ARTICLE

Clinical observation of the effect of nicotinamide mononucleotide on the improvement of insomnia in middle-aged and old adults

Baisong Zhao[1]*, Chengyi Liu[1], Long Qiang[1], Jinyang Liu[1], Zhehan Qiu[1], Zixin Zhang[1], Jian Zhang[2], Yiming Li[3], Mingjie Zhang[1]

[1]Hope Research Center for Life Sciences, Southern University of Science and Technology, Shenzhen 518000, China
[2]School of Medicine, Southern University of Science and Technology, Shenzhen 518000, China
[3]School of Innovation and Entrepreneurship, Southern University of Science and Technology, Shenzhen 518000, China

***Correspondence:**
Dr. Baisong Zhao, Hope Research Center for Life Sciences, Southern University of Science and Technology, Shenzhen 518000, China
Email: zhaobs@sustech.edu.cn

ABSTRACT

***β*-nicotinamide mononucleotide (NMN) has several beneficial effects. However, it remains unclear whether it has sleep-protective effects in middle-aged and old adults. Fifty-eight volunteers underwent a 12-week treatment period. They were randomly divided into NMN and control groups to observe and compare NMN's effect on insomnia in middle-aged and old adults. Its efficacy was evaluated using the Pittsburgh Sleep Quality Index (PSQI) and smart bands (Huawei Band 6) sleep data. Each group's PSQI total and item scores decreased before and after treatment. Significant differences were observed in the total PSQI score, sleep quality, sleep latency, and daytime dysfunction($P < 0.05$). The total effectiveness rate was significantly higher in the NMN group (65.52%) than in the control group (27.59%; $P < 0.05$). Sleep data recorded by their smart bands indicated better sleep quality in the NMN group. These findings show that NMN improves sleep quality in middle-aged and old adults. (Am J Transl Med 2022. 6(4):167-176).**

Keywords: *β*-nicotinamide mononucleotide; middle-aged and old adults; sleep quality; smart bands.

INTRODUCTION

Sleep quality is an important factor contributing to overall health (Mendonca et al., 2019) and is directly related to metabolism, immunity, glucose regulation,

cognition, and memory (Sharma et al., 2010). Decreasing nocturnal melatonin and total cortisol hormone secretion with increasing age can affect sleep. Cell numbers in the suprachiasmatic nucleus (SCN) are significantly lower in older than younger adults, making them less sensitive to external natural circadian rhythms (Garau et al., 2006; Leblanc et al., 2015). While the elderly has sufficient sleep time, it is difficult for them to feel satisfied with their sleep quantity and quality. Therefore, older adults are more likely to suffer from insomnia than young adults, with the prevalence increasing with age (Blay et al., 2008).

Nicotinamide adenine dinucleotide (NAD^+) is an important coenzyme in eukaryotic cells to maintain redox homeostasis. It is indispensable in various biological processes in the organism Ramjan (Okabe et al., 2019; Rajman et al., 2018). NAD^+ deficiency is closely associated with various pathophysiologies. Aging reduces NAD^+ levels in several organs, resulting in various age-related diseases (Camacho-Pereira et al., 2016), such as diabetes, obesity, heart failure, Alzheimer's disease, and insomnia correlated with circadian rhythm imbalance (Gomes et al., 2013; Mills et al., 2016; Mouchiroud et al., 2013; Poddar et al., 2019). β-nicotinamide mononucleotide (NMN) is a nucleotide best known for its role as an NAD^+ biosynthesis intermediate (Poddar et al., 2019). Supplementation of NAD^+ precursors is an effective approach to increase NAD^+ levels. (Yamamoto et al., 2014) investigated NAD^+ levels in a nicotinamide phosphoribosyltransferase (*Nampt*) gene knockout mouse model with cardiac ischemia-reperfusion, finding that they increased in cardiomyocytes after NMN administration. Kawamura et al. (2016) showed that NMN administration was more likely to increase NAD^+ levels in mice.

Intelligent wearable devices are increasingly used to detect important information, such as vital signs and movement, because of their convenience, intelligence, and real-time characteristics (Xu et al., 2022). They provide data supporting health status by monitoring the human body. As intelligent smart wearable devices such as FitBit and Apple Watch become more prevalent, intelligent wearable devices are gradually gaining popularity. Many different types of detectors, including skin sensors, electric sweat monitors, temperature and pressure sensors, and glucose detectors, are available to better detect body indicators (Bai et al., 2021). When exercising, smart wearable devices can help us more intuitively see information such as body heartbeat, breathing, and exercise distance to better control exercise amount and intensity.

