Appendix

Appendix 1 PGRN levels were corrected by inter-batch variation and corrected values were used for analyses

In order to harmonize the different analytical run and account for interplate variation, the MSD ELISA CSF PGRN concentrations were corrected based on the measurements of the four internal standards (IS) that were loaded on all plates. The concentration of each IS in an individual plate (plate x) was expressed as a percentage of the mean concentration across all plates, as follows:

a1 (%) in plate x = [(concentration of IS1 in plate x) / (mean concentration of IS1 in all plates)]×100

a2 (%) in plate x = [(concentration of IS2 in plate x) / (mean concentration of IS2 in all plates)]×100

a3 (%) in plate x = [(concentration of IS3 in plate x) / (mean concentration of IS3 in all plates)]×100

a4 (%) in plate x = [(concentration of IS4 in plate x) / (mean concentration of IS4 in all plates)]×100

The mean of the percentages (**Ax**) for all the IS (**a1, a2, a3, a4**) in plate x was calculated and the following correction factor was computed for each individual plate:

Correction factor for plate x = 100 / **Ax**

Table e-1 Classification of ADNI participants based on their biomarker profile and clinical stage.

		N = 965			N = 228		
		Clinical stage（C）			Clinical stage（C）		
		CDR = 0 (cognitively unimpaired)	**CDR = 0.5** (very mild dementia)	**CDR = 1** (mild dementia)	**CDR = 0** (cognitively unimpaired)	**CDR = 0.5** (very mild dementia)	**CDR = 1** (mild dementia)
Biomarker profile	**A-/TN-**	**Healthy controls** *n* = 121	n = 118	n = 2	**Healthy controls** *n* = 34	n = 14	n = 0
	A+/TN-	**Preclinical AD A+/TN-** n = 52	n = 89	n = 12	**Preclinical AD A+/TN-** n = 9	n = 13	n = 5
	A+/TN+	**Preclinical AD A+/TN+** n = 45	**AD CDR = 0.5** n = 270	**AD CDR = 1** n = 78	**Preclinical AD A+/TN+** n = 14	**AD CDR = 0.5** n = 83	**AD CDR = 1** n = 23
	A-/TN+	n = 73	n = 97	n = 8	n = 12	n = 20	n = 1
		Suspected non-Alzheimer's pathophysiology (SNAP)			**Suspected non-Alzheimer's pathophysiology (SNAP)**		

The ADNI participants were classified based on their clinical stage, as defined by the clinical dementia rating (CDR) score, and the biomarker-based A/T/N framework. The A/T/N framework comprises 3 biomarker groups: A Aβ pathology biomarker status, T tau pathology biomarker status, and N neurodegeneration biomarker status. Each of the biomarkers group have binarized into positive/abnormal (+) or negative/normal according the biomarkers cutoffs. T and N have been merged to simplify the classification and TN- indicates that both T and N are normal and TN+ indicates that T and/or N are abnormal.

Table e-2 Association results of CSF PGRN and neuroinflammatory markers with A/TN status in total population

	CSF markers	A status (A+ vs. A-)		TN status (TN+ vs. TN-)	
		beta	***p* value**	**beta**	***p* value**
	PGRN	-0.037	**1.15E-07**	0.042	**2.26E-10**
Anti-inflammatory markers	sTNFR1	-0.008	**2.67E-07**	0.12	**< 2e-16**
	sTNFR2	-0.064	**5.29E-06**	0.12	**< 2e-16**
	TGF-BETA1	-0.036	0.158	0.09	**0.0002**
	IL-10	-0.02	0.432	0.016	0.567
Pro-inflammatory markers	ICAM1	-0.046	0.14	0.089	**0.002**
	VCAM1	-0.117	**1.08E-05**	0.165	**5.96E-11**
	IL-6	-0.02	0.512	0.036	0.2982
	IL-7	0.128	0.051	0.023	0.704

