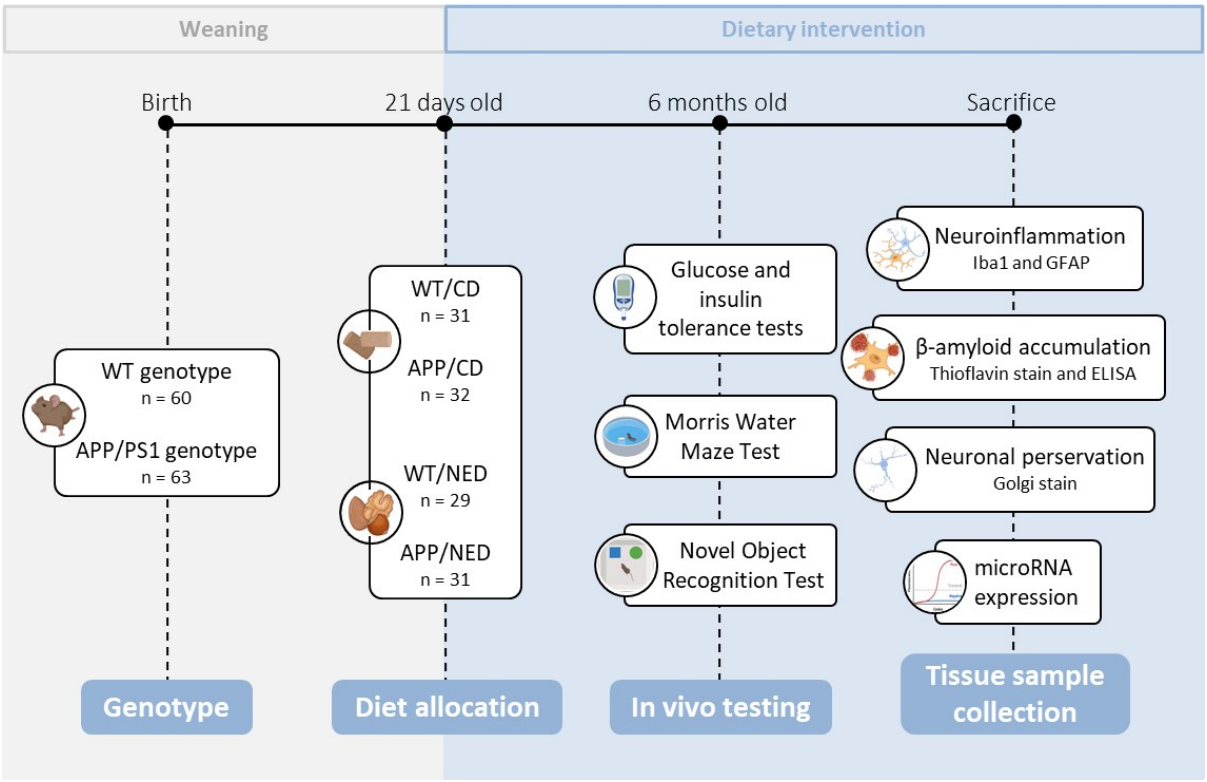

Figure S1. Graphical representation of experimental design. APP/PS1 (APP) and wild-type (WT) littermates were randomly assigned to either a conventional chow diet (CD) or a nut-enriched diet (NED) providing 10% of the energy from nuts at 21 days old. At 6 months, animals underwent glucose and insulin tolerance tests and followed by behavioural assessments (Morris Water Maze test and Novel Object Recognition Test). Animals were then sacrificed, and blood and brain samples were collected to evaluate neuroinflammation, β-amyloid accumulation, neuronal preservation and microRNA expression. Abbreviations: WT, wild-type; APP, APP/PS1 transgenic mice mutation; CD, control diet; NED, nuts-enriched diet; Iba1, ionized calcium binding adaptor molecule 1; GFAP, glial fibrillary acidic protein; ELISA, enzyme-linked immunosorbent assay.

Table S1. Nutritional composition of experimental diets.

