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SYSTEMATIC REVIEWS AND META-ANALYSES

Siddarth Singh, Section Editor

Rates of and Factors Associated With Placebo Response in Trials of Pharmacotherapies for Nonalcoholic Steatohepatitis: Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e37. Learning Objective–Upon completion of this activity, successful learners will be able to assess the natural history of the placebo group in nonalcoholic steatohepatitis (NASH) randomized clinical trials and identify changes that occur in this group over time.

BACKGROUND & AIMS: **It is important to know the extent of the placebo effect in designing randomized controlled trials for patients with nonalcoholic steatohepatitis (NASH), to accurately calculate sample size and define treatment endpoints.**

METHODS: **We performed a systematic review and meta-analysis of the placebo groups from randomized controlled trials of adults with NASH that provided histologic and/or magnetic resonance image-based assessments. We identified trials through a comprehensive search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Scopus, from each database's inception through January 2, 2018.**

RESULTS: **We identified 39 randomized controlled trials, comprising 1463 patients who received placebo. Histologic assessment data (the nonalcoholic fatty liver disease activity scores, NAS) were available from 956 patients; magnetic resonance spectroscopy data were available from 295 patients and magnetic resonance proton density fat fraction measurements from 61 patients. Overall, 25% of patients given placebo had an improvement in NAS by 2 or more points (95% CI, 21%–29%) with a small amount of heterogeneity (I_2 = 27%). There were improvements by at least 1 point in steatosis scores of 33% ± 3% of patients, in hepatocyte ballooning scores of 30% ± 3% of patients, in lobular inflammation scores of 32% ± 3% of patients, and in fibrosis scores of 21% ± 3% of patients, with a moderate amount of heterogeneity among trials (I_2 range, 51%–63%). Patients given placebo had a statistically significant improvement in NAS (by 0.72 ± 0.19), with a large amount of heterogeneity (I_2 = 96%). Univariate and multivariate meta-regression showed that trials with a higher baseline NAS, those conducted in South America, and those in which patients had a decrease in body mass index, were associated with greater improvements in NAS among patients given placebo. Patients given placebo had**

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Abbreviations used in this paper: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; IHTG, intrahepatic triglyceride; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PDFF, proton density fat fraction; RCTs, randomized-controlled trials; SD, standard deviation; SE, standard error of the mean.

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significant reductions in intrahepatic triglyceride, measured by magnetic resonance spectroscopy (by 1.45% ± 0.54%) with moderate heterogeneity (I_2 = 40%), and in magnetic resonance proton density fat fraction (by 2.43 ± 0.89), without heterogeneity (I_2 = 0). Mean serum levels of alanine and aspartate aminotransferases decreased significantly (by 11.7 ± 3.8 U/L and 5.9 ± 2.1 U/L, respectively; $P < .01$ for both).

CONCLUSIONS: **In a meta-analysis of randomized controlled trials of NASH, patients given placebo have significant histologic, radiologic, and biochemical responses. The placebo response should be considered in designing trials of agents for treatment of NASH.**

Keywords: MRS; MRI-PDFF; Trial Design; NAFLD.

See editorial on page 607.

Because nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, with a prevalence of 25% worldwide,[1] and has no approved therapy, there is great interest in clinical trials assessing possible treatments. Treatments currently being studied are generally tailored toward the advanced form of the disease, nonalcoholic steatohepatitis (NASH), which includes steatosis, inflammation, and hepatocyte ballooning and may progress to cirrhosis.[2,3] To assess the effectiveness of therapies for disease, the gold standard has long been a randomized, double-blind placebo-controlled clinical trial in which a treatment is considered beneficial if it is shown to be more effective than the placebo. However, it is important to remember that placebos may have effects, the likely extent of which may be important to consider for optimal trial design, including sample size calculations and definition of treatment endpoints.

The only previous meta-analysis to assess the biochemical and histologic effects of placebo on patients with NAFLD in randomized, placebo-controlled trials was carried out almost a decade ago.[4] That meta-analysis included a total of only 189 patients in the treatment arms of the studies and 162 patients in the placebo arms, and only 3 of the 5 studies included in the meta-analysis reported detailed histologic data both pretreatment and post-treatment. In that meta-analysis Loomba et al[4] showed that patients who received placebo had a significant decrease in the mean level of alanine aminotransferase (ALT) and 31% were found to have a 1-point improvement in the steatosis score. However, a 2-point improvement in NAFLD activity score (NAS), typically considered a meaningful clinical outcome, was rarely seen. Furthermore, that study did not examine the impact of placebo on liver fat content (intrahepatic triglycerides [IHTG]) as shown by magnetic resonance imaging (MRI) proton density fat fraction (PDFF), which measures the fat fraction in all liver segments, or magnetic resonance spectroscopy (MRS), which measures the fat fraction of a single location in the liver.[5] Since the previous meta-analysis, MRI-PDFF has been shown to be accurate for detection and quantification of steatosis degree and it is now being used to evaluate treatment efficacy in NASH clinical trials. In addition, substantially more NASH clinical trials using histologic outcomes have been conducted in recent years.[6] Our aim was to quantify the response to placebo using the current commonly used endpoints to clinical trials in NASH. We conducted a systematic review and meta-analysis of histologic changes, MRI-based IHTG changes, and biochemical changes observed in placebo-treated patients in randomized, placebo-controlled studies in adult patients with NASH.

Materials and Methods

This systematic review was conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[7] The investigators developed a protocol specifying eligibility criteria, outcomes of interest, and methods of analysis. Randomized-controlled trials (RCTs) that compared results between a control intervention and a pharmacologic intervention in adults diagnosed with NAFLD (based on histology or MRI) were included. The control intervention could be a placebo and/or a lifestyle intervention. Trials comparing different lifestyle interventions were excluded. Inclusion was limited to trials reporting histologic data using the NAS and/or IHTG or fat fraction assessed by MRS or MRI-PDFF. Trials had to report paired outcome data before and after placebo to be included. Trials reporting other histologic scores were excluded if they did not provide any of the previously mentioned outcomes. Trials using MRI-PDFF were excluded if they did not report measuring fat fraction in 3 regions of interest in each segment of the liver. We limited our eligibility criteria to trials reported in English. We excluded nonrandomized studies, noncomparative studies, commentaries, editorials, letters, reviews, and studies reported solely as abstracts.

Data Sources and Search Strategies

A comprehensive search was conducted of the following databases from each database's inception to January 2, 2018: MEDLINE Epub Ahead of Print, Medline In-Process & Other Non-Indexed Citations, MEDLINE,

EMBASE, Cochrane Central Register of Controlled Trials, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for RCTs of fat fraction in NAFLD. The actual strategy is available in the Supplementary Appendix.

Study Selection and Data Extraction

Independent reviewers (M.A.T.H., O.A., S.H., V.T., O.E.) reviewed the titles and abstracts of the identified references for full-text review. The retrieved full-text articles were then reviewed by the reviewers independently. Conflicts were resolved by consensus and consultation with an additional reviewer (M.N.). Data were extracted by the reviewers independently using a Microsoft Excel extraction form. Discrepancies were resolved by mutual discussion. The extracted data included inclusion criteria, study location, sample size, lifestyle modifications, frequency of follow-up visits, duration of trial, and the predetermined outcomes as below. If the published manuscript reported assessing 1 of our main outcomes in the methods but did not report the findings in the results, we contacted the corresponding and/or senior author to request the missing data.

Outcome Measures

We assessed 3 main outcomes: (1) histologic response, defined as a $\geq$2-point improvement in NAS; (2) histologic change, defined as the change in NAS from baseline to end of treatment; and (3) IHTG change, defined as the change in MRI-based liver fat content from baseline to end of treatment. Other outcomes included average changes in individual components of the NAS (degree of steatosis, lobular inflammation, hepatocyte ballooning); changes in fibrosis; percentage of patients with $\geq$1-point improvement in individual components of the NAS and fibrosis; changes in biochemical parameters including ALT, aspartate aminotransferase (AST), alkaline phosphatase, hemoglobin A_{1c}, and insulin resistance measured using the homeostatic model assessment for insulin resistance; and changes in body mass index (BMI).

We extracted the mean or mean difference and with the associated standard deviation (SD) for each of the previously mentioned continuous outcomes. If a trial reported the mean or mean difference with other measures of variability, such as the standard error (SE) and confidence intervals (CIs), we imputed the SD from them. If the study reported the mean or mean difference but did not report any measure of variability, we imputed the SD from the other studies. If the trial did not report the mean NAS, we used the NAS components, when provided, and calculated the mean and SD by summing the means and variances using linear combination after calculating the covariance from the trials. If the trial did not report any of the previously mentioned but reported the median with the upper and lower limits of the range and/or the first and third quartiles, we used them in addition to the sample size to impute the mean and SD using the methods proposed by Wan et al.[8] If they only provided the median with the interquartile range, we imputed the mean from the median and the SD as interquartile range/1.35. If none of the previously mentioned was reported, we attempted to contact the corresponding and/or senior author to obtain the missing data. If we did not receive a response from the authors within 4 weeks, we excluded the trial.

What You Need to Know

Background

The effect of placebo in randomized controlled trials of nonalcoholic steatohepatitis pharmacotherapy is not well-understood or estimated.

Findings

Placebo treatment is associated with statistically significant histological, biochemical, and radiological responses. Possible cofactors include the duration of trial, number of patients, change in weight, baseline severity of the disease, recommendation of lifestyle modifications, and the geographical region where the trial is conducted.

Implications for patient care

Designing and interpreting trials that assess the response to pharmacotherapy in patients with nonalcoholic steatohepatitis should consider the effect of placebo treatment and its cofactors.

Risk of Bias Assessment

We used the Cochrane risk of bias tool to evaluate risk of bias in the individual trials.[9] We evaluated the adequacy of randomization, allocation concealment, blinding (patients, providers, data collectors, and outcome assessors), extent of missing outcome data, and the funding source.

Statistical Assessment

We used the random-effects model to estimate the pooled proportion and mean difference of the primary and secondary outcomes before and after receiving the control intervention.[10] We used the Cochran Q test and I^2 statistic to assess heterogeneity, where $P \leq .10$ or $I^2 > 50\%$ indicated the presence of substantial heterogeneity.[11] We used univariable and multivariable meta-regression and/or subgroup analysis to explore causes of heterogeneity in the main outcomes using the

following explanatory variables: geographical region, change in BMI, duration of trial, baseline NAS or IHTG, number of included patients, central versus local biopsy reading, and/or recommendation of lifestyle modifications. For the purpose of the analysis, we categorized the lifestyle modification recommendation into 2 main categories: dietary recommendations and physical activity recommendations. The dietary recommendations were then dichotomized into recommendations that involved a dietitian (either throughout the trial duration or only at the beginning of the trial) in 1 category versus nondietitian dietary advice, trials that did not recommend dietary changes, and trials that did not report such recommendations as the other category. Similarly, physical activity recommendations were dichotomized into trials that recommended exercise (as an advice only or by implementing an exercise program) as one category versus trials that did not report or recommend physical activity recommendations as the other category. When appropriate, we assessed publication bias by visual inspection of funnel plots and using weighted Egger test.[12] To assess the robustness of our results, we conducted sensitivity analysis by excluding small trials (n <50), excluding trials at high risk for bias, excluding trials where we had to impute the mean and/or SD, and/or excluding trials that reported 2-point improvement in NAS but did clearly state that fibrosis was unchanged. We used the metafor (version 2.0-0) and meta (version 4.9-0) packages of R (version 3.4.3) in addition to Comprehensive Meta-Analysis (version 2.2.064) to conduct the different analyses.[13,14]

Results

With our search strategy we identified 3997 references. After reviewing the titles and abstracts of the identified references, 149 full-text articles were retrieved for review. After reviewing the full texts, 39 articles reporting 39 trials met the prespecified criteria and were included in the systematic review and meta-analysis (Supplementary Figure 1).[15-53] Of these, 14 trials were conducted in North America, 10 in Europe, 7 in East Asia, 2 in Australia, 2 in South America, 2 in the Middle East, and 2 trials in more than 1 region. A total of 1463 patients were randomized to receive the control intervention, including 956 patients from 30 trials who had paired histologic data using NAS reported, 830 patients from 24 trials who had a 2-point improvement in NAS reported, 295 patients from 13 trials who had paired MRS data reported, 61 patients from 3 trials who had paired MRI-PDFF data reported, and 245 patients from 28 trials who did not have any paired primary outcome data because of loss from follow-up or withdrawal. Among 31 trials that reported a histologic outcome, pathology slides were read centrally in 12 trials and locally in 19 trials. Pathologists were blinded in all trials. A total of 71.8% of the trials reported recommending or implementing lifestyle modifications, either dietary or physical activity. Dietitians were involved in the initial visit in 28.2% of trials, and followed the patients throughout the trial in 12.8% of the trials. A total of 43.6% of the trials reported providing dietary recommendations without reporting the involvement of a dietitian. Recommendations to increase physical activity were given in 59% of trials but only 18% of trials reported providing a specific regimen to the patients. The median duration of treatment was 48 weeks (range, 8–96 weeks). Characteristics of the included studies are described in Table 1. Excluded studies and the reason of exclusion are listed in Supplementary Table 1.

Risk of Bias

There was a moderate risk of bias in the individual trials overall. Most trials reported the randomization method but did not report how the allocation was concealed. Most of the trials blinded the patients, providers, and outcome assessors. The rate of missing or unreported primary outcome data in the control arm was less than 20% in 71.8% of the included trials. Most of the trials reported the different reasons behind the missing outcome data including patients lost to follow-up and/or withdrawn; however, some of them did not disclose or clarify that. There was contribution and/or support from for-profit organizations in 69% of the trials. Supplementary Figure 2 summarizes the risk of bias for each individual study using the Cochrane risk of bias tool.

Meta-Analysis of Paired Histologic Response

The pooled proportion of patients who had improvement of 2 or more points in the NAS was 25% (95% CI, 21%–29%) with minimal heterogeneity (I^2 = 27%; P = .11) (Figure 1). Sensitivity analysis limited to trials that reported ≥2-point improvement in NAS without worsening in fibrosis showed similar results with a pooled proportion of 25% (95% CI, 20%–30%) and with minimal heterogeneity (I^2 = 27%; P = .19) (Supplementary Figure 3).

Placebo treatment was associated with a statistically significant improvement in NAS of 0.72 points (95% CI, -1.09 to -0.34; P < .01) with considerable heterogeneity (I^2 = 96%; P < .01) (Figure 2). Using subgroup interaction tests (Figure 3), there was no significant difference between the pooled NAS change when the trials were subgrouped based on geographic region, trial duration, recommendation of lifestyle modifications, administration of placebo pill, number of patients in the placebo arm with paired biopsies, or the location where the biopsy was read (central vs local read; P > .1) (Supplementary Figure 4*A–F*). Using univariate meta-regression models (Figure 3), the heterogeneity was

Table 1. Baseline Characteristics of the Included Randomized Controlled Trials

Trial	Location	Number of patients enrolled in placebo arm (N) and trial duration (*wk*)	Lifestyle intervention	Outcome measures
Abdelmalek et al, 2009[15]	Country: United States Number of sites: 2	N: 29 Trial duration: 52	Diet: nondietitian advice Physical activity: NR	Histology
Alam et al, 2016[16]	Country: Bangladesh Number of sites: 1	N: 15 Trial duration: 52	Diet: nondietitian advice Physical activity: exercise regimen	Histology
Alam et al, 2017[17]	Country: Bangladesh Number of sites: 1	N: 10 Trial duration: 52	Diet: nondietitian advice Physical activity: advice only	Histology
Argo et al, 2015[18]	Country: United States Number of sites: 1	N: 21 Trial duration: 52	Diet: dietitian with follow-up Physical activity: exercise regimen	Histology
Armstrong et al, 2016[19]	Country: United Kingdom Number of sites: 4	N: 26 Trial duration: 48	Diet: nondietitian advice Physical activity: advice only	Histology
Belfort et al, 2006[20]	Country: United States Number of sites: 3	N: 25 Trial duration: 26	Diet: dietitian with follow-up Physical activity: NR	Histology and MRS-IHTG
Chachay et al, 2014[21]	Country: Australia Number of sites: 1	N: 10 Trial duration: 8	Diet: none Physical activity: none	MRS-IHTG
Chan et al, 2010[22]	Country: Australia Number of sites: 1	N: 10 Trial duration: 22	Diet: dietitian at initial visit Physical activity: NR	MRS-IHTG
Cui et al, 2016[23]	Country: United States Number of sites: 1	N: 25 Trial duration: 24	Diet: NR Physical activity: NR	MRS-IHTG and MRI-PDFF
Cusi et al, 2016[24]	Country: United States Number of sites: 1	N: 51 Trial duration: 78	Diet: dietitian at initial visit only Physical activity: NR	Histology and MRS-IHTG
Dasarathy et al, 2015[25]	Country: United States Number of sites: 2	N: 19 Trial duration: 48	Diet: dietitian with follow-up Physical activity: exercise regimen	Histology
Friedman et al, 2017[26]	Countries: Australia, Belgium, France, Germany, Hong Kong, Italy, Poland, Spain, the United Kingdom, and the United States Number of sites: 81	N: 144 Trial duration: 52	Diet: nondietitian advice Physical activity: advice only	Histology
Haukeland et al, 2009[27]	Country: Norway Number of sites: 1	N: 24 Trial duration: 26	Diet: nondietitian advice Physical activity: advice only	Histology
Heebøll et al, 2016[28]	Country: Denmark Number of sites: 1	N: 13 Trial duration: 26	Diet: nondietitian advice Physical activity: advice only	Histology and MRS-IHTG
Idilman et al, 2008[29]	Country: Turkey Number of sites: 1	N: 25 Trial duration: 48	Diet: dietitian with follow-up Physical activity: exercise regimen	Histology
Joy et al, 2017[30]	Country: Canada Number of sites: 1	N: 6 Trial duration: 24	Diet: NR Physical activity: NR	Histology
Kim et al, 2017[31]	Country: Korea Number of sites: 5	N: 22 Trial duration: 24	Diet: dietitian at initial visit only Physical activity: NR	MRS-IHTG
Le et al, 2012[32]	Country: United States Number of sites: 4	N: 25 Trial duration: 24	Diet: NR Physical activity: NR	Histology, MRS-IHTG, and MRI-PDFF
Leuschner et al, 2010[33]	Countries: Germany and Greece Number of sites: 25	N: 91 Trial duration: 78	Diet: NR Physical activity: NR	Histology
Loguercio et al, 2012[34]	Countries: Italy and Romania Number of sites: 13	N: 88 Trial duration: 52	Diet: nondietitian advice Physical activity: advice only	Histology
Loomba et al, 2015[35]	Country: United States Number of sites: 4	N: 25 Trial duration: 24	Diet: NR Physical activity: NR	Histology, MRS-IHTG, and MRI-PDFF

