Effects of Niacin on apolipoprotein A1 and B levels: A systematic review and meta-analysis of Randomised Controlled Trials

Running title: Niacin and apolipoprotein A1 and B: A meta-analysis

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Abstract

Niacin has been investigated for its potential impact on lipid metabolism and cardiovascular health. This meta-analysis aims to systematically evaluate the effects of Niacin interventions on apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B) levels, key regulators of lipoprotein metabolism and markers of cardiovascular risk. A comprehensive search of the literature was performed on five databases of PubMed, Scopus, Web of Science, Embase and Cochrane library, from inception up to 15 July 2023. This search identified 1452 publications, from which 12 randomized controlled trials (RCTs) met the inclusion criteria. The intervention dosages ranged from 500 to 3000 mg/day, and the study durations spanned 6 to 102.8 weeks. The Niacin intervention demonstrated a significant reduction in Apo B levels (WMD: -24.37 mg/dl, $p = 0.01$). Subgroup analyses indicated that intervention duration played a role, with trials of ≤16 weeks showing a greater reduction in Apo B. Regarding Apo A1, Niacin significantly increased its levels (WMD: 8.23 mg/dl, $p < 0.001$). Subgroup analyses revealed that the beneficial effects of Niacin on Apo A1 were observed at a dosage of >1500 mg/day ($p < 0.001$), and Extended-Release Niacin was more effective compared to other forms ($p < 0.001$). According to the

Begg's regression test, no publication bias was observed in this systematic review and meta-analysis. This meta-analysis highlights Niacin's potential role in improving lipid profiles and cardiovascular health. Further well-designed clinical trials are needed to elucidate and confirm optimal dosages and durations of Niacin interventions for influencing Apolipoproteins A1 and B.

Keywords: Niacin, Apolipoproteins, Apo B, Apo A1, Meta-analysis

Cardiovascular disease (CVD) is the primary contributor to global mortality and is expected to continue as the leading cause of death worldwide, with an estimated 23 million fatalities by 2030 from a value of 18.6 million in 2019[1; 2]. The likelihood of developing CVD is associated with unhealthy eating habits alongside lack of physical activity, being overweight or obese, experiencing stress, alcohol consumption, and smoking [3; 4]. Dyslipidaemia is considered a significant factor influencing atherosclerosis process[5] which is a major determinant of CVD. Low-density lipoprotein (LDL) is the primary apolipoprotein B (Apo B)-containing lipoprotein present in human plasma. An elevated level of LDL-cholesterol (LDL-C), known as hypercholesterolemia, is the most common form of dyslipidaemia and is associated with an increased risk of CVD[6]. While LDL contains varying amounts of cholesterol, each lipoprotein has only one Apo B protein. Consequently, Apo B serves as a more reliable predictor of the number of LDL particles compared to LDL-C which can predict

cardiovascular events, including myocardial infarction [7; 8]. On the other hand, apolipoprotein A1 (Apo A1) functions as a major structural protein of high-density lipoprotein (HDL). Its key role involves facilitating cholesterol transport by removing excess cholesterol from peripheral tissues and delivering it to the liver and maintaining cellular cholesterol homeostasis. Therefore, there is a negative correlation between Apo AI concentrations and the risk of cardiovascular diseases [9; 10].

Dyslipidaemia may be treated with the help of nutritional supplements including vitamins and other nutraceutical compounds[11; 12; 13; 14]. Two meta-analysis studies have evaluated the impacts of vitamins on Apolipoproteins B and A1. Both studies found that pooling the results of seven randomized controlled trials (RCTs) investigating the effects of vitamin D or vitamin E supplementation on Apo A1 and Apo B100 levels yielded non-significant effects[15; 16]. However, Niacin or nicotinic acid is a widely recognized treatment for lipid disorders, with efficacy in reducing plasma triglycerides, increasing high-density lipoprotein cholesterol (HDL-C) levels, reducing cardiovascular mortality rates, and improving vascular function[17; 18]. It is capable of reducing LDL particle numbers while increasing the size of LDL from small type B to large type A. Moreover, Niacin enhances Apo B degradation and lowers the fractional catabolic rate of HDL-Apo A1[19; 20].

Various vitamin B3 formulations are designed to control the gradual release of niacin. Immediate-release niacin (IRN) causes quick flushing, while intermediate-release niacin (IRN) lessens flushing intensity. Moderate-release niacin (MRN) enhances tolerability by controlled release. Extended-release niacin (ERN) minimizes flushing over an extended period.[21]. Several clinical trials are being conducted to assess the effects of different types of Niacin, administered at varying dosages, on apolipoproteins A1 and B. In a RCT conducted by Scoffone et al. on Thalassemic patients, it was demonstrated that a

12-week treatment with Extended-Release Niacin (ERN) resulted in an increase in HDL-C compared to the placebo treatment. Although there was no significant difference in the mean change of Apo AI between the study groups, the researchers reported a significant reduction in the ratio of LDL-C to HDL-C and apolipoprotein B to apo A1 in the Niacin-treated group when compared to patients who received the placebo[22]. An investigation focusing on diabetic patients with renal ischemia demonstrated that the combination of atorvastatin and ERN treatment significantly raised HDL-C and Apo A1 levels compared to patients who only received atorvastatin. However, this combination treatment did not have a significant reducing effect on LDL-C levels[23]. Superko et al. conducted a RCT on hypercholesterolemic patients to investigate the impacts of two forms of nicotinic Acid: immediate-release niacin (IRN) and ERN on apolipoproteins. The study revealed that both forms of nicotinic Acid significantly increased Apo A1 levels, while also significantly reducing Apo B levels compared to patients who received the placebo[24]. Findings from a meta-analysis study demonstrated that Niacin could have positive effects on the levels of LDL-C and HDL-C in individuals with type 2 diabetes[25]. Nonetheless, there has been a lack of meta-analysis investigating the extent of effectiveness of Niacin treatment on apolipoproteins A1 and B. In this study, we conducted a systematic review and meta-analysis of published clinical trials that utilized any form of this vitamin as an intervention, with blood levels of Apo B and Apo A1 as the measured outcomes.