Intelligent wearable devices can reflect some disease symptoms that the body cannot feel. Apple Watch's new electrocardiogram sensor can detect diseases such as arrhythmias, tachycardia, or bradycardia. In addition, its sleep detection function can also monitor the user's sleep quality (Saghir et al., 2020; Strik et al., 2020). Relevant literature shows that smart bands adopt photoelectric heart rate detection and three-axis acceleration motion monitoring methods. Photoelectric heart rate detection monitors the real-time heart rate in the blood vessels below the wrist through a red light emitted by the band. Three-axis acceleration motion monitoring monitors physical activity through a built-in three-axis accelerometer (Kolla et al., 2016). These technologies have matured in recent years. In general, wearable devices are increasingly enmeshed in people's lives, and more intelligent wearable devices are trending. The side effects of pharmacological treatment are still poorly received, especially by middle-aged and old adults who need more moderate and effective treatment options. Finding more reasonable, effective, and economical treatments is necessary. While NMN has shown many benefits in the human body, clinical trials on NMN's effects on sleep in the elderly remain to be performed. This study uses the Pittsburgh Sleep Quality Index (PSQI) scale with a wearable device (Huawei Band 6) to monitor NMN's effects on sleep in middle-aged and old adults.

MATERIALS AND METHODS

Ethical Approval and Participants

This research was approved by the Medical Ethics

Committee of the Southern University of Science and Technology (ethics approval no: 2021CXC115). Its subjects were recruited between September 2021 and March 2022 at the Department of Respiratory Medicine (Shenzhen University General Hospital) and Hope Research Center for Life Sciences (Southern University of Science and Technology). This clinical trial used a single-blind design. Subjects were not notified beforehand of their respective numbers, group status, or treatment regimen. Except for the necessary communication for data collection and NMN distribution, the researcher was not allowed to disclose any information about the experiment that might influence the volunteers to reduce the subjective bias in the results.

The inclusion criteria were: (1) aged 45–75 years with no other acute illness or major disease; (2) not taking relevant sedative or other sleep-aiding drugs within two weeks before treatment; (3) a PSQI score ≥5; (4) prolonged sleep time in the last three months; (5) ≥3 nights per week with a total sleep time of <6.5 h for the last three months; (6) decreased sleep quality, insufficient sleep depth, or excessive dreaming ≥3 times per week for the last three months; (7) ≥1 late sleep awakening per week for the last three months.

The exclusion criteria were: (1) not meeting the inclusion criteria; (2) significant primary conditions such as cardiovascular, respiratory, cardiac, hepatic, and renal disease; (3) poor cooperation and repeated unsuccessful communications; (4) poor compliance during the clinical trial; (5) failure to strictly follow the regulations.