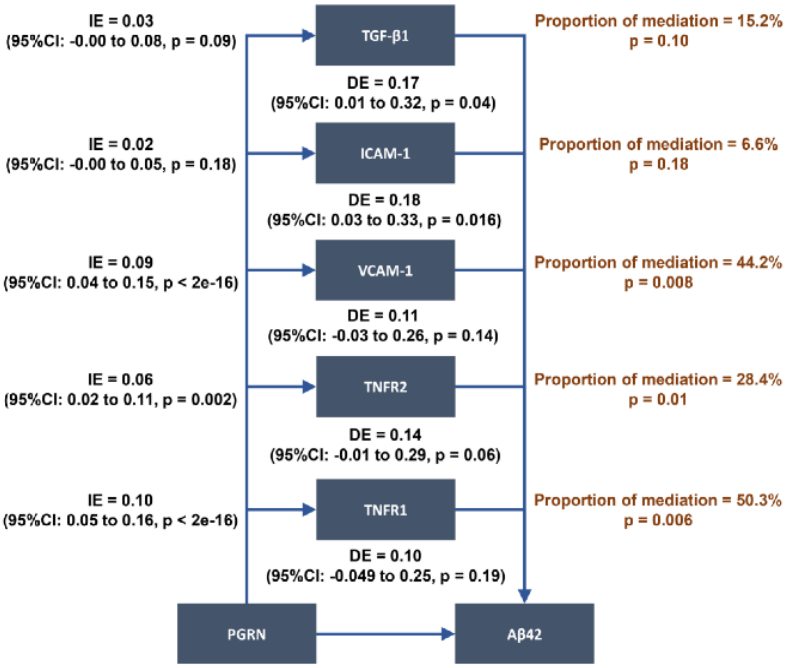
All analyses were adjusted for age, gender, education, apoe4 status, and CDR score. A and TN status were simultaneously included in the model.

Table e-3 The relationships of CSF PGRN and neuroinflammatory markers with Aβ deposition and the tau related neurodegeneration within the framework combining A/TN classification and clinical stage

CSF markers	CDR=0								CDR=0.5								CDR=1							
	A+ (TN+ vs TN-)		A- (TN+ vs TN-)		TN+ (A+ vs A-)		TN- (A+ vs A-)		A+ (TN+ vs TN-)		A- (TN+ vs TN-)		TN+ (A+ vs A-)		TN- (A+ vs A-)		A+ (TN+ vs TN-)		A- (TN+ vs TN-)		TN+ (A+ vs A-)		TN- (A+ vs A-)	
	F	P	F	P	F	P	F	P	F	P	F	P	F	P	F	P	F	P	F	P	F	P	F	P
PGRN	8.903	**3.66E-03**	25.874	**8.78E-07**	10.078	**1.94E-03**	1.849	1.76E-01	8.398	**3.99E-03**	9.779	**2.02E-03**	10.565	**1.26E-03**	5.392	**2.12E-02**	0.197	6.59E-01	na	na	3.355	7.00E-02	na	na
sTNFR1	4.831	**4.21E-02**	19.802	**5.42E-05**	6.754	**1.61E-02**	3.525	6.78E-02	44.924	**1.12E-09**	17.36	**2.68E-04**	7.93	**5.79E-03**	15.316	**6.55E-04**	12.995	**1.57E-03**	na	na	na	na	na	na
sTNFR2	3.352	8.47E-02	31.3	**1.17E-06**	3.679	6.70E-02	4.104	0.0495	39.961	**6.74E-09**	17.534	**2.54E-04**	3.876	5.16E-02	8.195	**8.50E-03**	8.488	**8.05E-03**	na	na	na	na	na	na
TGF-β1	2.193	1.57E-01	2.025	1.61E-01	1.03	3.19E-01	0.394	5.34E-01	12.346	**6.60E-04**	1.073	3.09E-01	1.112	2.94E-01	3.183	8.70E-02	11.872	**2.31E-03**	na	na	na	na	na	na
IL-10	0.82	3.78E-01	0.952	3.34E-01	11.287	**2.70E-03**	0.64095	6.41E-01	0.366	5.47E-01	0.134	7.17E-01	1.683	1.97E-01	0.131	7.20E-01	2.244	1.48E-01	na	na	na	na	na	na
ICAM1	1.134	3.02E-01	0.285	5.96E-01	0.228	6.38E-01	4.295	4.50E-02	0.723	3.97E-01	12.548	**1.41E-03**	2.04	1.56E-01	1.638	2.13E-01	0.001	9.72E-01	na	na	na	na	na	na
VCAM1	3.463	8.02E-02	43.87	**3.35E-08**	1.71	2.04E-01	3.262	7.85E-02	10.849	**1.36E-03**	6.486	**1.66E-02**	8.957	**3.44E-03**	4.101	5.41E-02	5.021	**3.55E-02**	na	na	na	na	na	na
IL-6	0.738	4.02E-01	0.513	4.77E-01	0.097	7.59E-01	0.596	4.45E-01	0.153	6.96E-01	1.206	2.82E-01	0.09	7.64E-01	0.28	6.02E-01	0.135	7.16E-01	na	na	na	na	na	na
IL-7	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	**1.00E-02**	ns	ns	ns	ns	na	na	na	na	na	na