Methods

This systematic review and meta-analysis adhered to the guidelines outlined in the PRISMA statement[26], ensuring comprehensive and transparent reporting of the study. The registration of this review was completed in PROSPERO under the reference number CRD42023444659.

Search strategy

A comprehensive search of the literature was performed across various online databases of PubMed, Scopus, Web of Science, Embase and Cochrane library, from inception up to July 2023. The search strategy incorporated the following keywords: (Niacin OR "nicotinic acid" OR "acipimox" OR niaspan) AND ("Apolipoprotein A1" OR " ApoA1" OR "Apo A1" OR "Apolipoprotein B" OR "ApoB" OR " Apo B") AND (Intervention OR "Intervention Study" OR "Intervention Studies" OR "controlled trial" OR randomized OR random OR randomly OR placebo OR assignment OR "clinical trial" OR Trial OR assignment OR "randomized controlled trial" OR "randomized clinical trial" OR RCT OR blinded OR "double blind" OR "double blinded" OR trial OR "clinical trial" OR trials OR "Pragmatic Clinical Trial" OR "Cross-Over Studies" OR "Cross-Over" OR "Cross-Over Study" OR parallel OR "parallel study" OR "parallel trial")(Supplementary Table 1). There were no limitations regarding language or time in the search process. To facilitate the screening process, all identified studies were imported into the EndNote software. After removing duplicate citations, the remaining studies from the initial search underwent screening based on their titles and abstracts. Subsequently, eligible studies were subjected to a thorough full-text review. Furthermore, to ensure inclusiveness, the reference lists of relevant studies were manually examined. The literature search and screening process were conducted by two separate investigators (EYR & SS) working independently.

Inclusion and exclusion criteria

The study selection process followed specific criteria, focusing on RCTs that involved adult participants aged 18 years or older. These trials investigated the impact of various forms of Niacin administration on serum Apo B and Apo A1 levels. To be included, the RCTs had to provide mean and standard deviations (SDs) at both the beginning and the end of the intervention for both the treatment and control groups. The selection process adhered to the PICO framework[27],

encompassing the following elements: Participants (adults ≥18 years), Intervention (Niacin), Comparison (placebo or no intervention group), and Outcomes (serum levels of Apo B and Apo A1).

Exclusions were made for in vitro studies, experimental and ecological studies, observational papers, and review articles. Additionally, trials without a placebo or control group were also excluded from the study. Furthermore, studies with a two-arm intervention duration or dosage were treated as two separate entities during the selection process.

Data extraction

Data extraction was conducted by two independent investigators (ES & SS). Any discrepancies or disagreements were resolved through discussion to reach a consensus. The relevant information from each study was carefully extracted into an Excel sheet. This included details such as the first author's name, publication year, participants' gender and mean age, study design, country of origin, sample sizes for both control and intervention groups, Niacin dosage, type of Niacin, type of control intervention, duration of the intervention, health status and disease conditions of the studied population, mean changes and SDs of Apo B and Apo A1 throughout the trials for both the intervention and control groups. When numerical estimates were presented in graphical format, we used the plot digitizer tool (http://plotdigitizer.sourceforge.net/) to extract the data accurately.

Quality assessment

The Cochrane quality assessment tool was employed to evaluate the potential bias risk in each study included in the current meta-analysis[28]. This tool comprises seven domains, which involve aspects like random sequence generation, allocation concealment, and various sources of bias (reporting, performance, detection, attrition, etc.). For each domain, a "high risk" score was assigned if the

study contained methodological errors that might have influenced its findings. Conversely, a "low risk" score was given if no defects were identified, and an "unclear risk" score was used when the available information was insufficient to determine the impact. The risk of bias assessment was conducted independently by two reviewers.

Statistical analysis

The overall effect sizes of apolipoproteins in the Niacin and control groups were calculated using the mean changes and their SDs. In cases where mean changes were not reported, they were computed based on the changes in apolipoproteins concentrations during the intervention. To ensure consistency, standard errors (SEs), 95% confidence intervals (CIs), and interquartile ranges (IQRs) were converted to SDs using the method described by Hozo et al.[29].

For the analysis, a random-effects model was utilized, which accounts for between-study variations. The effect sizes for variables were expressed as weighted mean differences (WMDs) with their respective 95% CIs. Heterogeneity was assessed using the I^2 statistic and Cochrane's Q test. An I^2 value greater than 50% or a p-value less than 0.05 for the Q-test indicated significant between-study heterogeneity. To explore potential sources of heterogeneity, we conducted subgroup analyses based on predefined variables, including intervention duration, type of Niacin used, Niacin dosage, and origin country where the study was conducted.

To assess the possibility of publication bias, we conducted Egger's and Begg's regression tests. Furthermore, we conducted a non-linear dose-response analysis to examine the relationship between the pooled effect size and Niacin dosage (mg/day) as well as the duration of the intervention (weeks). To ensure the strength of our findings, we performed a sensitivity analysis to identify if the overall effect size is influenced by any specific study. The meta-analysis was

carried out using Stata, version 14 (StataCorp), and a significance level of $p < 0.05$ was considered statistically significant.

Certainty Assessment

The overall certainty of evidence from the studies was evaluated based on the GRADE guidelines (Grading of Recommendations Assessment, Development, and Evaluation) working group. Using the corresponding evaluation criteria, the quality of evidence was categorized into four levels: high, moderate, low, and very low[30].

Results

Search results and study selection

In the initial phase of this meta-analysis, we identified a total of 1452 publications. After a thorough assessment, 585 articles were excluded due to duplication, and the study design of 800 articles did not meet the inclusion criteria as they encompassed animal studies, observational studies, and review articles. Additionally, during the research process, we found four more articles through a comprehensive reference check of relevant studies. After careful screening of the remaining records, 71 publications were eligible for full-text assessment of eligibility. During this full-text assessment, 35 articles were further excluded as they did not meet the predefined inclusion criteria. Additionally, 18 articles lacked a proper control group or placebo group, and six articles were excluded due to insufficient data for calculating the mean change and standard deviation of the mean change for our variables.

