Peripheral blood inflammatory cytokines in isolated REM sleep behavior disorder

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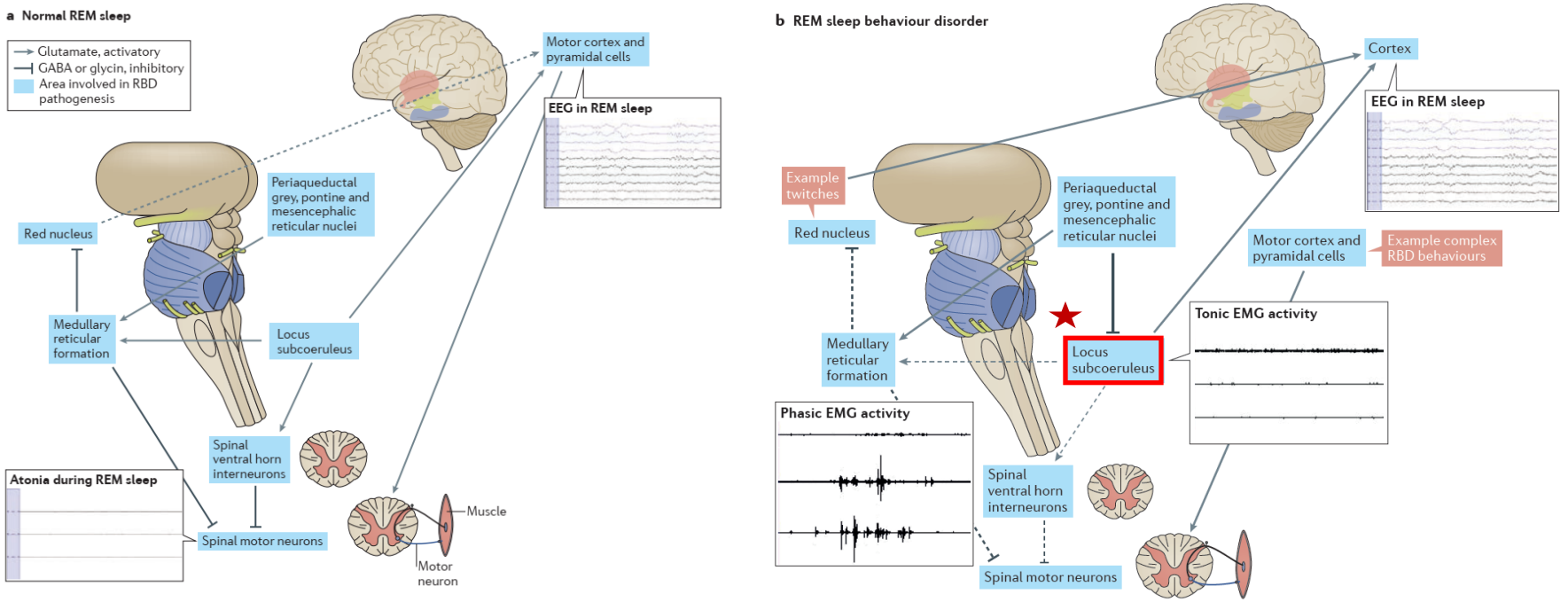
What is RBD?

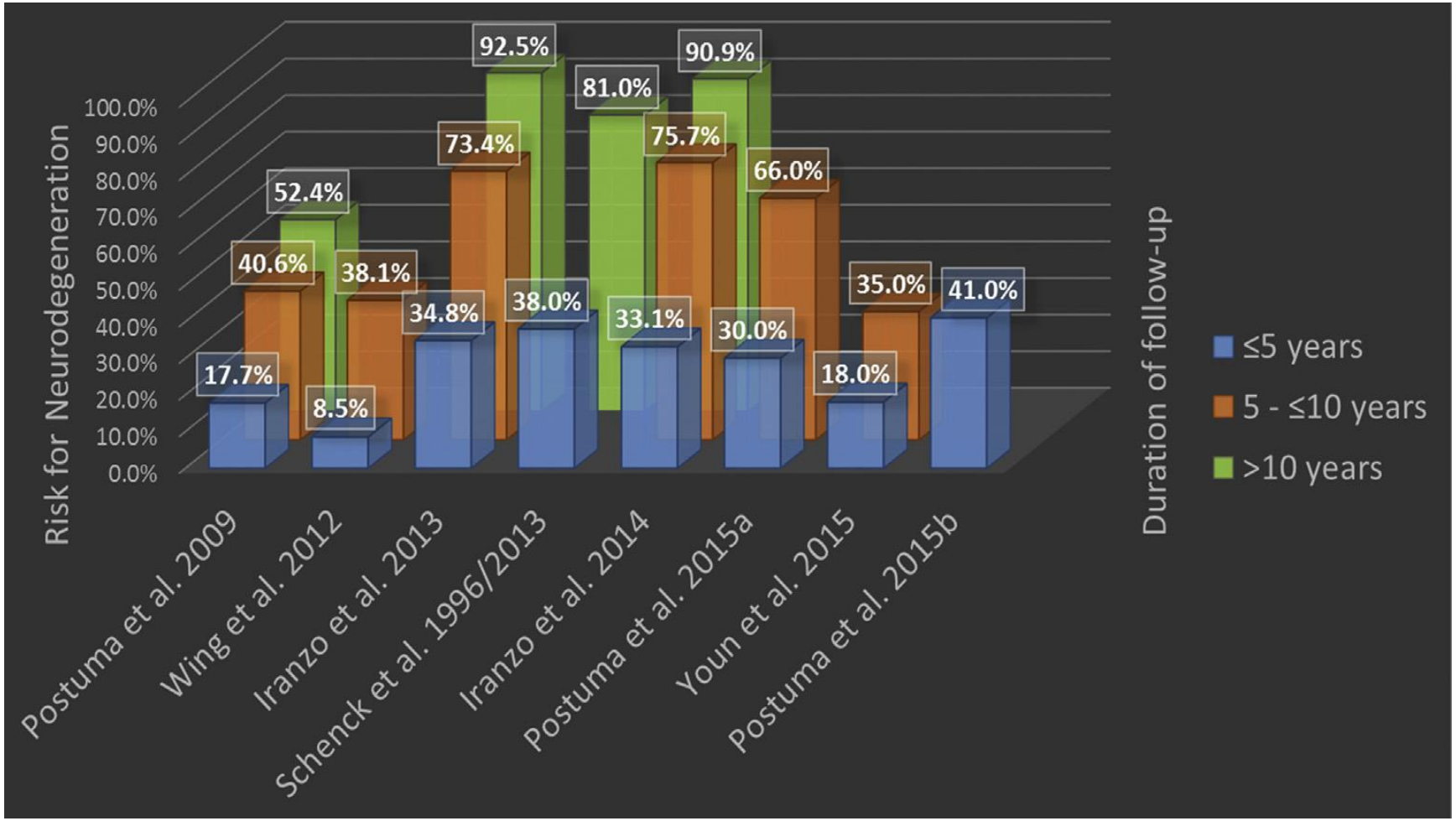
- **REM sleep behavior disorder (RBD)** is characterized by vocalizations and/or motor behaviors during REM sleep associated with REM-related dream content.