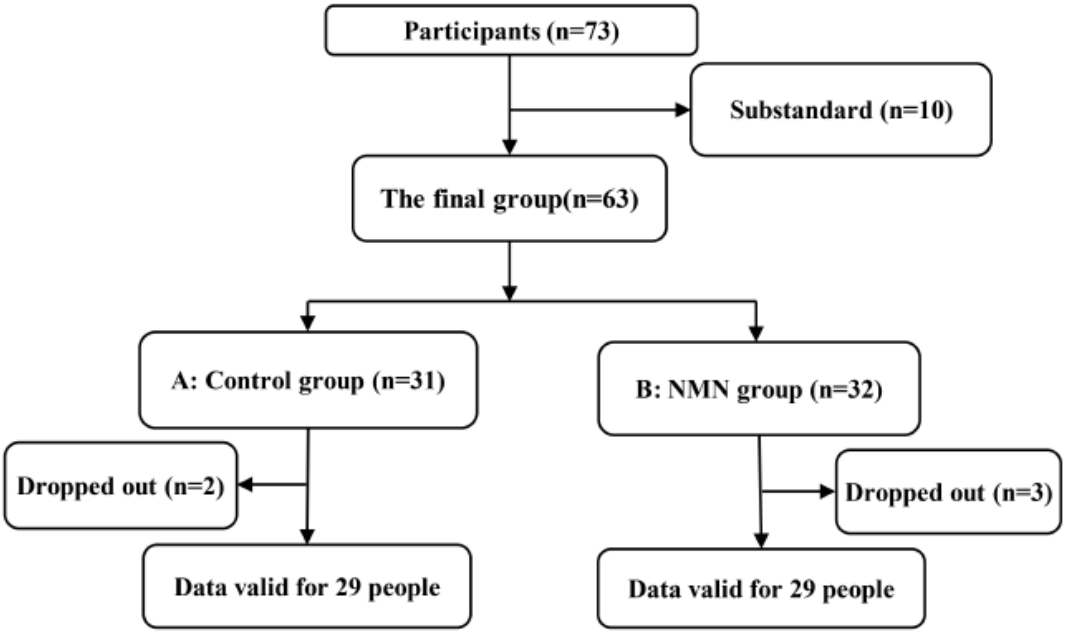

Figure 1. Flow chart of the experiment.

This trial included 63 registered subjects. Their enrollment status is shown in **Figure 1.** All subjects signed the informed consent form. The subjects were randomly divided into two groups using a random numbering method. Thirty-two subjects were enrolled in the NMN group, of which three withdrew due to personal reasons. Thirty-one subjects were enrolled in the control group, of which two withdrew due to personal reasons. Therefore, 58 subjects completed this trial: 29 in the NMN group and 29 in the control group. Their general information is shown in **Table 1.**

Effectiveness Analysis

The effectiveness analysis used the PSQI scale scores and the rate of change data from the smart bands.

Table 1. General characteristics of subjects in each group.

Group	Number of subjects	Sex[1]		Age (years)[2]
		Male	Female	
Control	29	13	16	57.21 ± 8.20
NMN	29	11	18	52.79 ± 7.36

Note: [1]Comparison of male and female numbers in each group using a Chi-square test ($\chi^2 = 0.28$, $P = 0.59$); [2]Comparison of subject ages in each group using an independent samples t-test ($t = 2.16$, $P = 0.35$).

Efficiency was calculated using Equation 1 below and categorized as follows: recovery, 75%–100%; effective, 50%–75%; less effective, 25%–50%; ineffective, <25%.

Efficiency = ([pre-use value − post-use value] / pre-use value) × 100 (1)

Data Collection

The trial was conducted for 12 weeks and involved three sessions and two PSQI questionnaires. The sleep data generated by the smart bands were uploaded at the end of each week. The weekly sleep data included the week before the trial (week 0) and continued until the end of the trial's last week (week 12), providing thirteen time points.

Table 2. PSQI total and item scores in each group before and after treatment

Projects	Control group		NMN group	
	Before treatment	After treatment	Before treatment	After treatment
Total PSQI score	8.62 ± 2.31	7.34 ± 2.28*	8.32 ± 2.46	5.72 ± 2.80*▲
Sleep quality	1.76 ± 0.57	1.28 ± 0.69*	1.72 ± 0.64	1.17 ± 0.46*
Sleep latency	1.86 ± 0.78	1.48 ± 0.90*	1.72 ± 0.64	0.93 ± 0.83*▲
Sleep duration	1.24 ± 0.43	1.24 ± 0.57	1.28 ± 0.58	0.97 ± 0.67
Sleep efficiency	0.86 ± 0.78	1.17 ± 0.95	0.86 ± 1.04	0.69 ± 0.95
Sleep disturbances	1.21 ± 0.48	0.97 ± 0.18*	1.07 ± 0.52	0.97 ± 0.49
Daytime dysfunction	1.69 ± 0.75	1.21 ± 0.61*	1.66 ± 0.84	1.00 ± 0.79*

Key: *, $P < 0.05$ in a paired sample t-test comparing values before and after treatment; ▲, $P < 0.05$ in an independent sample t-test comparing values between groups.

Intervention Methods

The NMN group took two 300 mg NMN capsules (180 mg NMN and 120 mg additives) at lunchtime daily. The control group took two 300 mg placebo capsules (the main ingredient was edible starch) at lunchtime daily. NMN was purchased from Hong Kong Genesleader (Hong Kong) Limited. The Huawei Band 6 smart bands were purchased from the Huawei Mall (http://www.vmall.com).

