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META-ANALYSIS

Effects of Nicotinamide Mononucleotide Supplementation on Muscle and Liver Functions Among the Middle-Aged and Elderly: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract: ***Introduction:*** Nicotinamide Mononucleotide (NMN) has gained attention as a precursor to Nicotinamide Adenine Dinucleotide (NAD^+) in recent years, commonly utilized in anti-aging therapies. The anti-aging effects of NMN on muscle and liver functions in middle-aged and elderly people are still unclear.

Objective: Based on available randomized controlled trials, we conducted a meta-analysis to evaluate the impact of NMN on muscle and liver functions in middle-aged and elderly individuals.

Methods: We conducted searches on three electronic databases (PubMed, Embase, Web of Science) for randomized controlled trials involving NMN interventions in middle-aged and elderly populations. Through the Cochrane Handbook, we assessed the specific methodological quality. All statistical analyses were obtained by Stata15, and statistical significance was set as $P<0.05$.

Results: There were 412 participants from 9 studies in this meta-analysis. Based on changes in gait speed (SMD: 0.34 m/s, 95%CI [0.03, 0.66] $p = 0.033$), NMN had significant effects on muscle mass. Moreover, NMN had a better effect on ALT (SMD: -0.29 IU/L, 95%CI [-0.55, -0.03] $p = 0.028$). Subgroup analysis indicated that administering a small dose of NMN exerted the most prominent impact on Homeostasis Model Assessment-Insulin Resistance (HOMA-IR).

Conclusion: NMN has positive efficacy in enhancing muscle function, reducing insulin resistance and lowering aminotransferase levels in middle-aged and elderly individuals. NMN is an encouraging and considerable drug for anti-aging treatment.

Keywords: Aging, nicotinamide mononucleotide, meta-analysis, muscle, liver.

1. INTRODUCTION

The global trend of increasingly aging societies has become one of the key issues facing public healthcare, bringing enormous challenges to the healthcare system and the social economy [1]. Around the globe, the proportion of the population aged over 60 is expected to rise from 10% in 2005 to 22% by 2050 [2]. Senescence refers to the decrease or deterioration (termed "de-tuning") in adaptation as one grows older, resulting in the gradual decline of tissue and organ functions. This decline contributes to the development of various chronic ailments, including cancer, ultimately diminishing the overall quality of life for elderly individuals [3-5]. For example, the reduction in muscle and physical capabilities among older individuals may exacerbate the onset of geriatric conditions, such as sarcopenia and frailty [6], and decreased muscle mass aggravates insulin resistance [7]. Due to the progress of aging, changes in liver function and decreased cytochrome P450 activity can affect metabolism, increasing susceptibility to liver injury and causing liver diseases [8]. The development of numerous age-related pathologies and diseases resulting from deficiencies in nuclear and mitochondrial functions is causally associated with the reduction in NAD^+ levels during aging [9].

Nicotinamide mononucleotide (NMN), originating from fruits and vegetables, is essential for the biosynthesis of NAD^+ and supports numerous physiological functions,

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which has shown promise in reversing age-related complications and slowing down the aging process by augmenting NAD^+ levels in the body [10]. NMN serves as an intermediary in the biosynthesis of NAD^+ [11]. NAD^+, a vital metabolic redox coenzyme in eukaryotic organisms, plays an essential role in numerous enzymatic reactions [10]. Intracellular NAD^+ levels lead to the activation of sirtuins [12]. The diverse cellular locations of sirtuins support their versatile functions, enabling cells to sense changes in energy levels across the nucleus, cytoplasm, and mitochondrion [13]. Sirtuins play a crucial role in various physiological and biochemical processes within the body, including apoptosis, aging, and gene or protein expression, which emphasizes the significant role of NAD^+ in longevity and overall health [14]. As reported by some recent studies [15, 16], NMN supplementation can compensate for NAD^+ deficiency and influence various pharmacological activities in diverse disease conditions.

In recent years, many studies have revealed that NMN can effectively alleviate age-related physiological decline in the middle-aged and elderly, indicating a promising approach for anti-aging therapies [17]. While NMN demonstrated analogous effects in animal models [18-20], there are currently limited clinical studies on NMN intervention, and the correlation between NMN and human aging remains uncertain. Hence, this meta-analysis relied on available randomized controlled trials (RCTs) to analyze and assess the impacts of different NMN supplementations on muscle and liver functions in middle-aged and elderly individuals.

2. MATERIALS AND METHODS

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement [21].

2.1. Data Sources and Search Strategy

Adhering to PRISMA guidelines, this meta-analysis study was meticulously conducted and reported. Until February 22, 2023, we extensively searched several electronic databases without limitations on language, region, or publication time, including PubMed, Embase, and Web of Science. Furthermore, we screened the reference lists of selected articles. The search keywords included NMN, mononucleotide nicotinamide, excluding animals, mice, mouse, and review.

Here is the search strategy used in the PubMed database:

((("Nicotinamide Mononucleotide"[Mesh]) OR (Mononucleotide, Nicotinamide[Title/Abstract])) OR (Nicotinamide Mononucleotide[Title/Abstract])) OR (NMN[Title/Abstract]) NOT "Animals"[Mesh Terms]) NOT "mice"[Title/Abstract]) NOT "mouse"[Title/Abstract]) NOT "review"[Title/Abstract]

2.2. Inclusion and Exclusion Criteria

We chose articles that met each of the following criteria:

(1) The type of study was an RCT.

