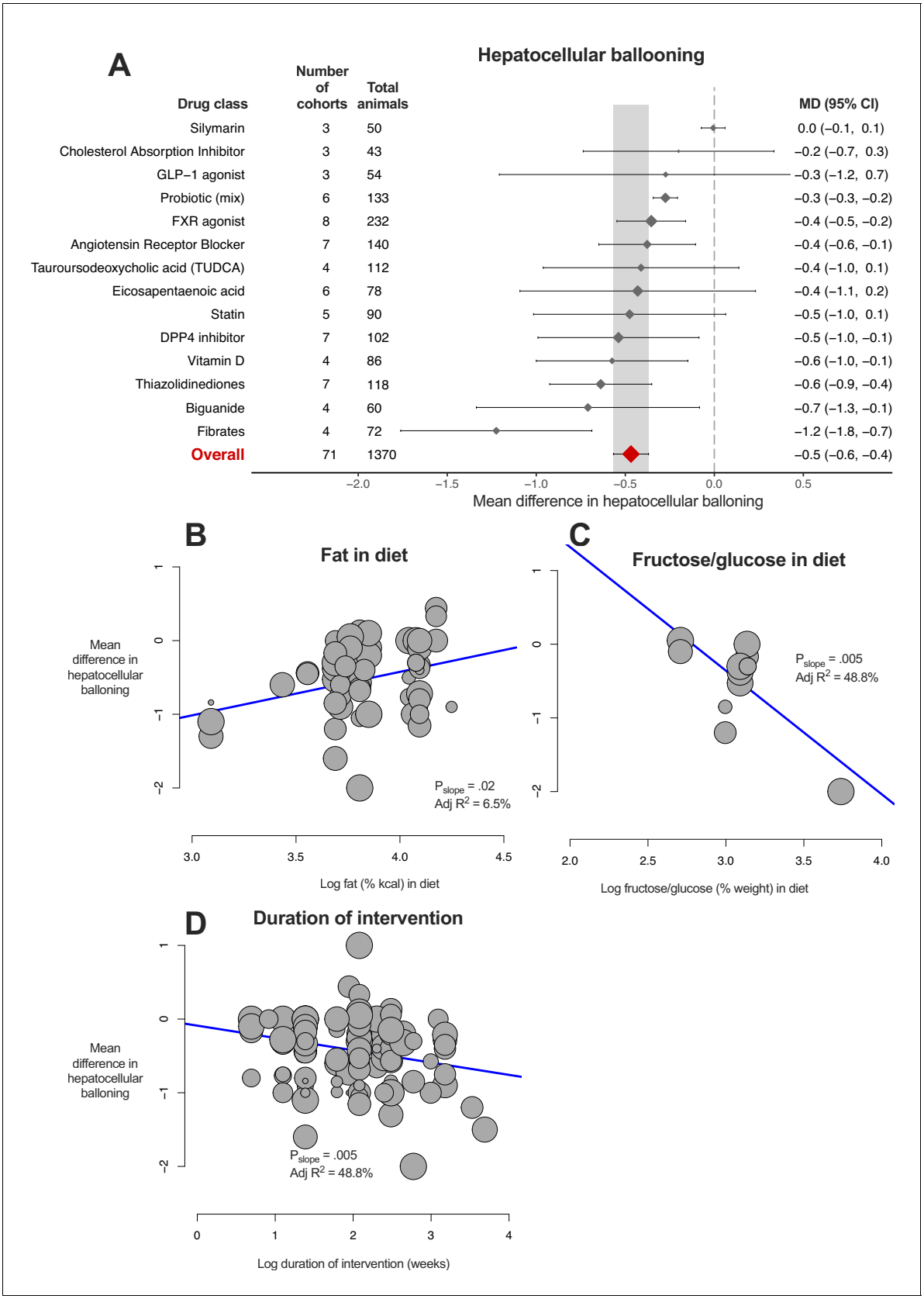

Figure 6. Meta-analysis of hepatocellular ballooning in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. The total number of animals is calculated from the sum of control and interventional

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animals for each subgroup. CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference; TUDCA, tauroursodeoxycholic acid. (**B**) Meta-regression bubble plot using (log) fat (%kcal) in diet for each cohort. (**C**) Meta-regression bubble plot using (log) fructose/glucose (% weight) in diet for each cohort. (**D**) Meta-regression bubble plot using (log) duration of intervention (in weeks) for each cohort.

