British Journal of Nutrition (2024), 131, 1225–1235 doi:10.1017/S000711452300288X

Effects of niacin on apo A1 and B levels: a systematic review and meta-analysis of randomised controlled trials

Somayeh Saboori[1,2], Esmaeil Yousefi Rad[1,2], Jonathan Tammam[1], Pariyarath Sangeetha Thondre[1] and Shelly Coe[1]*

[1]*Oxford Brookes Centre for Nutrition and Health (OxBCNH), Department of Sport, Health Sciences and Social Work, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford OX3 0BP, UK*
[2]*Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran*

(Submitted 4 September 2023 – Final revision received 20 November 2023 – Accepted 4 December 2023 – First published online 19 December 2023)

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 apo A1 and 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 twelve randomised controlled trials met the inclusion criteria. The intervention dosages ranged from 500 to 3000 mg/d, and the study durations spanned from 6 to 102·8 weeks. The niacin intervention demonstrated a significant reduction in apo B levels (weighted mean differences (WMD): −24·37 mg/dl, $P = 0{\cdot}01$). 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, $P < 0{\cdot}001$). Subgroup analyses revealed that the beneficial effects of niacin on apo A1 were observed at a dosage of > 1500 mg/d ($P < 0{\cdot}001$), and extended-release niacin was more effective compared with other forms ($P < 0{\cdot}001$). 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 apo A1 and B.

Keywords: **Niacin: apo: apo B: apo A1: Meta-analysis**

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. LDL is the primary apo B-containing lipoprotein present in human plasma. An elevated level of LDL-cholesterol, 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 with LDL-cholesterol, which can predict cardiovascular events, including myocardial infarction[7,8]. On the other hand, apo A1 functions as a major structural protein of high-density lipoprotein. 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 CVD[9,10].

Dyslipidaemia may be treated with the help of nutritional supplements including vitamins and other nutraceutical compounds[11–14]. Two meta-analysis studies have evaluated the impacts of vitamins on apo B and A1. Both studies found that pooling the results of seven randomised controlled trials (RCT) investigating the effects of vitamin D or vitamin E supplementation on apo A1 and apo B100 levels yielded nonsignificant effects[15,16]. However, niacin or nicotinic acid is a widely recognised treatment for lipid disorders, with efficacy in reducing plasma TAG, increasing HDL-cholesterol 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

Abbreviations: ERN, extended-release niacin; RCT, randomised controlled trials.

* **Corresponding author:** Dr Shelly Coe, email scoe@brookes.ac.UK

type A. Moreover, niacin enhances apo B degradation and lowers the fractional catabolic rate of HDL-apo A1[19,20].

Various vitamin B_3 formulations are designed to control the gradual release of niacin. Immediate-release niacin causes quick flushing, while intermediate-release niacin lessens flushing intensity. Moderate-release niacin enhances tolerability by controlled release. Extended-release niacin (ERN) minimises 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 apo A1 and B. In an RCT conducted by Scoffone *et al.* on Thalassemic patients, it was demonstrated that a 12-week treatment with ERN resulted in an increase in HDL-cholesterol compared with 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-cholesterol to HDL-cholesterol and apo B to apo A1 in the niacin-treated group when compared with patients who received the placebo[22]. An investigation focusing on diabetic patients with renal ischaemia demonstrated that the combination of atorvastatin and ERN treatment significantly raised HDL-cholesterol and apo A1 levels compared with patients who only received atorvastatin. However, this combination treatment did not have a significant reducing effect on LDL-cholesterol levels[23]. Superko *et al.* conducted an RCT on hypercholesterolemic patients to investigate the impacts of two forms of nicotinic acid: immediate-release niacin and ERN on apo. The study revealed that both forms of nicotinic acid significantly increased apo A1 levels, while also significantly reducing apo B levels compared with patients who received the placebo[24]. Findings from a meta-analysis study demonstrated that niacin could have positive effects on the levels of LDL-cholesterol and HDL-cholesterol 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 apo A1 and B. In this study, we conducted a systematic review and meta-analysis of published clinical trials that utilised 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') (online 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 RCT 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 RCT had to provide mean and SD 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 SD 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 digitiser 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

British Journal of Nutrition

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 apo in the niacin and control groups were calculated using the mean changes and their SD. In cases where mean changes were not reported, they were computed based on the changes in apo concentrations during the intervention. To ensure consistency, SE, 95 % CI and interquartile ranges were converted to SD using the method described by Hozo *et al.*[29]

For the analysis, a random-effects model was utilised, which accounts for between-study variations. The effect sizes for variables were expressed as weighted mean differences with their respective 95 % CI. 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/d) 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 categorised 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, seventy-one publications were eligible for full-text assessment of eligibility. During this full-text assessment, thirty-five articles were further excluded as they did not meet the predefined inclusion criteria. Additionally, eighteen 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 twelve clinical trials in this systematic review and meta-analysis. Among these studies, thirteen arms evaluated blood levels of apo B, and fourteen 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 Fig. 1.