(2) The study focused on certain clinical trials of NMN administration.

(3) Intervention: NMN supplementation with high doses (≥900mg/d) or low doses (≤300mg/d); Control: Placebo treatment or no therapy.

(4) The duration of the NMN supplementation was more than 4 weeks.

But we eliminated articles if:

(1) Its type was one animal study, one non-randomized trial, one observational study, one review, and one case report.

(2) It was a duplicate publication.

(3) The duration of the NMN intervention was less than 4 weeks.

2.3. Data Extraction

Two reviewers independently extracted data on the basis of the screening criteria. Some discrepancies were resolved through discussion and documentation. Any disagreements were discussed and documented. Consultation was sought for inconsistent data extraction to ensure a final decision, as the extracted data did not match. Each trial included in this study presented details, such as the author's name, country of origin, publication year, percentage of male participants, study type, sample size, average ages, interventions, and outcomes. We converted all the walking test data from the included studies on gait speed, and the relevant data were estimated on the basis of the Cochrane Handbook [22] for further analysis of the results. If the value of the change before and after the NMN intervention was not given in the study, we could use the formula ([SD change =√SD before 2 + SD after 2 − (2*R*SD before *SD after)] (R = 0.5)) to estimate the variation.

2.4. Statistical Analysis

By using Stata15 software, we conducted statistical meta-analyses, setting confidence intervals (CIs) at 95%. The standardized mean differences (SMD) and weighted mean differences (WMD) were calculated for continuous data, with CIs set at 95%. A random effects model was utilized to calculate SMD and WMD for all outcomes. A significance level of $P < 0.05$ was considered statistically significant. A heterogeneity test was performed by using I^2 and Q statistics, and $I^2 > 50.0\%$ or $P < 0.10$ was considered as significant heterogeneity. Stata15 software was utilized to identify publication bias, primarily employing the Egger test, where a $P > 0.05$ shows no significant publication bias.

3. RESULTS

3.1. Literature Search

In our search of the electronic databases, a total of 4305 documents were recorded. Among these, 1783 duplicate documents were excluded. The remaining 2522 studies were retrieved for title and abstract review, and 2,501 literatures were excluded because they did not conform to the topic. A total of 21 works of literature were retrieved in full text. Thirteen RCT studies in nine pieces of literature were selected for the final summary analysis. At the same time as retrieving the target documents, the relevant references were

also included in the corresponding classification. The PRISMA flowchart of the study selection is reported in Fig. (**1**).

3.2. Study Characteristics

Table **1** displays the baseline characteristics of the studies and populations. There were 412 participants enrolled in the thirteen included studies, all of whom were supplied with NMN. The published studies covered 2021-2023 from China, Japan, and the USA, with a follow-up of 4w to 24w.

3.3. Study Quality and Risk of Bias Assessment

Table **2** summarizes the risk of bias assessments of the included studies. Two independent reviewers (JPW and YDZ) were responsible for reviewing the quality of all included studies by using the modified risk of bias tool from Cochrane Collaboration. The risk of bias was evaluated in seven parts in each randomized controlled trial. Consequently, we used terms like "Low," "High," or "Unclear" to assess every part. Furthermore, if there were any discrepancies in the evaluation process, the final results were judged and resolved by the corresponding author.

3.4. Meta-analysis

3.4.1. Muscle Function

The gait speed was reported as an important outcome in five studies, with 8 trials including a total of participants (intervention = 143 and control = 143) (Fig. **2**). From the random-effects model, the administration of NMN led to a significant trend in gait speed (SMD: 0.34 m/s, 95%CI [0.03, 0.66] p = 0.033) with significant heterogeneity among the studies (I^2 = 48.4%, p = 0.059). This heterogeneity could be explained by the length of the intervention, the dose, and the age of the participants in these studies. After the consumption of NMN, there was a significant increase in gait speed in the ten weeks of intervention duration (SMD: 0.54 m/s, 95%CI [0.13, 0.94] p = 0.010 I^2 = 45.8%, p = 0.136), intervention dose, which was more than 900mg/day (SMD: 1.20 m/s, 95%CI [0.52, 1.87] p = 0.001), and subjects with an average age under 60 (SMD: 0.61 m/s, 95%CI [0.05, 1.17] p = 0.033 I^2 = 61.9%, p = 0.073) (Table **3**).