McPherson et al, 2017[36]	Country: United Kingdom Number of sites: 11	N: 21 Trial duration: 96	Diet: nondietitian advice Physical activity: advice only	Histology
Neuschwander-Tetri et al, 2015[37]	Country: United States Number of sites: 8	N: 142 Trial duration: 72	Diet: nondietitian advice Physical activity: advice only	Histology
Nogueira et al, 2016[38]	Country: Brazil Number of sites: 1	N: 28 Trial duration: 26	Diet: NR Physical activity: NR	Histology
Ratziu et al, 2008[39]	Country: France Number of sites: 1	N: 32 Trial duration: 52	Diet: nondietitian advice Physical activity: advice only	Histology
Ratziu et al, 2016[40]	Countries: Belgium, France, Germany, Italy, Romania, Spain, the Netherlands, the United Kingdom, and the United States Number of sites: 56	N: 92 Trial duration: 52	Diet: NR Physical activity: NR	Histology
Safadi et al, 2014[41]	Country: Israel Number of sites: 11	N: 20 Trial duration: 12	Diet: NR Physical activity: NR	MRS-IHTG
Sanyal et al, 2010[43]	Country: United States Number of sites: 11	N: 83 Trial duration: 96	Diet: nondietitian advice Physical activity: advice only	Histology
Sanyal et al, 2014[42]	Country: United States Number of sites: 37	N: 75 Trial duration: 52	Diet: NR Physical activity: NR	Histology
Scorletti et al, 2014[44]	Country: United Kingdom Number of sites: 1	N: 52 Trial duration: 78	Diet: nondietitian advice Physical activity: advice only	MRS-IHTG
Shields et al, 2009[45]	Country: United States Number of sites: 1	N: 10 Trial duration: 52	Diet: dietitian at initial visit only Physical activity: exercise program	Histology
Stefan et al, 2014[46]	Countries: Austria and Germany Number of sites: 4	N: 41 Trial duration: 12	Diet: none Physical activity: none	MRS-IHTG
Takeshita et al, 2014[47]	Country: Japan Number of sites: 1	N: 15 Trial duration: 26	Diet: dietitian at initial visit only Physical activity: exercise program	Histology
Van Wagner et al, 2011[48]	Country: United States Number of sites: 1	N: 9 Trial duration: 52	Diet: nondietitian advice Physical activity: advice only	Histology
Vilar Gomez et al, 2009[49]	Country: Cuba Number of sites: 1	N: 30 Trial duration: 26	Diet: dietitian with follow-up Physical activity: exercise regimen	Histology
Wah Kheong et al, 2017[50]	Country: Malaysia Number of sites: 1	N: 50 Trial duration: 48	Diet: nondietitian advice Physical activity: advice only	Histology
Wong et al, 2013[51]	Country: Hong Kong Number of sites: 1	N: 10 Trial duration: 26	Diet: nondietitian advice Physical activity: advice only	MRS-IHTG
Wong et al, 2013[52]	Country: Hong Kong Number of sites: 1	N: 20 Trial duration: 24	Diet: nondietitian advice Physical activity: advice only	Histology
Zein et al, 2011[53]	Country: United States Number of sites: 1	N: 29 Trial duration: 52	Diet: dietitian at initial visit only Physical activity: advice only	Histology

MRI-PDFF, magnetic resonance imaging–based proton density fat fraction; MRS-IHTG, magnetic resonance spectroscopy–based intrahepatic triglyceride quantification; NR, not reported.

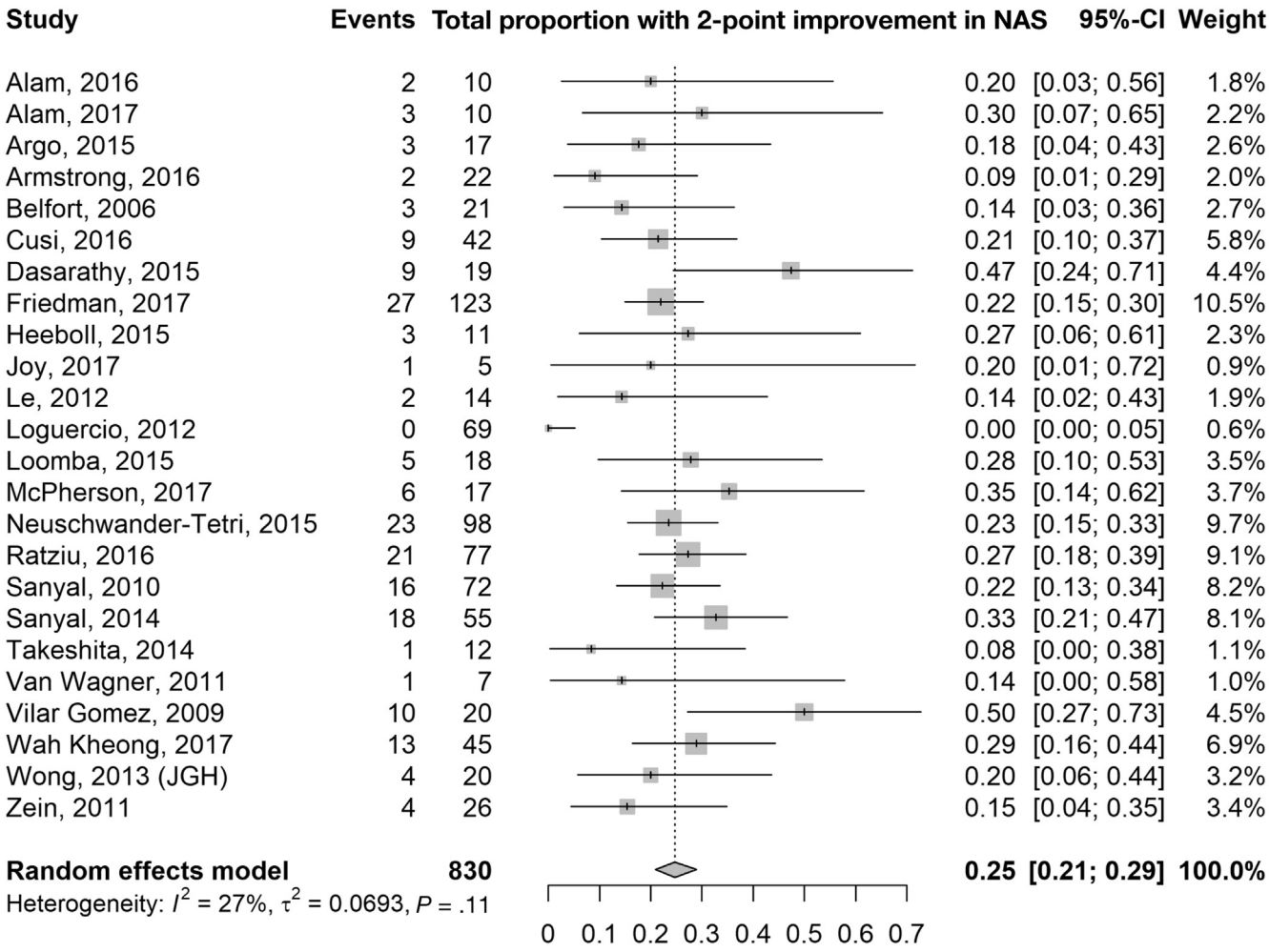

Figure 1. Meta-analysis of proportion of patients with histologic response. Forest plot of random-effects meta-analysis showing the proportion of patients with 2-point improvement in NAFLD activity score after receiving placebo intervention.

partially explained with a positive association between the change in NAS and the change in BMI (R^2 = 93%; P < .01), but not trial duration, baseline NAS, or visit frequency (R^2 range, 4%–28%; P > .1) (Supplementary Figure 5*A*–*D*). Multivariate meta-regression showed that trials from South America and trials with high baseline NAS were associated with more improvement in NAS (Supplementary Table 2). Testing for publication bias was not done because of the substantial heterogeneity. Sensitivity analyses showed statistically significant improvement of NAS when we used studies that included 50 or more patients with paired biopsies by 0.67 points (95% CI, -0.83 to -0.51; I^2 = 44%), excluded trials at high risk for bias by 0.5 points (95% CI, -0.61 to -0.39; I^2 = 0%), or excluded trials where we used imputation methods by 0.69 points (95% CI, -1.11 to -0.27; I^2 = 97%) (Supplementary Figure 6*A*–*C*).

The pooled proportion of patients with ≥1-point improvement in steatosis was 33% (95% CI, 27%–40%), in hepatocyte ballooning was 30% (95% CI, 24%–36%), in lobular inflammation was 32% (95% CI, 27%–38%), and in fibrosis was 21% (95% CI, 16%–26%). The pooled proportions were limited by moderate heterogeneity (I^2 range, 51%–63%; P < .01) (Supplementary Figure 7*A*–*D*).

There was a statistically significant improvement in steatosis of 0.35 points (95% CI, -0.45 to -0.25; P < .01), 0.16 points in ballooning (95% CI, -0.22 to -0.10; P < .01), and of 0.16 points in lobular inflammation score (95% CI, -0.23 to -0.09; P < .01). However, there was no statistically significant change in fibrosis. All the pooled mean differences were limited by substantial heterogeneity between the included trials (I^2 range, 52%–79%; P < .01) (Supplementary Figure 8*A*–*D*).

Meta-Analysis of MRI-Based IHTG Response

There was a statistically significant improvement in IHTG. When measured by MRS there was an improvement of 1.45% (95% CI, -2.51 to -0.40; P < .01) with moderate heterogeneity (I^2 = 40%; P = .07) and when MRI-PDFF was used, an improvement of 2.44% (95% CI, -4.16 to -0.73; P < .01) was seen, without heterogeneity (I^2 = 0%; P = .95) (Figure 4*A* and *B*). Testing for

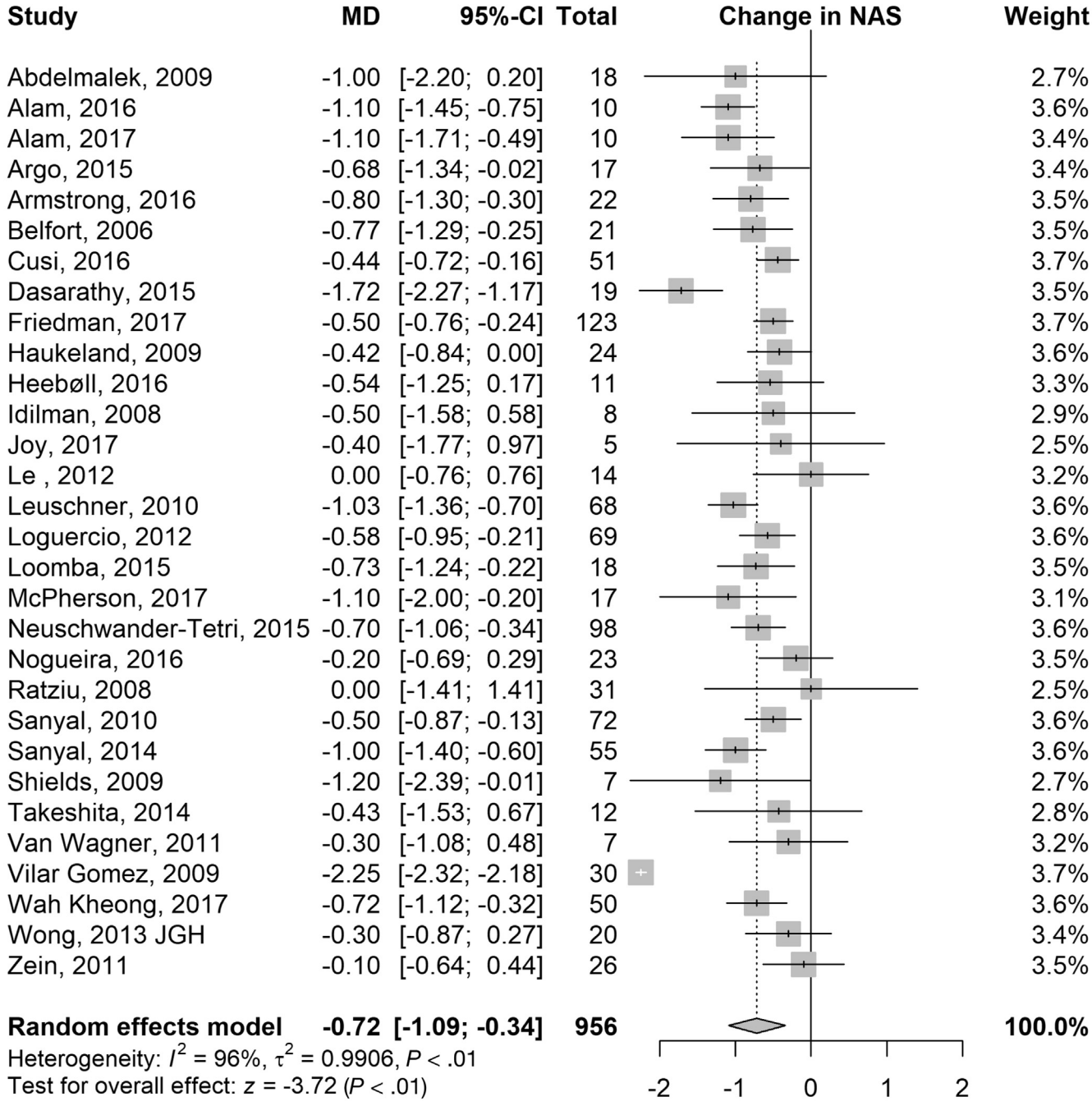

Figure 2. Meta-analysis of mean change in NAFLD Activity Score. Forest plot of random-effects meta-analysis of mean change in NAS after receiving placebo intervention measured as mean difference between values before and after receiving placebo. MD, mean difference.

publication bias was not done because of the heterogeneity in the MRS meta-analysis and small number of trials in the MRI-PDFF meta-analysis.