Characteristics of the included studies

Table 1 presents the characteristics of the RCT 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[8,22,24,31–34], 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 RCT varied significantly, ranging from fifteen 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/d and the duration of the intervention varied from 6 to 102·8 weeks.

Most of the studies utilised 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, nine studies administered ERN[18,22,24,31–34,37], one study used immediate-release niacin[24], one used nicotinic acid[38], one used acipomax[35] and one study used modified release niacin[36]. Additionally, four studies incorporated the use of statins[23,31,34] or *n*-3 fatty acids[33] in conjunction with the main niacin intervention.

The RCT 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], CVD[24,31,34,36], sickle cell anaemia with low HDL levels[22] and renal ischaemia[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 apo B. The pooled analysis of thirteen effect sizes using a random-effects model revealed a significant reduction in apo B level with the use of niacin

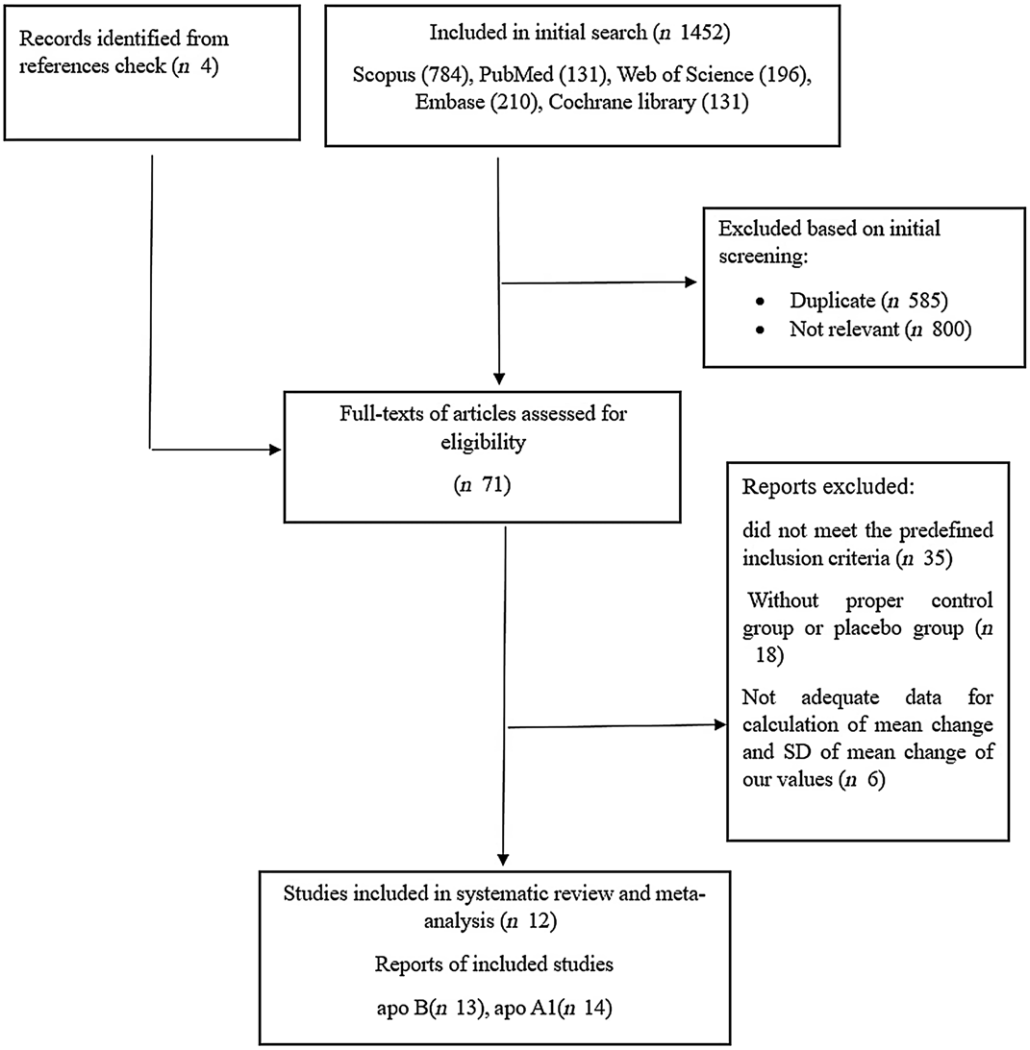

Fig. 1. Flowchart of the study selection for inclusion in the systematic review and meta-analysis.

compared with the control group (weighted mean differences: −24·38, 95 % CI: −43·97, −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 %) (Fig. 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 RCT that had an intervention duration of ≤ 16 weeks compared with those with > 16 week (weighted mean differences: −21·8, 95 % CI: −29·33, −14·28 mg/dl, *P*: < 0·001). Subgroup analysis according to the dosage of intervention (< 2000 mg/d *v.* ≥ 2000 mg/d), type of niacin (ERN *v.* other forms of niacin) and origin country (USA *v.* 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 ($P_{\text{non-linearity}} = 0·49$) and treatment duration ($P_{\text{non-linearity}} = 0·24$) on apo B levels (Fig. 3(a) and (b)).