Ultimately, we included 12 clinical trials in this systematic review and meta-analysis. Among these studies, 13 arms evaluated blood levels of Apo B, and 14 arms assessed blood levels of Apo A1, as some trials involved multiple dosages or intervention durations. For a visual representation of the study selection

process for inclusion in the systematic review, see the flowchart shown in Figure 1.

Characteristics of the included studies

Table 1 presents the characteristics of the RCTs included in our current systematic review and meta-analysis. These trials were published between 1998 and 2017 and were conducted in various regions, including the USA[8; 22; 24; 31; 32; 33; 34], UK[35; 36], Portugal[37], Pakistan[23], Korea[38], and Australia[18]. All of these studies involved both male and female participants. The sample sizes of the included RCTs varied significantly, ranging from 15 to 3115 participants, resulting in a total sample size of 5634 individuals. The participants' mean age across the studies ranged from 29 to 71 years. The Niacin dosages administered in the trials ranged from 500 to 3000 mg/day and the duration of the intervention varied from 6 to 102.8 weeks.

Most of the studies utilized a parallel design for their interventions, except for one study[37] that employed a cross-over design. In terms of the type of Niacin used, 9 studies administered ERN[18; 22; 24; 31; 32; 33; 34; 37], one study used IRN[24], one used nicotinic acid[38], one used acipomax[35], and one study used Modified Release Niacin (MRN)[36]. Additionally, 4 studies incorporated the use of statins[23; 31; 34] or n-3 fatty acids[33] in conjunction with the main Niacin intervention.

The RCTs covered a diverse range of participant groups, including those with diabetes and metabolic syndrome[18; 33; 35], patients with dyslipidaemia[37; 38], non-alcoholic fatty liver disease[32], CVDs[24; 31; 34; 36], sickle cell anaemia with low HDL levels[22], and renal ischemia[23].

According to the Cochrane Risk of Bias Assessment Tool, two studies obtained a high-quality rating[33; 38], demonstrating a low risk of bias across all domains. On the other hand, two other studies were deemed moderate-quality[35; 36], as they

had one domain with an unclear risk of bias, and the other studies were considered high risk of bias[18; 23; 24; 31; 32; 34; 37] with at least one domain having a high risk of bias (Table 2).

Meta-analysis

The effect of Niacin on apolipoprotein B

The pooled analysis of 13 effect sizes using a random-effects model revealed a significant reduction in Apo B level with the use of Niacin compared to the control group [WMD: -24.38, 95% CI: -43.97 to -4.78 mg/dl, p= 0.01]. However, there was considerable heterogeneity among the included studies (test for heterogeneity: $p < 0.001$, $I2 = 99.9\%$) (Figure 2). To explore the potential sources of heterogeneity, subgroup analyses were conducted based on the type of niacin, dosage, intervention duration, and origin country (Table 3).

Our findings revealed that the variation between studies could be attributed to dosage of Niacin used. Based on these subgroup analyses, we observed a significant reduction in Apo B concentrations with Niacin intervention in RCTs that had an intervention duration of ≤16 weeks compared to those with >16 week (WMD: -21.8, 95% CI: -29.33 to -14.28 mg/dl, p: <0.001). Subgroup analysis according to the dosage of intervention (<2000 mg/day vs ≥2000 mg/day), type of Niacin (ERN vs other forms of Niacin) and origin country (USA vs other countries) showed a significant effect in all subgroups.

In the sensitivity analysis, the exclusion of any individual study did not impact the overall estimate for the effect of Niacin on Apo B concentrations (CI range: -46.74, -2.78,). Additionally, based on the Begg's test and Egger's regression test there was no substantial evidence of publication bias (P=0.76 and 0.65 respectively). The dose-response analysis did not reveal any significant impact of Niacin dose ($P_{non\text{-}linearity} = 0.49$) and treatment duration ($P_{non\text{-}linearity} = 0.24$) on Apo B levels (Figures 3A and 3B).

The effect of Niacin on apolipoprotein A1

The meta-analysis included data from 12 RCTs and yielded 13 effect sizes. The findings indicated that Niacin had a significant increasing effect on Apo A1 concentrations [WMD: 8.24, 95% CI: 4.93, 11.54 mg/dl, P<0.001], as illustrated in Figure 4. Nevertheless, substantial heterogeneity was observed among the studies in this context (I^2=90.4%, P<0.001) (Figure 4).

Based on the subgroup analyses (Table 3), the variability between studies could be attributed to several factors, including the dosage and type of Niacin administered, intervention duration, and the country where the study was conducted. Notably, Niacin resulted in a significant increase in ApoA1 concentrations in RCTs that utilized ERN as the intervention, especially when the dosage of intervention exceeded 1500 mg/day. Furthermore, the effect of Niacin administration was particularly significant in studies conducted in the USA compared to those conducted in other countries. The sensitivity analyses demonstrated that excluding any individual study did not substantially impact the estimated pooled effect size (CI range: 2.90, 12.90).

Based on the Begg's test, no evidence of publication bias was observed (p = 0.82). However, Egger's regression test indicated the potential presence of publication bias concerning the impact of Niacin administration on Apo A1 levels. Consequently, we applied the trim-and-fill method, but no studies were added,

and the pooled effect size remained unchanged. The non-linear dose-response meta-analysis, which included 13 eligible effect sizes focusing on Apo A1 concentrations, revealed that neither Niacin dosage nor intervention duration had a significant impact on serum Apo A1 concentrations ($P_{non\text{-}linearity} = 0.18$ and 0.50, respectively) (Figures 3C and 3D).

Grading of evidence

An evaluation of the quality of evidence using the GRADE approach is presented in Table 4. Low quality of evidence was detected for Apo B and Apo A1 for a very serious inconsistency (I^2=99.9% and I^2=90.4% for heterogeneity, respectively).