Component	Nut-Enriched Diet	Control Diet
Energy Density (kcal/g)	3.1 (13.0 MJ/kg)	3.1 (13.0 MJ/kg)
Carbohydrates (%E)	45	58

Component	Nut-Enriched Diet	Control Diet
Fat (%E)	33	18
Protein (%E)	22	24
Crude Fiber (%)	4.5	3.5

The table compares energy density (kcal/g), the relative contribution of carbohydrates, fat, and protein to total energy intake (%E), and crude fiber content as a percentage of total composition (%).

Table S2. Neuroinflammation immunofluorescence primary and secondary antibodies.

Protein	Antibody
GFAP	Z0334 (Dako)
IBA1	O19-19741 (Wako)
Secondary Alexa Fluor 488 (Goat-Anti Mouse)	A11001 (Life Technologies)
Secondary Alexa Fluor 594 (Goat-Anti Rabbit)	A11080 (Life Technologies)

Primary and secondary to evaluate microglia and astrocyte activation in the brain. Glial fibrillary acidic protein (GFAP) was used to assess astrocyte reactivity, while ionized calcium binding adaptor molecule 1 (IBA1) was used for microglia assessment. Abbreviations: GFAP, glial fibrillary acidic protein; IBA1, ionized calcium binding adaptor molecule 1.

Table S3. Differences in the expression of miRNAs in serum, cortex and hippocampus.

	Comparison			
	APP/CD and WT/CD	WT/CD and WT/NED	APP/CD and APP/NED	WT/NED and APP/NED
Serum				
let-7b-3p	0,194	0,483	0,916	0,593
miR-122-5p	0,036	0,740	0,287	0,006
miR-187-3p	0,684	0,946	0,009	0,024
miR-214-3p	0,105	0,316	0,357	0,063
miR-338-5p	0,242	0,950	0,685	0,901
miR-429-3p	0,782	0,987	0,030	0,177
miR-451a	0,484	0,223	0,000	0,026
miR-6240	0,024	0,734	0,487	0,286
miR-669a-5p	0,029	0,275	0,033	0,165
miR-669o-5p	0,402	0,987	0,504	0,330
miR-702-3p	0,155	0,616	0,694	0,901
miR-19a-3p	0,433	0,278	0,091	0,175
miR-98-5p	0,011	0,022	0,038	0,038
miR-29c-3p	0,114	0,011	0,821	0,262
miR-338-3p	<0,001	0,399	0,052	0,420
miR-34a-5p	0,979	0,715	0,119	0,365
Cortex				
let-7b-3p	0,012	0,078	0,101	0,533
miR-122-5p	0,038	0,073	0,033	0,063
miR-153-3p	0,041	0,727	0,179	0,728
miR-187-3p	0,219	0,663	0,421	0,321
miR-214-3p	0,120	0,017	0,135	0,042
miR-218-2-3p	0,131	0,053	0,006	0,006
miR-338-5p	0,018	0,270	0,493	0,553
miR-3547-3p	0,045	0,988	0,850	0,098
miR-451a	0,035	0,029	0,019	0,026
miR-6240	0,010	0,399	0,907	0,051
miR-669o-5p	0,102	0,491	0,186	0,632
miR-702-3p	0,013	0,169	0,170	0,930
miR-19a-3p	0,184	<0,001	0,118	0,001
miR-98-5p	0,494	0,271	0,053	0,070
miR-29c-3p	0,031	0,032	0,258	0,358
miR-338-3p	0,079	0,850	0,595	0,175
Hippocampus				

let-7b-3p	0,813	0,715	0,042	0,159
miR-122-5p	0,333	0,257	0,406	0,286
miR-153-3p	0,163	0,017	0,774	0,338
miR-187-3p	0,576	0,302	0,683	0,317
miR-214-3p	0,778	0,385	0,461	0,313
miR-218-2-3p	0,086	0,209	0,314	0,702
miR-338-5p	0,050	0,319	0,099	0,037
miR-3547-3p	0,855	0,683	0,721	0,989
miR-451a	0,017	0,012	0,049	0,040
miR-6240	0,577	0,334	0,038	0,003
miR-669o-5p	0,842	0,650	0,799	0,443
miR-702-3p	0,466	0,638	0,005	0,002
miR-19a-3p	0,035	0,088	0,034	0,199
miR-98-5p	0,960	0,781	0,893	0,707
miR-29c-3p	0,813	0,357	0,667	0,318
miR-338-3p	0,355	0,020	0,860	0,101
miR-34a-5p	0,465	0,033	0,224	0,003

Differences between experimental groups were assessed by Student's T test or Mann-Whitney test according to normality. Statistical significance was set at p-value <0.05. Abbreviations: WT, wild-type; APP, APP/PS1; CD, control diet; NED, nuts-enriched diet.