The effect of niacin on apo A1. The meta-analysis included data from twelve RCT and yielded thirteen effect sizes. The findings indicated that niacin had a significant increasing effect on apo A1 concentrations (weighted mean differences: 8·24, 95 % CI: 4·93, 11·54 mg/dl, $P < 0·001$), as illustrated in Fig. 4. Nevertheless, substantial heterogeneity was observed among the studies in this context ($I^2 = 90·4$ %, $P < 0·001$) (Fig. 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 Apo A1 concentrations in RCT that utilised ERN as the intervention, especially when the dosage

Table 1. Summary of clinical trials on the effects of niacin on apo A1 and apo B levels

Outcome	Duration (week)	Final daily dosage (mg)	Intervention		Age, year	Sample size	Gender	Participants	Design	Country	Author, year
			Control	treatment							
apo A1	12	1500	Placebo	Extended-release niacin (ERN)+	Int:46·3 ± 12·02 Con:52·44 ± 9·55	Int: 8 Con:9	Both	Men or women, with serum HDL-C ≤ 40 mg/dl or ≤ 50 mg/dl	Cross-over trial	Portugal	Batuca *et al.* 2016
apo A1, apo B	8	1000	Placebo	Nicotinic acid	Int:57·4 ± 6·8 Con:61·8 ± 8·3	Int: 25 Con:21	Both	People with Mixed Dyslipidemia	RCT	Korea	Kim *et al.* 2011
apo B	16	2000	Placebo	Extended-release niacin (niaspan)	Int:43 ± 15 Con:45 ± 9	Int: 9 Con:9	Both	People with NAFLD	RCT	USA	Fabbrini *et al.* 2010
apo A1	8	1500	No inter-vention	Extended-release niacin	65	Int: 7 Con:8	Both	People with T2DM	RCT	Australia	Hamilton *et al.* 2010
apo A1, apo B	6	500	Placebo	Acipimox	Int:29 Con:31	Int: 29 Con:31	Both	People with Non-insulin-dependent diabetes mellitus	RCT	UK and Germany	Davoren *et al.* 1998
apo A1, apo B	16	2000	*n*-3 Fatty Acids Placebo	Extended-release niacin (ERN)+ *n*-3 Fatty Acids Extended-release niacin (ERN)	NR	Int: 13 Con:15 Int: 14 Con:14	Both	People with metabolic syndrome	RCT	USA	Savinova *et al.* 2015
apo A1	16	500	Atorvastatin	Niacin+ Atorvastatin	NR	Int: 51 Con:56	Both	patients with renal ischemia	RCT	Pakistan	Yasmeen *et al.* 2014
apo B	25/7 51·42	2000	Simvastatin	Extended-release niacin (ERN)+ simvastatin	Int:71 ± 7·4 Con:70·5 ± 14·8	Int: 22 Con:25	Both	Patients with carotid atherosclerosis	RCT	USA	Airan-Javia *et al.* 2009
apo A1	12	1500	Placebo	Extended-release niacin (ERN)	18–65	Int: 10 Con:14	Both	Adults with Sickle Cell Anemia and Low High-Density Lipoprotein Cholesterol Levels	RCT	USA	Scoffone *et al.* 2013
apo A1, apo B	51·42 102·85	1500–2000	Statin	Extended-release niacin (ERN)+ statin	Int:63·7 ± 8·8 Con: 63·7 ± 8·7	Int: 1561 Con:1554 Int: 865 Con:873	Both	patients with cardio-vascular disease	RCT	USA	Aim-High inves-tigators 2011
apo A1, apo B	25·7 51·4	2000	Placebo	Modified release NA (niaspan)	Int:65 ± 9 Con:65 ± 9	Int: 22 Con:29	Both	patients with low HDL-C (,40 mg/dl) and either: 1) type 2 diabetes with coronary heart dis-ease; or 2) carotid/ peripheral athero-sclerosis.	RCT	UK	Lee. J *et al.* 2009
apo A1, apo B	14	1500 3000	Placebo	Extended-release niacin (ERN) Immediate release niacin (IRN)	Int:53 ± 12 Con:55 ± 12 Int:53 ± 11 Con:55 ± 12	Int: 60 Con:61 Int: 59 Con:61	Both	patients with clinical his-tory of coronary dis-ease or at least two risk factors for coro-nary disease	RCT	USA	Superko. H *et al.* 2004