We analyzed data from 200 participants (intervention = 106 and control = 94) in four studies with 7 trials and used grip strength as a final parameter to assess muscle function

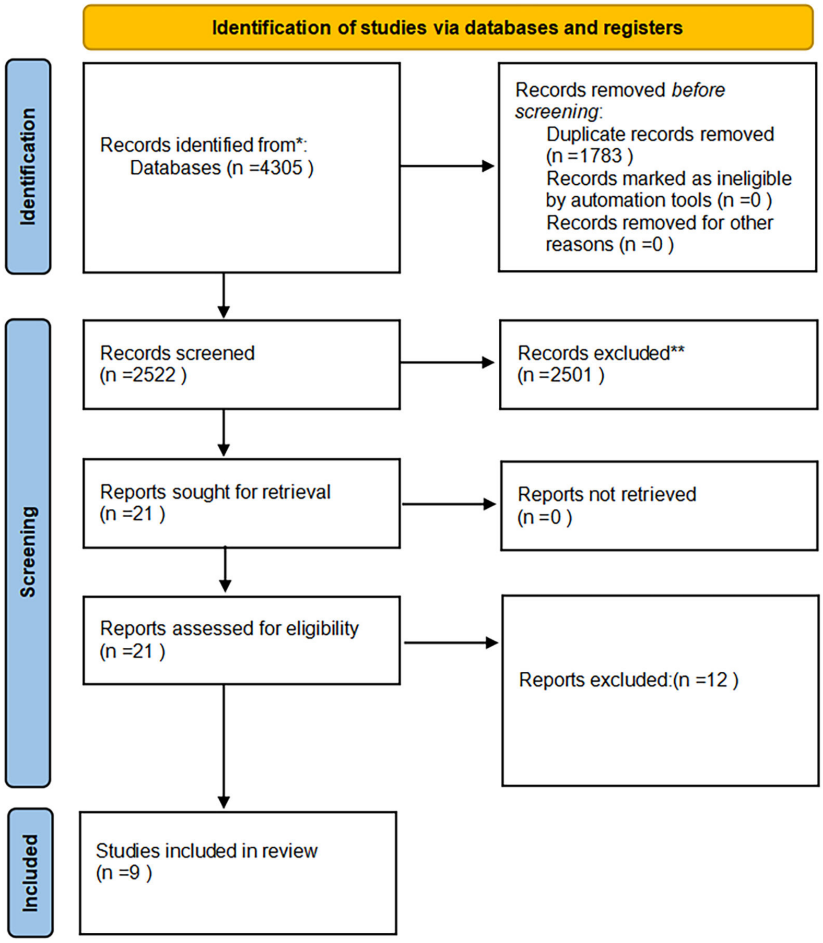

Fig. (1). Flowchart of study selection.

Table 1. Characteristics of the studies included in the systematic review.

Author (year)	Coun-try	Particip-ants	Sample size (T/C)	Age(y) (Mean+SD)	Study duration	Outcomes	Intervention	Control
Huang 2022	China	health	31/31	T:47.8±6.6 C:47.2±6.6	60 days	①④⑤⑥	NMN 300mg/d	PBO
Igarashi 2022 (A)	Japan	health	10/10	T:71.1±3.9 C:71.8±6.1	12 weeks	①②③④	NMN 250mg/d	PBO
Igarashi 2022 (B)	Japan	health	21/21	T:71.1±3.9 C:71.8±6.1	6 weeks	①②③④	NMN 250mg/d	PBO
Yi 2023 (A)	China	health	20/20	T:51.2±7.0 C:46.5±6.7	60 days	①④⑤⑥	NMN 300mg/d	PBO
Yi 2023 (B)	China	health	20/20	T:49.9±6.3 C:46.5±6.7	60 days	①④⑤⑥	NMN 900mg/d	PBO
Fukamizu 2022	Japan	health	16/15	T:35.1±7.0 C:35.7±7.2	4 weeks	⑤⑥	NMN 1250mg/d	PBO
Katayoshi 2023	Japan	health	17/17	T:48.1±5.4 C:47.9±5.5	12 weeks	⑤⑥	NMN 250mg/d	PBO
Akashaka 2022	Japan	diabetes	7/7	T:83.0±6.7 C:79.3±6.0	24 weeks	①②③	NMN 250mg/d	PBO
Kim 2022 (A)	Japan	health	27/27	T:72.2±5.1 C:72.5±4.6	12 weeks	①②③	NMN 250mg/d(AM)	PBO
Kim 2022 (B)	Japan	health	27/27	T:72.8±4.3 C:73.0±4.7	12 weeks	①②③	NMN 250mg/d(PM)	PBO
Yoshino 2021	USA	diabetes	13/12	T:62.0±4.0 C:61.0±5.0	10 weeks	⑤⑥	NMN 250mg/d	PBO
Liao 2021 (A)	China	health	12/12	T:37.0±5.7 C:36.1±6.0	6 weeks	②	NMN 300mg/d	PBO
Liao 2021 (B)	China	health	12/12	T:33.5±6..6 C:36.1±6.0	6 weeks	②	NMN 1200mg/d	PBO

Abbreviation: T: treatment group；C: control group；①gait speed ②grip strength ③5-STS ④HOMA-IR ⑤AST ⑥ALT.

Table 2. Quality assessment.

Study	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Sources of Bias	Blinding (Partic-ipants and Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome Data
Huang 2022	L	U	L	U	L	L	L
Igarashi 2022	L	U	H	U	L	L	H
Yi 2023	L	U	L	U	L	L	L
Fukamizu 2022	L	L	L	U	L	L	L
Katayoshi 2023	L	L	L	U	L	L	L
Akashaka 2022	L	L	L	U	L	L	L
Kim 2022	L	L	L	U	L	L	L
Yoshino 2021	L	U	H	U	U	U	L
Liao 2021	L	L	H	U	L	L	U

Abbreviation: L: Low risk H: High risk U: Unclear risk.