- RBD is accompanied by the absence of muscle atonia.



Högl et al. Nat Rev Neurol. 2018

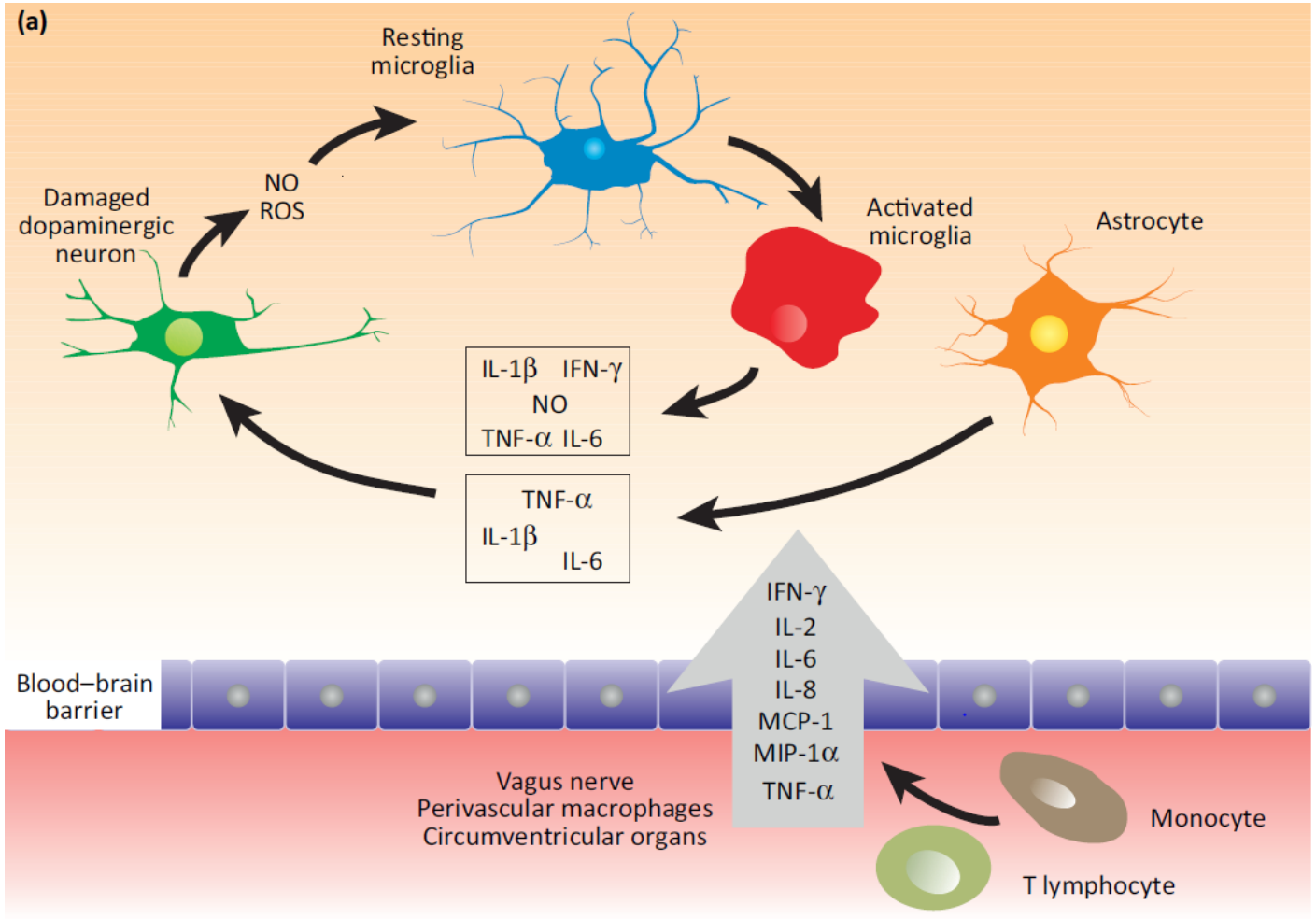
RBD and α-synucleinopathies



Conversion rate: 6-10 %/yr

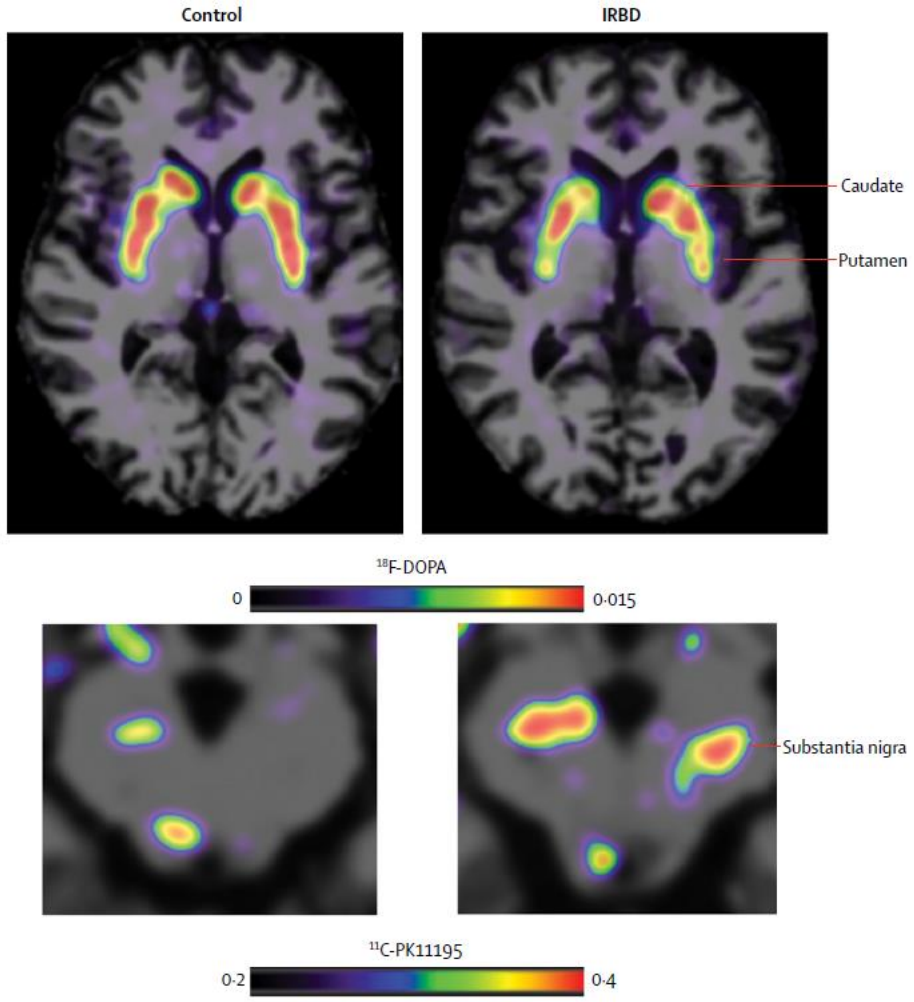
Gan-Or et al. Sleep Med Rev. 2018
Postuma et al. Ann Neurol. 2015