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

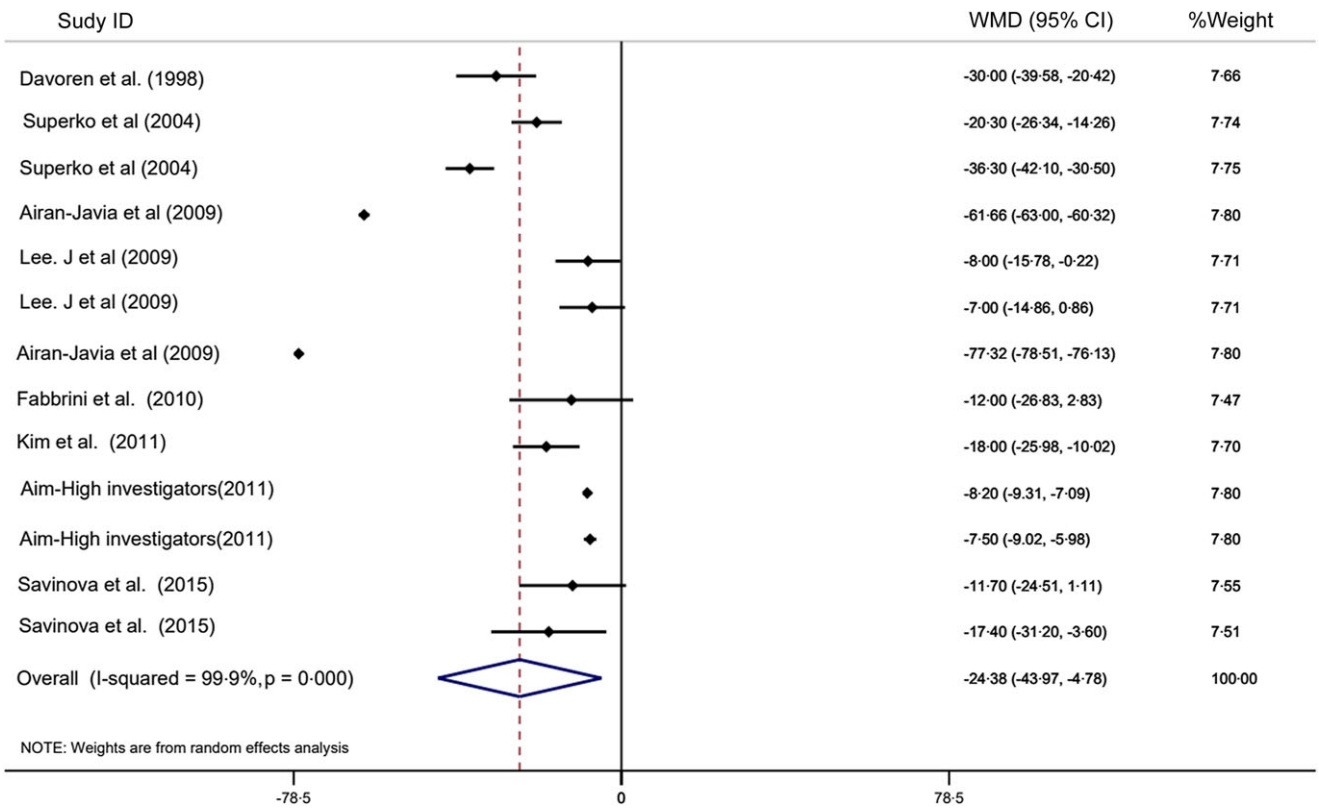

Fig. 2. Forest plot of a random effects meta-analysis of the effect of niacin on apo B. WMD, weighted mean difference

of intervention exceeded 1500 mg/d. Furthermore, the effect of niacin administration was particularly significant in studies conducted in the USA compared with 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 thirteen 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 ($P_{\text{non-linearity}} = 0·18$ and 0·50, respectively) (Fig. 3(c) and (d)).

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

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/d)						
< 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/d)						
≤ 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.

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 apo 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 apo, niacin could play a crucial role in decreasing the risk of CVD[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 with 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/d. 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 with 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-cholesterol levels by up to 35 %. Furthermore, ERN diminishes TAG 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 CVD[47]. The non-linear dose–response meta-analysis did not show any significant impact of niacin dosage or intervention duration on apo A1