(Fig. **2**). Comparing the outcomes from the random effects model, we found that NMN did not cause a significant improvement in grip strength (WMD: -0.07 kg, 95%CI [-0.70, 0.57] p = 0.841) without significant heterogeneity on the studies (I^2 = 23.1%, p = 0.253). However, we found that NMN significantly improved grip strength in subjects older than 60 years (WMD: 1.35 kg, 95%CI [0.04, 2.66] p = 0.043 I^2 = 0%, p = 0.917) (Table **3**) in the subgroup analysis.

After analyzing data from three studies with 5 trials including 164 participants (intervention = 82 and control = 82), we observed a change in 5-STS, and there was no significant statistical difference between the groups (SMD: -0.23 s, 95%CI [-0.52, 0.06] p = 0.12 I^2 = 0%, p = 0.818) (Fig. **2** and Table **3**).

3.4.2. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR)

From 142 participants (intervention = 81 and control = 61) in three studies with 4 trials, a forest plot was reported to compare the influence of NMN and PBO on HOMA-IR

Table 3. Subgroup analyses of the effects of NMN intervention on muscle and liver function

	NO	SMD/WMN (95%)	*p*-value	*p* Hetero-Geneity	I^2
Subgroup analyses of NMN intake on gait speed					
Overall effect	8	0.34 (0.03, 0.66)	0.033	0.059	48.40%
Trial duration (week)					
≥10	4	0.08 (-0.32, 0.47)	0.701	0.273	23.00%
<10	4	0.54 (0.13, 0.94)	0.01	0.136	45.80%
Intervention dose					
Lower dose (≤300mg/d)	7	0.19 (-0.04, 0.43)	0.107	0.423	0%
High dose (≥900mg/d)	1	1.20 (0.52, 1.87)	0.001		
Age					
≥60	5	0.13 (-0.19, 0.45)	0.426	0.321	14.70%
<60	3	0.61 (0.05, 1.17)	0.033	0.073	61.90%
Subgroup analyses of NMN intake on grip strength					
Overall effect	7	-0.07 (-0.70, 0.57)	0.841	0.253	23.10%
Trial duration (week)					
≥10	4	1.33 (-0.25, 2.90)	0.1	0.814	0.00%
<10	3	-0.34 (-0.93, 0.24)	0.247	0.259	26.00%
Intervention dose					
Lower dose (≤300mg/d)	6	0.48 (-0.68, 1.64)	0.415	0.17	35.60%
High dose (≥900mg/d)	1	-0.30 (-0.98, 0.38)	0.385		
Age					
≥60	5	1.35 (0.04, 2.66)	0.043	0.917	0.00%
<60	2	-0.45 (-0.93, 0.02)	0.058	0.532	0.00%
Subgroup analyses of NMN intake on 5-STS					
Overall effect	5	-0.23 (-0.52, 0.06)	0.12	0.818	0%
Trial duration (week)					
≥10	4	-0.17 (-0.50, 0.16)	0.315	0.812	0%
<10	1	-0.44 (-1.06, 0.17)	0.157		
Intervention dose					
Lower dose (≤300mg/d)	5	-0.23 (-0.52, 0.06)	0.12	0.818	0%
High dose (≥900mg/d)	0				
Age					
≥60	5	-0.23 (-0.52, 0.06)	0.12	0.818	0%
<60	0				

(Table 3) Contd….

	NO	SMD/WMN (95%)	*p*-value	*p* Hetero-Geneity	I^2
Subgroup analyses of NMN intake on HOMA-IR					
Overall effect	4	-0.29 (-0.60, 0.02)	0.066	0.731	0%
Trial duration (week)					
≥10	1	-0.24 (-1.12, 0.64)	0.588		
<10	3	-0.30 (-0.63, 0.03)	0.079	0.528	0%
Intervention dose					
Lower dose (≤300mg/d)	3	-0.38 (-0.74, -0.02)	0.036	0.868	0%
High dose (≥900mg/d)	1	-0.02 (-0.64, 0.60)	0.96		
Age					
≥60	1	-0.24 (-1.12, 0.64)	0.588		
<60	3	-0.30 (-0.63, 0.03)	0.079	0.528	0
Subgroup analyses of NMN intake on AST					
Overall effect	6	-0.16 (-0.42, 0.10)	0.227	0.881	0%
Trial duration (week)					
≥10	2	-0.01 (-0.52, 0.50)	0.967	0.859	0%
<10	4	-0.21 (-0.51, 0.09)	0.169	0.73	0%
Intervention dose					
Lower dose (≤300mg/d)	4	-0.07 (-0.37, 0.24)	0.678	0.968	0%
High dose (≥900mg/d)	2	-0.38 (-0.85, 0.09)	0.117	0.562	0%
Age	6				
≥60	1	-0.06 (-0.85, 0.72)	0.871		
<60	5	-0.17 (-0.44, 0.10)	0.221	0.79	0%
Subgroup analyses of NMN intake on ALT					
Overall effect	6	-0.29 (-0.55, -0.03)	0.028	0.859	0%
Trial duration (week)					
≥10	2	-0.03 (-0.54, 0.48)	0.909	0.87	0%
<10	4	-0.38 (-0.68, -0.08)	0.013	0.908	0%
Intervention dose					
Lower dose (≤300mg/d)	4	-0.27 (-0.58, 0.04)	0.092	0.669	0%
High dose (≥900mg/d)	2	-0.34 (-0,81, 0.13)	0.152	0.581	0%
Age					
≥60	1	0.02 (-0.76, 0.80)	0.96		
<60	5	-0.33 (-0.60, -0.05)	0.019	0.869	0%

