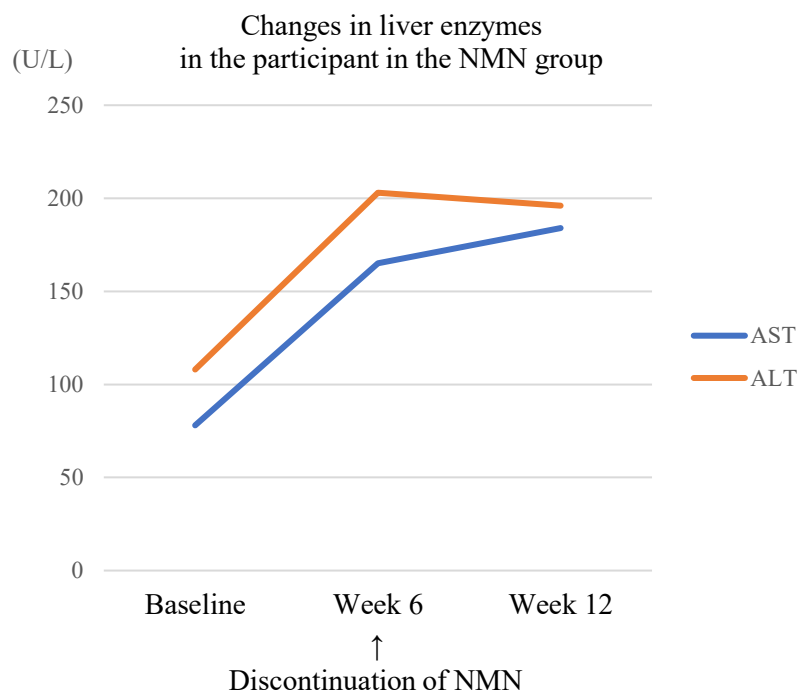




Supplementary Figure1. Changes in liver enzymes in the participant in the NMN group
This participant had mild liver enzyme elevation at baseline, with a further increase at week 6, leading to discontinuation of NMN as a precaution. Follow-up showed only slight improvement, suggesting that NMN-related liver injury was unlikely and that the findings were consistent with asymptomatic ALT/AST elevation associated with chronic liver disease.

	Baseline			Week 24			Change from Baseline to Week 24		
	NMN	Placebo	p-value	NMN	Placebo	p-value	NMN	Placebo	p-value
	median (n=31)	median (n=29)		median (n=30)	median (n=28)		median (n=30)	median (n=28)	
TP (g/dL)									
All (n=30/28)	7.1	7	0.48	7.0	7.1	0.623	-0.2	0.0	0.042*
Male (n=30/28)	7.1	7.1	0.66	7.0	7.2	0.606	-0.2	0.0	0.064
Female	7.1	6.8	0.62	7.0	7.0	0.73	-0.1	0.0	0.513
Age$\leq$70	7.3	6.9	0.141	7.0	7.2	0.87	-0.2	0.2	0.02*
Age$\geq$71	7	7	0.455	7.0	7.1	0.356	-0.1	-0.1	0.869
Albumin (g/dL)									
All	4.2	4.1	0.0245	4.1	4.1	0.45	-0.1	-0.1	0.504
Male	4.2	4.1	0.0244*	4.1	4.1	0.329	-0.1	0.0	0.351 ^a
Female	4.2	4.2	0.661	4.1	4.2	0.816	0.0	-0.1	0.788
Age$\leq$70	4.3	4.1	0.0207*	4.3	4.1	0.639	-0.1	0.1	0.182 ^a
Age$\geq$71	4.2	4.2	0.467	4.1	4.1	0.7	0.0	-0.1	0.711
AST (U/L)									
All	21	20	0.197	21	20	0.267	-1.0	-0.5	0.558
Male	21	19	0.101	22	20	0.249	-1.0	0.0	0.4
Female	22	22	0.944	21	19	0.731	-1.0	-1.0	0.969
Age$\leq$70	22.5	20	0.439	22	21	1	-3.0	-0.5	0.325
Age$\geq$71	21	19	0.269	21	19	0.111	-1.0	-0.5	0.986
ALT (U/L)									
All	18	16	0.11	17.5	15.5	0.426	-2.5	-0.5	0.275
Male	20	14.5	0.309	18	15	0.453	-1.0	-1.0	0.354
Female	18	17	0.304	16	16	0.909	-4.0	1.0	0.731
Age$\leq$70	26.5	16	0.341	16	18	0.848	-4.0	1.0	0.114
Age$\geq$71	18	16	0.133	18	14.5	0.2	-2.0	-1.0	0.914
γ-GTP (U/L)									
All	18	16	0.11	22.5	18.5	0.213	-1.0	-0.5	0.537
Male	20	14.5	0.309	26	19	0.123	-1.0	0.0	0.489
Female	18	17	0.304	15	16	0.819	0.0	-1.0	1
Age$\leq$70	26.5	16	0.341	23	18.5	0.149	-2.0	-0.5	0.413
Age$\geq$71	18	16	0.133	19	19	0.588	0.0	-0.5	0.899