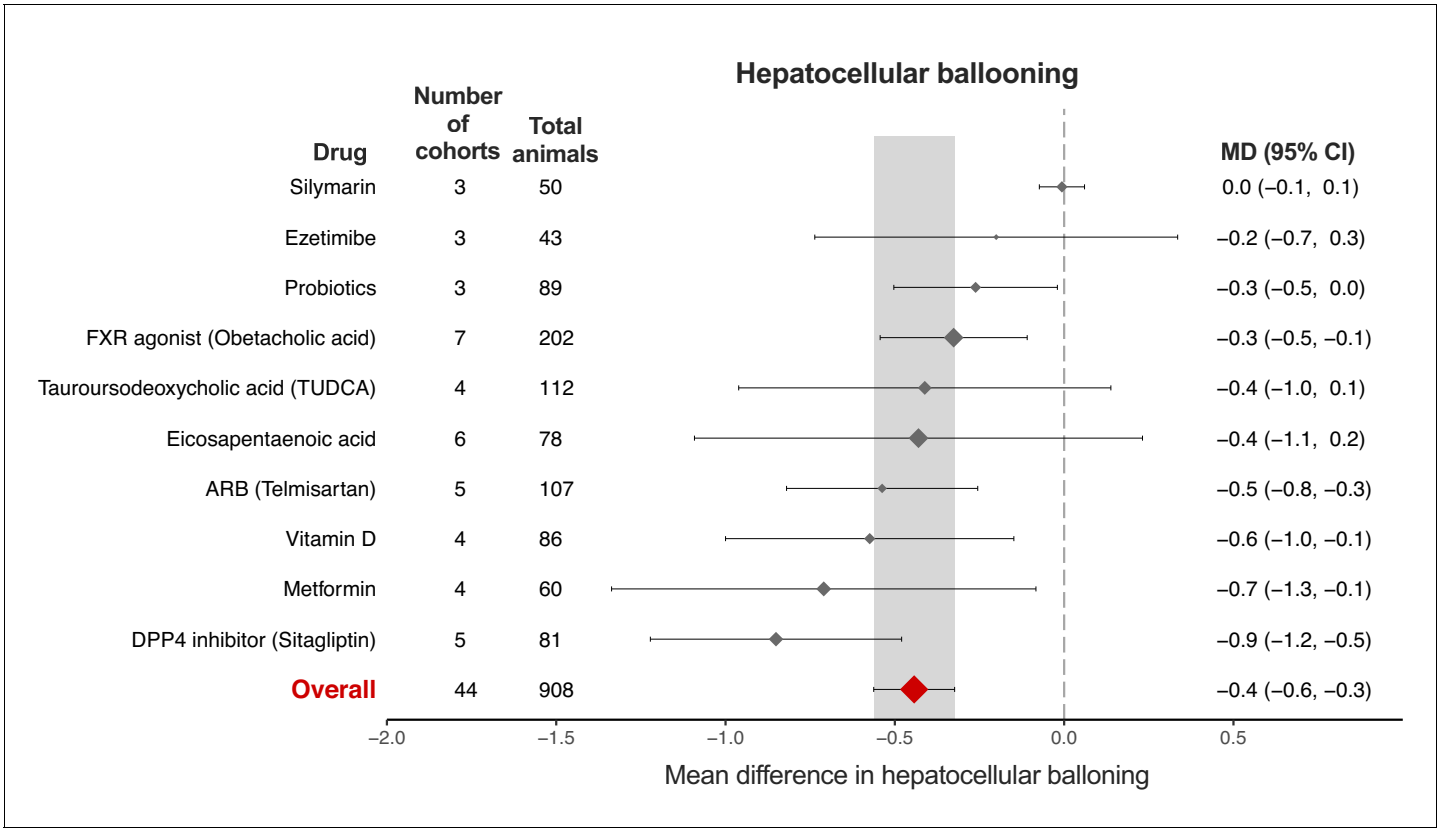

Figure 6—figure supplement 1. Meta-analysis of hepatocellular ballooning in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. Total animals is the sum of control and interventional animals for each subgroup. ARB, angiotensin receptor blocker; CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; MD, mean difference; TUDCA, tauroursodeoxycholic acid.