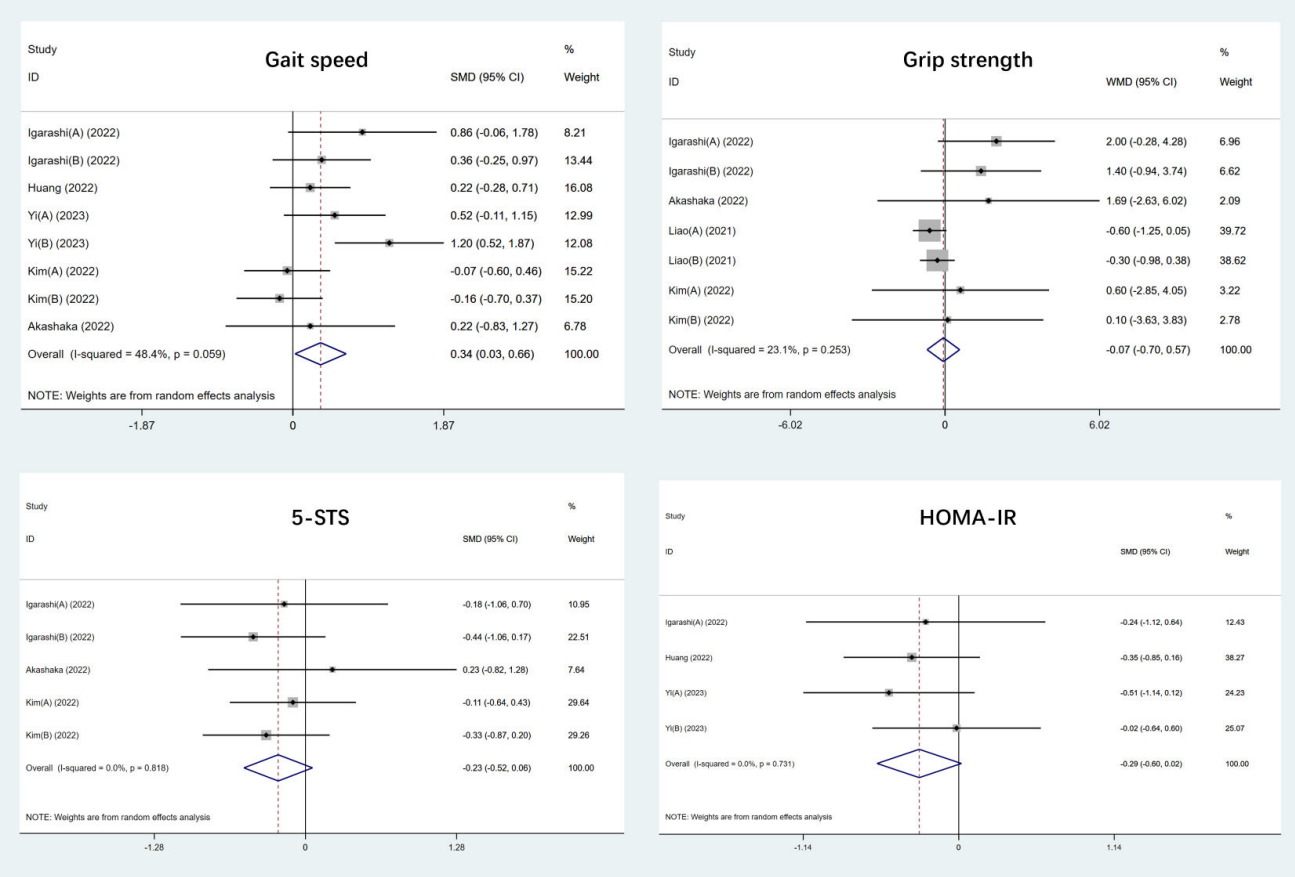

Fig. (2). Forest plot comparing the effects of NMN and PBO on muscle function and insulin resistance (the size of the box represents the weight of each study, and the lateral tips of the diamond shows the confidence interval of the pooled result)