Inflammation in neurodegenerative diseases



Nolan et al. Trends Mol Med. 2012

Neuroinflammation in iRBD



- F-DOPA: reduced in bilateral putamen
- PK11195: increased on the left SN

Stokholm et al. Lancet Neurol. 2017

Peripheral inflammation in iRBD

- There is considerable evidence suggesting that systemic inflammation is related to central neuroinflammatory processes.

- Given the accessibility and practicality of using peripheral blood, measurement of inflammatory markers in serum or plasma may be an attractive option to study and monitor the immune response in iRBD.

- **However, it remains unclear whether peripheral inflammation is involved in the pathogenesis of iRBD.**

Perry et al. Nat Rev Immunol. 2007

Peripheral inflammation in iRBD

Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

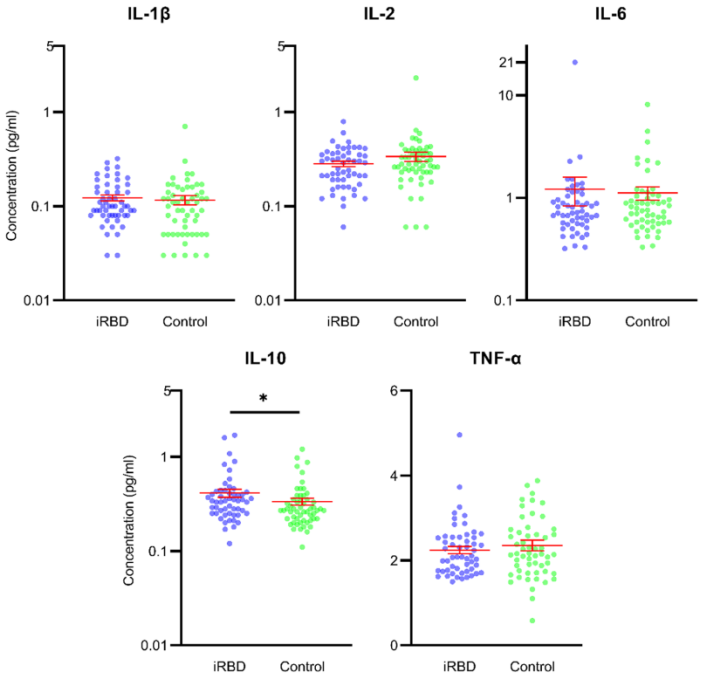
Brief Reports | Full Access

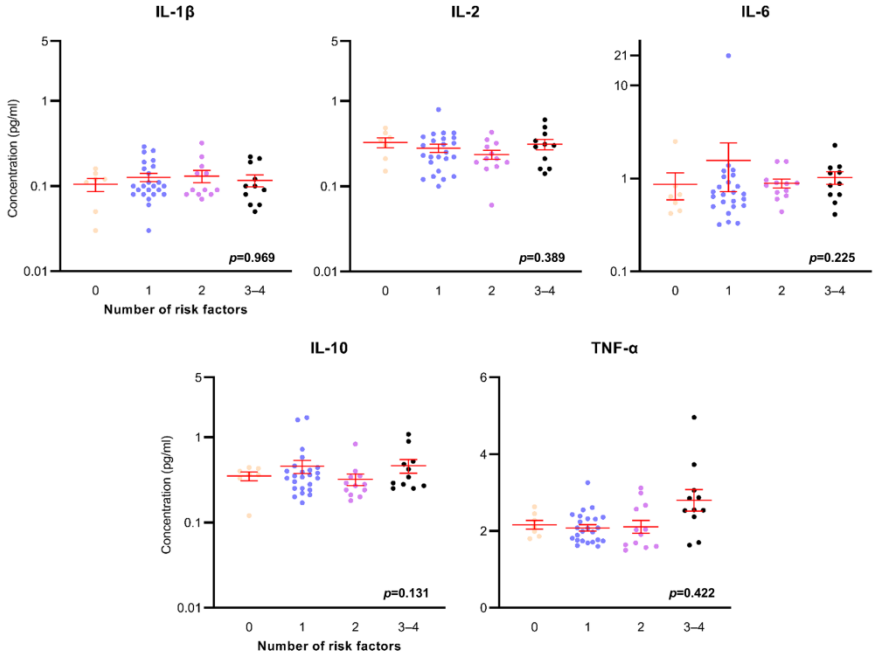
Peripheral Blood Inflammatory Cytokines in Idiopathic REM Sleep Behavior Disorder

Ryul Kim MD, Jin-Sun Jun MD, Han-Joon Kim MD, PhD, Ki-Young Jung MD, PhD, Yong-Won Shin MD, Tae-Won Yang MD, Keun Tae Kim MD ... See all authors

Limitations

1. Use of melatonin, which has anti-inflammatory properties, in many participants
2. Cross-sectional study design





Kim et al. Mov Disord. 2019

Objective

- To compare the serum cytokine profiles between iRBD patients and healthy control subjects using data made by stringent sample inclusion criteria and explored whether these biomarkers are related to phenoconversion risk.

- To assess longitudinal changes in serum cytokine levels in the iRBD patients.

Methods

- In this prospective cohort study, we analyzed serum samples from **patients with polysomnography-confirmed iRBD (n=30)** and **healthy controls (n=12)**.