Supplementary Table 1. Effect of NMN on clinical laboratory data (blood chemistry).

The results are median. Intergroup comparisons were performed using the Mann–Whitney U test.

^aInter-group comparisons were performed using ANCOVA to adjust baseline values.

Participants were stratified by sex and age (≤ 70 or ≥ 71 years). In the NMN group, 21 men and 10 women, with 14 participants were ≤ 70 years and 17 were ≥ 71 years. In the placebo group, 18 men and 11 women, with 12 participants were ≤ 70 years and 17 were ≥ 71 years.

*: $p < 0.05$, **: $p < 0.01$

NMN, nicotinamide mononucleotide; ANCOVA, analysis of covariance

	Baseline			Week 24			Change from Baseline to Week 24		
	NMN	Placebo	p-value	NMN	Placebo	p-value	NMN	Placebo	p-value
	median (n=31)	median (n=29)		median (n=30)	median (n=28)		median (n=30)	median (n=28)	
BUN (mg/dL)									
All	14.7	13.8	0.959	14.9	15.9	0.231	0.1	0.8	0.146
Male	13.1	14.2	0.352	14	15.9	0.091	0.2	1.5	0.109
Female	18.5	13.7	0.181	15.4	16.3	0.79	-0.6	-0.1	0.305
Age≤70	12	12.4	0.341	11.7	15.6	0.068	0.1	1.3	0.301
Age≥71	15.1	15.1	0.438	15.3	17.1	0.971	0.1	0.	0.28
Creatinine (mg/dL)									
All	0.8	0.78	0.569	0.82	0.77	0.919	-0.03	0.01	0.08
Male	0.89	0.91	0.746	0.86	0.94	0.378	-0.03	0.01	0.078
Female	0.65	0.6	0.378	0.59	0.58	0.909	-0.02	-0.02	0.731
Age≤70	0.82	0.81	0.237	0.86	0.79	0.605	-0.06	0.02	0.209
Age≥71	0.78	0.76	0.945	0.76	0.73	0.843	-0.02	0.00	0.205
Uric acid (mg/dL)									
All	5.8	5.6	0.225	5.6	5.7	0.913	-0.1	0.3	0.058
Male	6.2	5.8	0.455	6.0	6.8	0.49	-0.1	0.3	0.150
Female	5	4.7	0.289	4.9	5.4	0.675	0.0	0.3	0.209
Age≤70	6.2	5.8	0.471	5.7	5.7	0.957	-0.5	0.3	0.121
Age≥71	5.5	5.4	0.458	5.5	5.6	0.957	0.0	0.3	0.304
Na (mEq/L)									
All	140	140	0.304	141	141	0.949	1.0	1.0	0.644
Male	140	140	0.243	141	141	1	0.0	1.0	0.311
Female	140	140	0.943	141	141	0.752	1.0	1.0	0.212
Age≤70	140	139	0.037*	141	141	0.889	1.0	1.0	0.975 ^a
Age≥71	141	141	0.972	141	141	0.867	1.0	1.0	0.94
K (mEq/L)									
All	4.2	4.2	0.408	4.1	4.30.000403***		-0.1	0.2	0.007**
Male	4.3	4.3	0.348	4.1	4.4	0.00606**	-0.1	0.1	0.081
Female	4	4	0.769	4.1	4.3	0.0396*	0.0	0.2	0.051
Age≤70	4.3	4.3	0.604	4	4.5	0.0169*	-0.1	0.2	0.038*
Age≥71	4.1	4.2	0.42	4.1	4.3	0.01**	0.0	0.2	0.11

Supplementary Table 1. Effect of NMN on clinical laboratory data (blood chemistry).