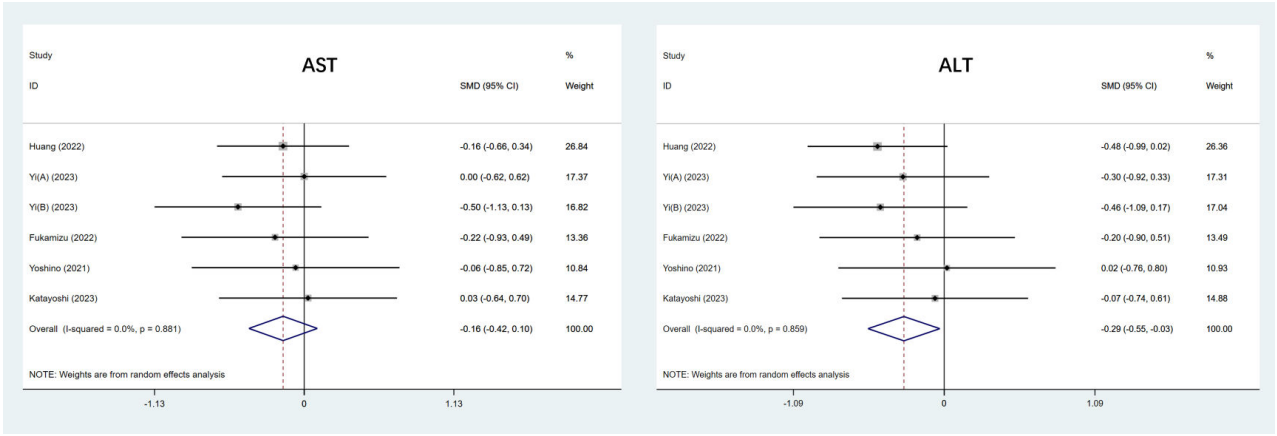

Fig. (3). Forest plot comparing the effects of NMN and PBO on hepatic enzyme (the size of the box represents the weight of each study, and the lateral tips of the diamond shows the confidence interval of the pooled result)

levels. Our results from the random effects model showed that the HOMA-IR after NMN administration did not change significantly (SMD: -0.29, 95%CI [-0.60, 0.02] p = 0.066) with no significant heterogeneity in the studies (I^2 = 0%, p = 0.731). After analysis of subgroups, we noticed that the intake of NMN significantly reduced the levels of HOMA-IR when the intervention dose was less than 300mg/day (SMD: -0.38, 95%CI [-0.74, -0.02] p = 0.036 I^2 = 0%, p = 0.868), indicating that the small doses of NMN were more effective for improving insulin resistance (Fig. **2** and Table **3**).

3.4.3. Liver Function

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were provided as a result after analyzing 5 studies with 6 trials with a total of 212 participants (intervention = 117, and control = 95) (Fig. **3**). The parameter of AST was not significantly improved after NMN intervention analyzing results from random effects models (SMD: -0.16 IU/L, 95%CI [-0.42, 0.10] p = 0.227), and there was no significant heterogeneity in the studies (I^2 = 0%, p = 0.881).

However, the data of ALT following NMN administration changed significantly, reporting results from the random effects model (SMD: -0.29 IU/L, 95%CI [-0.55, -0.03] p = 0.028), and significant heterogeneity was unable to be observed in the studies (I^2 = 0%, p = 0.8559).

After subgroup analysis was given, we noticed that supplementation with NMN significantly reduced the level of ALT while intervention duration was less than 10 weeks (SMD: -0.38 IU/L, 95%CI [-0.68, -0.08] p = 0.013 I^2 = 0%, p = 0.908). Significantly, a reduction in ALT was reported in healthy subjects under 60 years (SMD: -0.33 IU/L, 95%CI [-0.60, -0.05] p = 0.019 I^2 = 0%, p = 0.8869) (Table **3**).

3.5. Publication bias

Using the visual observations from the funnel plot and Egger's test data, we evaluated the publication bias of these studies and concluded that there was no clear evidence for publication bias in the meta-analysis of NMN administration in gait speed (p = 0.220); 5-STS (p = 0.339); HOMA-IR (p = 0.837) and AST (p = 0.8825). However, there was significant publication bias for grip strength (p = 0.035) ALT (p = 0.027) (Fig. **4**).

3.6. Sensitivity Analysis

We individually excluded each study to validate the reliability of our findings. We decided to do a sensitivity analysis of gait speed in middle-aged and elderly populations in order to further clarify the high heterogeneity of the findings. The final result indicated that 900mg/d of NMN contributed greatly to the evident heterogeneity in the study carried out by Yi (B) [23]. The statistical heterogeneity, as indicated by the I^2 value, significantly decreased to 0% within that subgroup after the study was excluded. Thus, it was rational to confirm the therapeutic effects of NMN in enhancing gait speed.

4. DISCUSSION

This systematic review and meta-analysis evaluated the effect of NMN in the treatment of people in the progress of aging. Our study included 9 trials [17, 23-30] with a total of 412 subjects with the intention to illustrate the clinical value of NMN. The results showed that supplementation with NMN led to a statistically significant improvement in muscle and liver functions and was an effective treatment strategy for middle-aged and elderly individuals compared to a placebo. Participants taking the NMN had enhanced gait speed and lowered ALT levels significantly. In middle-aged and elderly people, supplementing with NMN to increase the level of NAD^+ in the body can play a role in resisting aging and preventing age-related diseases [31].

4.1. Effects of NMN on Muscle Function and Insulin Resistance

The administration of NMN in rodent models counteracts age-related alterations in gene expression in peripheral tissues and boosts mitochondrial respiratory capacity in skeletal muscle [18, 32, 33]. The efficient increase of NAD^+ levels from Nmnat3 overexpression in mice has been associated with protection against age-associated insulin resistance [34]. In humans, only a few controlled studies or clinical trials have been included to examine the efficacy of NMN on muscle function [25, 28, 30] and insulin sensitivity [29, 35], which is far from sufficient to verify the effect of NMN intake in the middle-aged and elderly people.