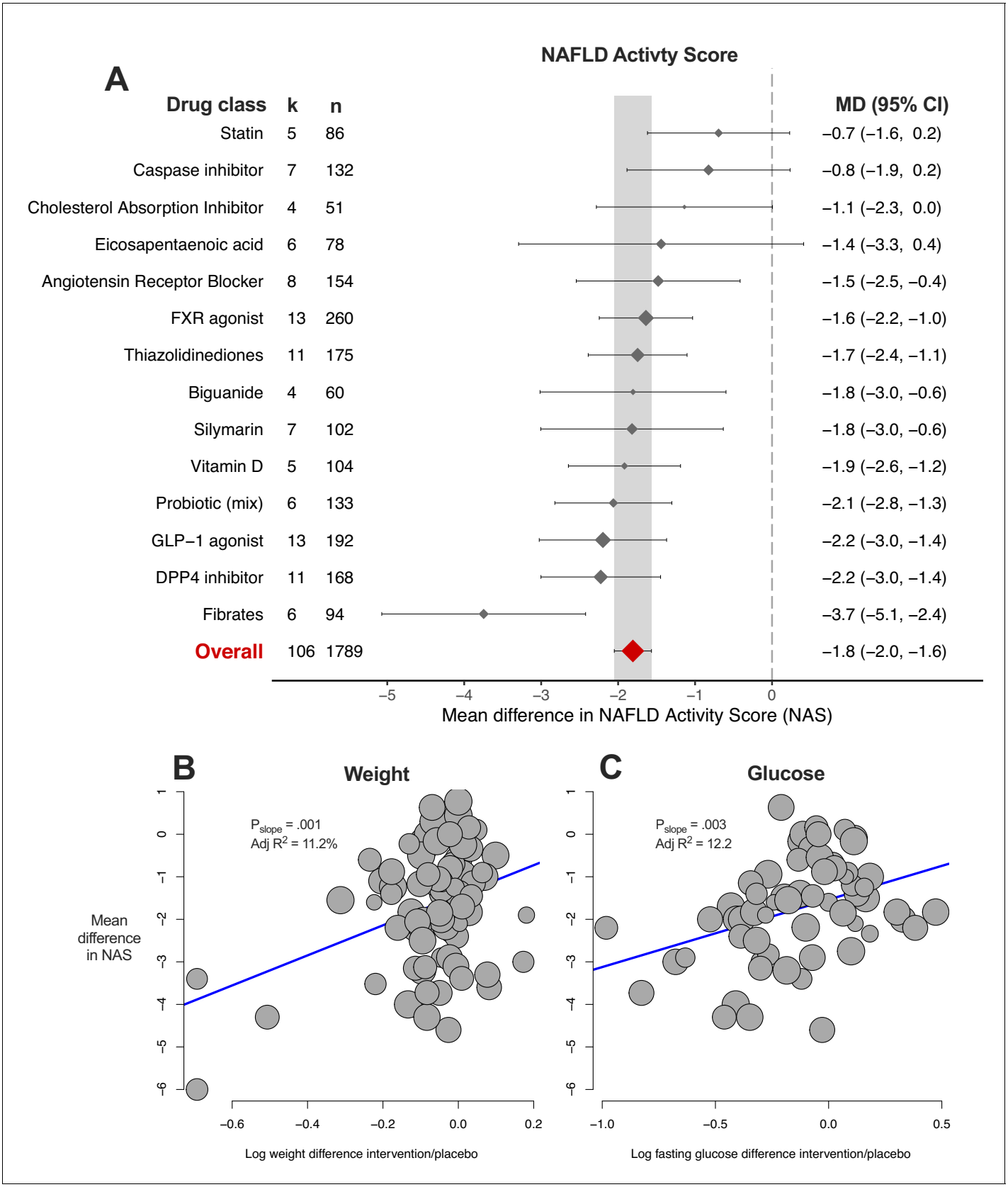

Figure 7. Meta-analysis of NAFLD Activity Score (NAS) in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. k represents the number of cohorts in each subgroup. The total number of animals is

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calculated from the sum of control and interventional animals for each subgroup. CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference. (**B**) Meta-regression bubble plot using (log) difference in weight between interventional and control animals, after removal of studies using models that induce weight loss. (**C**) Meta-regression bubble plot using (log) difference in glucose between interventional and control animals, after removal of studies using models that induce weight loss.