Discussion

The current systematic review and meta-analysis aimed to assess the effects of Niacin treatment on apolipoproteins A1 and B. The results indicate that Niacin intervention leads to a significant reduction in Apo B levels and a significant increase in Apo A1 concentrations. Niacin exerts its hypocholesterolemic effects through various mechanisms that affect lipid metabolism, including alterations in lipoprotein synthesis, lipolysis, and clearance [32; 39]. By influencing these Apolipoproteins, Niacin could play a crucial role in decreasing the risk of cardiovascular diseases [40]. However, it is essential to interpret these findings in light of the considerable heterogeneity observed among the included studies. Performing subgroup analyses revealed that the duration of Niacin treatment significantly influenced its effect on Apo B concentrations. Notably, Niacin intervention for ≤16 weeks showed a more substantial reduction in Apo B levels compared to interventions lasting >16 weeks. This

suggests that shorter-term use of Niacin might be more effective in lowering Apo B levels due to its immediate impact on lipid profiles. When Niacin interventions extend beyond 16 weeks, they might trigger compensatory mechanisms that counteract the initial reduction in Apo B levels. These mechanisms could entail alterations in receptor expression or cellular signalling pathways[41], ultimately diminishing Niacin's ability to lower Apo B levels over time. Moreover, variations in patient adherence and compliance during longer interventions could play a role[42]. The subgroup analyses based on Niacin dosage, type of Niacin, and origin country also indicated a significant effect in both subgroups. This suggests that regardless of the specific Niacin type, dosage, or country of origin, Niacin consistently exerts a favourable impact on Apo B levels. Regarding Niacin effects on Apo A1, subgroup analyses revealed that ERN was particularly effective in increasing Apo A1 concentrations, especially at dosages exceeding 1500 mg/day. This suggests that the type and dosage of Niacin could significantly influence its impact on Apo A1 levels. It seems that as the dosage of Niacin increases, its mechanisms of action might be more robustly engaged, leading to a greater stimulation of Apo A1 synthesis and subsequently higher levels[43]. However, the dose-response analysis in our meta-analysis did not show significant impacts of Niacin dose on Apo A1 levels. Additionally, the effect of Niacin on Apo A1 was more pronounced in studies conducted in the USA compared to those conducted in other countries. This observation could be attributed to differences in study populations, genetic factors, lifestyle, or dietary habits across different geographical regions[44]. Moreover, the use of ERN in studies conducted in the USA, which seems more potent in influencing lipid particles, could be another contributing factor. This type of Niacin stands as the most powerful

pharmaceutical option currently used in clinical settings to elevate HDL-C levels by up to 35%. Furthermore, ERN diminishes triglycerides levels while it can modify both the size and quantity of LDL particles[45]. Moreover, Sahebkar et al., in one systematic review and meta-analysis showed that ERN could significantly reduce lipoprotein(a) levels[46], another important risk factor for CVDs[47]. The non-linear dose-response meta-analysis did not show any significant impact of Niacin dosage or intervention duration on Apo A1 levels. This suggests that within the range of dosages and intervention durations studied, increasing the dosage or duration of Niacin treatment may not lead to a proportional increase in Apo A1 concentrations.

The effects of Niacin on apolipoproteins A1 and B are closely related to its impact on lipoprotein metabolism. One of the primary mechanisms by which Niacin improves lipid profile is by inhibiting the synthesis and secretion of very-low-density lipoprotein (VLDL) particles from the liver [48; 49]. Niacin reduces the availability of free fatty acids in the liver, thereby diminishing the substrate for VLDL synthesis. As a result, there is a reduction in VLDL particle production, leading to decreased levels of triglycerides in the circulation[32]. Niacin also promotes the lipolysis of triglycerides within circulating VLDL and intermediate-density lipoprotein (IDL) particles by activating lipoprotein lipase (LPL)[50]. Niacin could decrease the production of small, dense LDL particles, which are considered more atherogenic. It accomplishes this by reducing the activity of hepatic diacylglycerol acyltransferase-2 (DGAT2), an enzyme involved in the synthesis of triglycerides within hepatocytes[51]. Lower triglyceride availability results in the formation of larger, less atherogenic LDL particles. Additionally, Niacin downregulates the expression of proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that promotes the degradation of hepatic LDL receptors. The reduction in PCSK9 levels enhances LDL receptor recycling and increases LDL clearance from the circulation[52; 53]. Niacin reduces Apo B levels

by lowering the production of VLDL particles in the liver. Since each VLDL particle contains one molecule of Apo B, the reduction in VLDL synthesis results in decreased Apo B production[54]. Additionally, Niacin increases HDL cholesterol levels by inhibiting the activity of cholesteryl ester transfer protein (CETP). CETP facilitates the transfer of cholesteryl esters from HDL to other lipoproteins (such as VLDL and LDL) in exchange for triglycerides. By inhibiting CETP, Niacin reduces the transfer of cholesteryl esters from HDL, thereby increasing HDL cholesterol levels. The rise in HDL levels is often accompanied by an increase in apolipoprotein A1 as its major protein component[43; 48]. These mechanisms collectively lead to improvements in lipid profile, including reductions in LDL cholesterol and triglycerides, along with increases in HDL-C and Apo A1 levels, while also reducing Apo B levels.

This study represents the first systematic review and meta-analysis investigating the impact of Niacin on Apolipoproteins A1 and B. Nonetheless, it is not without its limitations. Firstly, the presence of substantial heterogeneity saw in meta-analysis could restrict the degree to which the findings can be generalized. The majority of included studies also had a high risk of bias. Moreover, another limitation of this meta-analysis stems from the inclusion of participants who encompass a variety of underlying pathological conditions, genetic backgrounds, and lifestyle factors, which can cause difficulty in interpreting the outcomes derived from this systematic review and meta-analysis.

In conclusion, this systematic review and meta-analysis provide evidence that Niacin treatment leads to a significant reduction in Apo B levels and a significant increase in Apo A1 concentrations. The results suggest that short-term Niacin intervention may be more effective in reducing Apo B levels, while ERN at higher dosages appears to be more effective in increasing Apo A1 concentrations. However, the substantial heterogeneity among studies should be acknowledged as limitations that may affect the overall confidence in these findings. Further

389 research and well-designed randomized controlled trials are needed to
390 corroborate and refine these results and to better understand the optimal dosing
391 and duration of Niacin treatment for favourable effects on apolipoproteins B and
392 A1.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Author contributions

JT, SC and PT designed and EYR and SS searched systematically for the study. EYR and SS reviewed and selected the articles and extracted data from articles. SS performed data analysis and interpretation. EY and SS drafted the manuscript. SC, JT and PT revised the article for important intellectual content.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Figure legends

Figure 1. Flowchart of the study selection for inclusion in the systematic review and meta-analysis.