On the one hand, further subgroup and sensitivity analyses indicated that the dose of NMN greatly influenced the result regardless of the short or long-term time of follow-up. Although the reduction in gait speed after NMN treatment was statistically significant, the dose played a crucial role. Since only one of the studies included had a dose greater than or equal to 900mg/day, this outcome was not further evaluated. However, larger doses of NMN may lead to more significant improvements in gait speed in middle-aged and elderly people. In subgroup analyses of gripping strength, the size of the NMN dose may not have a therapeutic effect on improving gripping strength. It is interesting to notice that the effect of NMN treatment is more pronounced in older people over the age of 60.

In addition, as reported by Igarashi *et al*.[25], the intervention duration of NMN is one of the factors that influence treatment outcomes, at least in terms of walking speed and grip strength. The performance on the 5-chair standing Test (5-CST) can indicate the strength of the lower limb muscles. According to Dodds *et al*.[36], the relationship between the 5-CST and gait speed may be positively correlated. As with gait speed, the effect of NMN on the 5-CST may also be reflected in the dose and duration of intervention. As is known to us all, enhancing muscle function is an enduring process, and the intervention duration and dosage of NMN play crucial roles in determining the final outcomes. It is reasonable to expect that indicators linked to muscle function will improve with a well-considered dosage regimen in future research endeavors. In conclusion, overall, NMN supplementation is beneficial for muscle function.

On the other hand, subgroup analyses reported that small doses of NMN can reduce insulin resistance in healthy middle-aged and elderly people. In flies, nematodes, and mice, regulating insulin-related signaling pathways has been shown to delay the progression of biological aging and extend lifespan [37, 38]. Clinical studies have confirmed the effectiveness of this strategy [24]. Yoshino *et al*. [29] reported in their study that NMN (250 mg/day) increases muscle insulin sensitivity in obese or pre-diabetic people. In the study of Yi *et al*. [23], the NMN doses of 300mg/day, 600mg/day, and 900mg/day showed decreasing effectiveness in reducing the variation in HOMA-IR. Therefore, lower doses of NMN may have a better effect on improving insulin resistance coming from aging [39].

Skeletal muscle aging is marked by loss of muscle mass and strength, decreased regenerative capacity, and impaired physical performance, which are often accompanied by muscle mitochondrial dysfunction and insulin resistance [40]. Based on the above studies, we aimed to determine the optimal anti-aging treatment strategy for NMN in middle-aged and elderly individuals, focusing on identifying the most effective dose and treatment duration. However, the current research evidence of NMN's effects on skeletal muscle is limited, indicating a need for more clinical trials.