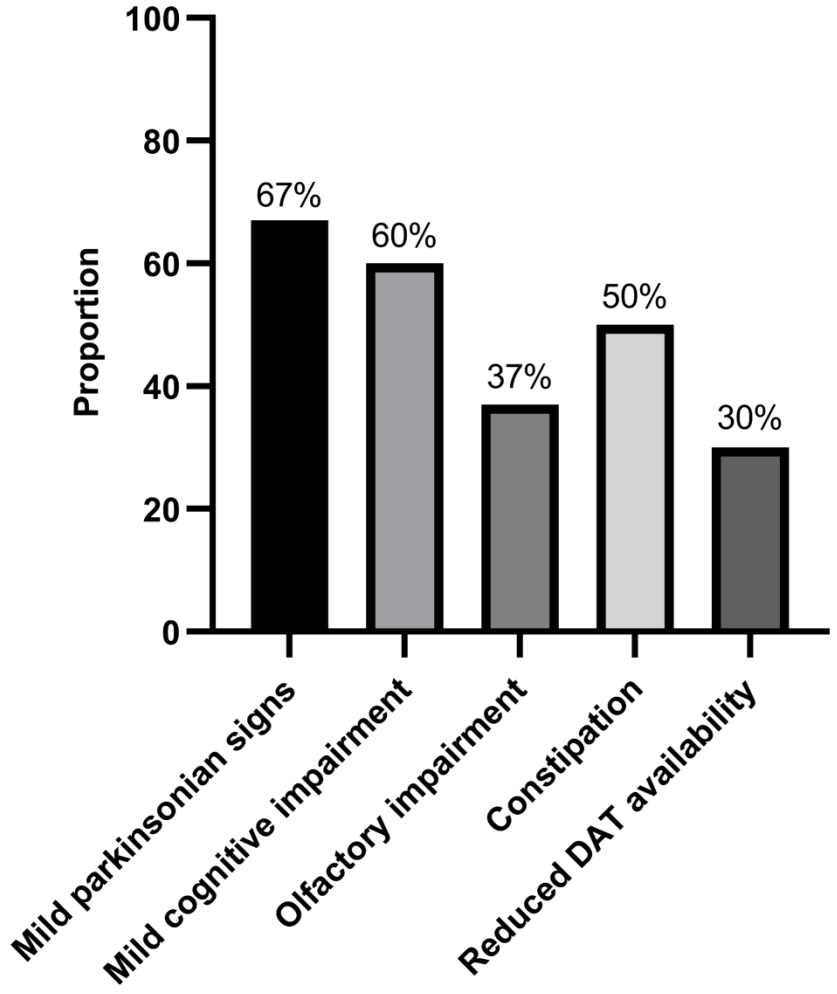
- We measured the following cytokines: interleukin (IL)-1β, IL-2, IL-6, IL-10, and tumor necrosis factor-α (TNF-α).

- All patients underwent motor and non-motor evaluations and dopamine transporter imaging at baseline for predicting the phenoconversion risk. We prospectively followed the patients quarterly a year over up to 6 years to identify disease conversion.

- We also assessed longitudinal changes in cytokine levels from baseline at the 2- and 4-year follow-up visits.

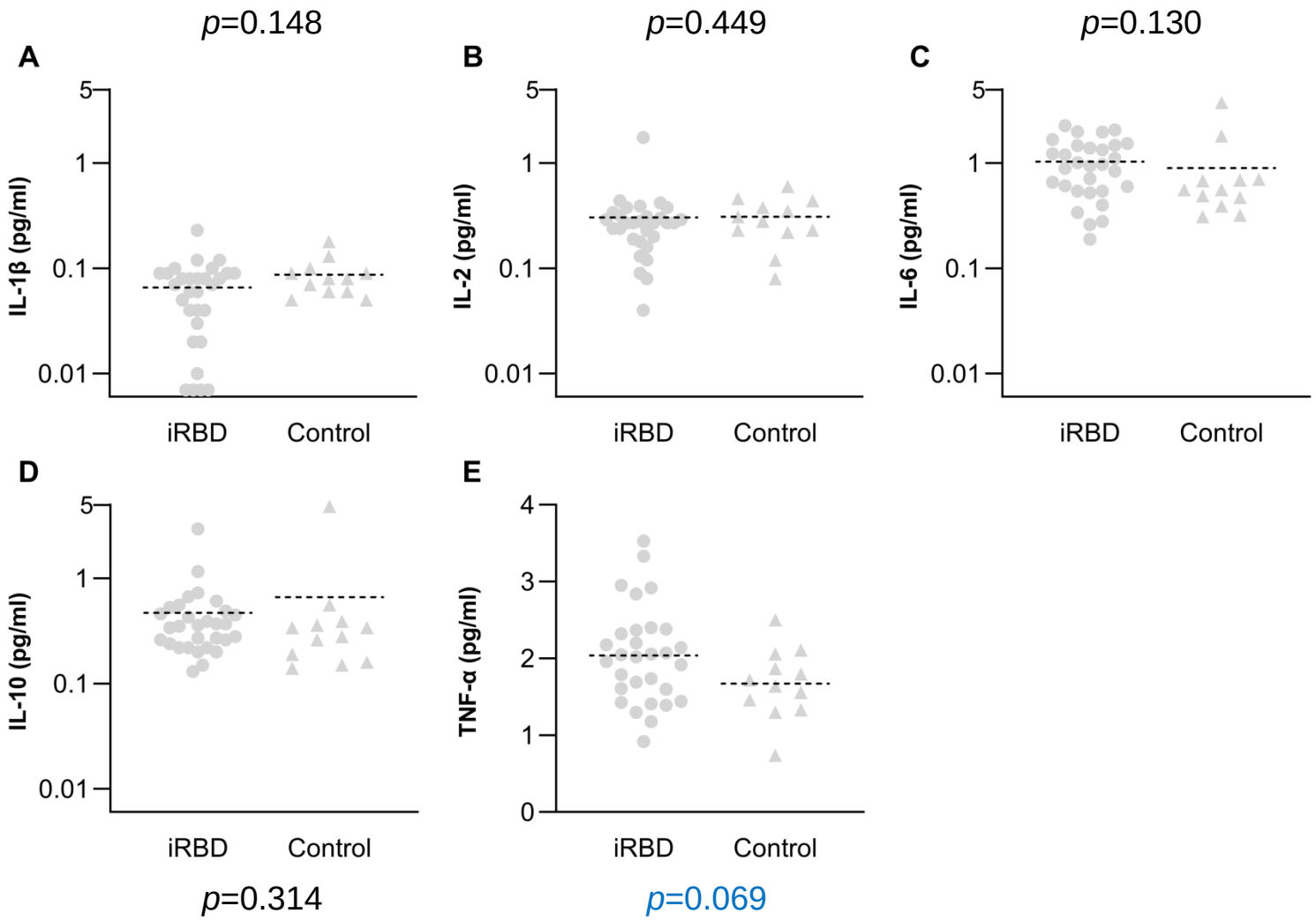
Variables	iRBD (*n*=30)	Control (*n*=12)	*P* value
Age, years	68.6 (5.9)	67.9 (4.6)	0.670
Male sex, %	19 (63%)	6 (50%)	0.498
RBD duration, years	5.1 (4.5)	–	–
MDS-UPDRS Part III	7.1 (5.5)	0.2 (0.4)	**<0.001**
NMSS score	25.8 (21.4)	18.8 (10.8)	0.562
GDS-15 score	6.1 (3.0)	5.2 (3.5)	0.356
Olfactory test			
B-SIT score	6.4 (2.7)	8.7 (1.8)	**0.017**
BTT score	4.7 (2.2)	6.8 (1.3)	**0.042**
Neuropsychological test, z-score			
TMT-A	-0.51 (1.07)	0.11 (0.54)	0.073
TMT-B	-1.13 (2.05)	0.60 (0.23)	**0.001**
CWST (color reading)	-0.88 (1.03)	-0.17 (0.96)	0.100
COWAT (semantic)	-0.28 (1.01)	-0.21 (0.79)	0.613
COWAT (phonemic)	-0.70 (0.96)	-0.45 (0.79)	0.497
RCFT (copy)	-1.78 (1.66)	-0.99 (0.98)	0.154
SVLT (immediate recall)	-0.27 (0.97)	0.33 (0.98)	0.133
SVLT (delayed recall)	-0.69 (1.12)	0.28 (0.85)	**0.019**
SVLT (recognition)	-0.22 (1.06)	0.86 (0.64)	**0.002**
K-BNT	0.02 (1.16)	0.59 (0.55)	0.184
DAT imaging, binding ratio			
Anterior putamen	4.59 (1.60)	5.81 (0.96)	**0.013**
Posterior putamen	3.85 (1.61)	4.97 (0.92)	**0.030**
Caudate nucleus	3.64 (1.33)	4.45 (0.91)	0.068