Using subgroup interaction tests (Figure 5), there was a significant difference between pooled MRS-IHTG change when the trials were subgrouped based on the number of included patients with paired MRS-IHTG and trial duration ($P < .01$), but not by recommendation of lifestyle modifications, administration of placebo pill, or geographic region ($P > .1$) (Supplementary Figure 9*A–E*). Trials with 40 or more patients and trials with longer duration were associated with more improvement in MRS-IHTG. Univariate meta-regression models (Figure 5) showed that trial duration explained the moderate heterogeneity noticed between MRS trials ($R^2 = 98\%$; $P = .003$), but not BMI change, baseline MRS-IHTG, or visit frequency (R^2 range 0%–27%; $P > .1$) (Supplementary Figure 10*A–D*). The multivariate meta-regression model showed that trials with longer duration and that did not report or recommend lifestyle modifications were

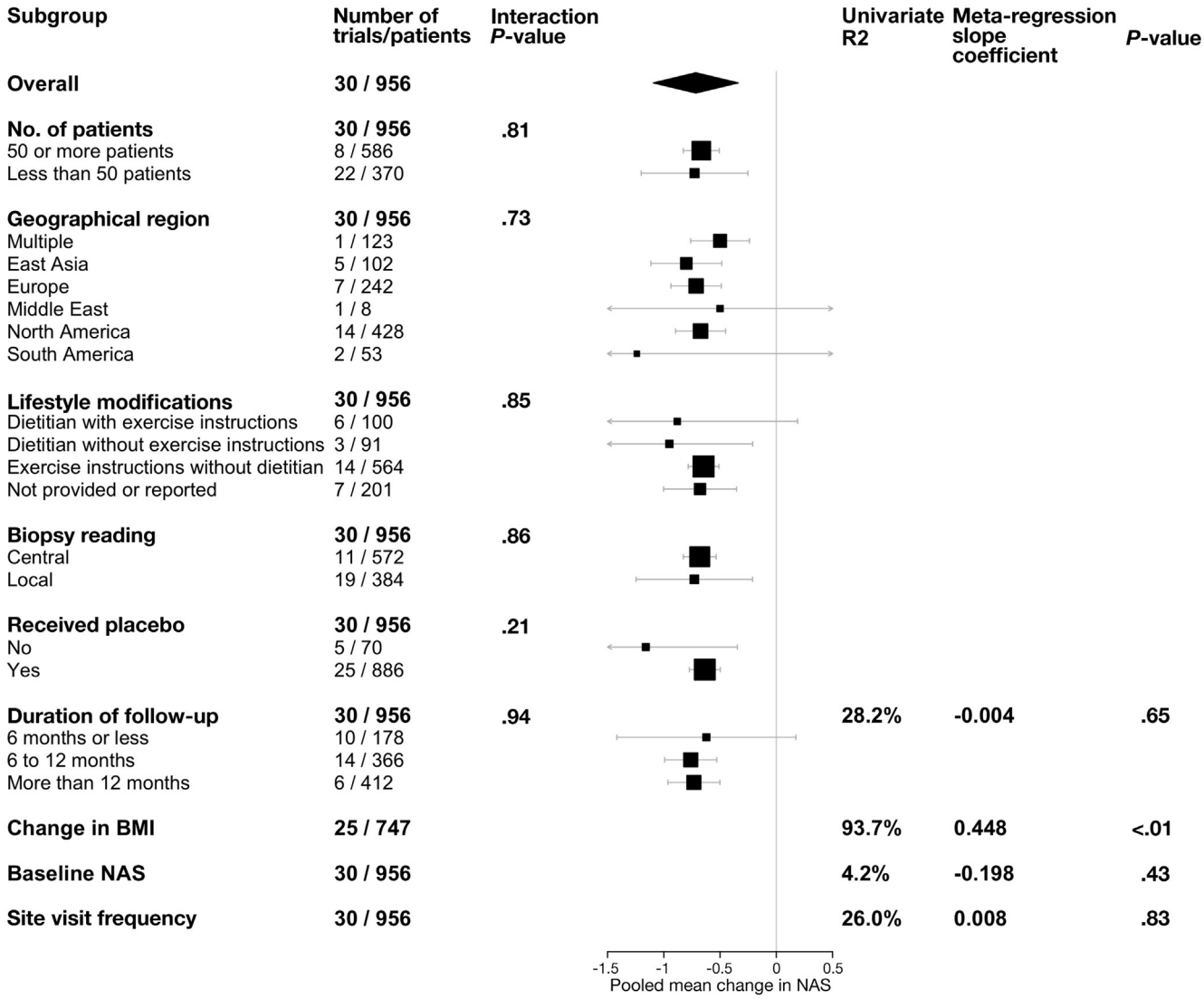

Figure 3. Investigating the heterogeneity observed in the pooled mean change in NAS in patients receiving placebo ($I^2 = 97\%$; $P < .01$; number of trials = 30).

associated with more improvement in MRS-IHTG, whereas trials from the Middle East were associated with worsening of MRS-IHTG (Supplementary Table 3).

Meta-Analysis of Biochemical and Anthropometric Response

Mean serum ALT and AST decreased significantly in placebo-treated patients (by 11.7 U/L ± SE 1.9 and 5.9 U/L ± SE 1.1, respectively; $P < .05$). However, there was no statistically significant change in mean serum alkaline phosphatase ($P = .55$) (Supplementary Figure 11A–C). There was a statistically significant reduction in BMI of 0.28 ± SE 0.10 ($P < .01$) and an increase in hemoglobin A_{1c} of 0.05 ± SE 0.02 in placebo-treated patients ($P = .02$), but no significant change in homeostatic model assessment for insulin resistance ($P = .87$) (Supplementary Figure 12*A–C*).

Discussion

In this systematic review and meta-analysis we found and quantified the improvement in histologic, radiologic, and biochemical features in patients with NASH treated with placebo, an important finding that could impact the assessment of the relative effectiveness of various interventions observed in NASH clinical trials. The key finding of our work was that in patients with NASH treated with placebo there was a significant improvement in the mean NAS. Although some might not consider the NAS change of 0.72 points clinically significant, it is important to consider that this level of change might occur in the placebo arm when designing NASH clinical trials. Also, because a 2-point change in NAS without change in fibrosis is currently considered to be clinically meaningful, the possible contribution of a placebo effect of 0.72 (35% of a 2-point change) is important. A total of 1 in 4 placebo-treated patients achieved a

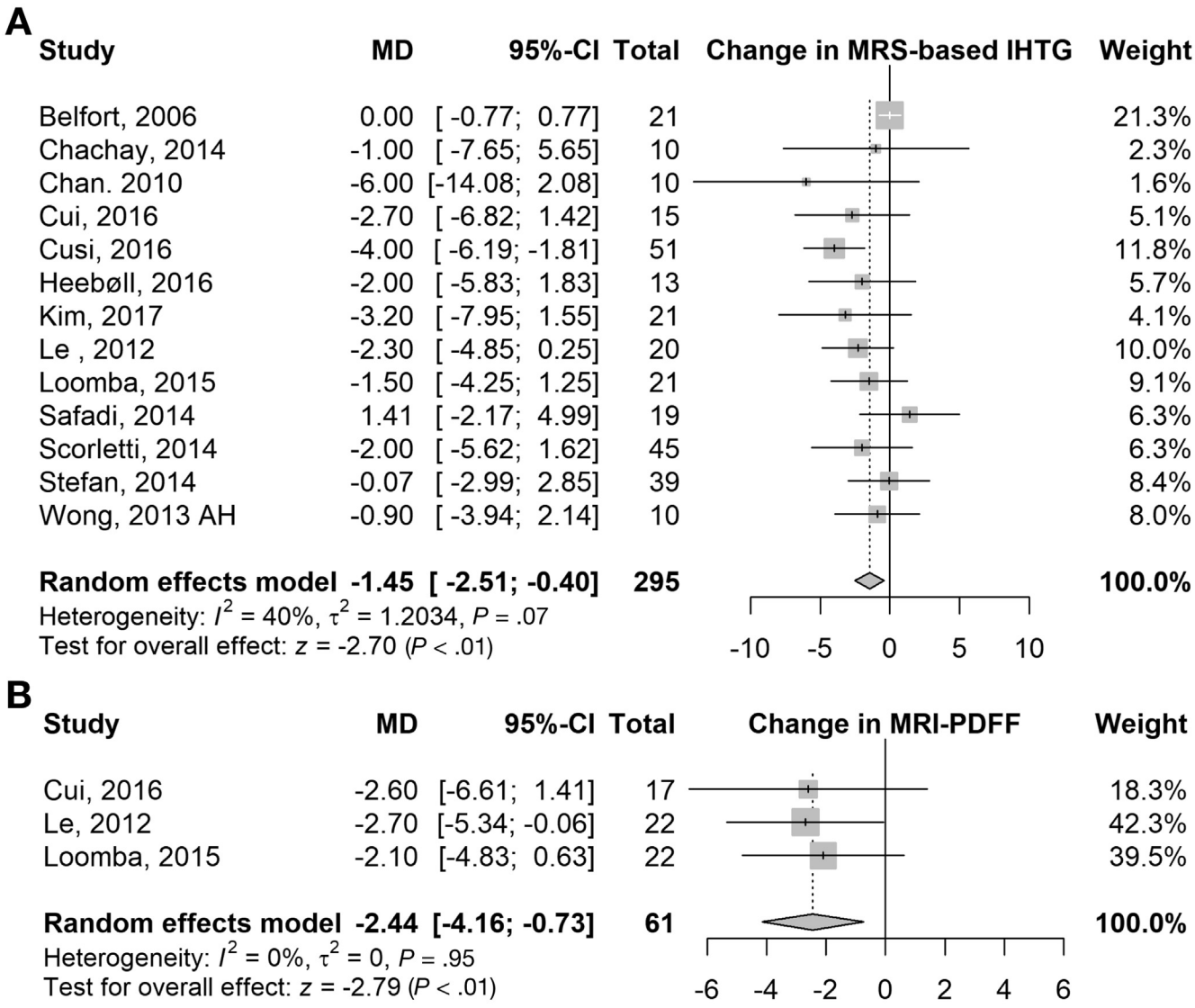

Figure 4. Meta-analyses of change in MRS-based and IHTG. Forest plots of random-effects meta-analyses of mean change in MRS-based IHTG (*A*) and MRI-PDFF based IHTG (*B*) after receiving placebo intervention measured as mean difference between values before and after receiving placebo. MD, mean difference.

2-point reduction in NAS. There was also a significant reduction in liver fat, as shown by MRI-based assessment of IHTG, and significant reductions in ALT and AST in placebo-treated patients.

With the large and increasing number of clinical trials testing NASH treatments in recent years, this meta-analysis was able to obtain data from a much larger number of trials and placebo patients compared with the only previous meta-analysis on this topic published in 2008[4] (39 trials vs 5; and 1463 placebo patients vs 162). In contrast to the previous report, our study showed statistically significant improvement in the individual NAS components, including steatosis, ballooning, and lobular inflammation. Both studies showed a change in ALT levels but, in contrast to the previous report, we also found a change in AST level that is plausible. We defined improvement as a change of $\geq$2 points in NAS without worsening of fibrosis, which is currently considered 1 of the main outcomes for NASH clinical trials. This was not the case in the previous report. Finally, we found a 25% pooled proportion of patients who had improvement of $\geq$2 points in the NAS in comparison with 14.3% in the previous meta-analysis. This updated analysis with a much larger sample size should more accurately represent the changes that can be expected in the placebo arms of NASH clinical trials.

The analysis was limited by some heterogeneity, which we investigated extensively using different possible explanatory variables. All the studies used NAS, eliminating diversity of scoring systems as a contributor to the heterogeneity. Sensitivity analyses excluding small trials and trials at high risk of bias showed statistically significant improvement without substantial heterogeneity. Using univariate meta-regression, there was a statistically significant positive correlation between the change in BMI and change in NAS in placebo-treated patients. This is

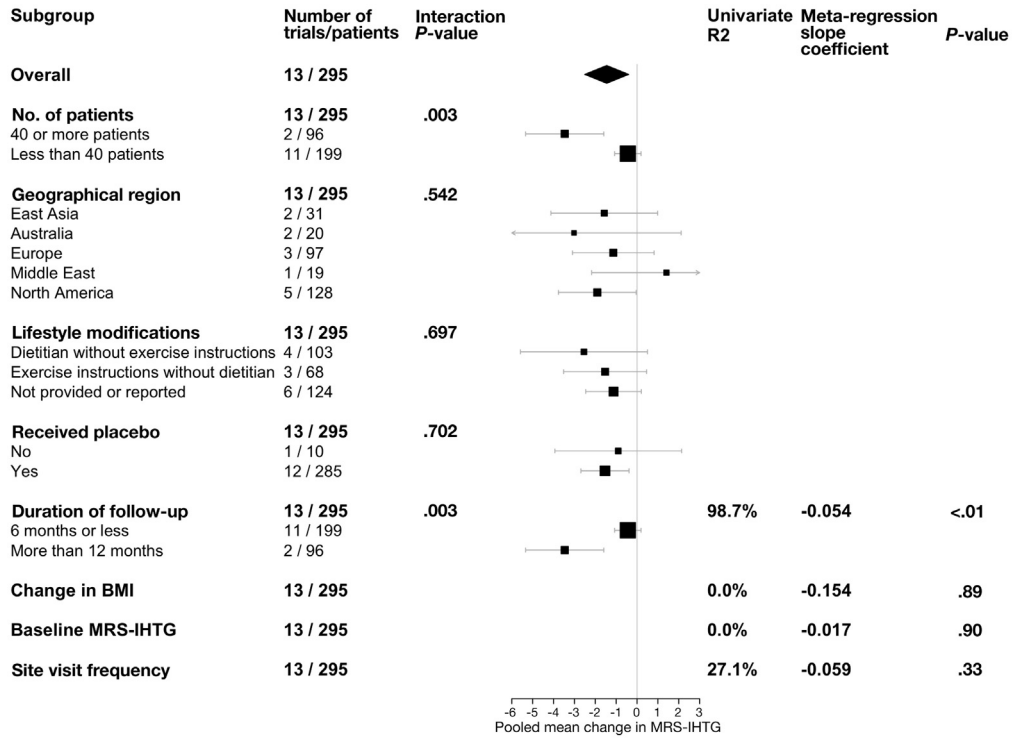

Figure 5. Investigating the heterogeneity observed in the pooled mean change in MRS-IHTG in patients receiving placebo ($I^2 = 40\%$; $P < .07$; number of trials = 13).

consistent with previous studies showing the association of weight loss with steatosis or NAS reductions.[54]

We investigated the possible etiologies of the placebo effect with univariate and multivariate meta-regression models. It has long been thought possible that patients in placebo arms may modify their behavior in response to their awareness of being observed (the Hawthorne effect), which in these NASH trials might have led to decreased BMI over time. It has been also thought that a greater number of follow-up visits in an RCT may influence patient behavior because of the increased attention perceived by the patient, which could potentially increase the likelihood of a behavioral change.[55] However, there was no statistically significant correlation between the frequency of follow-up visits and change in NAS. Additionally, when we subgrouped the MRS trials based on including 40 or more patients with paired measurements, the interaction test was significant. This indicated a difference in the outcome based on the number of included patients, another factor that could explain the heterogeneity. Additionally, the NAS trials were less heterogeneous after excluding trials with sample sizes less than 50. This is consistent with previous work showing that heterogeneity tends to be greater between small studies compared with larger studies.[56]

The significant correlation of baseline NAS with the observed change in NAS in the multivariate metaregression suggests that subjects with a higher baseline NAS might be more likely to respond to placebo or lifestyle modification. There was a similar statistically significant correlation between the improvement in IHTG and trial duration. These correlations might indicate that the spontaneous improvement is related to the natural history of the disease or that it reflects regression to the mean. Multivariable metaregression models of the NAS and MRS-IHTG showed that the geographic region where the trial was conducted was another factor that explained the observed heterogeneity after adjusting for all the other variables that we evaluated. This could be related to differences in lifestyles, research methodology, or underlying pathophysiologic variances in different populations. The lack of heterogeneity in the MRI-PDFF studies despite the small number of studies and short follow-up may be attributed to the high accuracy of these techniques in capturing even small changes in hepatic steatosis. This was shown previously[5,57] and needs to be explored in future studies.

The decline in ALT in placebo-treated patients in our study supports previously described results.[4] The improvement parallels the histologic and radiologic responses. Serum enzymes are known to fluctuate in NASH over time as part of the natural history of the disease. There is concern for selection bias in favor of recruiting patients who had higher serum liver enzymes into clinical trials because patients with higher transaminase levels are more likely to be referred to a tertiary care center and enrolled into trials compared with those with lower levels. Additionally, the phenomenon of regression to the mean, or the effect of repeated measurements, might have contributed to the observed responses.

The current study showed that specific variables could explain the differences in the placebo effect. Those variables should be considered when conducting future trials. The change of BMI and weight of the patients is a

cofactor that should be considered when analyzing and interpreting the results of NASH trials. The number of included patients is another factor that should be considered, because the results of trials with small sample sizes were, not surprisingly, heterogeneous compared with studies with larger sample sizes. Additionally, recommendation of lifestyle modifications, baseline NAS scores, and trial duration should be considered and/or standardized in future trials because they might affect the changes seen in the placebo population of NASH trials. Such variability can add noise and hide important signals, and subsequently affect the power of these trials to detect significant changes. Finally, the geographic region where the study is being conducted should also be considered when interpreting the results of NASH trials.

This study has multiple strengths. In trials reporting biopsy-based outcomes, all the patients had biopsy-proven NASH and the sample size exceeded 900 patients. We only included trials that used NAS as a histologic outcome to eliminate the difficulty in comparing the magnitude of change in histologic parameters across trials using different scoring systems. NAS has been extensively validated and is currently the leading histologic scoring system used for outcome measurement in NASH trials. We also summarized the evidence of the placebo effect on NASH assessed by MRI-based measures. Because of the variability in MRI-PDFF protocols and to ascertain reproducible consistent results between the included trial, we only included trials that clearly stated using 3 regions of interest per segment. We excluded trials that used different protocols, such as using 1 region of interest per segment as in Joy et al,[30] or did not clearly describe their protocol (Supplementary Table 1). We also conducted comprehensive analyses and used several variables to explain the heterogeneity between studies and we hope that this information may be useful for design of future trials.

There are several limitations to this systematic review. The risk of bias of the included trials was moderate overall with evidence of some heterogeneity; thus, the results should be interpreted with caution. The adequacy of biopsy specimens was not described in some of the studies. Although we contacted corresponding authors, there were still trials that could not be included because of missing data and lack of response from the authors. The smaller number of studies using MRI-PDFF limits the interpretation and generalization of those results. We could not assess the publication bias because of the presence of substantial heterogeneity or small number of trials.

Finally, it is important to recognize the limitations of the statistical tests that we conducted to investigate the heterogeneity and acknowledge their observational nature with the possibility of false negatives and false positives. For example, the baseline NAS severity and geographic region were not statistically significant in univariate analyses but significant in the multivariate metaregression. This observation could be related to the exclusion of the 5 trials that did not report BMI changes from the multivariate metaregression model, or could be caused by confounding or model fitting. Another example is the MRS-IHTG multivariate metaregression, which showed that trials that did not report or perform lifestyle modification recommendations were associated with more improvement in MRS-IHTG after adjusting for all the other variables included in our model. This may need to be explored in future MRS-IHTG studies, although they are less commonly conducted now.