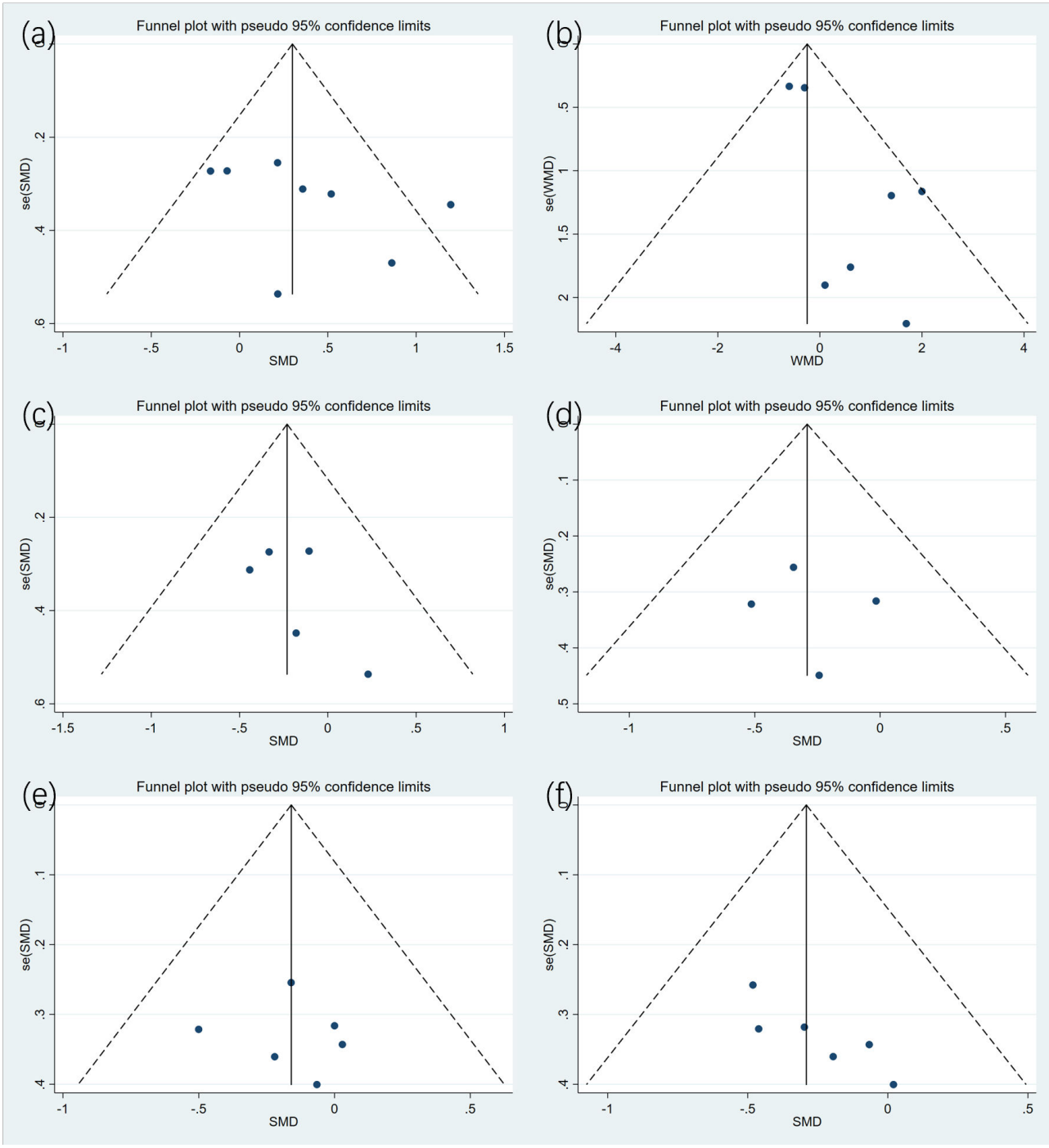

Fig. (4). Funnel plot for the effect of NMN on: (**a**) Gait speed; (**b**) Grip strength; (**c**) 5-STS; (**d**) HOMA-IR; (**e**) AST; and (**f**) ALT.

4.2. Effects of NMN on Hepatic Transaminase

The reduction in ALT was statistically significant, but changes in AST did not differ between groups after NMN intervention. These results showed that NMN could enhance hepatic repair and anti-damage capabilities by reducing the level of transaminase in middle-aged and elderly people, thus improving liver function.

In previous animal models, NMN reduced AST and ALT levels only in mice with liver injury or fibrosis, and aging mice could increase ALT and AST levels compared to young mice [41, 42]. Although NMN has so far not been reported to significantly reduce liver transaminase levels in aging mice, it can decline the level of AST and ALT in RCTs regardless of giving different doses of NMN. Based on the results of studies in humans and animals, it can be confirmed that NMN has a beneficial effect of NMN on liver damage and repair. Due to fewer studies included, we could not analyze the optimal dose of NMN from a dosing perspective. Hence, more RCTs and further basic research are needed.

According to Porter *et al*. [43], increased alanine aminotransferase levels are linked with a growing risk of hypertension, diabetes, metabolic syndrome, impaired fasting blood sugar, and insulin resistance. The age-associated changes in liver function contribute to the systemic susceptibility to these age-related diseases [44-46]. For example, the liver regulates systemic energy homeostasis through glucose and lipid metabolism and insulin signaling pathways [47]. Although liver aging does not manifest itself in the form of liver disease in healthy people, the risks and susceptibilities associated with an aging liver remain and can evolve into disease at any time under certain conditions. In this study, NMN improved liver function by reducing ALT levels and subsequently had a certain preventive and therapeutic effect on diseases caused by aging liver.

In conclusion, NMN, a drug with proven safety and without serious adverse drug reactions [48], could serve as a safe alternative treatment for alleviating aging in middle-aged and elderly individuals. Considering the scarcity of available data and the suboptimal quality of completed trials, it is necessary to conduct further well-designed, multi-center randomized controlled trials (RCTs) to specifically investigate the influence of NMN treatment.

4.3. Limitations

There are certain limitations in our study. The first one is the size of the dose of NMN among the trials for different durations of intervention. Therefore, the subgroup analysis was used for merging in this study. Second, the number of randomized controlled trials meeting the inclusion criteria was small, and the sample size was not large enough. Moreover, this study highlighted variable parameters (gait speed, grip strength, 5-STS, HOMA-IR, etc.), and could not fully evaluate the influence of NMN on aging, especially because data on cognitive memory levels were lacking.

CONCLUSION

In conclusion, NMN has positive efficacy in enhancing muscle function, reducing insulin resistance, and lowering hepatic aminotransferase levels in middle-aged and elderly individuals. Although the current meta-analysis showed a statistical benefit, we would like to pay attention to potential drawbacks associated with the quality, heterogeneity, and small sample size of the studies included. Therefore, further long-range clinical trials are required to evaluate the influence of NMN on muscle and liver functions in middle-aged and elderly populations.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study conception, design, and interpretation of the data. All the authors took responsibility for the integrity and accuracy of the data analysis and approved the manuscript for submission.

CONSENT FOR PUBLICATION

Not applicable.

AVAIALABILITY OF DATA

All the data and supportive information are provided within the article.

STANDARD OF REPORTING

PRISMA guidelines and methodology were followed.

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CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

PRISMA checklist is available as supplementary material on the publisher's website along with the published article.

Supplementary material is available on the publisher's website along with the published article.

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