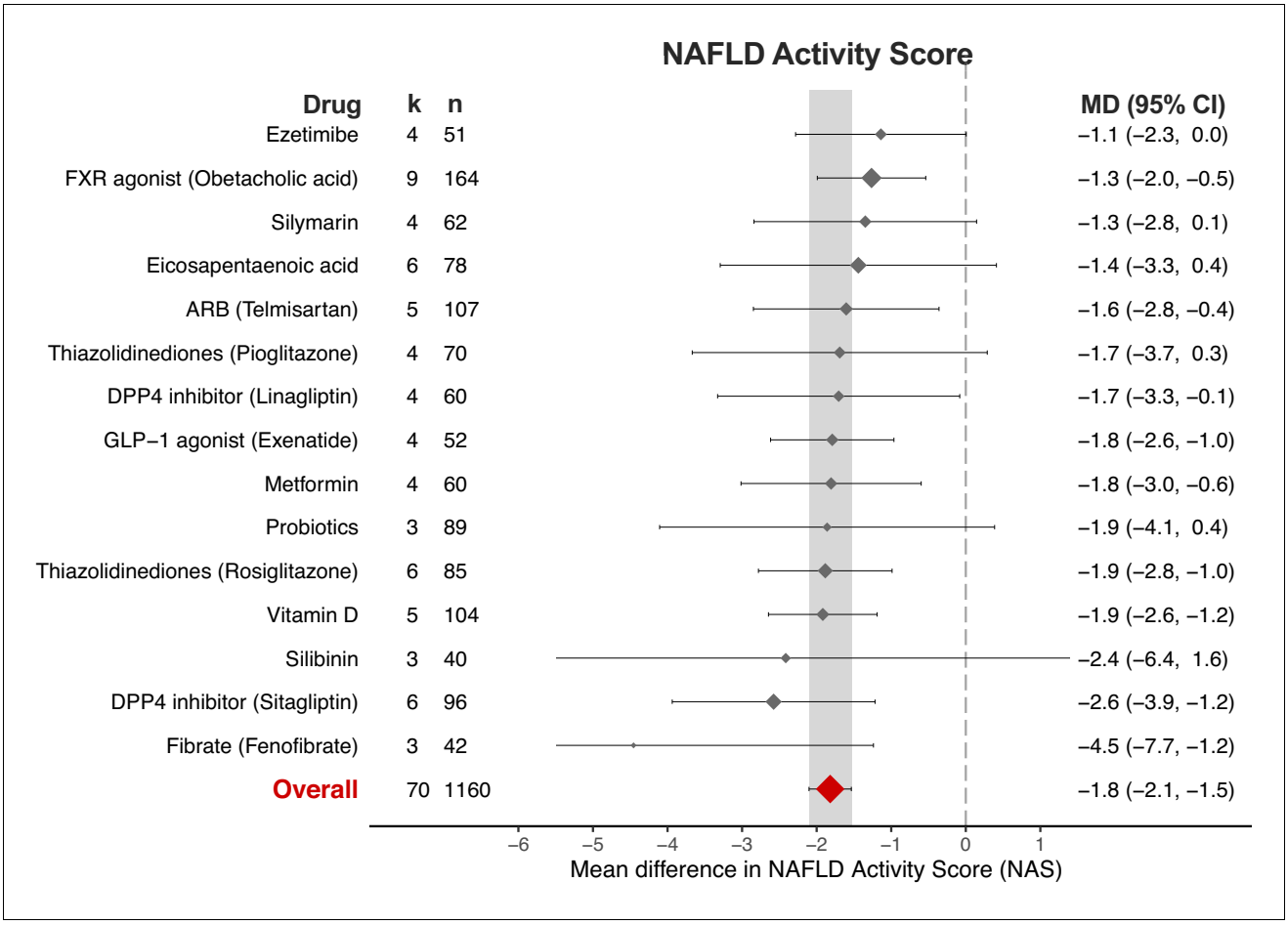

Figure 7—figure supplement 1. Meta-analysis of NAFLD Activity Score (NAS) in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. k represents the number of cohorts in each subgroup. Total animals is the sum of control and interventional animals for each subgroup. ARB, angiotensin receptor blocker; CI, confidence interval; DPP4, Dipeptidyl peptidase-4; FXR, Farnesoid X receptor; MD, mean difference.