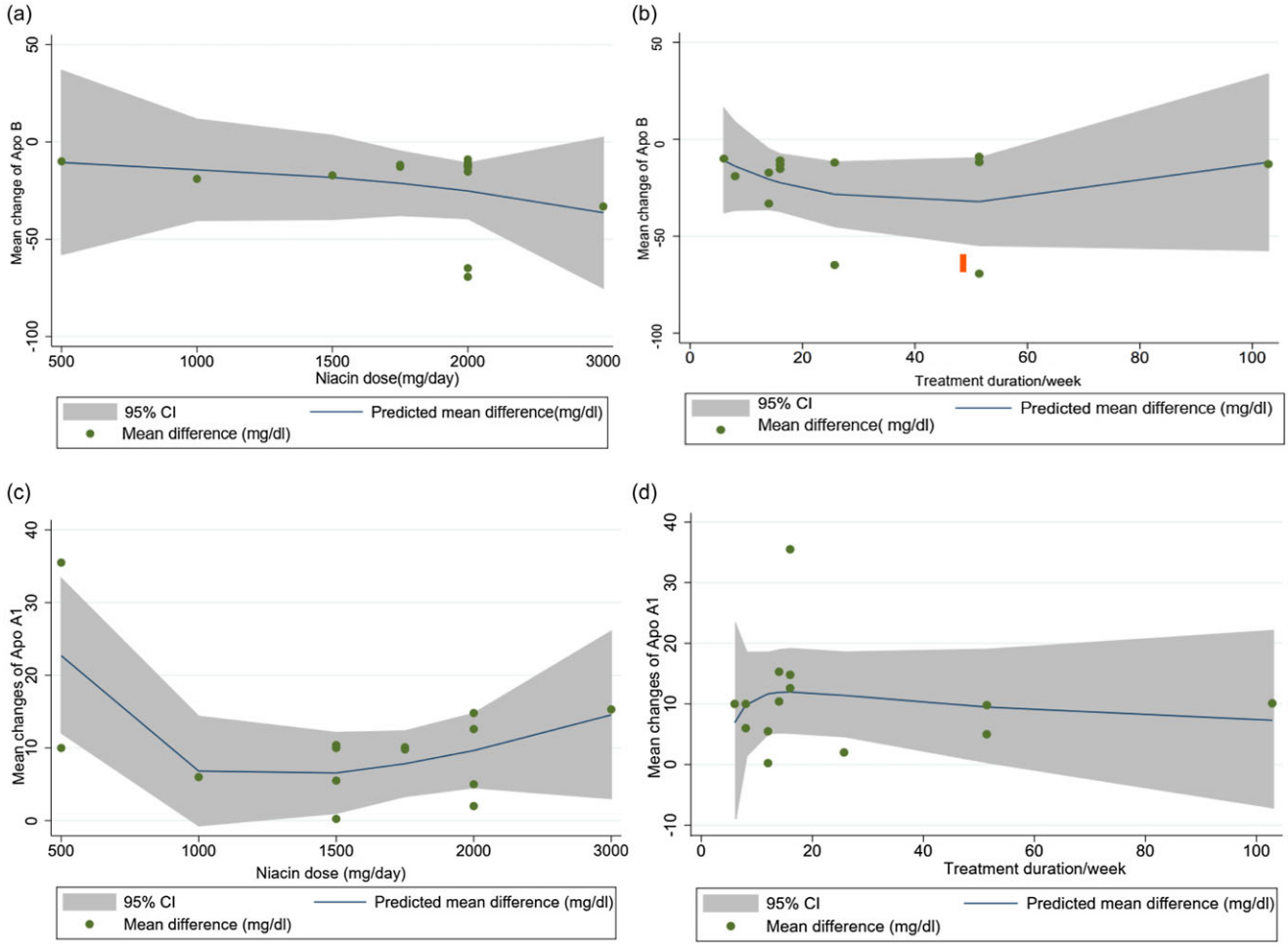

Fig. 3. Non-linear dose–response effects of niacin dosage (mg/d) on apo B (a), apo A1, (c) and treatment duration on apo B (b) apo A1(D). The 95 % CI is demonstrated in the shaded regions.

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 apo 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 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 TAG in the circulation[32]. Niacin also promotes the lipolysis of TAG within circulating VLDL and intermediate-density lipoprotein particles by activating lipoprotein lipase[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, an enzyme involved in the synthesis of triglycerides within hepatocytes[51]. Lower TAG availability results in the formation of larger, less atherogenic LDL particles. Additionally, niacin downregulates the expression of proprotein convertase subtilisin/kexin type 9, a protein that promotes the degradation of hepatic LDL receptors. The reduction in proprotein convertase subtilisin/kexin type 9 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. Cholesteryl ester transfer protein facilitates the transfer of cholesteryl esters from HDL to other lipoproteins (such as VLDL and LDL) in exchange for TAG. By inhibiting cholesteryl ester transfer protein, 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 apo A1 as its major protein component[43,48]. These mechanisms collectively lead to improvements in lipid profile, including reductions in LDL-cholesterol and TAG, along with increases in HDL-cholesterol 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 apo A1 and B.