Each subject was issued one smart band (Huawei Band 6), worn on the wrist before nighttime sleep. They had to install the Huawei Sports Health App on their phone. The band was connected to the phone using Bluetooth. After monitoring their nightly sleep, the band generated daily bedtime, night waking frequency, deep sleep ratio, light sleep ratio, rapid eye movement (REM)

sleep ratio, total sleep duration, and night waking time-frequency data and their weekly averages.

All subjects were given sleep health education and related data uploading operation methods and requirements one week before the trial began. They were prohibited from drinking alcohol, strong tea, and other sleep-disrupting beverages during the trial. They were asked to avoid overly spicy or fatty foods in their diet. They were required to submit their smart band data on time.

Statistical Methods

All *t*-tests and Friedman tests were performed with the SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Data are presented as their mean ± standard deviation. A paired sample *t*-test was used to assess intra-group differences. An independent samples *t*-test was used to assess inter-group differences. Chi-square tests were used in the effectiveness analysis. All results with $P < 0.05$ were considered statistically significant.

RESULTS

PSQI and Smart Band Data Analysis

PSQI scores before and after treatment are shown in **Table 2**. Total PSQI scores and sleep latencies differed significantly between the NMN and control groups after ($P < 0.05$) but not before ($P > 0.05$) treatment. Pre- and post-treatment total PSQI scores, sleep qualities, sleep latencies, sleep disorders, and daytime dysfunction differed significantly in the control group ($P < 0.05$). Pre- and post-treatment total PSQI scores, sleep qualities, sleep latencies, and daytime dysfunction differed significantly in the NMN group ($P < 0.05$).

Thirteen weeks of weekly sleep data were generated (**Figure 2**). During the 12 weeks of treatment, the sleep time and REM sleep ratio changed after the third week. The deep sleep and light sleep ratios changed significantly after the sixth week. The waking frequency and the light sleep ratio decreased. In contrast, the REM sleep and deep sleep ratios increased.

Effectiveness Analysis

We analyzed NMN's effectiveness using the PSQI (**Table 3**). Total PSQI scores differed significantly between the NMN and control groups ($P < 0.05$). The NMN group's effectiveness was 65.52%, significantly higher than that of the control group (27.59%; $P < 0.05$). No other items differed significantly.

Table 3. Effectiveness analysis of PSQI total and item scores

Item	Group	Recovery	Effective	Less effective	Ineffective	Efficiency	*P*
Total PSQI score	Control	0	1	7	21	27.59%	0.03*
	NMN	1	3	15	10	65.52%	
Sleep quality	Control	3	12	2	12	58.62%	0.22
	NMN	1	18	0	10	65.52%	
Sleep latency	Control	4	7	4	14	51.72%	0.20
	NMN	9	9	1	10	65.52%	
Sleep duration	Control	2	1	0	26	10.34%	0.24
	NMN	5	3	0	21	27.59%	
Sleep efficiency	Control	3	3	0	23	20.69%	0.38
	NMN	6	1	1	21	27.59%	
Sleep disturbances	Control	1	5	0	23	20.69%	0.25
	NMN	2	1	1	25	13.79%	
Daytime dysfunction	Control	2	10	4	12	55.17%	0.41
	NMN	6	8	4	11	62.07%	

Key: *, $P < 0.05$ in a Chi-square test comparing effectiveness between groups.