The results are median. Intergroup comparisons were performed using the Mann–Whitney U test.

^aInter-group comparisons were performed using ANCOVA to adjust baseline values.

Participants were stratified by sex and age (≤70 or ≥71 years). In the NMN group, 21 men and 10 women, with 14 participants were ≤70 years and 17 were ≥71 years. In the placebo group, 18 men and 11 women, with 12 participants were ≤70 years and 17 were ≥71 years.

*: p<0.05 , **: p<0.01

NMN, nicotinamide mononucleotide; ANCOVA, analysis of covariance

	Baseline			Week 24			Change from Baseline to Week 24		
	NMN median	Placebo median	p-value	NMN median	Placebo median	p-value	NMN median	Placebo median	p-value
	(n=31)	(n=29)		(n=30)	(n=28)		(n=30)	(n=28)	
WBC ($\times 10^3$counts/μL)									
All	5.5	5.7	0.819	5.2	5.1	0.767	-0.4	-0.6	0.907
Male	5.7	5.6	0.714	5.3	4.7	0.402	-0.5	-0.8	0.597
Female	5.4	6.3	0.944	5.1	5.4	0.518	-0.2	0.0	0.402
Age ≤ 70	5.8	5.1	0.157	5.3	4.4	0.252	-0.5	-0.3	0.586
Age ≥ 71	5.3	6.3	0.326	5.1	5.2	0.505	-0.3	-0.6	0.759
RBC ($\times 10^3$counts/μL)									
All	458	434	0.07	450	433	0.441	-12.0	2.0	0.085
Male	464	454	0.526	458	471	0.692	-12.0	7.0	0.212
Female	442.5	420	0.02*	431	427	0.37	-12.0	-4.0	0.648 ^a
Age ≤ 70	473.5	434.5	0.009**	465	430	0.077	-19.0	2.0	0.562 ^a
Age ≥ 71	442	434	0.756	437	437.5	0.705	-2.0	1.5	0.505
Hemoglobin (g/dL)									
All	14.1	13.6	0.058	13.9	13.4	0.225	-0.4	-0.3	0.264
Male	14.4	14	0.108	14.3	14	0.557	-0.4	-0.3	0.517
Female	13.3	12.5	0.29	12.9	13	0.97	-0.4	-0.3	0.399
Age ≤ 70	14.6	13.6	0.011*	14.2	13.5	0.086	-0.5	-0.4	0.933 ^a
Age ≥ 71	13.8	13.6	0.692	13.3	13.3	0.986	-0.2	-0.3	0.456
Hematocrit (%)									
All	42.3	41.2	0.108	41.7	41.1	0.396	-1.1	-0.1	0.161
Male	43.1	42.6	0.226	42.5	41.9	0.814	-1.4	-0.2	0.297
Female	40.2	39.5	0.359	39.1	39.8	0.97	-0.5	0.0	0.518
Age ≤ 70	43.8	41	0.01*	42.1	40.7	0.097	-1.7	-0.3	0.849 ^a
Age ≥ 71	41.3	41.4	0.918	40.8	41.3	0.986	-0.4	0.0	0.589
Platelet ($\times 10^3$counts/μL)									
All	25.2	26.2	0.451	24.8	27.2	0.074	-1.3	0.1	0.02*
Male	24.9	25.8	0.545	23.8	36.6	0.163	-0.9	0.4	0.069
Female	27	27.4	0.605	25.7	27.4	0.27	-2.9	-0.2	0.068
Age ≤ 70	26.6	25.7	0.625	25.6	27.2	0.532	-1.5	0.5	0.068
Age ≥ 71	23.3	27.4	0.143	21.3	26.9	0.035	-1.0	-0.6	0.144

Supplementary Table 2. Effect of high-dose NMN on clinical laboratory data (hematology).