Figure 2. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo B

Figure 3. Non-linear dose–response effects of Niacin dosage (mg/day) on Apo B (A), Apo A1, (C) and treatment duration on Apo B (B) Apo A1(D). The 95% CI is demonstrated in the shaded regions.

Figure 4. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo A1

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Figure 1: Flowchart of the study selection for inclusion in the systematic review and meta-analysis.

Figure 2. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo B

WMD: weighted mean difference

Figure 3. Non-linear dose–response effects of Niacin dosage (mg/day) on Apo B (A), Apo A1, (C) and treatment duration on Apo B (B) Apo A1(D). The 95% CI is demonstrated in the shaded regions.

Figure 4. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo A1

WMD: weighted mean difference

Author, year	Country	Design	Participants	Gender	Sample size	Age, year	Intervention		Final daily dosage (mg)	Duration (week)	Outcome
							Treatment	Control			
Batuca et al. 2016	Portugal	Cross-over trial	Men or women, with serum HDL-C ≤ 40 mg/dl or ≤ 50 mg/dl	Both	Int: 8 Con:9	Int:46.3±12.02 Con:52.44±9.55	Extended-release niacin (ERN)+	Placebo	1500	12	Apo A1
Kim et al. 2011	Korea	RCT	People with Mixed Dyslipidemia	Both	Int: 25 Con:21	Int:57.4±6.8 Con:61.8±8.3	Nicotinic Acid	Placebo	1000	8	Apo A1, Apo B
Fabbrini et al. 2010	USA	RCT	People with NAFLD	Both	Int: 9 Con:9	Int:43±15 Con:45±9	Extended-release niacin (Niaspan)	Placebo	2000	16	Apo B
Hamilton et al. 2010	Australia	RCT	People with T2DM	Both	Int: 7 Con:8	65±7	Extended-release niacin	No intervention	1500	8	Apo A1
Davoren et al. 1998	UK and Germany	RCT	People with Non-insulin-dependent diabetes mellitus	Both	Int: 29 Con:31	Int:29 Con:31	Acipimox	Placebo	500	6	Apo A1, Apo B
Savinova et al. 2015	USA	RCT	People with metabolic syndrome	Both	Int: 13 Con:15	NR	Extended-release niacin (ERN)+ Omega-3 Fatty Acids	Omega-3 Fatty Acids	2000	16	Apo A1, Apo B
					Int: 14 Con:14		Extended-release niacin (ERN)	Placebo			
Yasmeen et al. 2014	Pakistan	RCT	patients with renal ischemia	Both	Int: 51 Con:56	NR	Niacin+ Atorvastatin	Atorvastatin	500	16	Apo A1
Airan-Javia et al.2009	USA	RCT	Patients with carotid atherosclerosis	Both	Int: 22 Con:25	Int:71±7.4 Con:70.5±14.8	Extended-release niacin (ERN)+ simvastatin	simvastatin	2000	25/7 51.42	Apo B

Scoffone et al.2013	USA	RCT	Adults with Sickle Cell Anemia and Low High-Density Lipoprotein Cholesterol Levels	Both	Int: 10 Con:14	18-65	Extended-release niacin (ERN)	Placebo	1500	12	Apo A1
Aim-High investigators 2011	USA	RCT	patients with cardiovascular disease	Both	Int: 1561 Con:1554	Int:63.7±8.8 Con: 63.7±8.7	Extended-release niacin (ERN)+ statin	statin	1500-2000	51.42	Apo A1, Apo B
					Int: 865 Con:873					102.85	
Lee. J et al.2009	UK	RCT	patients with low HDL-C (,40 mg/dl) and either: 1) type 2 diabetes with coronary heart disease; or 2) carotid/peripheral atherosclerosis.	Both	Int: 22 Con:29	Int:65±9 Con:65±9	Modified Release NA (Niaspan)	Placebo	2000	25.7	Apo A1, Apo B
										51.4	
Superko. H et al.2004	USA	RCT	patients with clinical history of coronary disease or at least two risk factors for coronary disease	Both	Int: 60 Con:61	Int:53±12 Con:55±12	Extended-release niacin (ERN)	Placebo	1500	14	Apo A1, Apo B
					Int: 59 Con:61	Int:53±11 Con:55±12	Immediate release niacin (IRN)		3000		

Table 1. Summary of clinical trials on the effects of Niacin on Apo A1 and Apo B levels.

Int: intervention group, Con: control group, T2DM: type 2 diabetes mellitus, NAFLD: non-alcoholic fatty liver disease, NR: not reported

Table 2. Methodological quality score for included studies using Cochrane quality assessment tool

author name	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Batuca et al. 2016	low	low	low	low	low	low	high
Kim et al. 2011	low	low	low	low	low	low	low
Fabbrini et al. 2010	low	unclear	low	high	low	low	unclear
Hamilton et al. 2010	unclear	high	unclear	low	high	high	low
Davoren et al. 1998	low	unclear	low	low	low	low	low
Savinova et al. 2015	low	low	low	low	low	low	low
Yasmeen et al. 2014	low	unclear	low	high	unclear	unclear	low
Airan-Javia et al.2009	low	unclear	low	low	low	low	high
Scoffone et al.2013	low	low	high	high	low	low	low
Aim-High investigators 2011	low	unclear	low	low	high	high	low
Lee. J et al.2009	low	low	unclear	low	low	low	low
Superko. H et al.2004	low	unclear	low	high	unclear	unclear	unclear

Table 3. Subgroup analyses of Niacin effect on Apo B and Apo A1 levels.