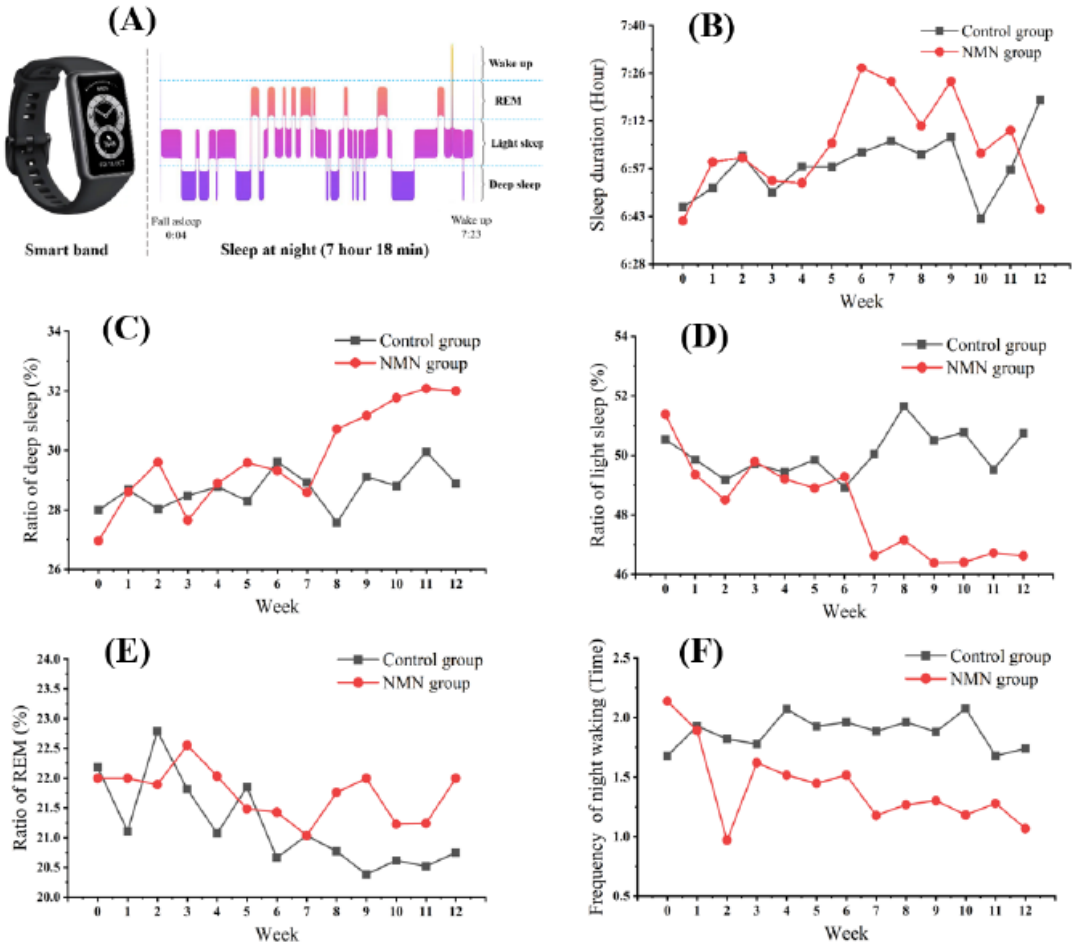

Figure 2. Smart band sleep data analysis. **(A)** A Smart Band 6 and an example of sleep data collection in the App. Changes in **(B)** sleep duration, **(C)** deep sleep ratio, **(D)** light sleep ratio, **(E)** REM sleep ratio, and **(F)** night waking frequency between weeks 0 and 12.

DISCUSSIONS

Sleep and wakefulness are humans' most common and indispensable physiological cycles, accounting for about one-third of their lives (Meyer et al., 2022). Sleep is a normal physiological activity crucial for the human body to remain healthy. The sleep process of an average human can be divided into awake, REM, and non-REM (NREM) based on different biological signals. NREM sleep can also be divided into four states (N1–N4). The time spent in REM, N3, and N4 states gradually decreases from childhood to old age with humans' growth, development, and aging. After the age of 60, the N4 state disappears, and the waking frequency at night increases significantly (Rechtschaffen et al., 1968). During this experiment, we found that after taking NMN, the sleep duration, deep sleep ratio, and REM sleep ratios increased, and the light sleep ratio and waking frequency decreased significantly (**Figure 2**). These are all benign responses and indicate that the sleep quality of elderly individuals improved after taking NMN. Some interesting phenomena were found in the intra-group analysis (**Table 2**). Post-treatment scores were significantly lower than pre-treatment scores for five indicators in the control group: total PSQI score, sleep quality, sleep latency, sleep disturbance, and daytime dysfunction. The NMN announcement to all volunteers

may have positively affected the control group due to the psychological suggestion factor. (Steptoe et al., 2008) found that positive and eudaimonic well-being are directly associated with good sleep.