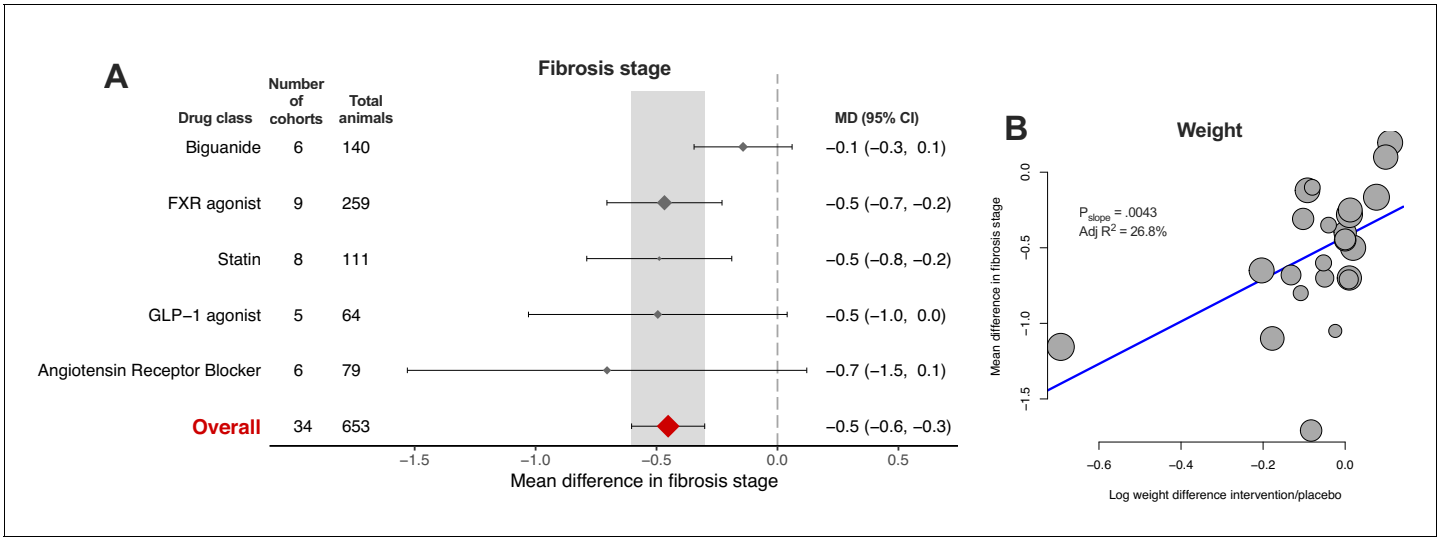

Figure 8. Meta-analysis of fibrosis stage in rodent studies of NAFLD. (**A**) Forest plot with subgrouping by class of drug. Individual studies have been hidden and only subgroup summaries are illustrated. The total number of animals is calculated from the sum of control and interventional animals for each subgroup. CI, confidence interval; FXR, Farnesoid X receptor; GLP-1, Glucagon-like peptide-1; MD, mean difference. (**B**) Meta-regression bubble plot using (log) difference in weight between interventional and control animals, after removal of studies using models that induce weight loss.