	No	WMD (95% CI)	P-within group	I^2 (%)	P-heterogeneity
Niacin effect on Apo B(mg/dl)					
Type of Niacin					
Extended-Release Niacin (ERN)	8	-27.19 (-52.69, -1.69)	0.002	99.9	<0.001
Other forms of Niacin	5	-19.90(-32.37, -7.43)	0.03	92.5	<0.001
Dosage of Niacin (mg/day)					
<2000	3	-22.09(-28.34, -15.84)	<0.001	48.9	0.14
≥2000	10	-24.86(-47.51, -2.21)	0.031	99.9	<0.001
Intervention duration (week)					
≤16	7	-21.80(-29.33, -14.28)	<0.001	79.4	<0.001
>16	6	-28.35(-57.82,1.11)	0.059	99.9	<0.001
Origin country					
USA	9	-15.47(-25.29, -5.65)	0.002	82.3	0.001
Other countries	4	-28.21(-52.02, -4.41)	0.02	99.9	<0.001
Niacin effect on Apo A(mg/dl)					
Type of Niacin					
Extended-Release Niacin (ERN)	8	6.21(5.52, 6.90)	<0.001	0.0	0.0
Other forms of Niacin	6	8.56(-0.45, 17.58)	0.06	91.8	<0.001
Dosage of Niacin (mg/day)					
≤1500	7	6.79(-2.88, 16.47)	0.16	90.6	<0.001
>1500	7	6.48(5.34, 7.61)	<0.001	25.1	0.23
Intervention duration (week)					
≤16	10	8.6(1.88, 15.32)	0.01	86.7	<0.001
>16	4	8.23(4.92, 11.54)	<0.001	0.0	0.83

Origin country					
USA	7	6.54(5.43, 7.66)	<0.001	24.6	0.24
Other countries	7	6.93(-2.93, 16.8)	0.16	90.7	<0.001

WMD: weighted mean difference

Table 4. GRADE profile of Niacin administration on Apo B and Apo A1.

Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Number of intervention / controls	WMD (95%CI)	Quality of evidence
Apo B	No serious limitation	Very serious [a] limitation	No serious limitation	No serious limitation	No serious limitation	5425(2701/2724)	-24.37 (-43.96, -4.78)	⊕⊕◯◯ Low
Apo A1	No serious limitation	Very serious [a] limitation	No serious limitation	No serious limitation	No serious limitation	5522 (2747/2776)	8.23(4.92, 11.54)	⊕⊕◯◯ Low

[a] There is high heterogeneity for Apo B (I^2=99.9%) and Apo A1 (I^2=90.4%).

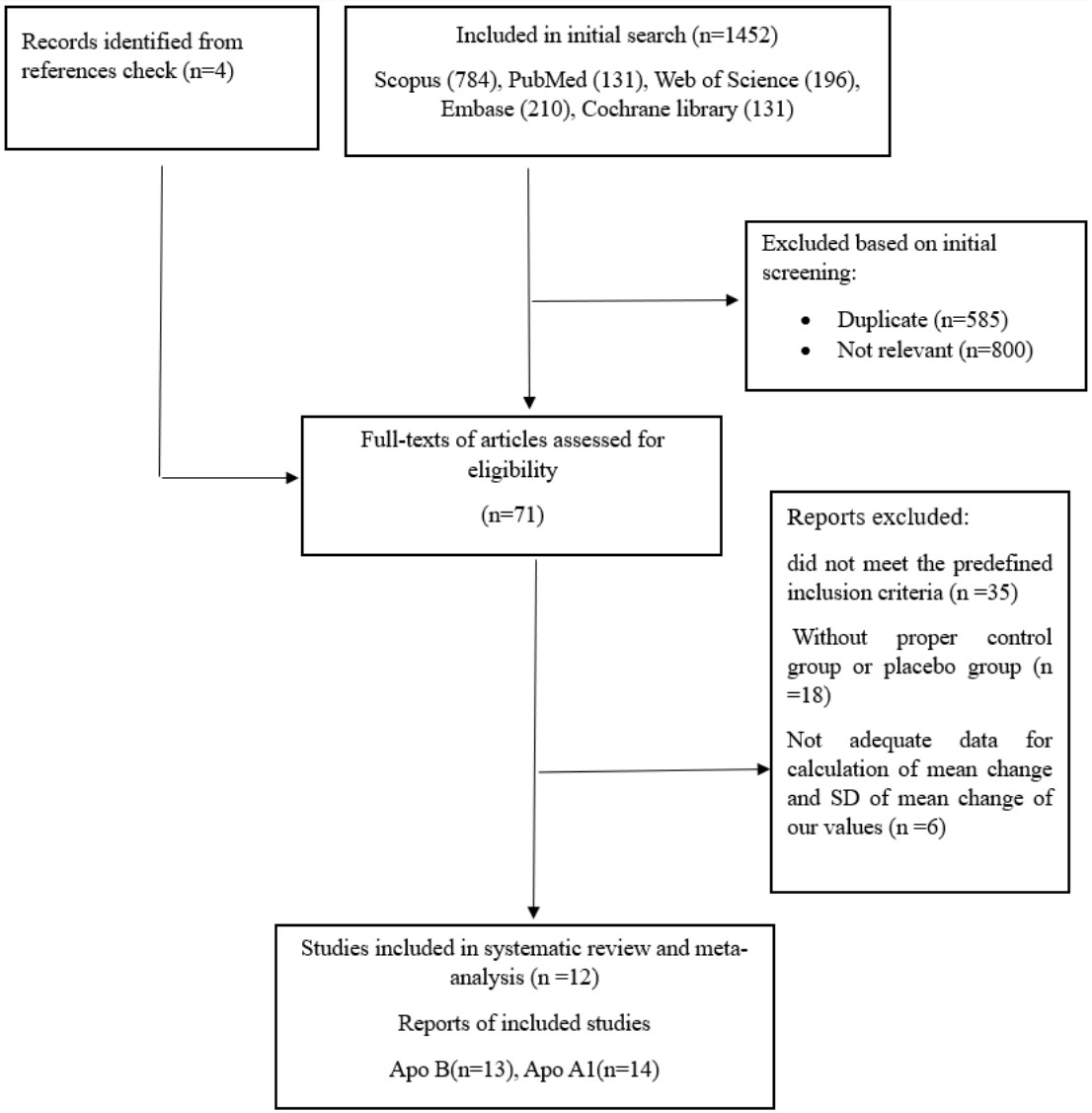

Records identified from references check (n=4)
Included in initial search (n=1452)
Scopus (784), PubMed (131), Web of Science (196), Embase (210), Cochrane library (131)
Excluded based on initial screening:
Duplicate (n=585)
Not relevant (n=800)
Full-texts of articles assessed for eligibility
(n=71)
Reports excluded:
did not meet the predefined inclusion criteria (n =35)
Without proper control group or placebo group (n =18)
Not adequate data for calculation of mean change and SD of mean change of our values (n =6)
Studies included in systematic review and meta-analysis (n =12)
Reports of included studies
Apo B(n=13), Apo A1(n=14)