In summary, placebo treatment in NASH is associated with histologic, radiologic, and biochemical responses. This may reflect the Hawthorne effect and/or the variability of these measures based on changes in weight, baseline severity of disease, trial duration, sample size, recommendation of lifestyle modification, geographic location, or the natural history of NAFLD. The response to placebo should be considered when designing and interpreting the results of RCTs assessing treatment response in patients with NASH.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.06.011.

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Conflicts of interest
These authors disclose the following: Eric Lefebvre was the Vice President and the Head of Clinical Research and Development – NASH at Allergan. Rifaat Safadi has been on the advisory board or a speaker for Intercept, Gilead, CanFite, and MedImmune; has received research support from Novartis, Galmed, BioLine, and CanFite; and is a minor shareholder of CanFite. Vlad Ratziu is a consultant for Boehringer, Bristol Myers Squibb, Galmed, Genfit, Intercept, Pfizer, and Alergan. Mazen Noureddin has been on the advisory board or a speaker for EchoSens, OWL, Intercept, Gilead, and Abbott; has received research support from Gilead, Galmed, Galectin, Genfit, Conatus, Zydus, and Shire; and is a minor shareholder of Anaetos. The remaining authors disclose no conflicts.

Supplementary Appendix

Actual Search Strategy

Ovid

Database(s): Embase 1988 to 2018 Week 01, EBM Reviews - Cochrane Central Register of Controlled Trials November 2017, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Search Strategy:

#	Searches	Results
1	exp Non-alcoholic Fatty Liver Disease/	37546
2	((("non-alcoholic" or nonalcoholic) and ("fatty liver*" or steatohepatit* or (liver and steatos*) or "visceral steatos*")) or NAFLD).mp.	55849
3	1 or 2	55849
4	exp nuclear magnetic resonance imaging/	788407
5	exp Magnetic Resonance Imaging/	1229061
6	((mr adj tomograph*) or (nmr adj tomograph*) or "chemical shift imaging*" or fmri or fmris or "magnetic resonance" or "magnetization transfer imaging*" or "mr imaging*" or "MR spectroscop*" or mri or mris or nmr or nmrs or "proton spin tom").mp.	2001062
7	4 or 5 or 6	2011632
8	(adipose or adiposity or fat or HFF or lipid* or PDFF or steatosis).mp.	1797148
9	7 and 8	82346
10	(biopsies or biopsy or histolog* or laboratory or pathologist*).mp.	3588323
11	3 and (9 or 10)	19839
12	exp controlled study/	6128459
13	exp Randomized Controlled Trial/	988876
14	exp triple blind procedure/	184
15	exp Double-Blind Method/	423044
16	exp Single-Blind Method/	75429
17	exp latin square design/	351
18	exp Placebos/	335640
19	exp Placebo Effect/	10652
20	((control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or random*).mp,pt.	9247173
21	or/12-20	9247238
22	11 and 21	6585
23	(exp animals/ or exp nonhuman/) not exp humans/	9465408
24	((alpaca or alpacas or amphibian or amphibians or animal or animals or antelope or armadillo or armadillos or avian or baboon or baboons or beagle or beagles or bee or bees or bird or birds or bison or bovine or buffalo or buffaloes or buffalos or "c elegans" or "Caenorhabditis elegans" or camel or camels or canine or canines or carp or cats or cattle or chick or chicken or chickens or chicks or chimp or chimpanze or chimpanzees or chimps or cow or cows or "D melanogaster" or "dairy calf" or "dairy calves" or deer or dog or dogs or donkey or donkeys or drosophila or "Drosophila melanogaster" or duck or duckling or ducklings or ducks or equid or equids or equine or equines or feline or felines or ferret or ferrets or finch or finches or fish or flatworm or flatworms or fox or foxes or frog or frogs or "fruit flies" or "fruit fly" or "G mellonella" or "Galleria mellonella" or geese or gerbil or gerbils or goat or goats or goose or gorilla or gorillas or hamster or hamsters or hare or hares or heifer or heifers or horse or horses or insect or insects or jellyfish or kangaroo or kangaroos or kitten or kittens or lagomorph or lagomorphs or lamb or lambs or llama or llamas or macaque or macaques or macaw or macaws or marmoset or marmosets or mice or minipig or minipigs or mink or minks or monkey or monkeys or mouse or mule or mules or nematode or nematodes or octopus or octopuses or orangutan or "orang-utan" or orangutans or "orang-utans" or oxen or parrot or parrots or pig or pigeon or pigeons or piglet or piglets or pigs or porcine or primate or primates or quail or rabbit or rabbits or rat or rats or reptile or reptiles or rodent or rodents or ruminant or ruminants or salmon or sheep or shrimp or slug or slugs or swine or tamarin or tamarins or toad or toads or trout or urchin or urchins or vole or voles or waxworm or waxworms or worm or worms or xenopus or "zebra fish" or zebrafish) not (human or humans)).mp.	8305148
25	22 not (23 or 24)	5356
26	limit 25 to (editorial or erratum or letter or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	102
27	25 not 26	5254
28	remove duplicates from 27	3852

Scopus

1 TITLE-ABS-KEY(((“non-alcoholic” or nonalcoholic) and (“fatty liver*” or steatohepatit* or (liver and steatos*) or “visceral steatos*”)) or NAFLD)

2 TITLE-ABS-KEY((mr W/1 tomograph*) OR (nmr W/1 tomograph*) OR “chemical shift imaging*” OR fmri OR fmris OR “magnetic resonance” OR “magnetization transfer imaging*” OR “mr imaging*” OR “MR spectroscop*” OR mri OR mris OR nmr OR nmrs OR “proton spin tom”)

3 TITLE-ABS-KEY(adipose OR adiposity OR fat OR “fatty acid*” OR HFF OR lipid* OR PDFF OR steatosis)

4 TITLE-ABS-KEY(biopsies OR biopsy OR histolog* OR laboratory OR pathologist*)

5 1 and ((2 and 3) or 4)

6 TITLE-ABS-KEY((control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or “pragmatic clinical trial” or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or “latin square” or placebo* or nocebo* or random*)

7 5 and 6

8 TITLE-ABS-KEY((alpaca OR alpacas OR amphibian OR amphibians OR animal OR animals OR antelope OR armadillo OR armadillos OR avian OR baboon OR baboons OR beagle OR beagles OR bee OR bees OR bird OR birds OR bison OR bovine OR buffalo OR buffaloes OR buffalos OR “c elegans” OR “Caenorhabditis elegans” OR camel OR camels OR canine OR canines OR carp OR cats OR cattle OR chick OR chicken OR chickens OR chicks OR chimp OR chimpanze OR chimpanzees OR chimps OR cow OR cows OR “D melanogaster” OR “dairy calf” OR “dairy calves” OR deer OR dog OR dogs OR donkey OR donkeys OR drosophila OR “Drosophila melanogaster” OR duck OR duckling OR ducklings OR ducks OR equid OR equids OR equine OR equines OR feline OR felines OR ferret OR ferrets OR finch OR finches OR fish OR flatworm OR flatworms OR fox OR foxes OR frog OR frogs OR “fruit flies” OR “fruit fly” OR “G mellonella” OR “Galleria mellonella” OR geese OR gerbil OR gerbils OR goat OR goats OR goose OR gorilla OR gorillas OR hamster OR hamsters OR hare OR hares OR heifer OR heifers OR horse OR horses OR insect OR insects OR jellyfish OR kangaroo OR kangaroos OR kitten OR kittens OR lagomorph OR lagomorphs OR lamb OR lambs OR llama OR llamas OR macaque OR macaques OR macaw OR macaws OR marmoset OR marmosets OR mice OR minipig OR minipigs OR mink OR minks OR monkey OR monkeys OR mouse OR mule OR mules OR nematode OR nematodes OR octopus OR octopuses OR orangutan OR “orang-utan” OR orangutans OR “orang-utans” OR oxen OR parrot OR parrots OR pig OR pigeon OR pigeons OR piglet OR piglets OR pigs OR porcine OR primate OR primates OR quail OR rabbit OR rabbits OR rat OR rats OR reptile OR reptiles OR rodent OR rodents OR ruminant OR ruminants OR salmon OR sheep OR shrimp OR slug OR slugs OR swine OR tamarin OR tamarins OR toad OR toads OR trout OR urchin OR urchins OR vole OR voles OR waxworm OR waxworms OR worm OR worms OR xenopus OR “zebra fish” OR zebrafish) AND NOT (human OR humans))

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10 DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

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13 11 and not 12

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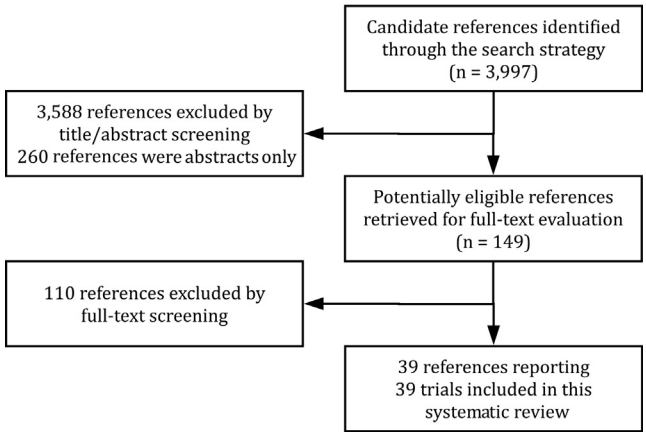
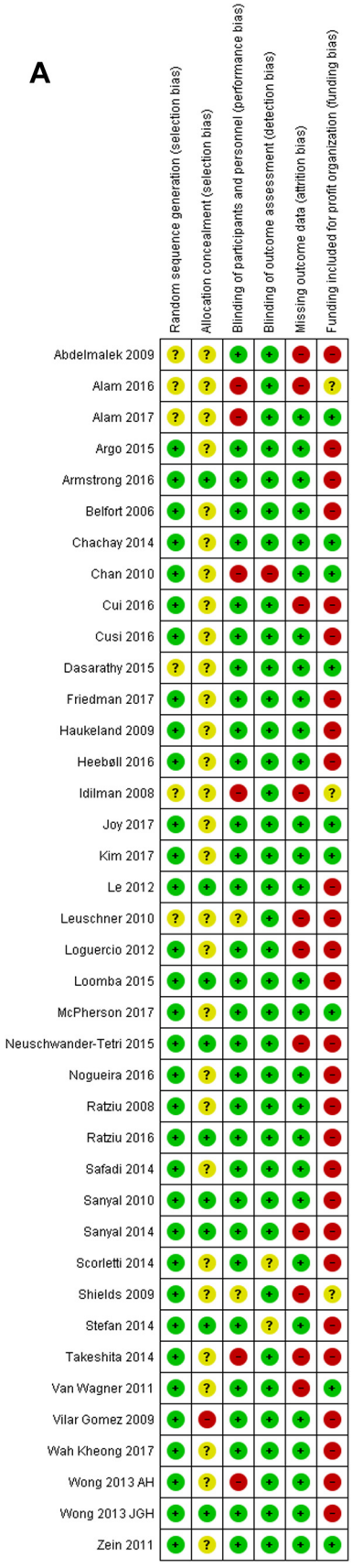
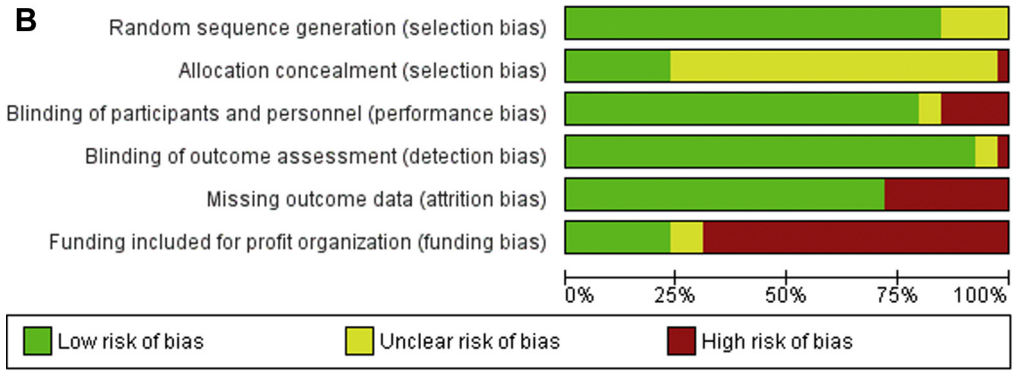


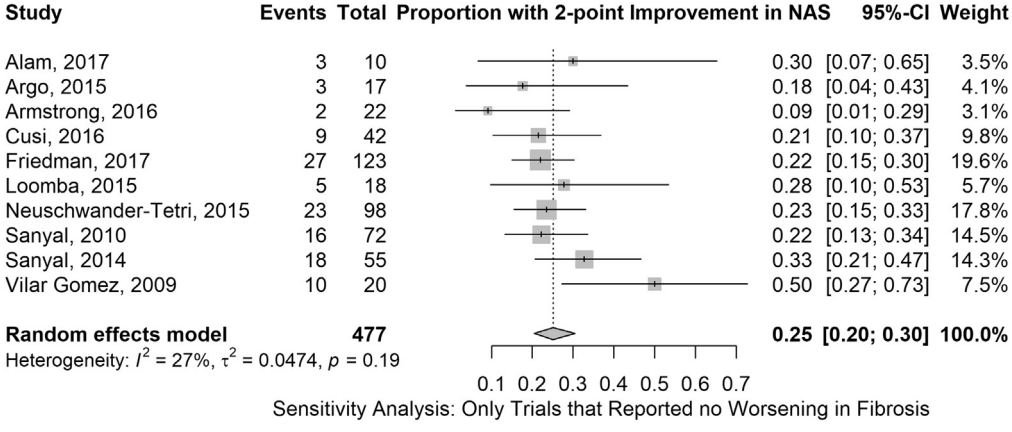
Supplementary Figure 1. Flow chart of study selection process.



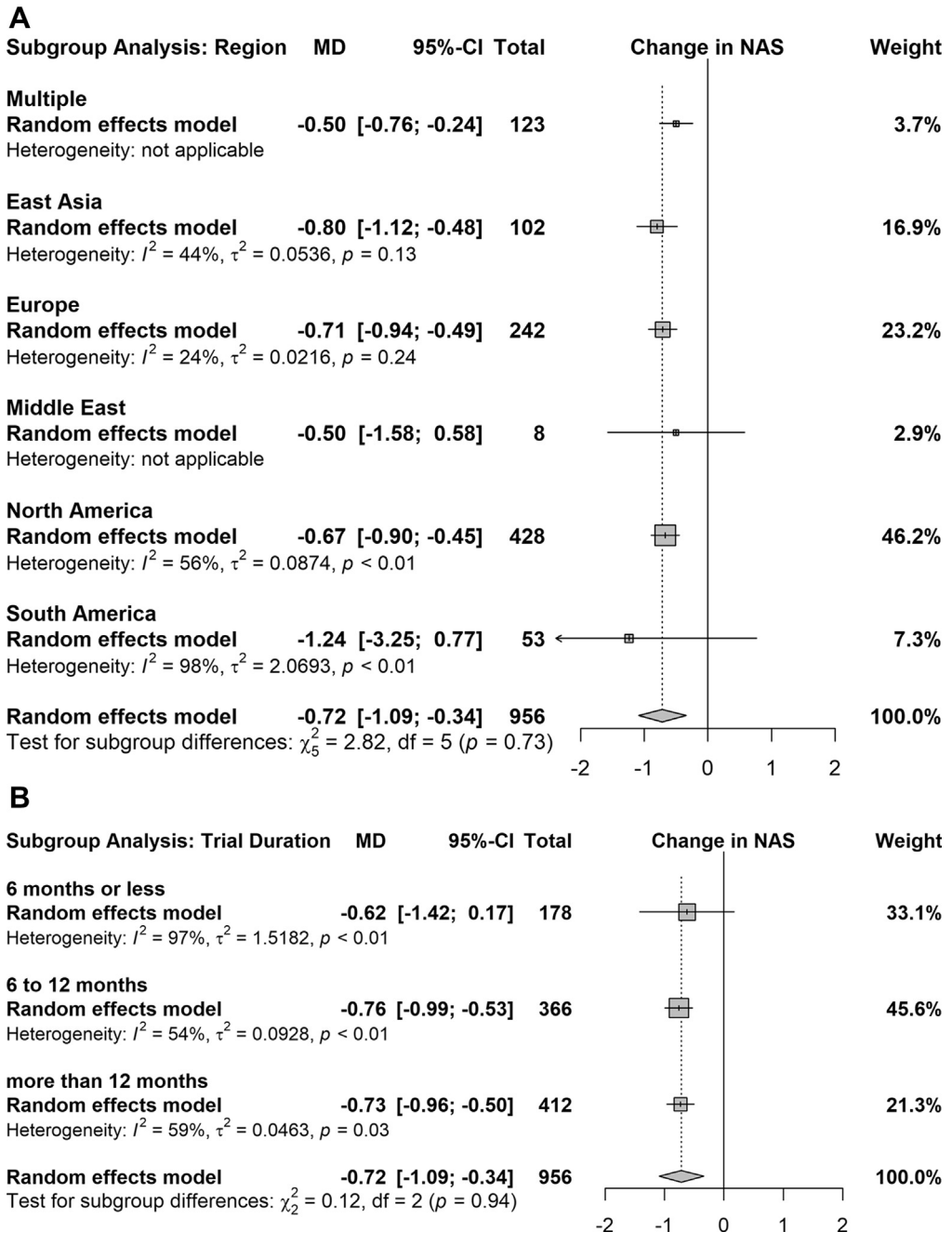
Supplementary Figure 2. Assessment of risk of bias in the individual studies. Risk of bias summary (*A*) and graph (*B*) based on the Cochrane risk of bias tool.