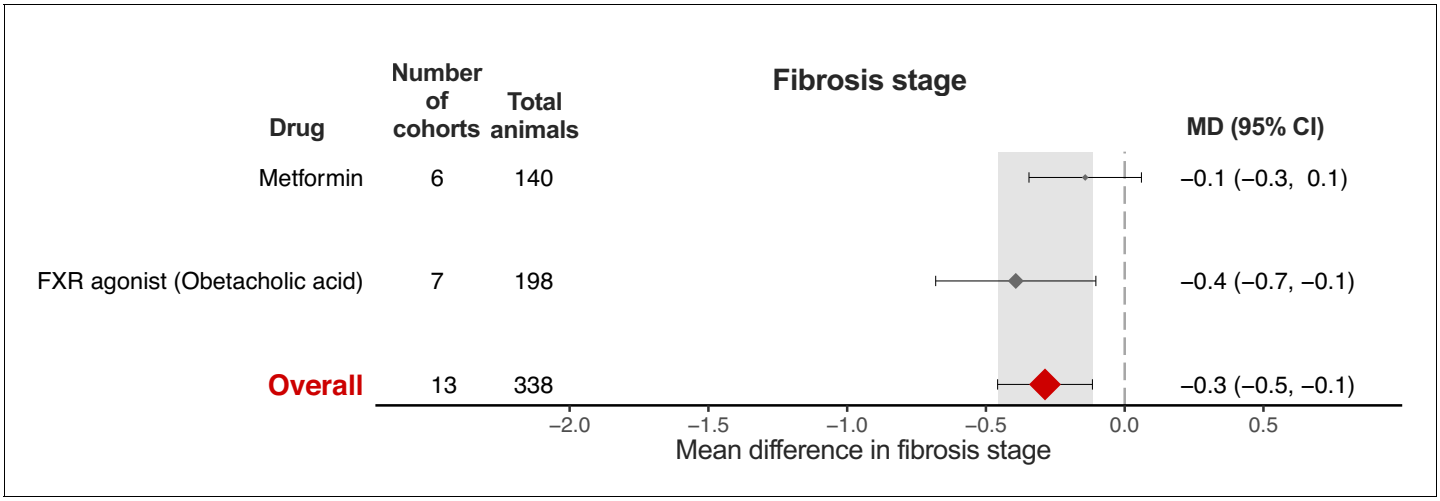

Figure 8—figure supplement 1. Meta-analysis of fibrosis stage in rodent studies of NAFLD by individual drug. Forest plot with subgrouping by individual drug. Individual studies have been hidden and only subgroup summaries are illustrated. Total animals is the sum of control and interventional animals for each subgroup. CI, confidence interval; FXR, Farnesoid X receptor; MD, mean difference.