Baseline characteristics

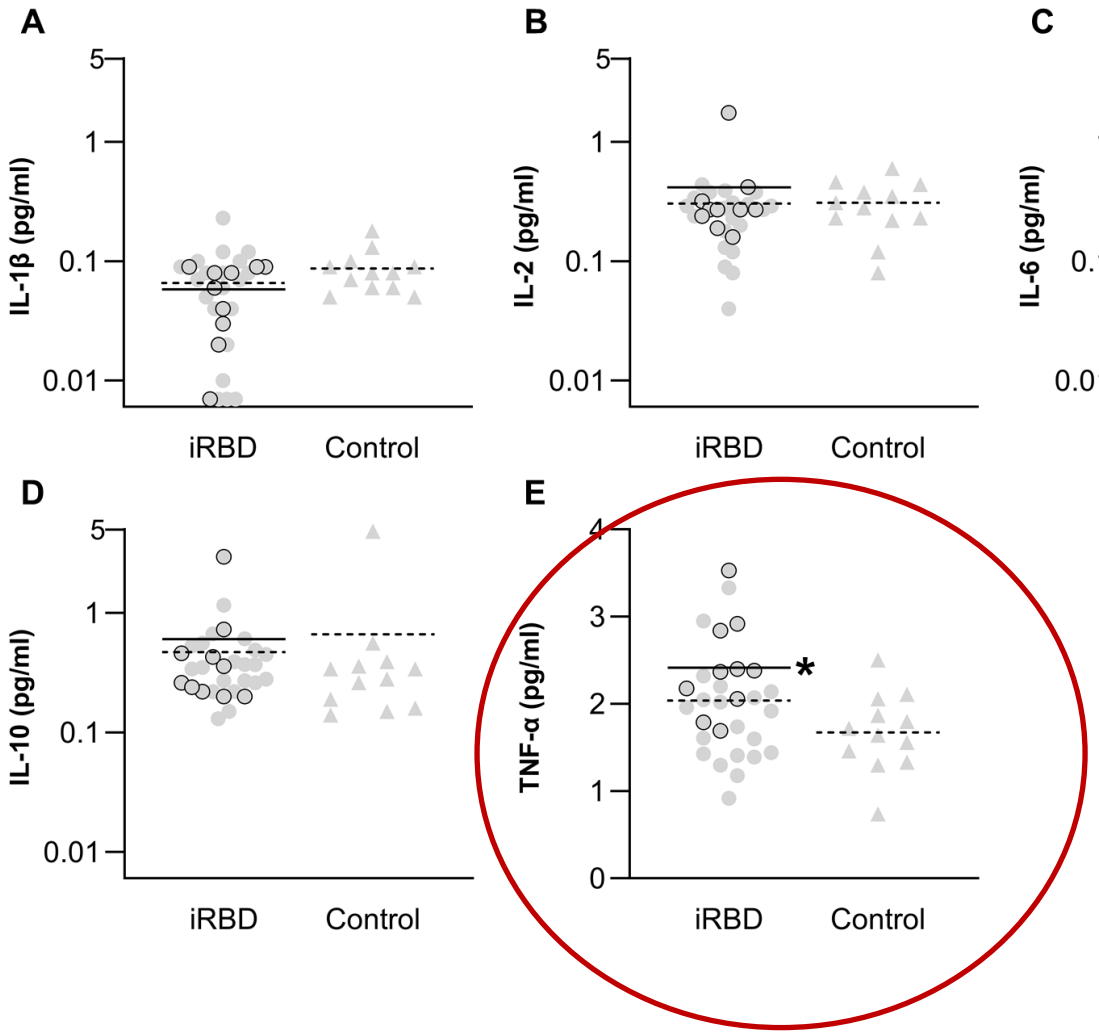


High-risk phenoconversion: 3 or more risk factors

Cytokine levels



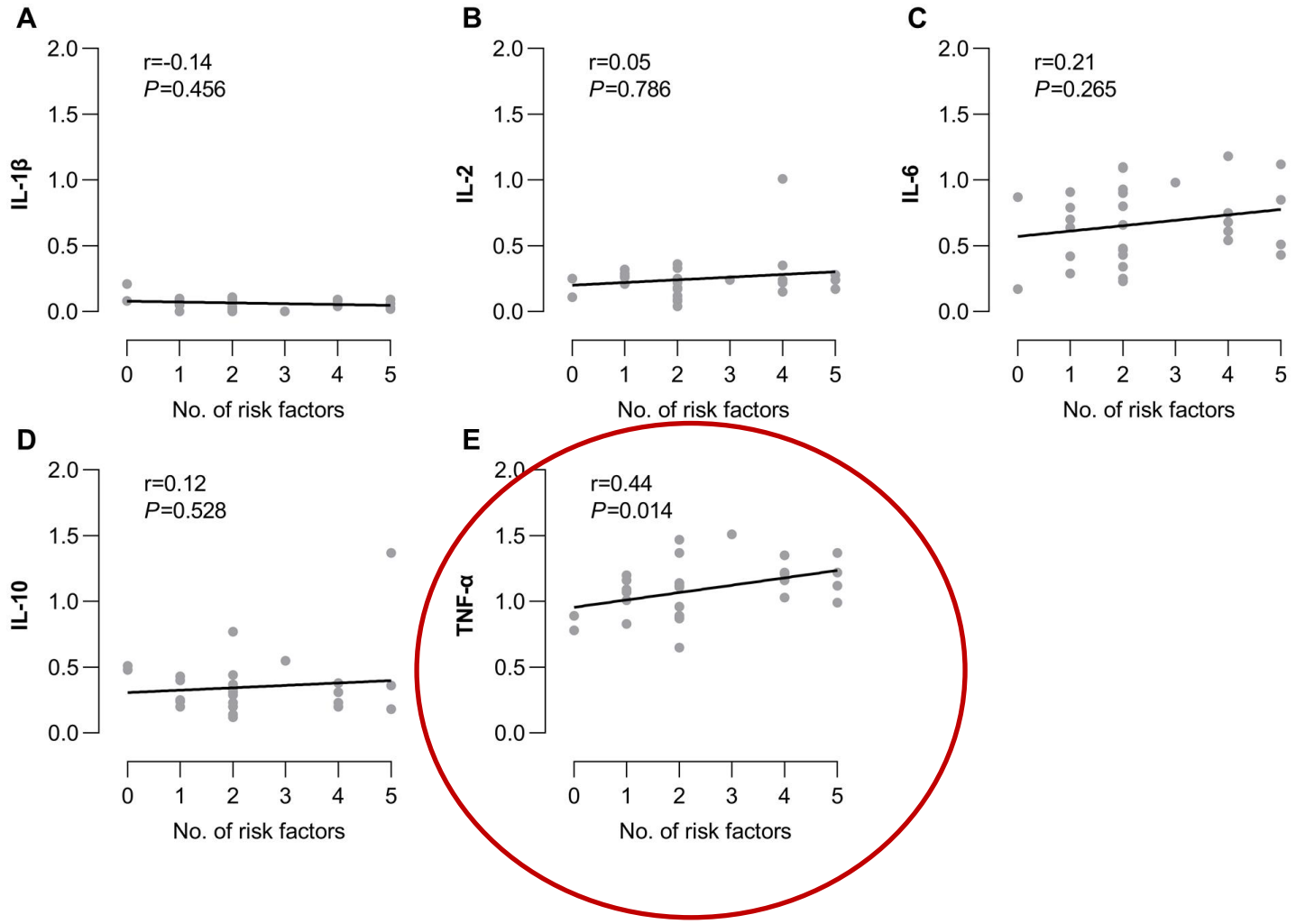
Cytokine levels in high-risk phenoconversion