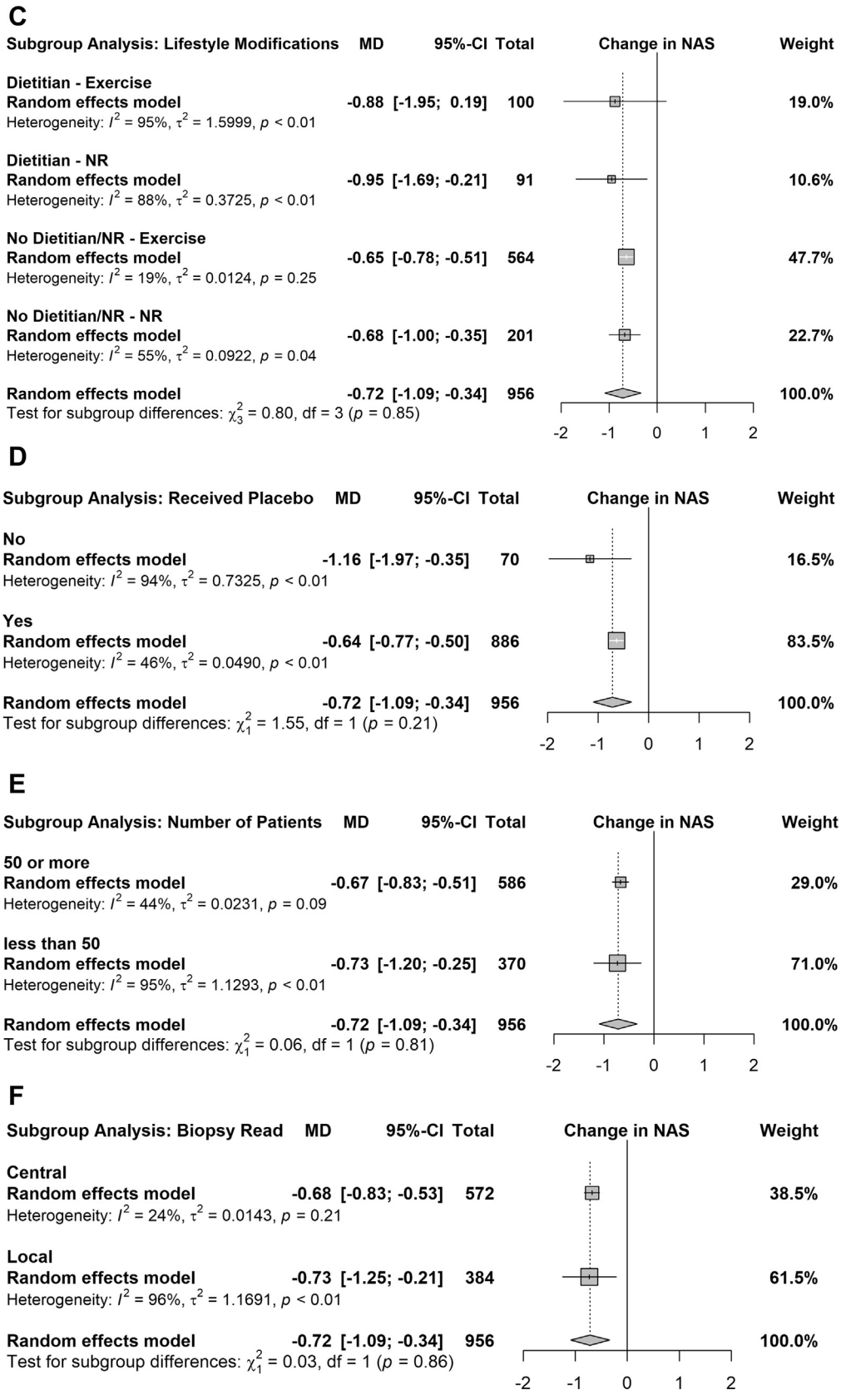
Supplementary Figure 2. (*continued*).



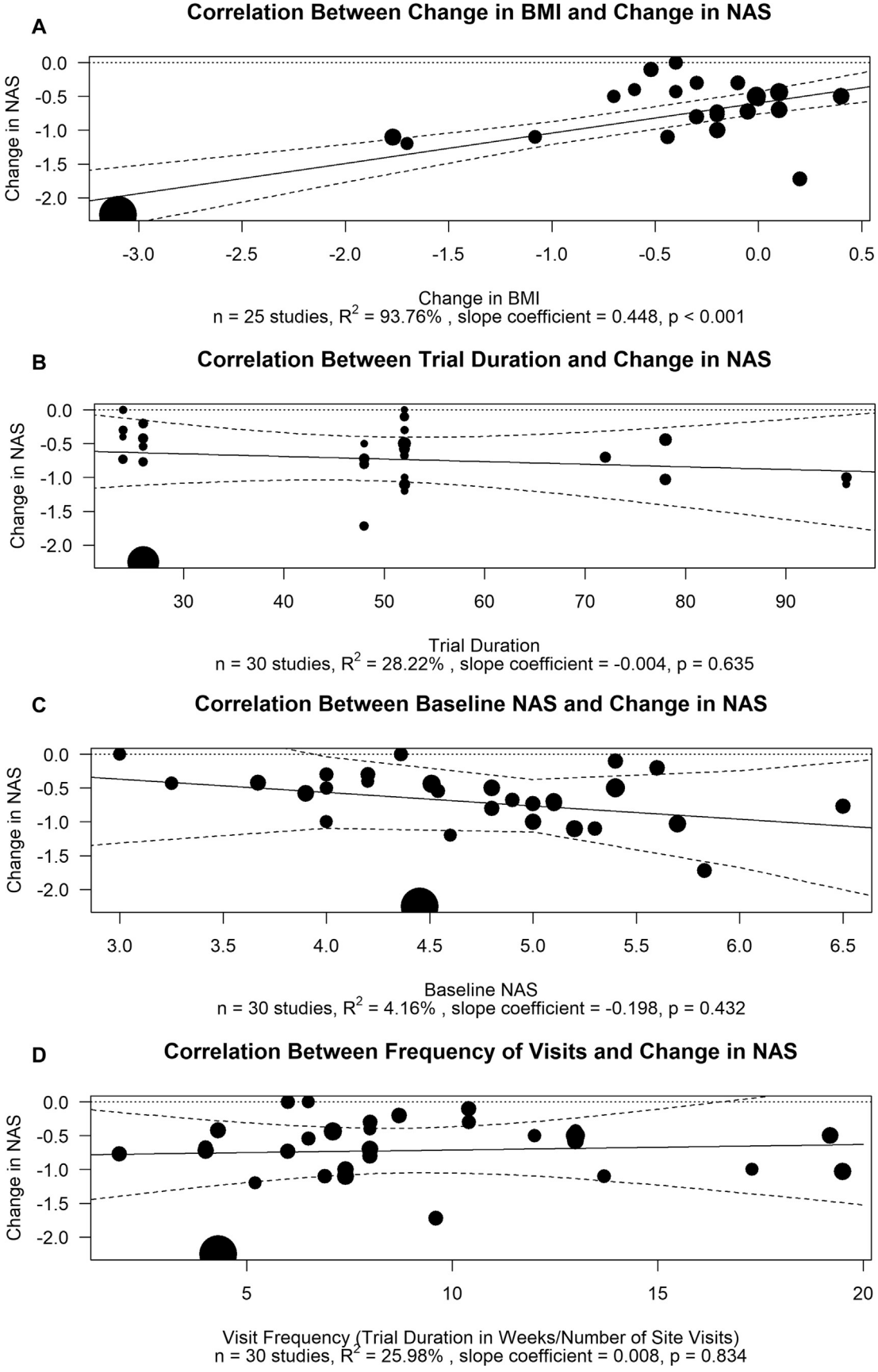
Supplementary Figure 3. Sensitivity analysis of meta-analysis of proportion of patients with histologic response. Sensitivity analysis using random-effects meta-analysis of the proportion of patients with 2-point improvement in NAFLD activity score without worsening in fibrosis after receiving placebo intervention.



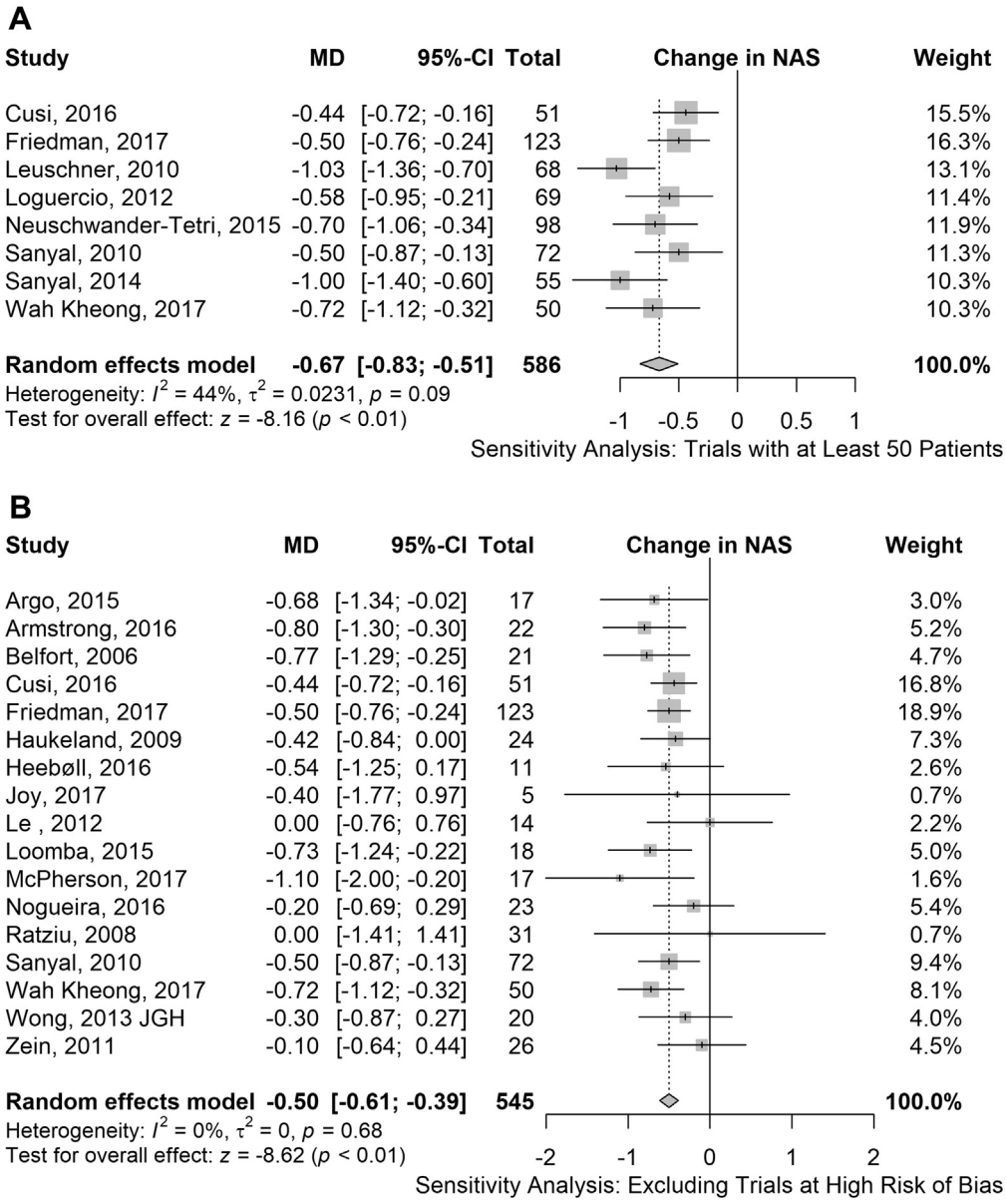
Supplementary Figure 4. Subgroup analyses to assess heterogeneity in the meta-analysis of change in NAS. Exploratory analyses to investigate the heterogeneity noted in the meta-analysis of mean change in NAS after receiving placebo intervention. Subgroup interaction tests based on geographic region where the trial was conducted (*A*), trial duration (*B*), lifestyle modification (*C*), receiving placebo versus lifestyle interventions only (*D*), number of patients with paired preplacebo and postplacebo data in the placebo arm (*E*), and the location where the biopsy was read, central versus local (*F*). MD, mean difference; NR, not recommended or reported.



Supplementary Figure 4. (*continued*).

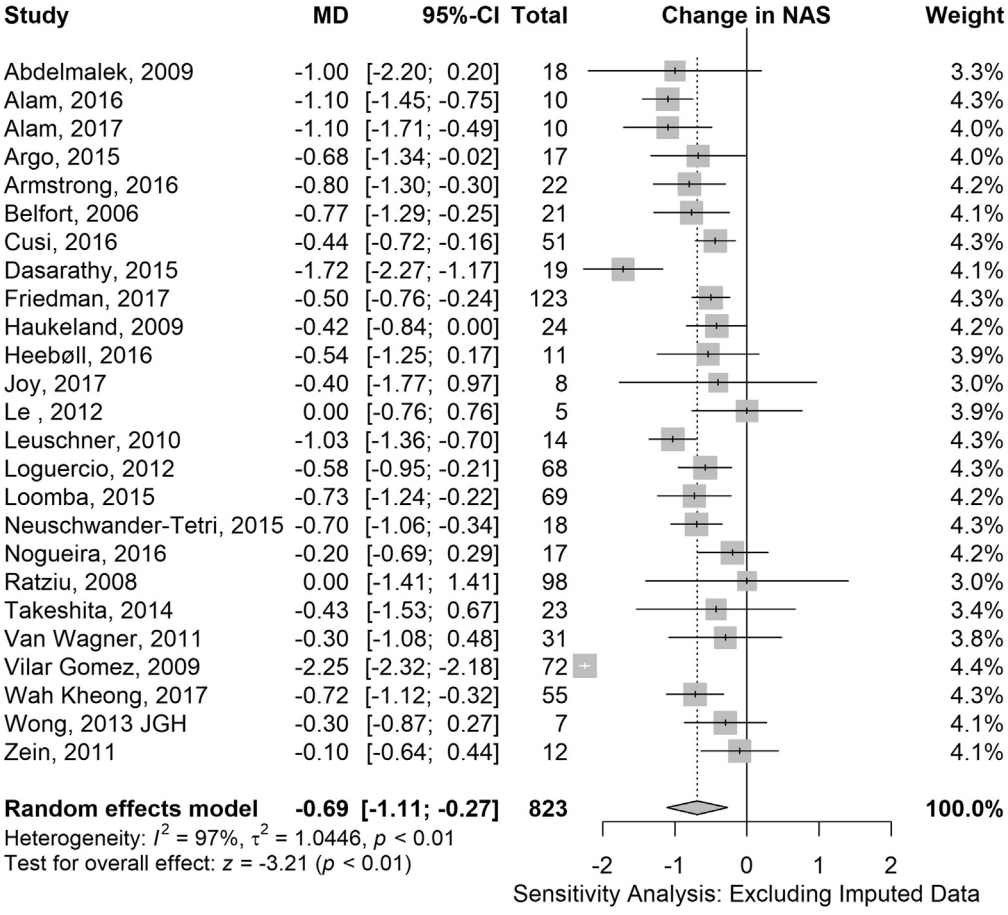


Supplementary Figure 5. Meta-regression to assess heterogeneity in the meta-analysis of change in NAS. Exploratory analyses to investigate the heterogeneity noted in the meta-analysis of mean change in NAS after receiving placebo intervention. Bubble plots of meta-regression using change in BMI (*A*), trial duration (*B*), baseline NAS (*C*), and frequency of site visit (*D*) as explanatory variables.