Recent animal clinical trials have shown that using NMN-based supplements can compensate for the decrease in body function brought about by NAD^+ deficiency and that NMN-based supplements can exert their flexible pharmacological activity in different diseases (Shen et al., 2022). Previous clinical trials on NMN have focused on various yeast, drosophila, and mouse models. Recently published clinical results show that NMN is a safe and metabolically-enhancing human supplement. (Yoshino et al., 2021) published the world's first clinical trial on NMN administration. Their results showed that serine 473 and threonine 308 phosphorylation levels were significantly increased in subjects taking NMN, suggesting that NMN significantly enhanced the skeletal muscle's regenerative and restorative capacity. (Igarashi et al., 2022) completed a second human clinical trial on NMN, finding that subjects taking NMN showed significant improvements in muscle strength, exercise capacity, and even hearing. (Liao et al., 2021) also completed a human clinical trial on NMN, showing that their subjects' muscles' ability to use oxygen was substantially enhanced after six weeks of NMN administration.

Weakened circadian regulation with age is associated with decreased SCN neuronal cells (Mattis et al., 2016) and with the sirtuin (SIRT) pathway. SIRT1 is the most studied mammalian silent regulatory protein member, which deacetylates the central clock component in the liver to negatively regulate circadian rhythms (Asher et al., 2008; Nakahata et al., 2008). Cellular NAD^+ levels are biologically dependent on the silent information regulatory protein family (SIRT1–7) (Rajman et al., 2018). SIRT1 function is lost with age, leading to attenuation of the clock component and deterioration of circadian rhythm regulation. The activities of SIRTs are directly dependent on NAD^+ activity and increase with increasing intracellular NAD^+ levels. Since NAD^+ levels decrease with age, NAMPT and SIRTs activities also decrease (Carlos et al., 2013). Increased NAD^+ depletion pathway expression, decreased biosynthesis rates, decreased SCN neuroblasts, and sleep misperceptions with increasing age all contribute to decreased regulation of circadian rhythms and altered phasing, leading to sleep deterioration (Albrecht, 2012). Therefore, NMN administration can regulate circadian rhythm to a certain extent and improve sleep.

Among objective sleep data evaluation methods, polysomnography (PSG) has become the gold standard for diagnosing many sleep disorders (Chi et al., 2020). The continuous development of medical technology and increasing understanding of sleep has led to various sleep monitoring devices being developed in recent years, such as human motion recorders, sports bands/watches, and smartphone applications. While PSG has become the most authoritative method in the industry, it has inevitable limitations. PSG must be performed in a designated outpatient department, and PSG instruments are costly and complicated to operate. It should also be noted that the subjects' discomfort in an unfamiliar environment and after installing electrodes for the first time interferes with sleep monitoring authenticity (Browman et al., 1980). In recent years, wearable electronic devices have impacted the medical health monitoring field, and the application of smart bands has become topical (An et al., 2017). Ma et al. used ePM/eP pod wearable devices to record sleep time. Their results showed no statistically significant differences in sleep time recorded by the Fitbit band and a wearable monitoring device. The sleep times recorded by the two methods were positively correlated in the healthy and postoperative groups. (Xie et al., 2018) compared Apple's Watch 2, Samsung's Gear S3, Jawbone's Up3, Fitbit's Surg, Huawei's Band B3, and Xiaomi's Band 2. Their results showed that the average percentage error of wearable devices in measuring heart rate, walking steps, exercise distance, and sleep time was about 0.10%. Smart bands, as new wearable devices in the health detection field, have, after years of rapid research and development, good potential for sleep monitoring.

CONFLICT OF INTERESTS

The authors report no conflicts of interest.

INFORMED CONSENT STATEMENT

Written informed consent was obtained from all subjects in this study.

AUTHORS' CONTRIBUTIONS

Study conduct: Baisong Zhao, Jian Zhang, Yiming Li, and Mingjie Zhang. Data collection and analysis: Long Qiang and Chengyi Liu. Data interpretation: Baisong Zhao and Chengyi Liu. Manuscript drafting: Baisong Zhao, Chengyi Liu, Long Qiang, Jinyang Liu, Zhehan Qiu, and Zixin Zhang. Manuscript revision: Baisong Zhao and Chengyi Liu. Final manuscript approval: Baisong Zhao and Cheng-Yi Liu.

DATA AVAILABILITY STATEMENT

All data supporting this study's findings are available from the corresponding author upon reasonable request.

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