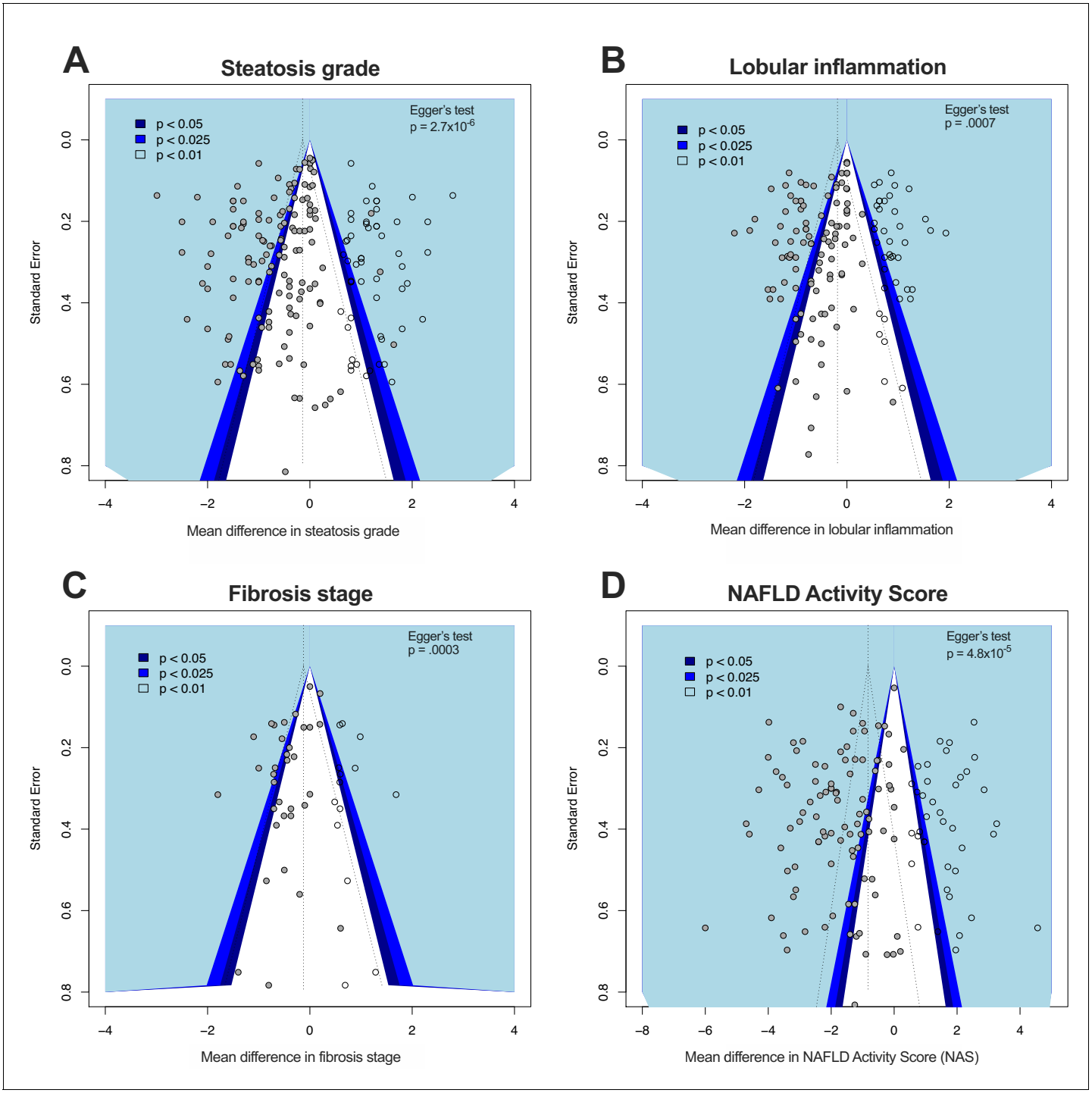

Figure 9. Funnel plots illustrating study distribution bias from meta-analyses of histological features. (**A**) Funnel plot illustrating study distribution (publication) bias in 145 original studies (solid grey circles) with 54 added studies (from trim-and-fill) for meta-analysis of steatosis grade. The statistical significance associated with each study is illustrated with the coloured background. Egger's test p-value indicates the likelihood that the original studies came from a symmetrical distribution. (**B**) Funnel plot for lobular inflammation meta-analysis with 103 original studies and 42 added studies. (**C**) Funnel plot for fibrosis stage meta-analysis with 34 original studies and 14 added studies. (**D**) Funnel plot for NAS meta-analysis with 106 original studies and 43 added studies.

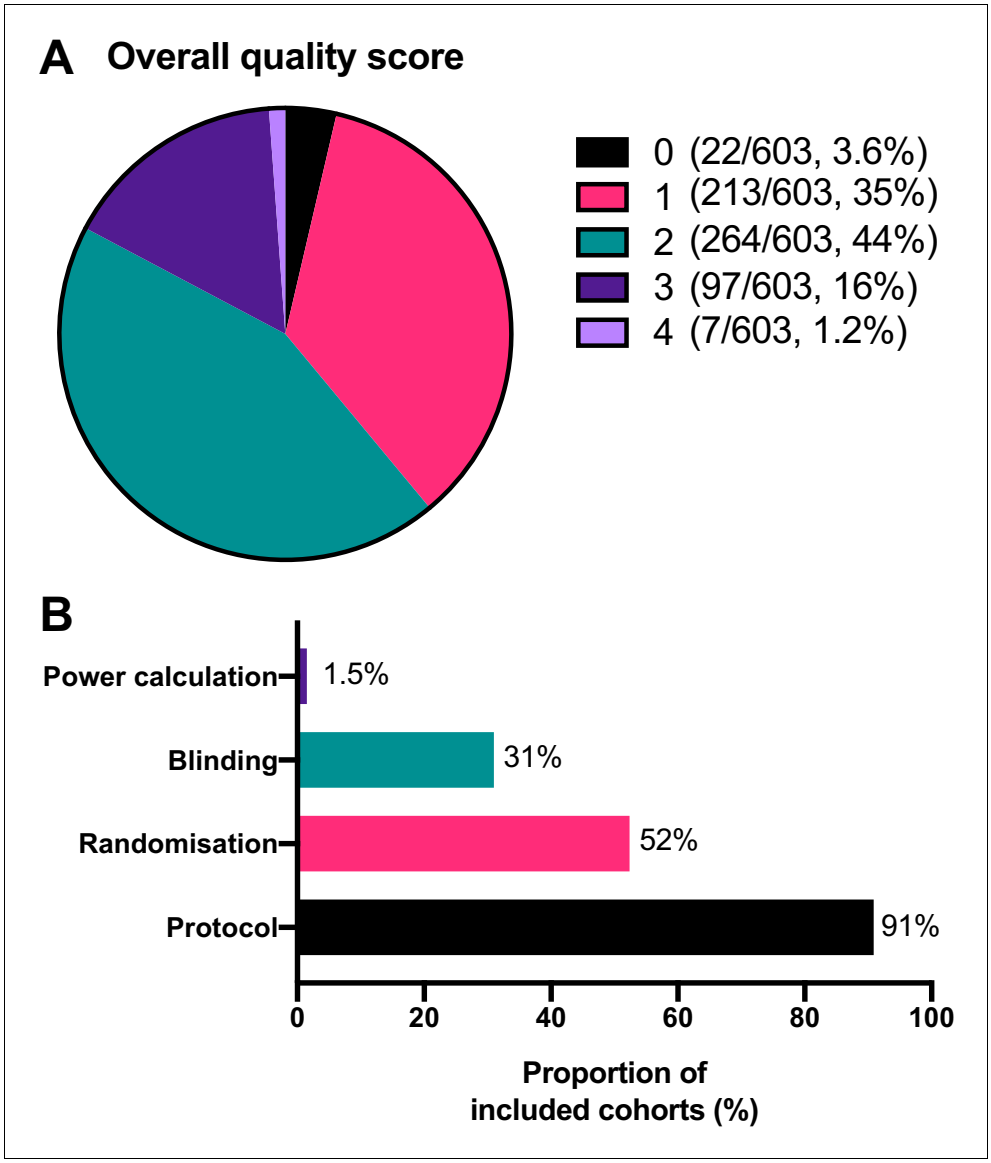

Figure 9—figure supplement 1. Quality assessment of included cohorts. (**A**) Distribution of overall quality scores from a four-point scale, composed of the use of a power calculation, use of blinding, randomisation, and referring to a predefined protocol, with 1-point awarded for presence of each factor. (**B**) Proportion of cohorts achieving each factor is shown in B.