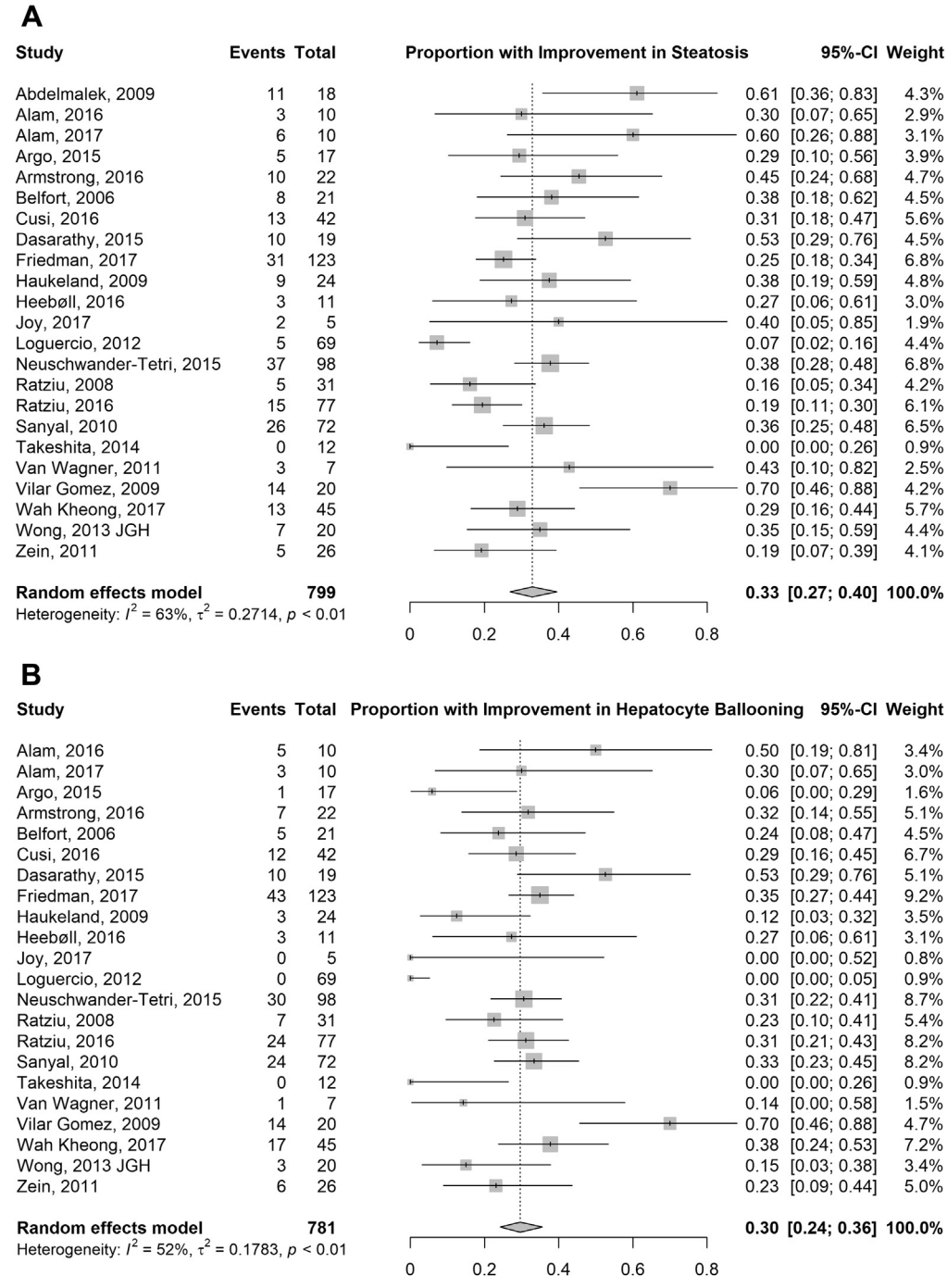


Supplementary Figure 6. Sensitivity analyses of meta-analysis of change in NAS. Sensitivity analyses using random-effects meta-analyses of the mean change in NAS after receiving the placebo intervention by excluding trials that had less than 50 patients with paired pre-placebo and post-placebo intervention data (*A*), excluding trials at high- and moderate-risk of bias (*B*), and excluding imputed data (*C*). MD, mean difference.

C

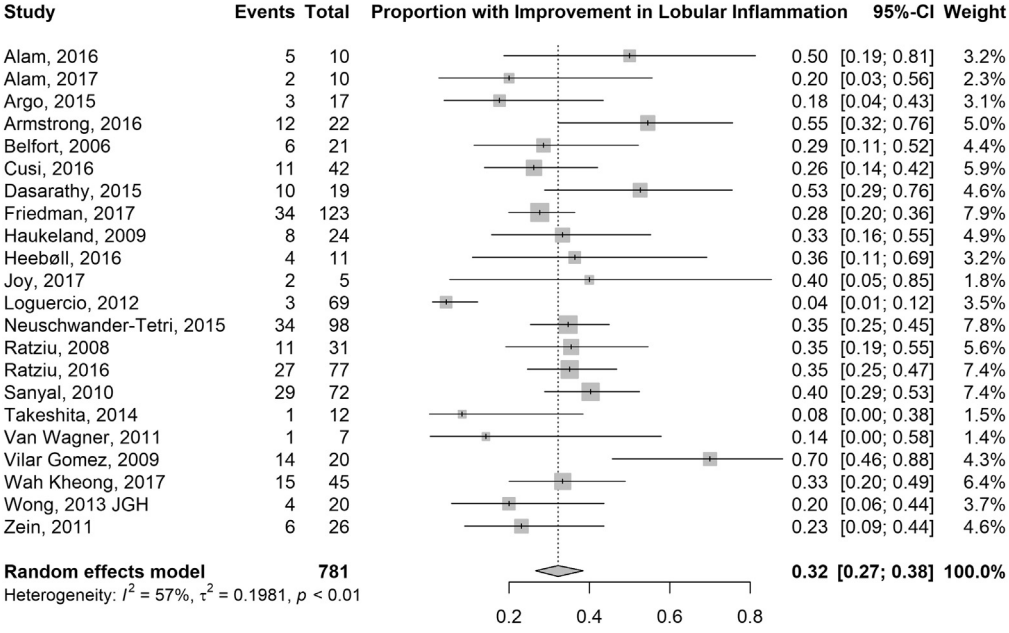


Supplementary Figure 6. (*continued*).

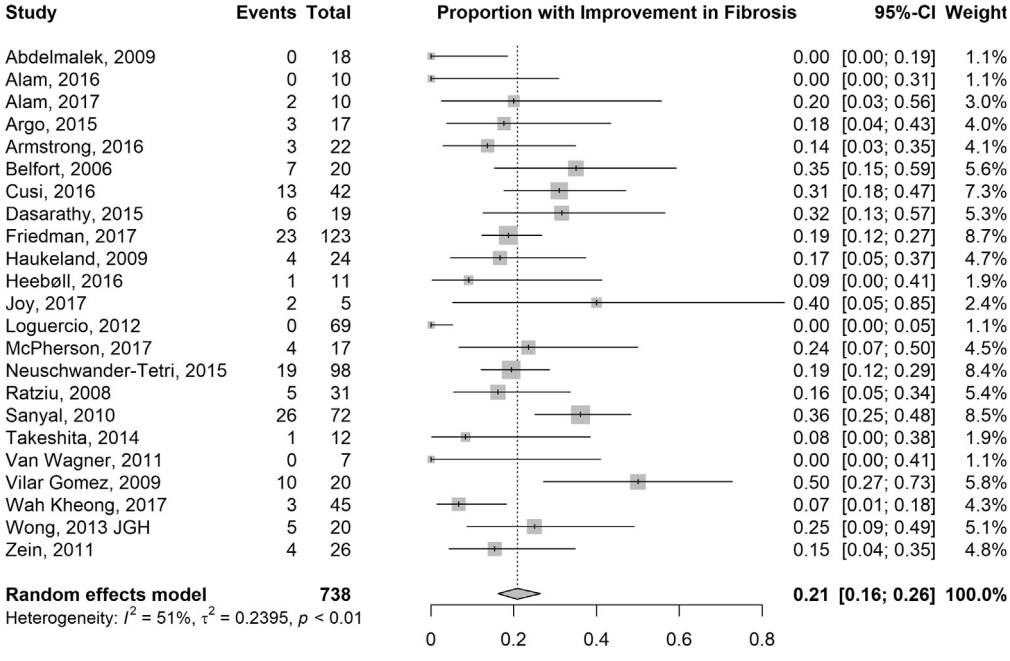


Supplementary Figure 7. Meta-analyses of proportion of patients with improvement in individual histologic scores. Forest plots of random-effects meta-analyses showing the proportions of patients with 1-point improvement in steatosis score (*A*), hepatocyte ballooning score (*B*), lobular inflammation score (*C*), and fibrosis grade (*D*) after receiving placebo intervention.

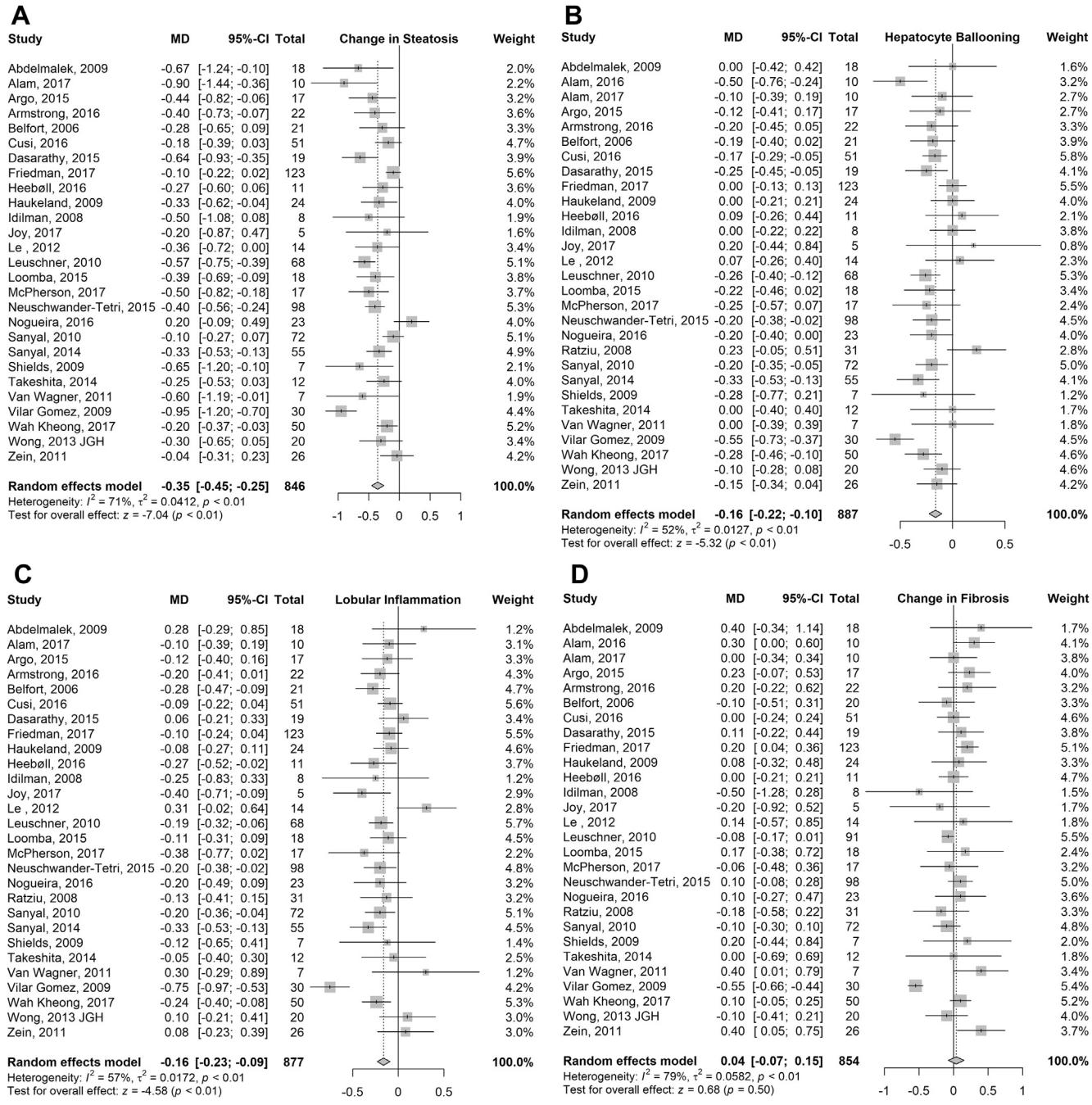
C



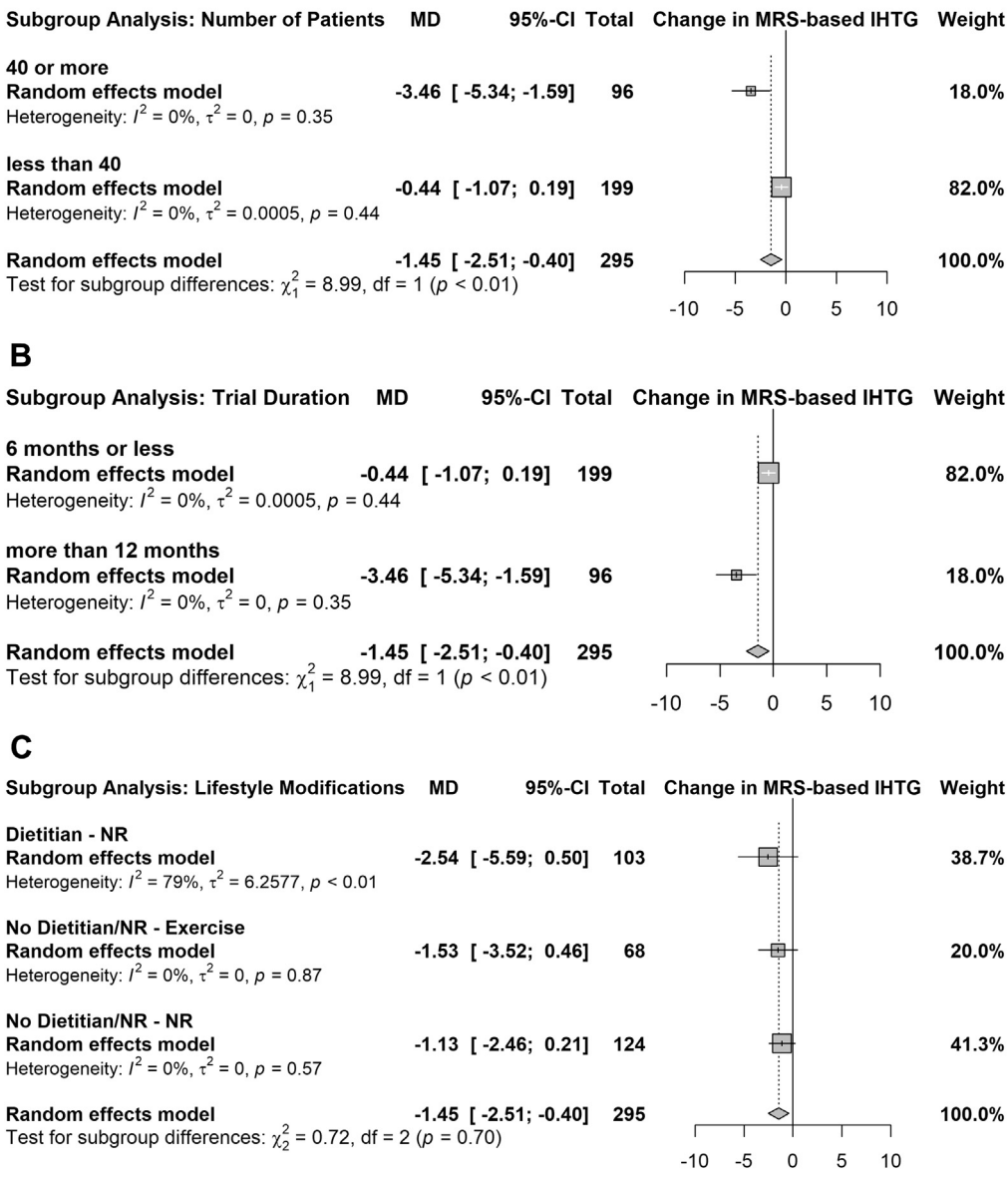
D



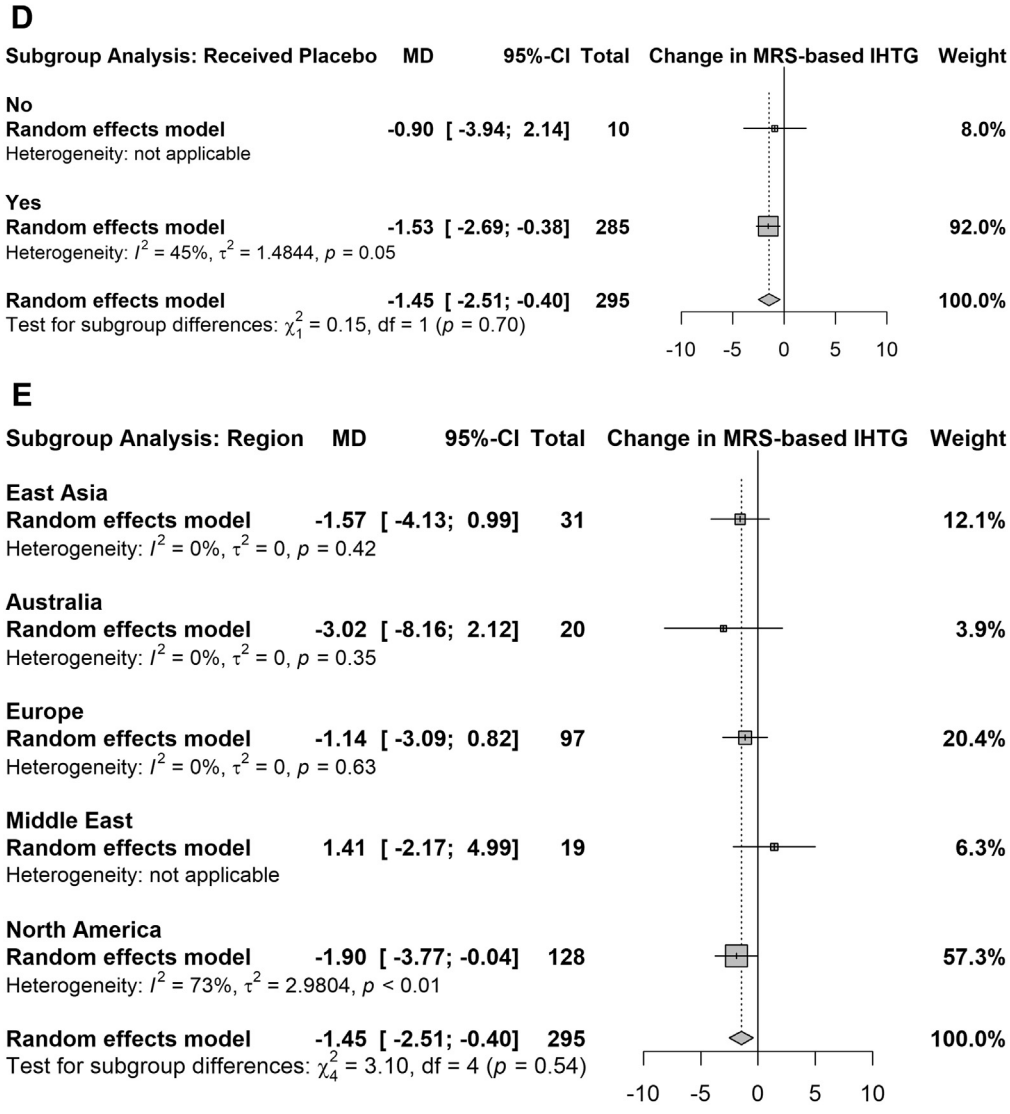
Supplementary Figure 7. (*continued*).