Figure 1: Flowchart of the study selection for inclusion in the systematic review and meta-analysis.

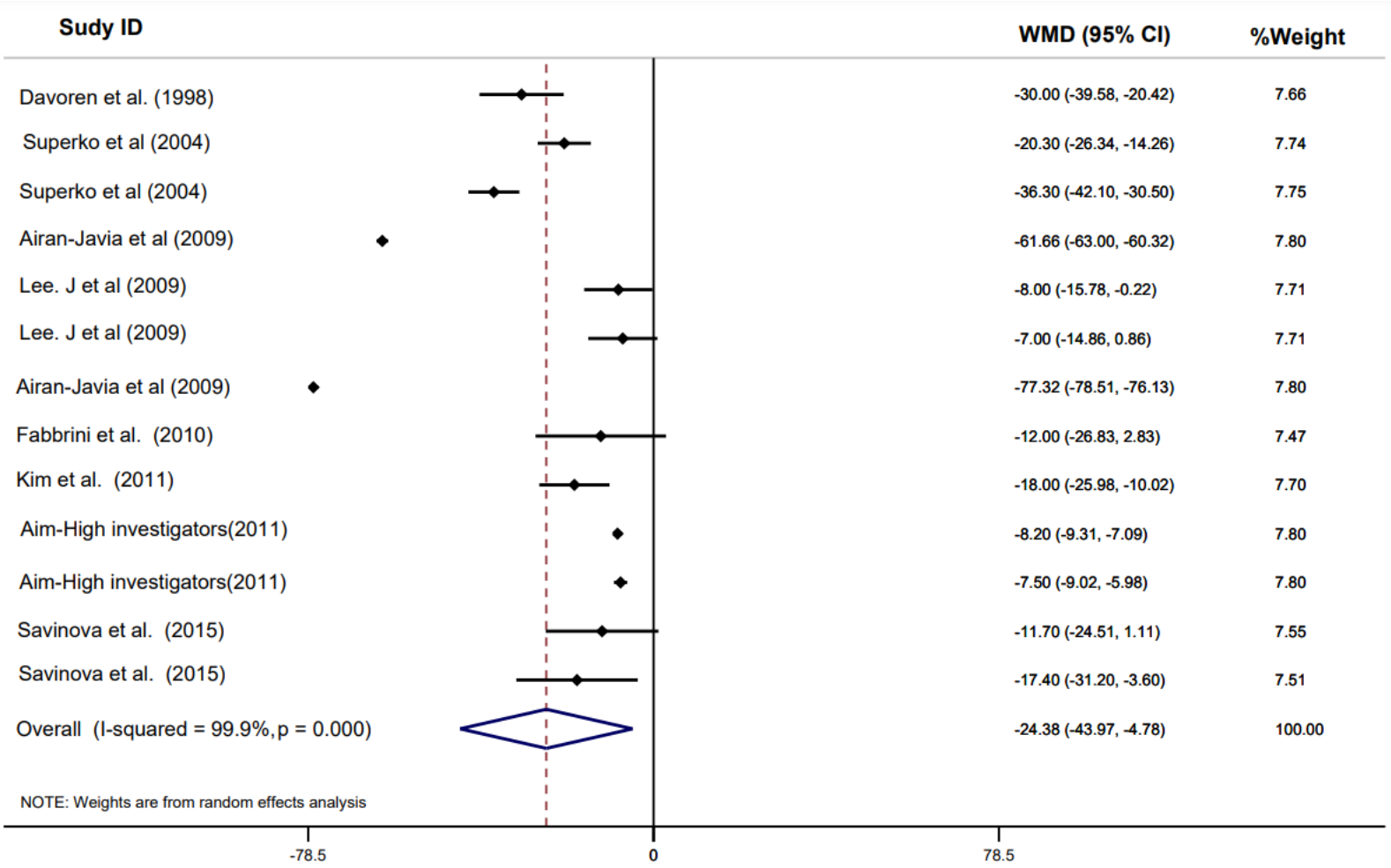
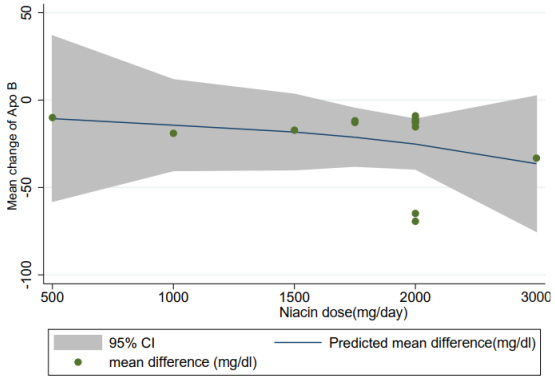


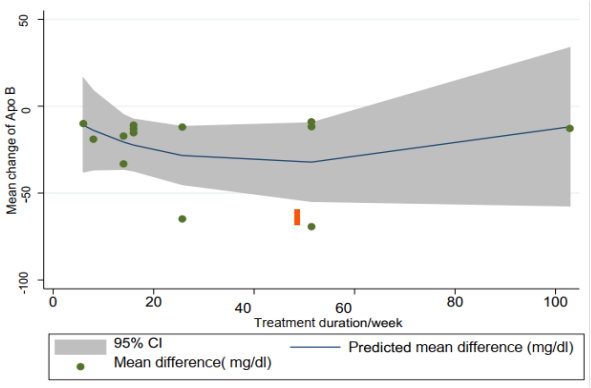
Figure 2. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo B

