METHODS

Data Sources and Searches

We searched PubMed, Cochrane Library, MEDLINE, EMBASE, clinicaltrials.gov through November 2011. using the terms: NAFLD, NASH, non-alcoholic fatty liver, steatosis, liver enzymes, AST, ALT, GGT, transaminases, liver fat, treatment, therapy, efficacy, trial. We also reviewed abstracts from American Association for the Study of Liver Disease (AASLD), American Gastroenterological Association (AGA), European Association for the Study of Liver (EASL), American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and Digestive Disease Week (DDW) meetings, which were subjected to the same quality assessment as regular articles.

Study Selection

Inclusion criteria: English and non-English articles with participants of any sex or ethnic origin with NAFLD/NASH, diagnosed on the basis of radiological/histological evidence of steatosis according to accepted criteria [reference 1 of main text]. Relevant meta-analyses were also included if following PRISMA guidelines[1].

Exclusion criteria were: non-human studies, non-randomized trials, letters/case reports or studies enrolling <10 subjects, articles not reporting outcomes of interest or primary data (editorials, reviews), studies using inadequate case definitions or enrolling secondary steatosis (i.e. drug-induced, total parenteral nutrition-induced steatosis, etc).

Data were extracted from each study by 2 authors (GM, MC) independently and in duplicate; agreement was assessed by a kappa statistic and disagreements resolved by mutual discussion. Authors were contacted to acquire further data information and to verify methodological quality.

Data Synthesis and Analysis. When a given outcome was assessed by ≥ 2RCTs using the same methods to assess outcomes, their results were pooled-together and meta-analyzed; otherwise, a narrative approach was followed. We used Review Manager (RevMan Version 5.0 163 Copenhagen: The Cochrane Collaboration 2008). The analysis was carried out according to the Cochrane Handbook of Systematic Reviews [ref 5 of main text]. Dichotomous variables were presented as odds ratios (OR) with 95% CI, continuous variables as weighted mean differences (WMD) with 95% CI. The fixed-effect
model was used, with significance set at $P = 0.05$. Statistical heterogeneity was assessed using the $I^2$ statistic: with $I^2$ values $\geq 50\%$, we used a random-effects model and explored individual study characteristics and those of subgroups of the main body of evidence. Sensitivity analysis was performed by removing 1 study at a time and repeating the meta-analysis to assess whether any one study significantly affected pooled estimates. Additionally, we planned a priori subgroup analysis according to the following criteria: NASH vs. NAFLD population, diabetic vs. non-diabetic population, treatment duration $\leq 1$ year vs. $>1$ year, different drugs of the same class or different doses of the same drug, addition or not of lifestyle intervention to drug, for high vs. low risk of bias RCT and for each item of the Cochrane Risk-of-Bias Tool.

Management of missing data.

Missing data were managed by contacting the corresponding authors of the RCTs. Where this was unsuccessful, missing histological scores were calculated from the raw numbers given in tables and/or estimated from bar charts. For missing standard deviations of mean change in scores, and where the $p$ value was provided for a comparison between treated and control groups, the standard deviation was calculated by converting the $p$ value into a $t$ value with appropriate degrees of freedom, and then calculating standard error and standard deviation. If neither the standard deviations nor the $p$ values were supplied, imputation of a standard deviation from studies with similar measurement methods, duration and measurement error was used if available [1] and tested in a sensitivity analysis and reported if the estimate differed meaningfully from previous estimates. If no similar studies were available, a narrative approach was used to summarize the data.

REFERENCES