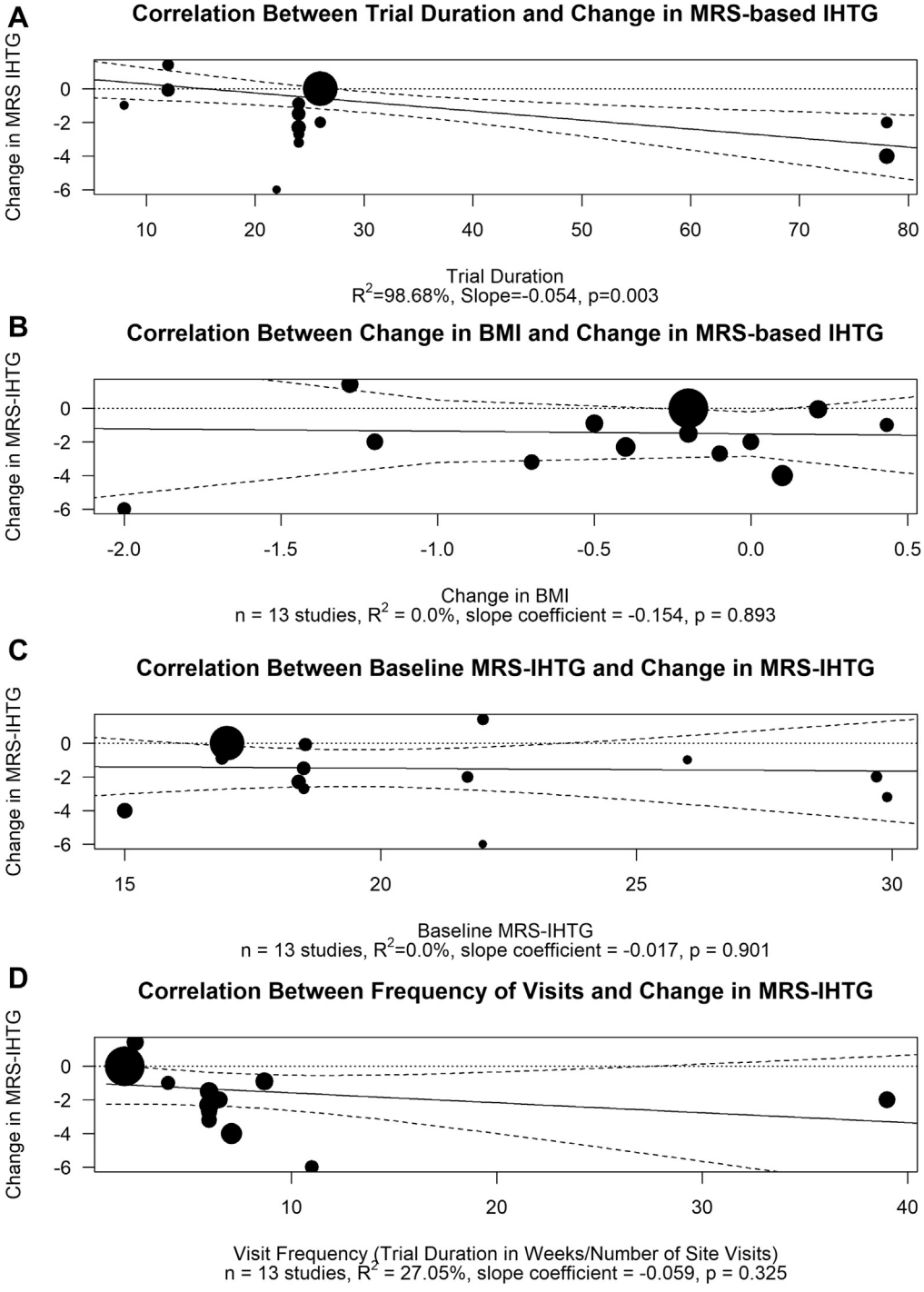
Supplementary Figure 8. Meta-analyses of change in individual histologic scores. Forest plots of random-effects meta-analyses of the mean change in steatosis score (*A*), hepatocyte ballooning score (*B*), lobular inflammation score (*C*), and fibrosis grade (*D*) after receiving placebo intervention measured as mean difference between values before and after receiving placebo. MD, mean difference.



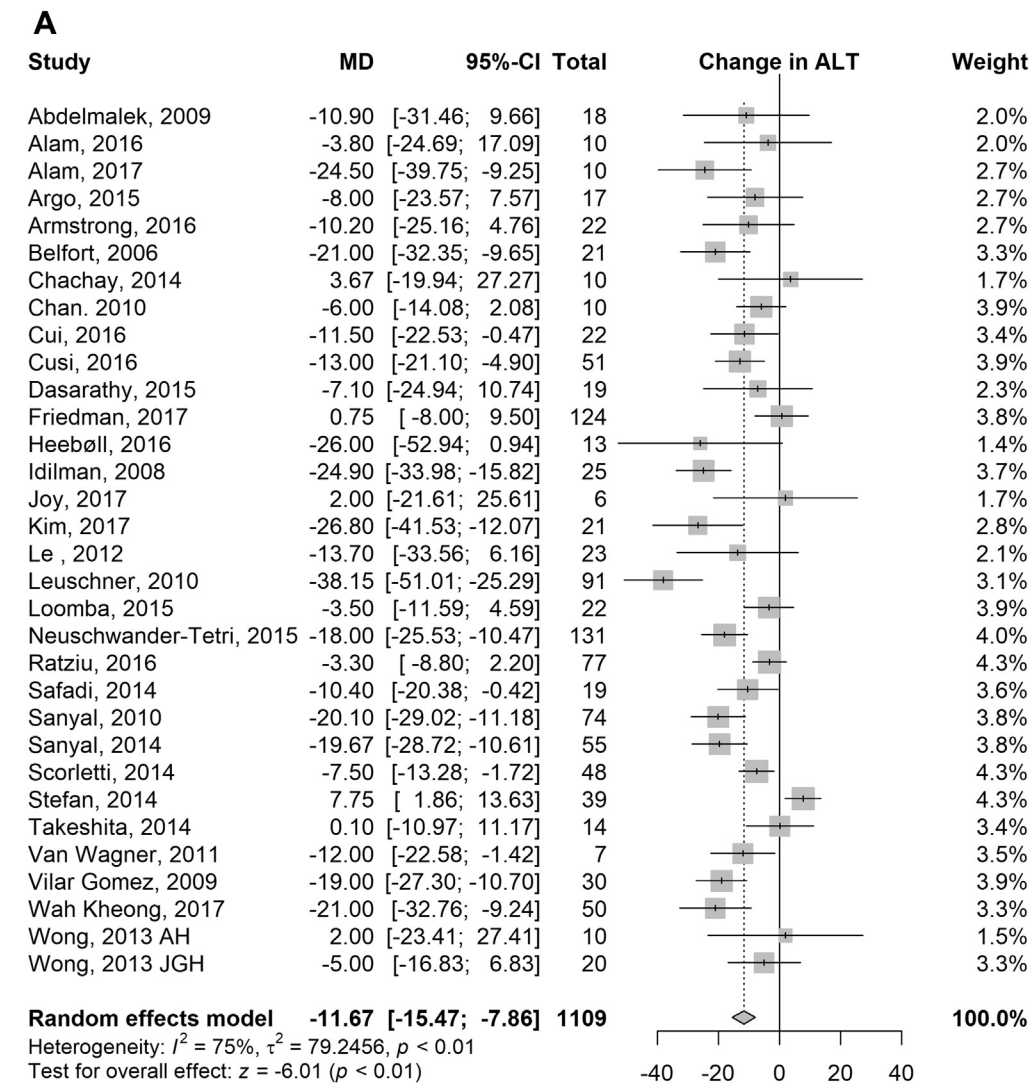
Supplementary Figure 9. Subgroup analyses to assess heterogeneity in the meta-analysis of change in MRS-based IHTG. Exploratory analyses to investigate the heterogeneity noted in the meta-analysis of the mean change in MRS-based IHTG after receiving placebo intervention. Subgroup interaction tests based on number of patients in the placebo arm (*A*), trial duration (*B*), recommendation of lifestyle modification (*C*), receiving placebo versus lifestyle interventions only (*D*), and the geographic region where the trial was conducted (*E*). MD, mean difference; NR, not recommended or reported.



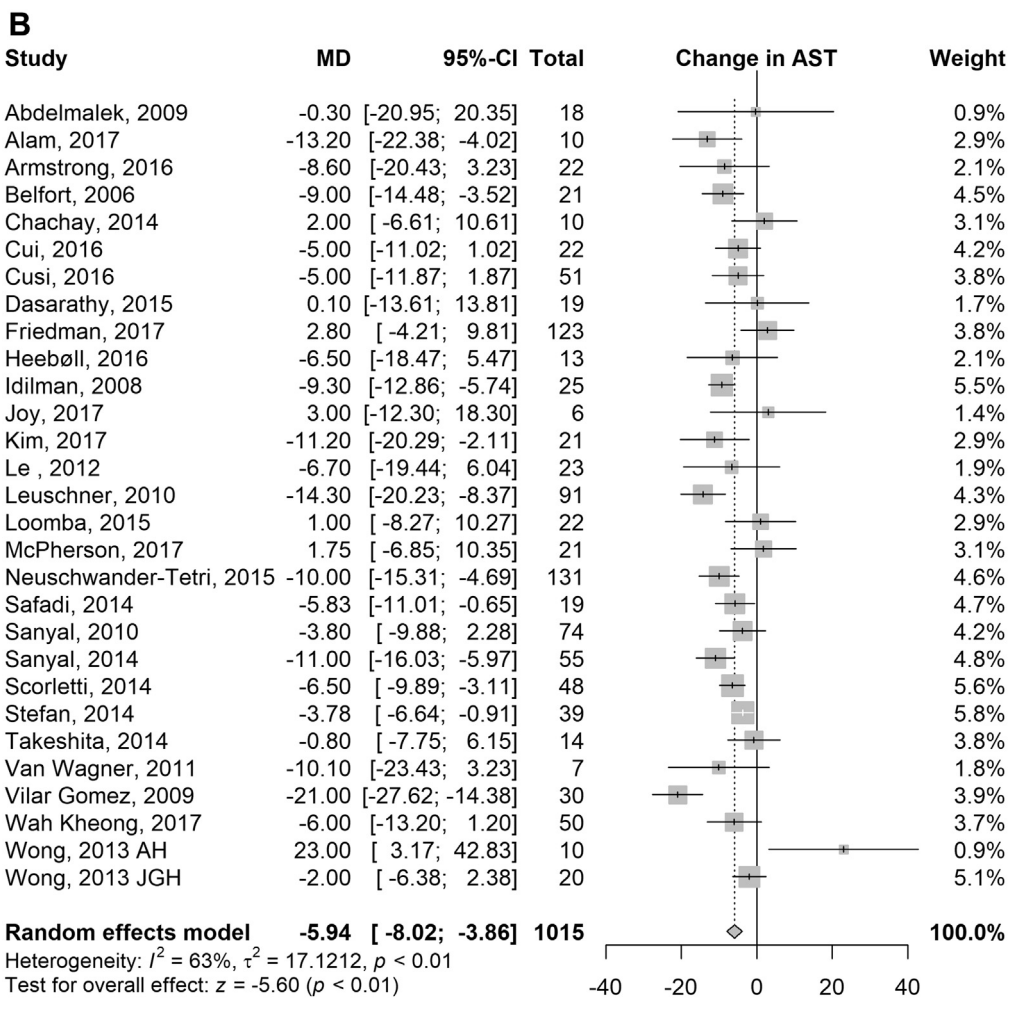
Supplementary Figure 9. (*continued*).

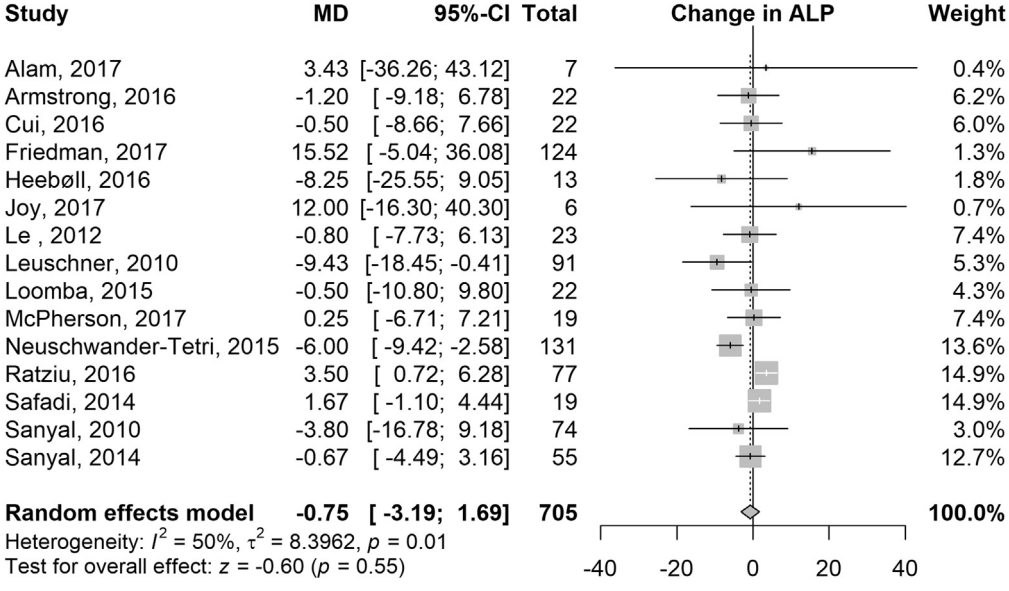


Supplementary Figure 10. Meta-regression to assess heterogeneity in the meta-analysis of mean change in MRS-based IHTG. Exploratory analyses to investigate the heterogeneity noted in the meta-analysis of the mean change in MRS-based IHTG after receiving placebo intervention. Bubble plots of meta-regression using trial duration (*A*), change in BMI (*B*), baseline MRS-based IHTG (*C*), and frequency of site visit (*D*) as explanatory variables.