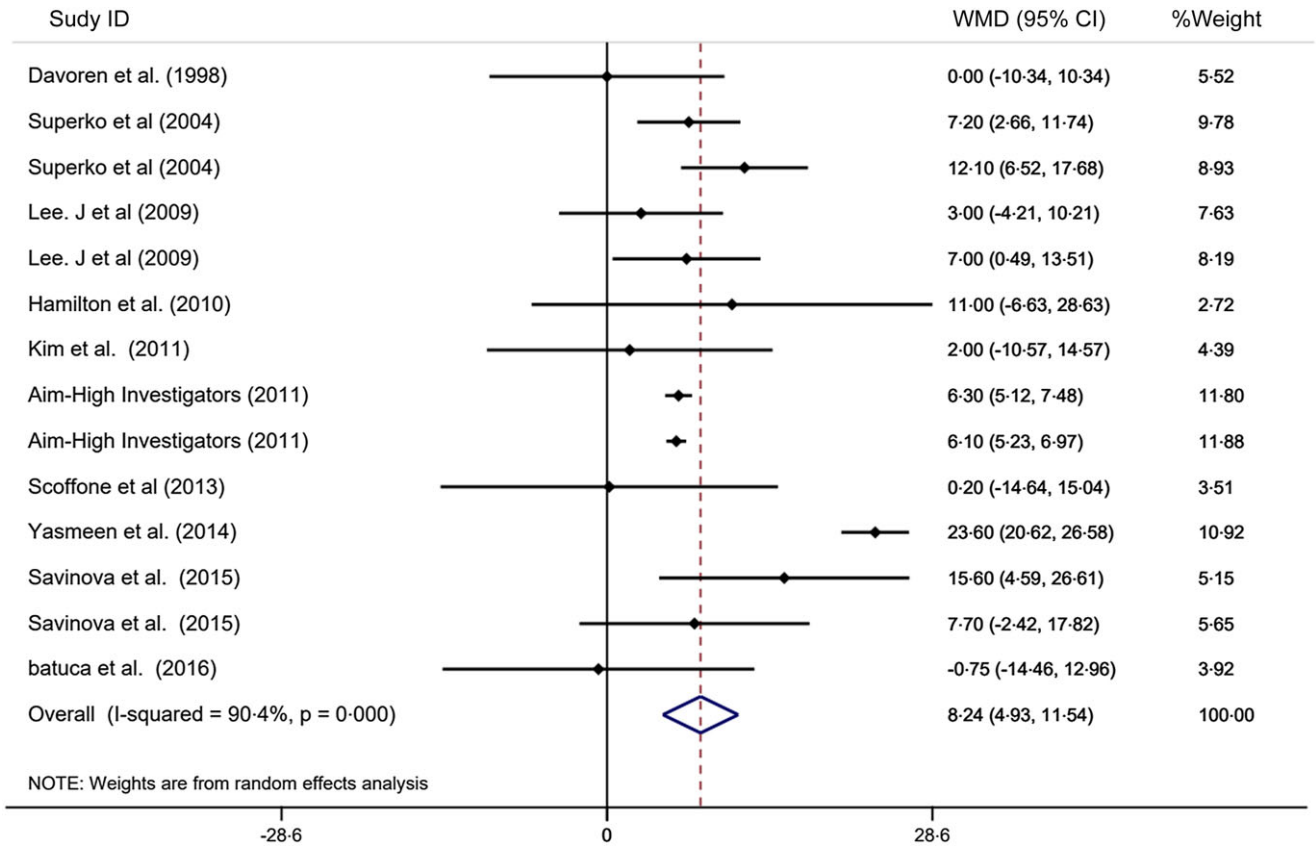

Fig. 4. Forest plot of a random effects meta-analysis of the effect of niacin on apo A1. WMD, weighted mean difference.

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 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 limitation*	No serious limitation	No serious limitation	No serious limitation	5522	2747/2776	8·23	4·92, 11·54	⊕⊕◯◯ Low

* There is high heterogeneity for apo B ($I^2 = 99·9$ %) and apo A1 ($I^2 = 90·4$ %).

Nonetheless, it is not without its limitations. First, the presence of substantial heterogeneity saw in meta-analysis could restrict the degree to which the findings can be generalised. 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 research and well-designed randomised controlled trials are needed to corroborate and refine these results and to better understand the optimal dosing and duration of niacin treatment for favourable effects on apo B and A1.

Acknowledgements

This work had no source of funding.

J. T., S. C. and P. S. T. designed and E. Y. R. and S. S. searched systematically for the study. E. Y. R. and S. S. reviewed and selected the articles and extracted data from articles. S. S. performed data analysis and interpretation. E. Y. R. and S. S. drafted the manuscript. S. C., J. T. and P. S. T. revised the article for important intellectual content.