Results are presented as medians. Intergroup comparisons were performed using the Mann–Whitney U test.

^aInter-group comparisons were performed using ANCOVA to adjust baseline values.

Participants were stratified by sex and age (≤ 70 or ≥ 71 years). In the NMN group, 21 men and 10 women, with 14 participants were ≤ 70 years and 17 were ≥ 71 years. In the placebo group, 18 men and 11 women, with 12 participants were ≤ 70 years and 17 were ≥ 71 years.

*: $p < 0.05$

NMN, nicotinamide mononucleotide; ANCOVA, analysis of covariance

	Baseline			Week 24			Change from Baseline to Week 24		
	NMN median (n=31)	Placebo median (n=29)	p-value	NMN median (n=30)	Placebo median (n=28)	p-value	NMN median (n=30)	Placebo median (n=28)	p-value
NAD (μM)									
All	14.07673	12.01565	0.0363*	51.172537	9.367093	1.87E-14***	38.628526	-3.142367	2.12E-13a***
Male	13.48428	12.35242	0.394	50.45664	10.25827	4.86E-10***	38.57237	-2.8222	2.78E-10***
Female	17.57812	11.86613	0.0357*	59.490898	8.794689	0.0000476***	42.20052	-3.4205	0.0000851a***
Age≤70	12.73694	11.58724	0.347	50.456643	9.970839	0.000000385***	38.68468	-3.3195	4.46E-08a***
Age≥71	14.8565	12.14605	0.0261*	53.466437	9.137956	3.86E-08***	38.57237	-2.96953	3.96E-06a***
NMN (μM)									
All	0.09813715	0.08601876	0.21	0.12121033	0.07707693	0.00000303***	0.024958	-0.00773	2.89E-09***
Male	0.09813715	0.08552753	0.364	0.1243105	0.07723563	0.0000188***	0.031121	-0.00635	2.43E-08***
Female	0.09790059	0.09424017	0.387	0.1199177	0.0676927	0.0381*	0.015341	-0.01589	0.00744**
Age≤70	0.1037077	0.08989172	0.347	0.13811104	0.07791235	0.000587***	0.042317	-0.00737	0.000000769a***
Age≥71	0.08970142	0.08140015	0.339	0.11405833	0.07246416	0.00216**	0.017638	-0.01126	0.000248***
NAM (μM)									
All	13.62803	15.23464	0.0437*	25.24926	20.22737	0.000672***	11.89161	4.642239	1.19E-07a***
Male	13.97185	17.11573	0.0239*	26.54766	21.42519	0.000925***	12.61056	4.801039	1.11E-05a***
Female	13.27067	13.25516	0.809	21.55375	18.86006	0.23	8.329969	4.239801	0.00566**
Age≤70	14.03179	16.24991	0.16	28.0511	20.22737	0.000194***	12.28402	4.893138	0.00000154a***
Age≥71	10.92769	14.23663	0.182	23.37706	20.24667	0.146	10.77969	4.494287	0.00000967***
NA (μM)									
All	0.08695209	0.09217586	0.628	0.1058007	0.1173605	0.763	0.030788	0.031451	0.705