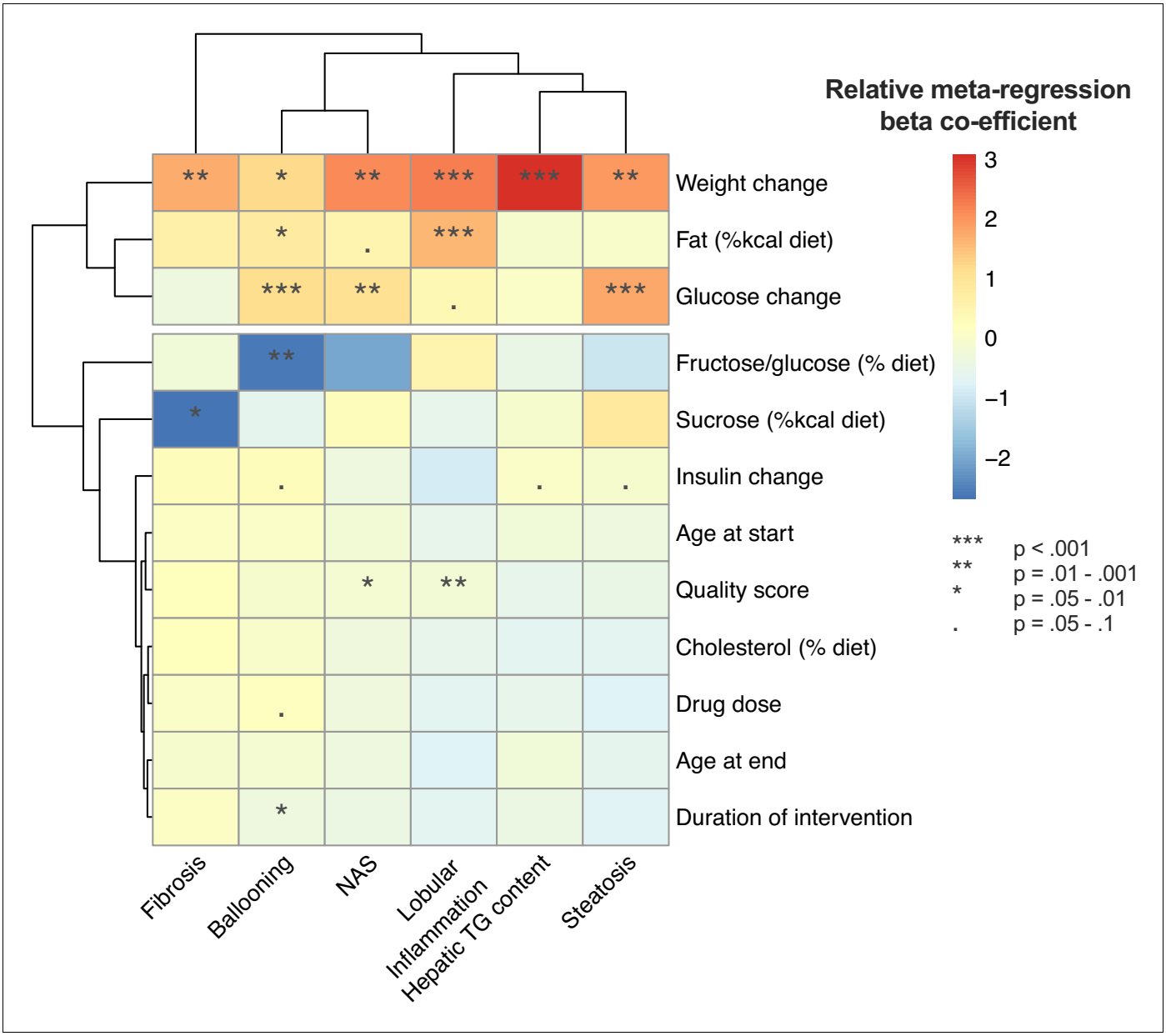

Figure 10. Summary of univariable meta-regression results across all outcomes.