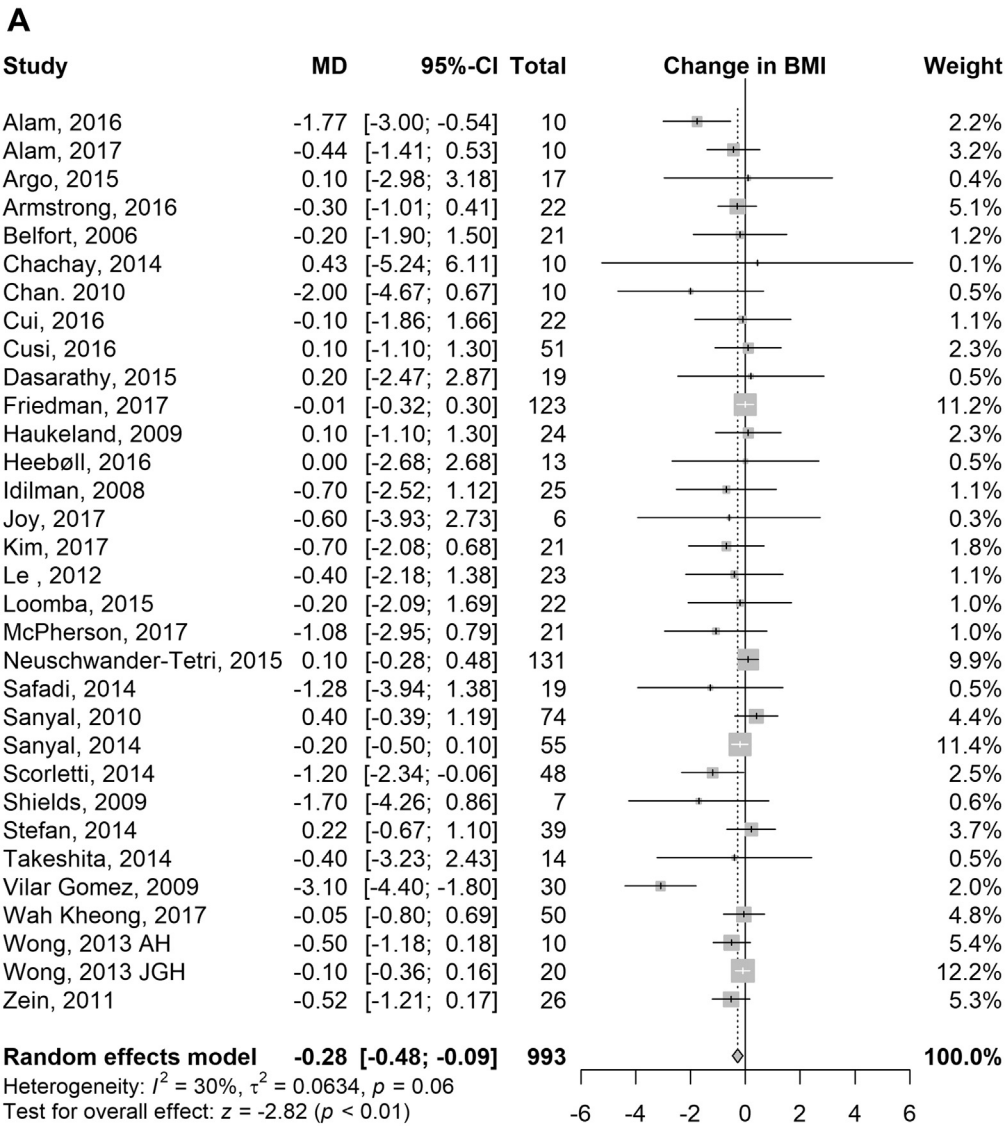


Supplementary Figure 11. Meta-analyses of change in liver enzymes. Forest plots of random-effects meta-analyses of the mean change in alanine aminotransferase (*A*), aspartate aminotransferase (*B*), and alkaline phosphatase (*C*) after receiving placebo intervention measured as mean difference between values before and after receiving placebo. ALP, alkaline phosphatase; MD, mean difference.



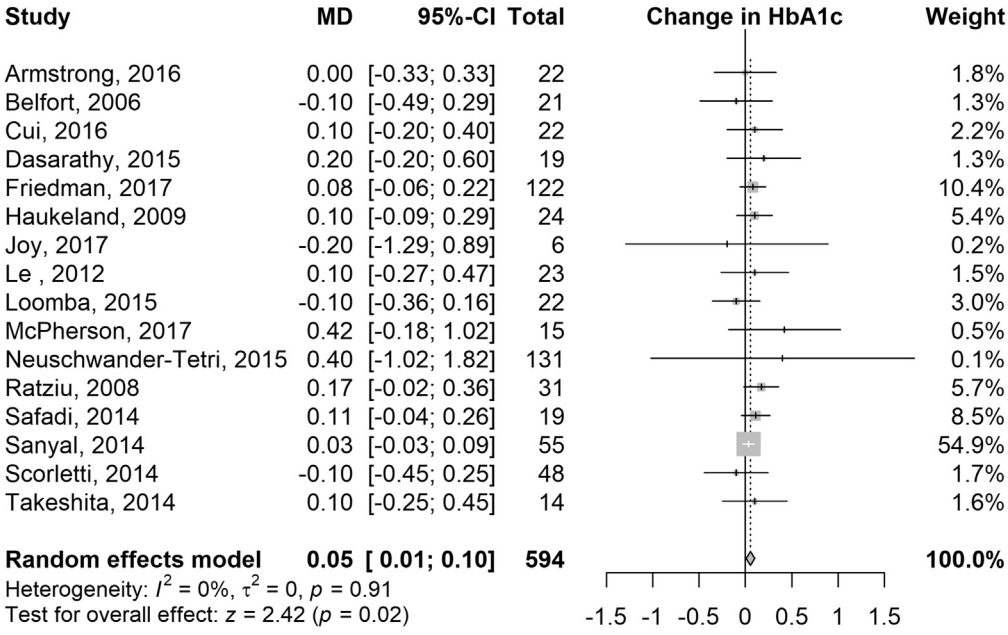


Supplementary Figure 11. (*continued*).

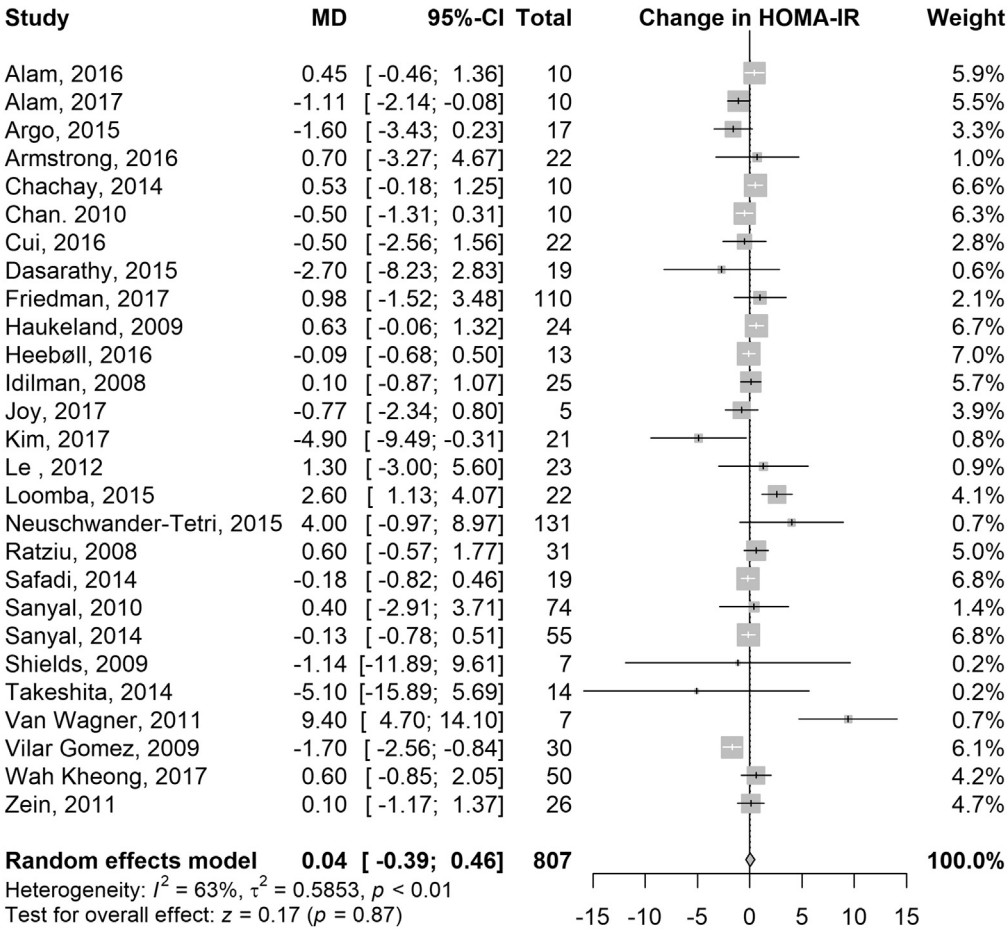


Supplementary Figure 12. Meta-analyses of change in BMI and biochemical parameters. Forest plots of random-effects meta-analyses of the mean change in body mass index (*A*), hemoglobin A_{1c} (*B*), and homeostatic model assessment of insulin resistance (*C*) after receiving placebo intervention measured as mean difference between values before and after receiving placebo. HbA1c, hemoglobin A_{1c}; HOMA-IR, homeostatic model assessment for insulin resistance; MD, mean difference.

B



C



Supplementary Figure 12. (*continued*).

Supplementary Table 1. Excluded References and Reason for Exclusion

Reference	Reason for exclusion
Adams 2015[1]	Did not clearly report the methods used in calculating MRI PDFF. No other outcomes of interest reported.
Aithal 2008[2]	Did not report any of the main outcomes of interest. The reported histologic outcome was not reported according to the NAFLD Activity Score.
Alisi 2014[3]	Did not report any of the main outcomes of interest. Pediatric population.
Aller 2011[4]	Did not report any of the main outcomes of interest.
Aller 2015[5]	Did not report any of the main outcomes of interest.
Amin 2009[6]	Did not report any of the main outcomes of interest.
Arendt 2011[7]	A commentary.
Athyros 2006[8]	No placebo group.
Balas 2007[9]	Did not report any of the main outcomes of interest.
Balmer 2008[10]	Did not report any of the main outcomes of interest.
Barchetta 2016[11]	Used 1 region of interest per liver segment when measuring MRI PDFF.
Bugianesi 2005[12]	Did not report any of the main outcomes of interest.
Cariou 2013[13]	Did not report any of the main outcomes of interest.
Celinski 2014[14]	No placebo group.
Chen 2015[15]	Did not report any of the main outcomes of interest.
Cichoz-Lach 2010[16]	No placebo group.
Charles 2016[17]	Having NAFLD was not 1 of the inclusion criteria.
Choi 2014[18]	Did not report any of the main outcomes of interest.
Coskun 2015[19]	No placebo group.
Cotrim 2009[20]	Did not report any of the main outcomes of interest.
Cussons 2009[21]	Not all patients had nonalcoholic fatty liver disease because it was not 1 of the inclusion criteria.
Daubioul 2005[22]	No placebo group.
Della 2016[23]	Pediatric population.
Dufour 2006[24]	Did not report any of the main outcomes of interest. The reported histologic outcome was not reported according to the NAFLD Activity Score.
Ekhlasi 2016[25]	Did not report any of the main outcomes of interest.
Ersoz 2005[26]	No placebo group.
Fard 2016[27]	Did not report any of the main outcomes of interest.
Federico 2016[28]	Did not report any of the main outcomes of interest.
Fernández Vega 2014[29]	Not in English language.
Ferolla 2016[30]	Some patients had baseline MRI PDFF less than 5%.
Georgescu 2009[31]	No placebo group.
Gianturco 2013[32]	Did not report any of the main outcomes of interest.
Gonciarz 2010[33]	Did not report any of the main outcomes of interest.
Gonciarz 2012[34]	Did not report any of the main outcomes of interest.
Han 2014[35]	No placebo group.
Harrison 2003[36]	Did not report any of the main outcomes of interest. The reported histologic outcome was not reported according to the NAFLD Activity Score.
Harrison 2009[37]	No placebo group.
Harrison 2016[38]	Did not report any of the main outcomes of interest.
Hashemi 2009[39]	Did not report any of the main outcomes of interest.
Hickman 2012[40]	No placebo group.
Hoofnagle 2013[41]	A secondary analysis of an included trial.[42]
Hussain 2016[43]	Did not report any of the main outcomes of interest.
Hussein 2007[44]	No placebo group.
Janczyk 2015[45]	Did not report any of the main outcomes of interest. Pediatric population.
Jeong 2017[46]	Not all the patients had NAFLD/NASH.
Ji 2008[47]	No placebo group.
Junker 2015[48]	Not a randomized controlled trial. Did not report any of the main outcomes of interest.
Junker 2016[49]	Not a randomized controlled trial. Did not report any of the main outcomes of interest.
Kakazu 2013[50]	Did not report any of the main outcomes of interest.
Kargiotis 2015[51]	No placebo group.
Kazemi 2012[52]	Did not report any of the main outcomes of interest.
Kedarisetty 2014[53]	No placebo group.
Khoo 2017[54]	Did not specify how many regions per liver segment when measuring MRI.
Komshilova 2015[55]	Did not report any of the main outcomes of interest.
Lalazar 2015[56]	Did not report any of the main outcomes of interest.
Lalazar 2017[57]	Did not use Kleiner histologic score.
Lavine 2011[58]	Pediatric population.
Lee 2008[59]	Did not report any of the main outcomes of interest.
Li 2015[60]	Did not report any of the main outcomes of interest.

Supplementary Table 1. Continued

Reference	Reason for exclusion
Lin 2017[61]	A secondary analysis of an included trial.[62]
Lindor 2004[63]	Did not report any of the main outcomes of interest. The reported histologic outcome was not reported according to the NAFLD Activity Score.
Loguercio 2010[64]	Did not report any of the main outcomes of interest.
Loomba 2017[65]	No placebo group.
Merat 2003[66]	Did not report any of the main outcomes of interest.
Malaguarnera 2010[67]	Did not report any of the main outcomes of interest.
Malaguarnera 2011[68]	Did not report any of the main outcomes of interest.
Morita 2005[69]	Use Brunt histology score.
Naganuma 2016[70]	Did not report any of the main outcomes of interest.
Nelson 2009[71]	Did not report any of the main outcomes of interest.
Nobili 2006[72]	Did not report any of the main outcomes of interest.
Nobili 2008[73]	Pediatric population.
Nobili 2011[74]	Did not report any of the main outcomes of interest.
Omer 2010[75]	No placebo group.
Pacifico 2015[76]	Pediatric population.
Pan 2013[77]	Did not report any of the main outcomes of interest.
Panahi 2017[78]	Did not report any of the main outcomes of interest.
Polyzos 2011[79]	No placebo group.
Petit 2017[80]	Having NAFLD was not 1 of the inclusion criteria.
Ratziu 2010[81]	An extension of a previous trial[82] with no more placebo group.
Ratziu 2011[83]	Did not report any of the main outcomes of interest.
Ratziu 2012[84]	Did not report any of the main outcomes of interest.
Razavizade 2013[85]	No placebo group.
Rosqvist 2016[86]	No placebo group.
Samson 2011[87]	No placebo group.
Santos 2003[88]	Did not report any of the main outcomes of interest.
Sanyal 2004[89]	No placebo group.
Savvidou 2015[90]	No placebo group.
Scherer 2017[91]	Healthy volunteers.
Scorletti 2014[92]	A duplicate publication of an included trial.[93]
Sharma 2012[94]	No placebo group.
Shavakhi 2013[95]	Did not report any of the main outcomes of interest.
Shavakhi 2015[96]	No placebo group.
Shenoy 2014[97]	Did not report any of the main outcomes of interest.
Smits 2016[98]	Having NAFLD was not 1 of the inclusion criteria.
Soleimani 2016[99]	Did not report any of the main outcomes of interest.
Taniai 2009[100]	Did not report any of the main outcomes of interest.
Targher 2007[101]	The comparison group consisted of healthy volunteers.
Torres 2011[102]	No placebo group.
Troisi 2013[103]	Did not report any of the main outcomes of interest.
Tuncer 2003[104]	Did not report any of the main outcomes of interest.
Uygun 2000[105]	Could not obtain full text.
Uygun 2004[106]	Did not report any of the main outcomes of interest.
Vajro 2011[107]	Pediatric population. Did not report any of the main outcomes of interest.
Valenti 2014[108]	Did not report any of the main outcomes of interest
Vos 2016[109]	Pediatric population. Did not report any of the main outcomes of interest.
Watanabe 2015[110]	No placebo group.
Yari 2016[111]	Did not report any of the main outcomes of interest.
Zelber-Sagi 2006[112]	Did not report any of the main outcomes of interest.
Zhang 2015[113]	Did not report any of the main outcomes of interest.

MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PDFF, proton density fat fraction.

Supplementary Table 2. Multivariable Meta-Regression of Trials That Used NAS ($P < .0001$)

Variable	Slope coefficient	*P* value
Intercept	1.1330	.2669
BMI	0.0574	.8055
Follow-up duration	-0.0016	.7419
Baseline NAS	**-0.3300**	**.0242**
Visit frequency	-0.0072	.7764
Lifestyle: dietitian – NR	-0.4365	.2541
Lifestyle: no dietitian/NR – exercise	0.0454	.8905
Lifestyle: no dietitian/NR – NR	-0.2922	.3505
Placebo pill provided	0.2808	.4972
Region: East Asia	-0.6617	.2085
Region: Europe	-0.5940	.1416
Region: Middle East	-0.4313	.6094
Region: North America	-0.2482	.4665
Region: South America	**-1.9855**	**.0063**
Biopsy read: local	0.3215	.3273

NOTE. Boldface indicates statistical significance.
BMI, body mass index; NAS, nonalcoholic fatty liver disease activity score; NR, not recommended or reported.

Supplementary Table 3. Multivariable Meta-Regression of Trials That Used MRS ($P = .0351$)

Variable	Slope coefficient	*P* value
Intercept	5.9662	.1200
BMI	3.3667	.1857
Follow-up duration	**-0.1321**	**.0020**
Region: Australia	-1.1416	.7299
Region: Europe	0.4507	.8377
Region: Middle East	**7.5872**	**.0356**
Region: North America	0.6451	.7405
Baseline MRS IHTG	-0.1799	.2309
Visit frequency	0.2894	.1239
Lifestyle: no dietitian/NR – exercise	-1.4898	.5148
Lifestyle: no dietitian/NR – NR	**-2.9858**	**.0147**

NOTE. Boldface indicates statistical significance.
BMI, body mass index; IHTG, intrahepatic triglyceride; MRS, magnetic resonance spectroscopy; NR, not recommended or reported.