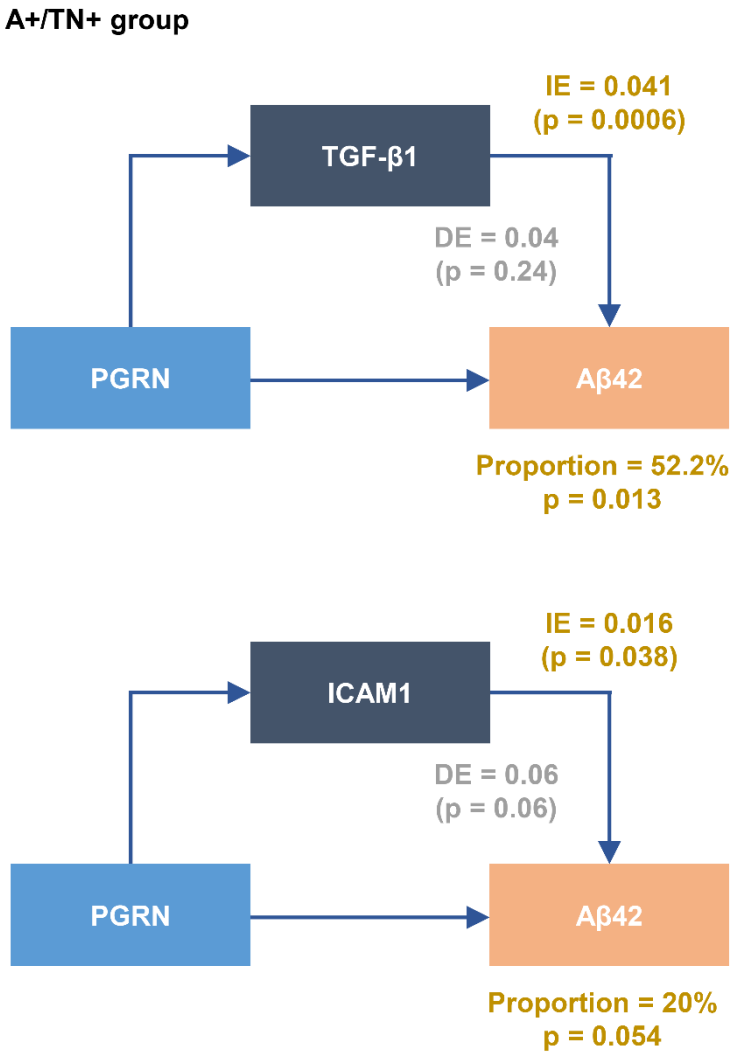
P-values were assessed by a one-way ANCOVA adjusted for age, gender, education, and *APOE*4 status.

Figure e-1 Mediation effects of CSF PGRN on amyloid pathologies via neuroinflammation within the A-T-N framework in total population



Higher levels of CSF PGRN alleviated cerebral amyloid deposition via stimulating neuroinflammatory markers, including sTNFR1 (proportion = 50.3%, p = 0.006), sTNFR2 (proportion = 28.4%, p = 0.01), and VCAM1 (proportion = 44.2%, p = 0.008)

Figure e-2 Mediation effects of CSF PGRN on amyloid via TGF-β1 and ICAM1 in A+/TN+



Mediation effects of TGF-β1 and ICAM1 on the relationships of PGRN with CSF amyloid pathology were found in A+/TN+ profile.