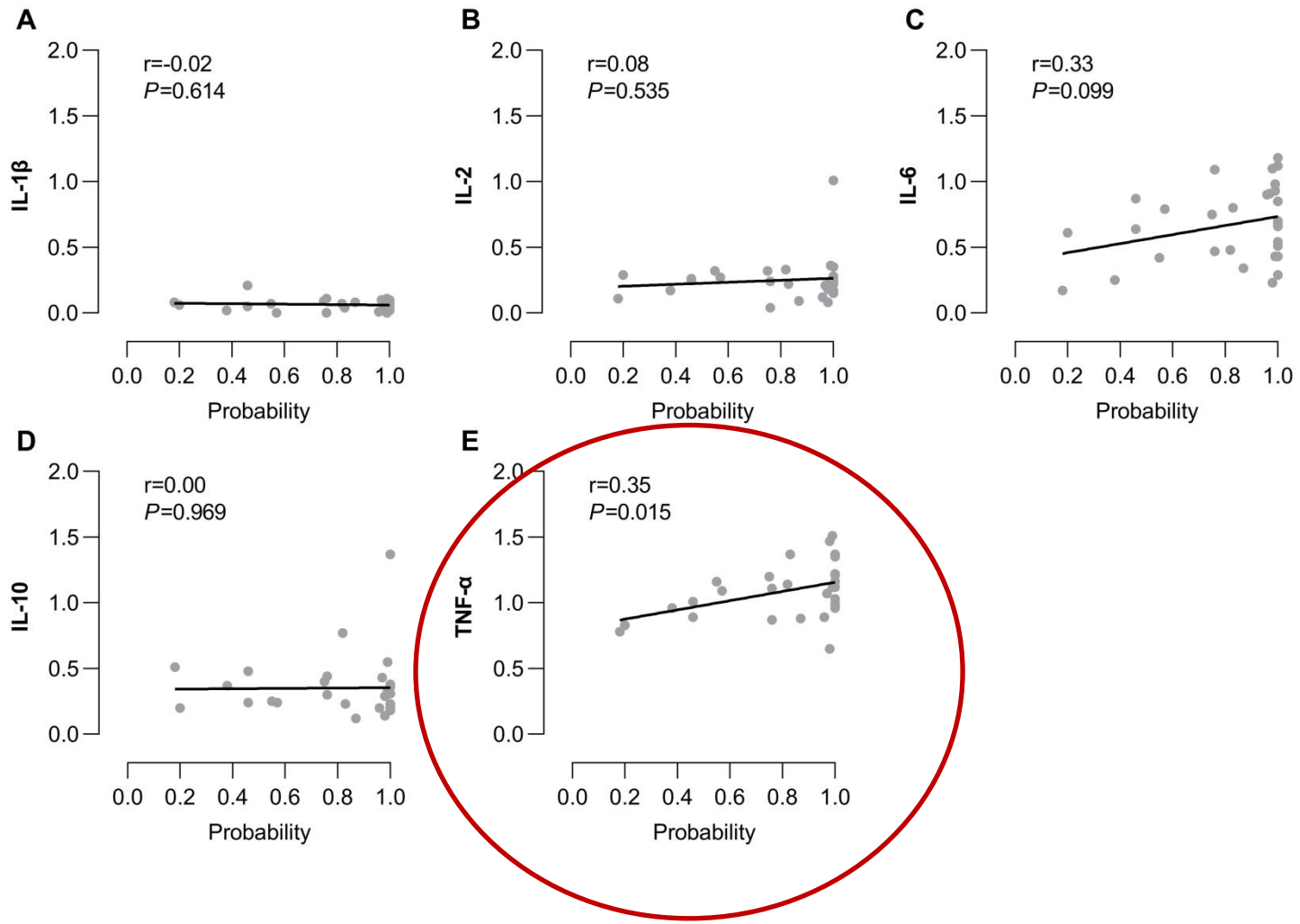
vs. without high-risk: p=0.008

vs. healthy controls: p=0.003

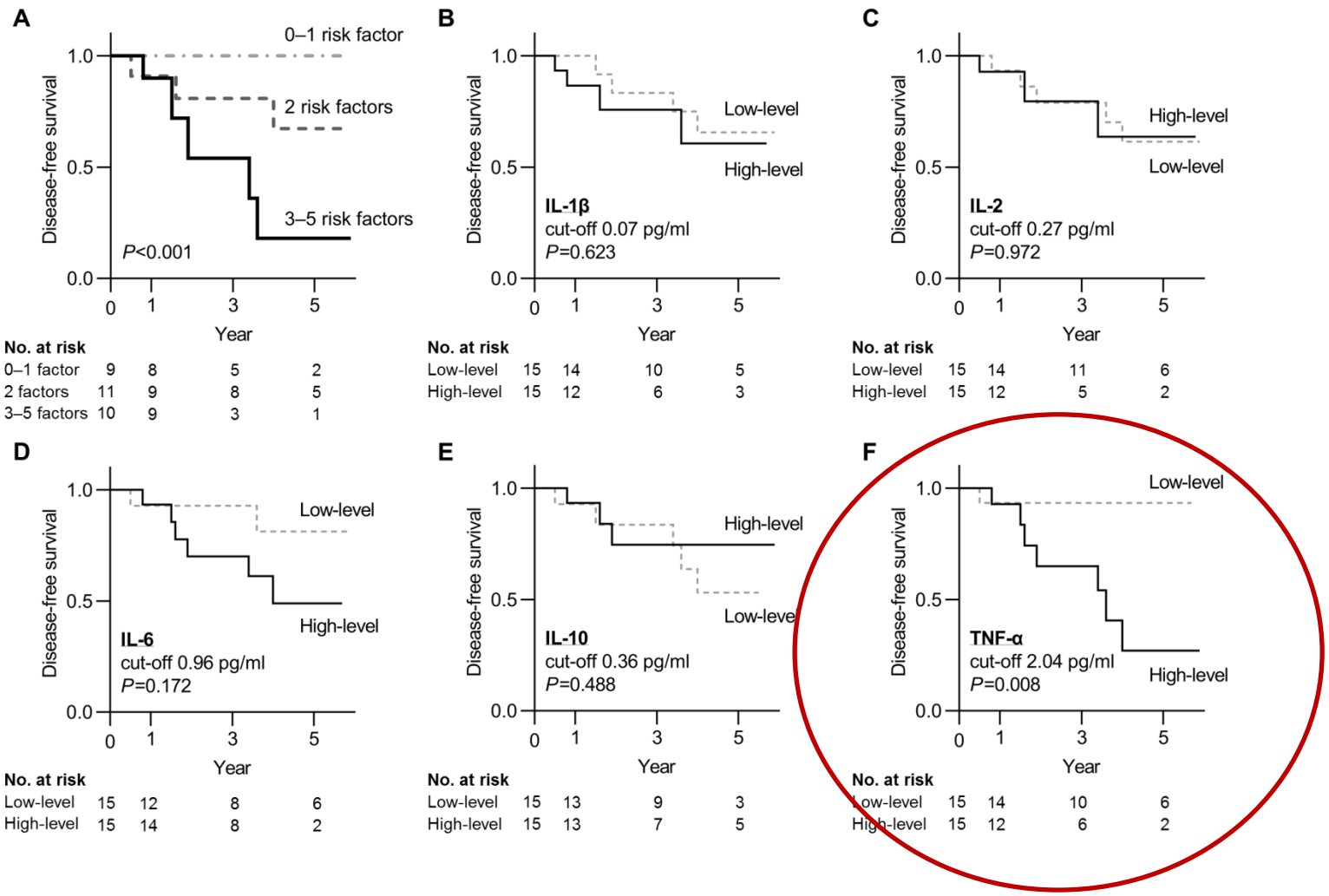