Male	0.09384701	0.09434318	0.791	0.1230495	0.1233647	0.416	0.031922	0.030975	0.383
Female	0.07712759	0.08966142	0.756	0.08773841	0.10694831	0.412	0.000946	0.033263	0.295
Age≤70	0.09944692	0.09662883	0.94	0.1485184	0.1188805	0.0398*	0.048391	0.011856	0.0298*
Age≥71	0.07726023	0.09069237	0.375	0.08789786	0.11736048	0.0805	0.000946	0.040357	0.102
NR (μM)									
All	0.00832977	0.00941674	0.436	0.01648165	0.01329453	0.482	0.004645	0.005413	0.552
Male	0.00832977	0.00936175	0.922	0.01684399	0.01887686	0.931	0.005864	0.007076	0.816
Female	0.00784229	0.00991178	0.197	0.01340333	0.00880482	0.261	0.001203	0.00078	0.23
Age≤70	0.00851314	0.00885608	0.705	0.01684399	0.0179641	0.689	0.003427	0.006983	0.47
Age≥71	0.00723012	0.00941674	0.193	0.01487277	0.01088665	0.118	0.005864	0.001453	0.146
NAR (μM)									
All	0.01860792	0.01709817	0.988	0.0605652	0.01932215	1.34E-14***	0.0436	-0.00082	6.88E-17***
Male	0.01775284	0.01695261	0.813	0.05775659	0.01712663	8.34E-10***	0.042944	-0.00073	6.95E-11***
Female	0.01977985	0.02208039	0.605	0.06337381	0.02138796	0.0000119***	0.044255	-0.00095	0.0000119***
Age≤70	0.01765378	0.01707687	1	0.05151331	0.01764374	0.00000154***	0.003382	-0.00113	0.000000385***
Age≥71	0.02044125	0.02168778	0.973	0.06337381	0.02145849	6.86E-09***	0.044255	-0.0008	1.71E-09***
NAMN (μM)									
All	0.03674273	0.03772364	0.918	4.36127862	0.04139846	2.75E-16***	4.29553	0.005511	1.38E-16***
Male	0.05400095	0.0343274	0.0115*	4.71287643	0.03145584	1.39E-10***	4.651611	0.000745	0.00000439a***
Female	0.02303537	0.06499389	0.00365**	3.8010804	0.0499879	0.0000119***	3.739733	0.00692	0.0000685a***
Age≤70	0.04375514	0.0374558	0.56	3.51349136	0.04180706	0.000000385***	3.483629	0.003668	0.000000385***
Age≥71	0.03674273	0.04478427	0.518	4.71287643	0.04139846	3.43E-09***	4.651611	0.005511	1.71E-09***
NAAD (μM)									
All	0.01645491	0.01563676	0.597	0.22475053	0.01407285	4.82E-16***	0.204126	0.000558	4.88E-09***
Male	0.0169395	0.01504663	0.512	0.26627638	0.01480795	4.86E-10***	0.218784	-0.00103	4.86E-10***
Female	0.01613297	0.01563676	0.973	0.18065426	0.01209103	0.0000119***	0.163009	0.000996	0.00871***
Age≤70	0.01788163	0.01504663	0.252	0.23447584	0.01446394	0.000000385***	0.214827	0.001772	0.000216***
Age≥71	0.01619519	0.01563676	0.892	0.21531273	0.01326322	1.20E-08***	0.201867	-0.00045	0.00000934***