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

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

References

1. Cd M (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* **3**, 2011–2030.
2. Roth GA, Mensah GA, Johnson CO, *et al.* (2020) Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *J Am Coll Cardiol* **76**, 2982–3021.
3. Anand SS, Hawkes C, De Souza RJ, *et al.* (2015) Food consumption and its impact on cardiovascular disease: importance of solutions focused on the globalized food system: a report from the workshop convened by the World Heart Federation. *J Am Coll Cardiol* **66**, 1590–1614.
4. Artinian NT, Fletcher GF, Mozaffarian D, *et al.* (2010) Interventions to promote physical activity and dietary lifestyle changes for cardiovascular risk factor reduction in adults: a scientific statement from the American Heart Association. *Circulation* **122**, 406–441.
5. Mendis S, Puska P, Norrving BE, *et al.* (2011) *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva: World Health Organization.
6. Arca M, Pigna G & Favoccia C (2012) Mechanisms of diabetic dyslipidemia: relevance for atherogenesis. *Curr Vasc Pharmacol* **10**, 684–686.
7. Carr SS, Hooper AJ, Sullivan DR, *et al.* (2019) Non-HDL-cholesterol and apolipoprotein B compared with LDL-cholesterol in atherosclerotic cardiovascular disease risk assessment. *Pathology* **51**, 148–154.
8. Walldius G, Jungner I, Holme I, *et al.* (2001) High apolipoprotein B, low apolipoprotein AI, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* **358**, 2026–2033.
9. Karthikeyan G, Teo KK, Islam S, *et al.* (2009) Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. *J Am Coll Cardiol* **53**, 244–253.
10. Walldius G & Jungner I (2005) Rationale for using apolipoprotein B and apolipoprotein AI as indicators of cardiac risk and as targets for lipid-lowering therapy. *Eur Heart J* **26**, 210–212.
11. Cicero AFG, Colletti A, Bajraktari G, *et al.* (2017) Lipid-lowering nutraceuticals in clinical practice: position paper from an international lipid expert panel. *Nutr Rev* **75**, 731–767.
12. Shidfar F, Aghasi M, Vafa M, *et al.* (2010) Effects of combination of zinc and vitamin A supplementation on serum fasting blood sugar, insulin, apoprotein B and apoprotein A-I in patients with type I diabetes. *Int J Food Sci Nutr* **61**, 182–191.
13. Shidfar F, Ebrahimi SS, Hosseini S, *et al.* (2012) The effects of berberis vulgaris fruit extract on serum lipoproteins, apoB, apoA-I, homocysteine, glycemic control and total antioxidant capacity in type 2 diabetic patients. *Iran J Pharm Res* **11**, 643–652.
14. Shidfar F, Keshavarz A, Hosseyni S, *et al.* (2008) Effects of *n*-3 fatty acid supplements on serum lipids, apolipoproteins and malondialdehyde in type 2 diabetes patients. *East Mediterr Health J* **14**, 305–313.
15. Hamedi-Kalajahi F, Zarezadeh M, Dehghani A, *et al.* (2021) A systematic review and meta-analysis on the impact of oral vitamin E supplementation on apolipoproteins A1 and B100. *Clin Nutr ESPEN* **46**, 106–114.
16. Radkhah N, Shabbidar S, Zarezadeh M, *et al.* (2021) Effects of vitamin D supplementation on apolipoprotein A1 and B100 levels in adults: systematic review and meta-analysis of controlled clinical trials. *J Cardiovasc Thoracic Res* **13**, 190.
17. Florentin M, N Liberopoulos E, Kei A, *et al.* (2011) Pleiotropic effects of nicotinic acid: beyond high density lipoprotein cholesterol elevation. *Curr Vasc Pharmacol* **9**, 385–400.
18. Hamilton SJ, Chew GT, Davis TM, *et al.* (2010) Niacin improves small artery vasodilatory function and compliance in statin-treated type 2 diabetic patients. *Diabetes Vasc Dis Res* **7**, 296–299.
19. Ruparelia N, Digby JE & Choudhury RP (2011) Effects of niacin on atherosclerosis and vascular function. *Curr Opin Cardiol* **26**, 66.
20. Al-Mohaissen M, Pun S & Frohlich J (2010) Niacin: from mechanisms of action to therapeutic uses. *Mini Rev Med Chem* **10**, 204–217.
21. Superko HR, McGovern ME, Raul E, *et al.* (2004) Differential effect of two nicotinic acid preparations on low-density lipoprotein subclass distribution in patients classified as low-density lipoprotein pattern A, B, or I. *Am J Cardiol* **94**, 588–594.
22. Scoffone HM, Krajewski M, Zorca S, *et al.* (2013) Effect of extended-release niacin on serum lipids and on endothelial function in adults with sickle cell anemia and low high-density lipoprotein cholesterol levels. *Am J Cardiol* **112**, 1499–1504.
23. Yasmeen G, Dawani ML & Mahboob T (2014) Adding niacin with atorvastatin in patients with renal ischemia: a comparative study. *Int J Pharm Sci Res* **5**, 3496–3501.
24. Superko HR, McGovern ME, Raul E, *et al.* (2004) Differential effect of two nicotinic acid preparations on low-density lipoprotein subclass distribution in patients classified as low-density lipoprotein pattern A, B, or I. *Am J Cardiol* **94**, 588–594.
25. Ding Y, Li Y & Wen A (2015) Effect of niacin on lipids and glucose in patients with type 2 diabetes: a meta-analysis of randomized, controlled clinical trials. *Clin Nutr* **34**, 838–844.
26. Page MJ, Moher D, Bossuyt PM, *et al.* (2021) PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ* **372**, n160.
27. Higgins JP & Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions 5.1.0. *The Cochrane Collaboration* 2011. https://training.cochrane.org/handbook/current (accessed June 2023).
28. Higgins JP, Altman DG, Gøtzsche PC, *et al.* (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928.
29. Hozo SP, Djulbegovic B & Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Method* **5**, 1–10.
30. Guyatt GH, Oxman AD, Vist GE, *et al.* (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* **336**, 924–926.
31. Airan-Javia SL, Wolf RL, Wolfe ML, *et al.* (2009) Atheroprotective lipoprotein effects of a niacin-simvastatin combination compared to low-and high-dose simvastatin monotherapy. *Am Heart J* **157**, 687.e681–687.e688.
32. Fabbrini E, Mohammed BS, Korenblat KM, *et al.* (2010) Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. *J Clin Endocrinol Metab* **95**, 2727–2735.
33. Savinova OV, Fillaus K, Harris WS, *et al.* (2015) Effects of niacin and *n*-3 fatty acids on the apolipoproteins in overweight patients with elevated triglycerides and reduced HDL cholesterol. *Atherosclerosis* **240**, 520–525.
34. Investigators A-H (2011) Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* **365**, 2255–2267.