Cytokine levels and the number of risk factors



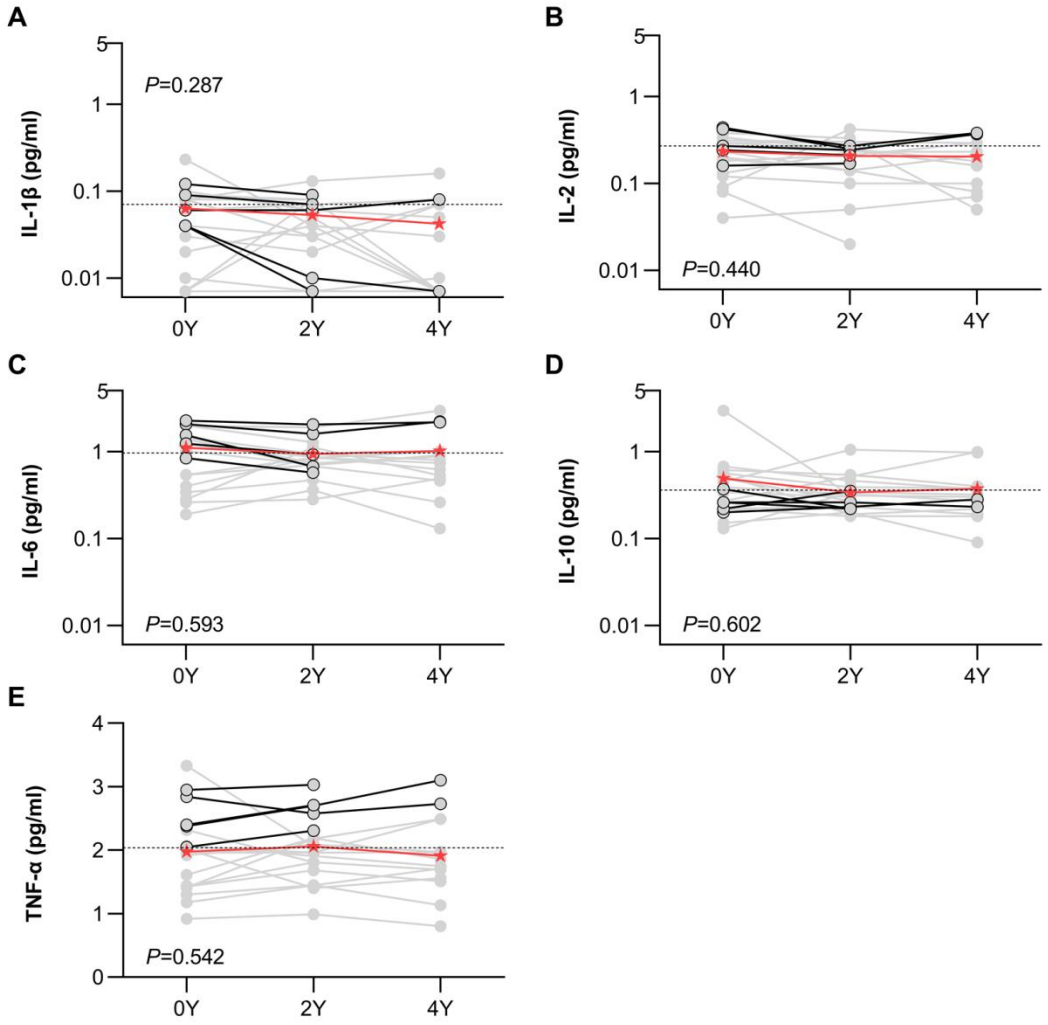
Cytokine levels and the probability of prodromal PD