WMD: weighted mean difference

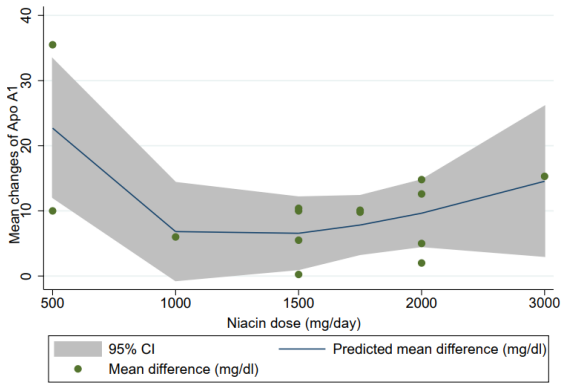
A.



B.



C.



D.

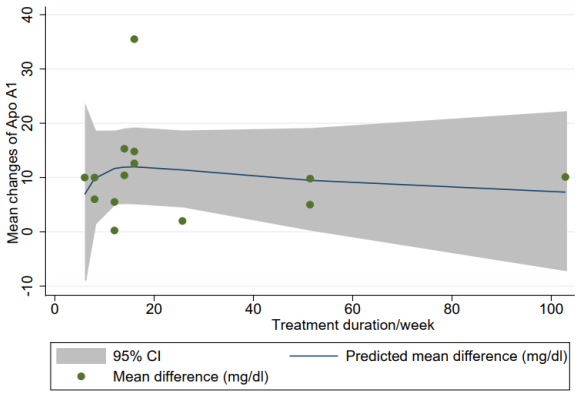


Figure 3. Non-linear dose–response effects of Niacin dosage (mg/day) on Apo B (A), Apo A1, (C) and treatment duration on Apo B (B) Apo A1(D). The 95% CI is demonstrated in the shaded regions.

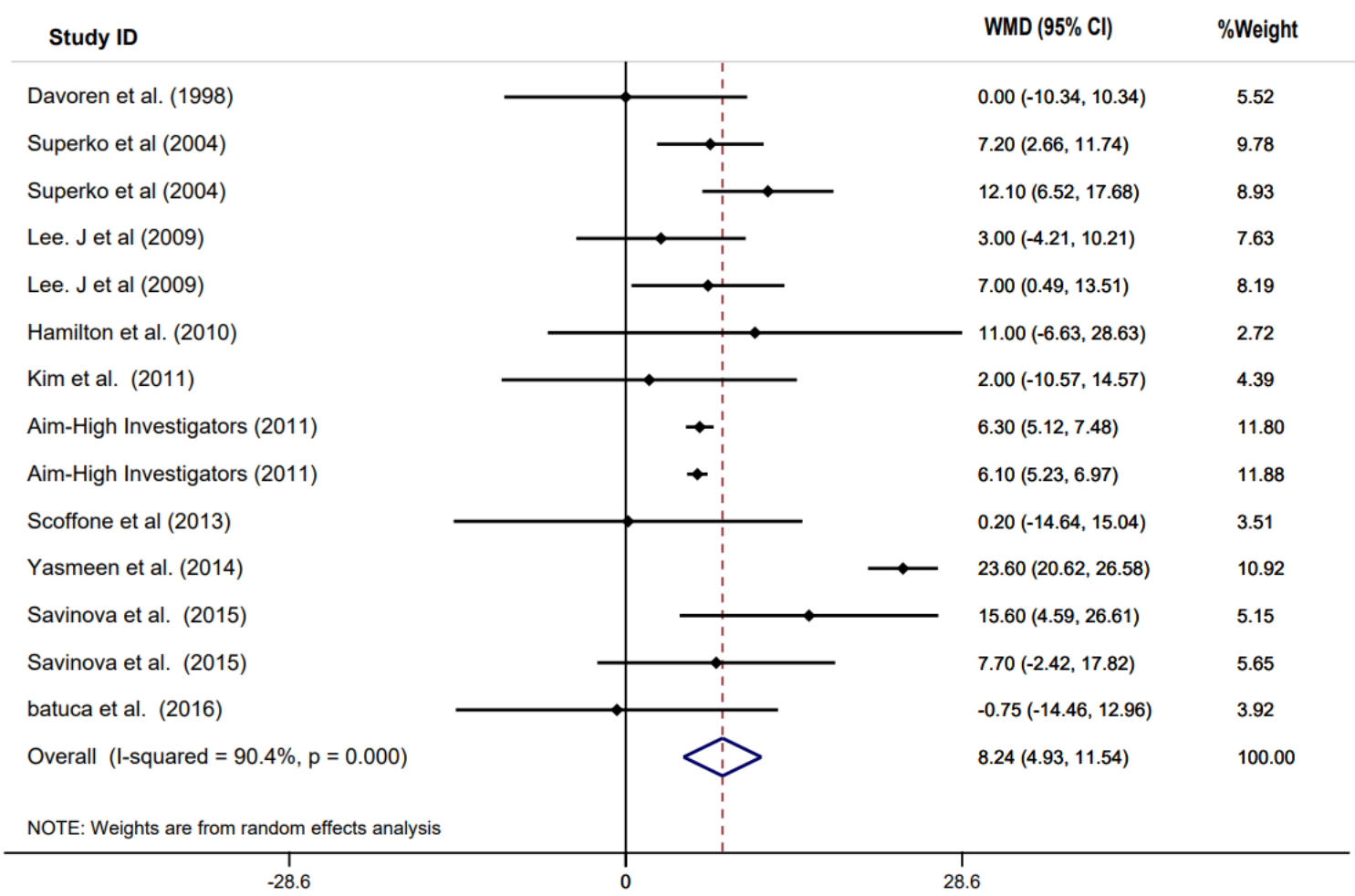


Figure 4. Forest plot of a random effects meta-analysis of the effect of Niacin on Apo A1

WMD: weighted mean difference