Supplementary Table 3. Effect of high-dose NMN on whole blood NAD+ and NAD+-related metabolite levels

Results are presented as medians. Intergroup comparisons were performed using the Mann–Whitney U test.

^aInter-group comparisons were performed using ANCOVA to adjust baseline values. The FDR-adjusted P values (q values) are presented in Figure 2.

Participants were stratified by sex and age (≤70 or ≥71 years). In the NMN group, 21 men and 10 women, with 14 participants were ≤70 years and 17 were ≥71 years. In the placebo group, 18 men and 11 women, with 12 participants were ≤70 years and 17 were ≥71 years.

*: p<0.05, **: p<0.01, ***: p<0.001 NMN, nicotinamide mononucleotide; ANCOVA, analysis of covariance

	Baseline			Week 24			Change from Baseline to Week 24		
	NMN median (n=31)	Placebo median (n=29)	p-value	NMN median (n=30)	Placebo median (n=28)	p-value	NMN median (n=30)	Placebo median (n=28)	p-value
Adiponectin (µg/ml)									
All	15.58	14.69	0.953	17.21	15.76	0.92	0.63	0.12	0.206
Male	14.17	13.23	0.549	13.41	12.44	0.581	0.02	-0.17	0.45
Female	27.61	22.42	0.918	23.67	22.66	0.882	2.57	0.99	0.331
Age≤70	13.53	14.68	0.347	12.33	15.41	0.225	0.01	0.21	0.936
Age≥71	18.48	16.67	0.357	20.99	16.09	0.347	2.57	0.12	0.094
FGF-21 (pg/ml)									
All	194.05	117.88	0.089	188.03	138.82	0.357	-3.79	14.97	0.195
Male	194.05	149.26	0.269	2008	157.89	0.523	-1.2	-3.34	0.337
Female	170.72	96.82	0.197	120.08	109.88	0.552	-6.37	31.21	0.503
Age≤70	243.76	75.89	0.085	225.66	122.29	0.32	-1.2	16.01	0.152
Age≥71	173.95	168.2	0.61	171.07	160.46	0.851	-6.37	9.94	0.736
Irisin (ng/ml)									
All	9.96	9.85	0.792	9.94	9.55	0.945	-0.61	0.0	0.178
Male	10.33	9.64	0.945	9.98	9.12	0.601	-0.21	-0.23	0.907
Female	7.73	10.06	0.557	5.29	9.78	0.456	0.91	-0.78	0.00622*
Age≤70	10.48	6.54	0.145	11.3	7.9	0.086	0.27	0.17	0.437
Age≥71	8.94	10.11	0.085	8.58	9.97	0.075	-0.61	-0.24	0.296
IGF-1 (ng/ml)									
All	95.17	91.58	0.344	92.94	92.26	0.982	-4.53	2.25	0.255
Male	97.18	95.38	0.602	94.49	97.28	0.383	-4.84	2.4	0.144
Female	92.84	84.82	0.314	81.53	77.25	0.456	-1.7	-1.86	1
Age≤70	97.84	99.45	0.857	95.26	99.38	0.247	-2.8	3.85	0.0457*
Age≥71	94.82	82.51	0.14	82.38	76.15	0.484	-5.38	-2.09	0.901
GDF-8 (ng/ml)									
All	2.08	2.25	0.402	2.12	2.21	0.799	0.12	-0.03	0.323
Male	2.1	2.45	0.282	2.22	2.42	0.862	0.14	-0.03	0.24
Female	1.7	1.87	0.314	1.69	2.06	0.175	0.1	0.0	0.79
Age≤70	2.07	2.13	0.94	2.21	2.29	0.728	0.04	0.24	0.807
Age≥71	2.08	2.25	0.29	2.04	2.18	0.932	0.18	-0.05	0.0688
IL-6 (pg/ml)									
All	77.91	77.03	0.75	77.89	80.92	0.339	-0.85	2.35	0.058
Male	81.48	78.27	0.662	79.7	83.14	0.445	0.05	4.49	0.103
Female	77.44	77.03	0.778	71.88	80.51	0.362	-0.87	0.02	0.224
Age≤70	72.96	71.8	0.705	77.95	75.18	0.47	0.05	2.65	0.27
Age≥71	78.8	77.03	0.343	77.01	80.92	0.381	-0.87	2.35	0.056
NAMPT (ng/ml)									
All	9.3	9.85	0.597	9.21	10.11	0.349	-0.11	0.24	0.889
Male	8.88	9.68	0.364	8.93	10.28	0.601	-0.06	0.11	0.639
Female	10.07	9.85	0.809	10.01	9.77	0.503	-1.09	0.73	0.882
Age≤70	8.99	10.42	0.16	8.93	9.85	0.406	-0.48	-0.87	0.503
Age≥71	10.05	8.08	0.892	9.9	10.75	0.551	-0.06	0.82	0.657

Supplementary Table 4. Effect of high-dose NMN on biomarkers measured by ELISA

Results are presented as medians. Intergroup comparisons were performed using the Mann–Whitney U test.

Participants were stratified by sex and age (≤70 or ≥71 years). In the NMN group, 21 men and 10 women, with 14 participants were ≤70 years and 17 were ≥71 years. In the placebo group, 18 men and 11 women, with 12 participants were ≤70 years and 17 were ≥71 years.

*: p<0.05

NMN, nicotinamide mononucleotide; ANCOVA, analysis of covariance