British Journal of Nutrition

35. Davoren P, Kelly W, Gries F, *et al.* (1998) Long-term effects of a sustained-release preparation of acipimox on dyslipidemia and glucose metabolism in non—insulin-dependent diabetes mellitus. *Metabolism* **47**, 250–256.
36. Lee JM, Robson MD, Yu L-M, *et al.* (2009) Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol* **54**, 1787–1794.
37. Batuca J, Amaral M, Favas C, *et al.* (2016) Extended release-niacin increases anti-ApoA-I antibodies that block the antioxidant effect of HDL-C: the EXPLORE clinical trial. *Br J Clin Pharmacol* **83**, 1002–1010.
38. Kim S-H, Kim M-K, Lee H-Y, *et al.* (2011) Efficacy and tolerability of a new extended-release formulation of nicotinic acid in Korean adults with mixed dyslipidemia: an 8-week, multicenter, prospective, randomized, double-blind, and placebo-controlled trial. *Clin Ther* **33**, 1357–1364.
39. Croyal M, Ouguerram K, Passard M, *et al.* (2015) Effects of extended-release nicotinic acid on apolipoprotein (a) kinetics in hypertriglyceridemic patients. *Arterioscler Thromb Vasc Biol* **35**, 2042–2047.
40. Chapman MJ, Redfern JS, McGovern ME, *et al.* (2010) Niacin and fibrates in atherogenic dyslipidemia: pharmacotherapy to reduce cardiovascular risk. *Pharmacol Ther* **126**, 314–345.
41. Santolla MF, De Francesco EM, Lappano R, *et al.* (2014) Niacin activates the G protein estrogen receptor (GPER)-mediated signalling. *Cell Signalling* **26**, 1466–1475.
42. Beintner I, Vollert B, Zarski A-C, *et al.* (2019) Adherence reporting in randomized controlled trials examining manualized multisession online interventions: systematic review of practices and proposal for reporting standards. *J Med Internet Res* **21**, e14181.
43. Zhang L-H, Kamanna VS, Ganji SH, *et al.* (2012) Niacin increases HDL biogenesis by enhancing DR4-dependent transcription of ABCA1 and lipidation of apolipoprotein AI in HepG2 cells. *J Lipid Res* **53**, 941–950.
44. Volgman AS, Palaniappan LS, Aggarwal NT, *et al.* (2018) Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. *Circulation* **138**, e1–e34.
45. Birjmohun RS, Hutten BA, Kastelein JJ, *et al.* (2005) Efficacy and safety of high-density lipoprotein cholesterol-increasing compounds: a meta-analysis of randomized controlled trials. *J Am Coll Cardiol* **45**, 185–197.
46. Sahebkar A, Reiner Ž, Simental-Mendia LE, *et al.* (2016) Effect of extended-release niacin on plasma lipoprotein (a) levels: a systematic review and meta-analysis of randomized placebo-controlled trials. *Metabolism* **65**, 1664–1678.
47. Nordestgaard BG, Chapman MJ, Ray K, *et al.* (2010) Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* **31**, 2844–2853.
48. Kamanna VS & Kashyap ML (2008) Mechanism of action of niacin. *Am J Cardiol* **101**, S20–S26.
49. Guo L & Fisher EA (2011) Niacin (vitamin B3, nicotinic acid) decreases apolipoprotein B (ApoB) and VLDL secretion from mouse hepatocytes. *FASEB J* **25**, lb174.
50. Kang I, Kim S-W & Youn JH (2011) Effects of nicotinic acid on gene expression: potential mechanisms and implications for wanted and unwanted effects of the lipid-lowering drug. *J Clin Endocrinol Metab* **96**, 3048–3055.
51. Hu M, Chu WCW, Yamashita S, *et al.* (2012) Liver fat reduction with niacin is influenced by DGAT-2 polymorphisms in hypertriglyceridemic patients. *J Lipid Res* **53**, 802–809.
52. Warden BA, Minnier J, Watts GF, *et al.* (2019) Impact of PCSK9 inhibitors on plasma lipoprotein (a) concentrations with or without a background of niacin therapy. *J Clin Lipidol* **13**, 580–585.
53. Watts GF, Chan DC, Pang J, *et al.* (2020) PCSK9 Inhibition with alirocumab increases the catabolism of lipoprotein (a) particles in statin-treated patients with elevated lipoprotein (a). *Metabolism* **107**, 154221.
54. Kamanna VS & Kashyap ML (2000) Mechanism of action of niacin on lipoprotein metabolism. *Curr Atheroscler Rep* **2**, 36–46.

British Journal of Nutrition