Table S4. KEGG pathway and GO functional enrichment analysis.

Gene Set	Description	Size	Expect	Ratio	P Value	FDR
KEGG Pathways						
mmu04930	Type II diabetes mellitus	48	9.8743	2.0255	7.07E-04	0.010731
mmu04929	GnRH secretion	63	12.96	1.929	3.94E-04	0.0090867
mmu04213	Longevity regulating pathway	61	12.549	1.9126	0.00059355	0.010357
mmu04068	FoxO signaling pathway	131	26.949	1.8925	9.72E-07	1.81E-04
mmu04720	Long-term potentiation	67	13.783	1.8864	4.59E-04	9.43E-03
mmu04350	TGF-beta signaling pathway	110	22.629	1.8561	0.000015183	0.0007941
mmu04721	Synaptic vesicle cycle	77	15.84	1.7677	0.00095652	0.011781
mmu04971	Gastric acid secretion	75	15.429	1.75	0.0013919	0.014038
mmu04360	Axon guidance	181	37.234	1.7457	1.04E-06	0.000181
mmu03083	Polycomb repressive complex	84	17.28	1.7361	0.00090136	0.011781
mmu04140	Autophagy	166	34.149	1.7277	4.72E-06	0.00041179
mmu04910	Insulin signaling pathway	139	28.594	1.7136	0.000037752	0.0016469
mmu04150	mTOR signaling pathway	157	32.297	1.7029	0.000015927	0.0007941
mmu04912	GnRH signaling pathway	90	18.514	1.6744	0.0014782	0.01433
mmu04015	Rap1 signaling pathway	214	44.023	1.6582	2.1495E-06	0.00025006
mmu05206	MicroRNAs in cancer	162	33.326	1.6504	0.000043787	0.001698
mmu04725	Cholinergic synapse	112	23.04	1.6493	0.00064158	0.010662
mmu04722	Neurotrophin signaling pathway	121	24.892	1.6471	0.00041253	0.0090867
mmu04152	AMPK signaling pathway	127	26.126	1.6459	0.00030751	0.0089434
mmu05414	Dilated cardiomyopathy	101	20.777	1.6364	0.0014078	0.014038
GO Biological processes						
GO:0016482	cytosolic transport	122	27.229	1.9097	4.09E-07	0.00004967
GO:0098876	vesicle-mediated transport to the plasma membrane	148	33.032	1.7862	1.0816E-06	0.00009194
GO:0099072	regulation of postsynaptic membrane neurotransmitter receptor levels	129	28.791	1.7714	7.4799E-06	0.00027768
GO:1902414	protein localization to cell junction	127	28.345	1.7287	0.000024168	0.00064197
GO:0016358	dendrite development	299	66.733	1.7233	1.46E-10	1.24E-07
GO:0002065	columnar/cuboidal epithelial cell differentiation	133	29.684	1.7181	0.000020283	0.00055614
GO:0050803	regulation of synapse structure or activity	303	67.626	1.671	1.77E-09	7.50E-07
GO:0016331	morphogenesis of embryonic epithelium	177	39.504	1.6707	0.000004084	0.00020372
GO:0035148	tube formation	172	38.388	1.6672	6.1547E-06	0.00026157
GO:0099173	postsynapse organization	252	56.243	1.6357	1.77E-07	0.000030044
GO:0030534	adult behavior	176	39.281	1.6038	0.000029558	0.00076136
GO:0097485	neuron projection guidance	234	52.226	1.5892	2.66E-06	0.00018821
GO:0031503	protein-containing complex localization	233	52.003	1.5768	4.3141E-06	0.00020372
GO:0048167	regulation of synaptic plasticity	240	53.565	1.5682	4.2439E-06	0.00020372
GO:0006813	potassium ion transport	227	50.664	1.5593	0.000010266	0.00033562
GO:0070085	glycosylation	232	51.78	1.545	0.000013303	0.00038993
GO:0060485	mesenchyme development	302	67.403	1.543	7.77E-07	0.000073379
GO:0048638	regulation of developmental	372	83.026	1.5417	4.51E-08	9.5813E-06

	growth					
GO:1905475	regulation of protein localization to membrane	208	46.423	1.5294	0.000057517	0.0012222
GO:0099003	vesicle-mediated transport in synapse	258	57.583	1.5282	8.2437E-06	0.00029196
GO molecular functions						
GO:0098918	structural constituent of synapse	38	8.3603	2.3922	0.00003437	0.001644
GO:0106222	lncRNA binding	21	4.6202	2.3809	0.0021977	0.045052
GO:0046332	SMAD binding	79	17.381	1.9562	0.000022577	0.0012959
GO:0003727	single-stranded RNA binding	94	20.681	1.7891	1.03E-04	3.70E-03
GO:0030165	PDZ domain binding	111	24.421	1.597	1.02E-03	2.43E-02
GO:0019902	phosphatase binding	222	48.842	1.5151	5.89E-05	0.0024164
GO:0106310	protein serine kinase activity	341	75.023	1.4929	1.91E-06	2.74E-04
GO:0060589	nucleoside-triphosphatase regulator activity	419	92.184	1.4428	1.74E-06	2.74E-04
GO:0005516	calmodulin binding	183	40.262	1.4406	1.43E-03	0.031504
GO:0046873	metal ion transmembrane transporter activity	416	91.524	1.4313	3.30E-06	3.15E-04
GO:0004674	protein serine/threonine kinase activity	411	90.424	1.4045	1.30E-05	0.00093364
GO:0003729	mRNA binding	313	68.863	1.365	4.96E-04	1.42E-02
GO:0001217	DNA-binding transcription repressor activity	334	73.483	1.3609	3.76E-04	0.012003
GO:0051020	GTPase binding	311	68.423	1.3592	6.19E-04	0.016151
GO Cellular component						
GO:0060077	inhibitory synapse	26	5.9303	2.3608	0.00056701	0.0080254
GO:0060076	excitatory synapse	93	21.212	1.98	0.000001448	0.000053285
GO:0031201	SNARE complex	44	10.036	1.8932	0.0020987	0.020613
GO:0098982	GABA-ergic synapse	122	27.827	1.7968	5.0279E-06	0.00015075
GO:0044309	neuron spine	232	52.916	1.7575	1.95E-09	8.98E-08
GO:0043198	dendritic shaft	70	15.966	1.6911	0.0021285	0.020613
GO:0098685	Schaffer collateral - CA1 synapse	135	30.792	1.6563	0.000057376	0.001173
GO:0098984	neuron to neuron synapse	440	100.36	1.6341	1.79E-12	3.30E-10
GO:0099572	postsynaptic specialization	431	98.306	1.5564	6.79E-10	4.17E-08
GO:0097060	synaptic membrane	494	112.68	1.5531	4.54E-11	4.18E-09
GO:0044306	neuron projection terminus	210	47.898	1.5241	0.000046218	0.001063
GO:0048786	presynaptic active zone	117	26.686	1.4614	0.0057784	0.04849
GO:0035770	ribonucleoprotein granule	262	59.759	1.4224	0.0001868	0.0030793
GO:0031252	cell leading edge	455	103.78	1.3876	5.7349E-06	0.00015075
GO:0150034	distal axon	388	88.498	1.3673	0.000066154	0.0012172
GO:0061695	transferase complex, transferring phosphorus-containing groups	278	63.408	1.3563	0.00095069	0.012495
GO:0030139	endocytic vesicle	229	52.232	1.321	0.0057977	0.04849
GO:0010008	endosome membrane	470	107.2	1.306	0.00020082	0.0030793
GO:0043235	receptor complex	383	87.358	1.2935	0.0011714	0.01437
GO:0045178	basal part of cell	338	77.094	1.2842	0.0029334	0.026987