Kaplan-Meier plot of disease-free survival



Longitudinal changes of cytokine levels



Discussion (1)

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Plasma immune markers in an idiopathic REM sleep behavior disorder cohort

Hui Zhang[a,b,1], Ting Wang[b,c,1], Yuan Li[a,b,1], Wei Mao[a,**], Shuwen Hao[b,c], Zhaoyang Huang[a], Piu Chan[a,b,c,d], Yanning Cai[b,c,e,*]

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[b] Department of Neurobiology, Xuanwu Hospital of Capital Medical University, Beijing, China
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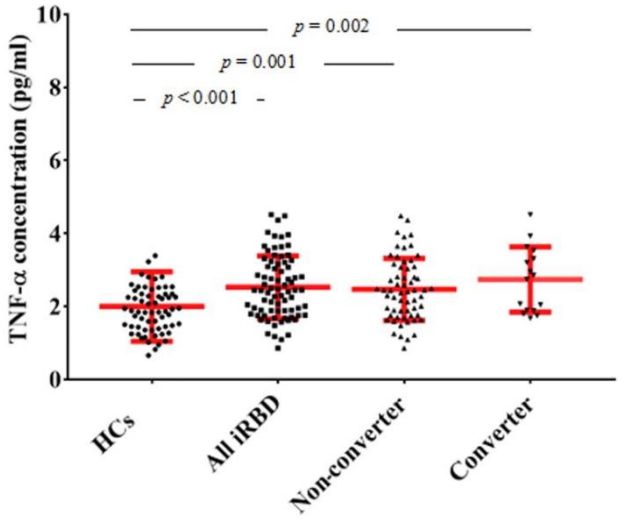
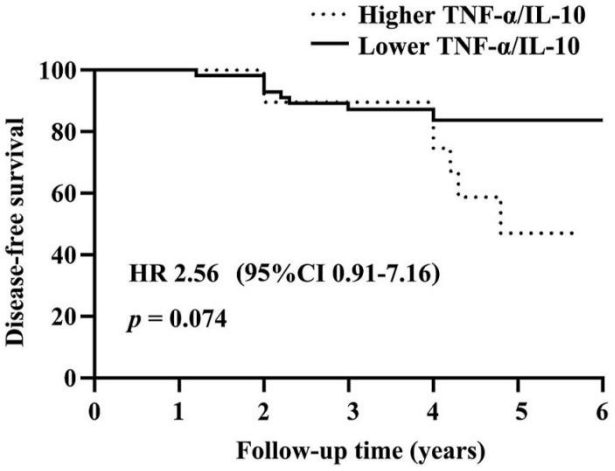
[e] Department of Biobank, Xuanwu Hospital of Capital Medical University, Beijing, China

	iRBD (n = 77)	HCs (n = 64)	*p*-value
IFN-γ (pg/ml)	3.95 (4.85)	3.77 (3.26)	0.764
IL-6 (pg/ml)	0.69 (0.57)	0.72 (0.62)	0.846
IL-8 (pg/ml)	4.99 (2.76)	5.55 (3.44)	0.461
IL-10 (pg/ml)	0.31 (0.28)	0.20 (0.18)	< **0.001**
TNF-α (pg/ml)	2.44 (1.35)	1.87 (0.91)	< **0.001**
IFN-γ/IL-10	12.57 (15.71)	17.63 (21.50)	0.024
IL-6/IL-10	2.28 (2.84)	3.51 (3.88)	**0.001**
IL-8/IL-10	13.65 (20.18)	25.53 (20.97)	< **0.001**
TNF-α/IL-10	7.18 (6.78)	8.21 (6.56)	0.076





Zhang et al. Park Relat Disord. 2020

Discussion (2)

JAMA Neurology | Original Investigation

Anti–Tumor Necrosis Factor Therapy and Incidence of Parkinson Disease Among Patients With Inflammatory Bowel Disease

Inga Peter, PhD; Marla Dubinsky, MD; Susan Bressman, MD; Andrew Park, PhD, MPH; Changyue Lu, MS; Naijun Chen, MS; Anthony Wang, PhD, MPH

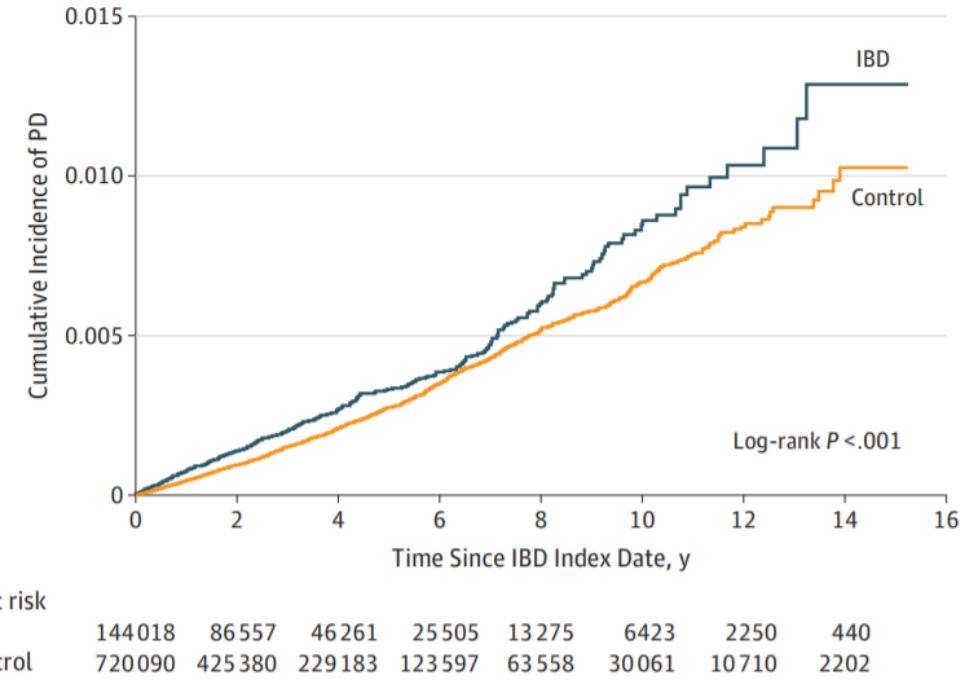


Table 3. Incidence Analysis of PD Among Patients With IBD by Anti-TNF Exposure

				Univariate Poisson Model[c]		Multivariate Poisson Model[d]	
Anti-TNF Exposure[a]	PD Event	Person-years	Rate[b]	Crude IRR (95% CI)	*P* Value	Adjusted IRR (95% CI)	*P* Value
Yes	2	23 610	0.08	0.11 (0.03-0.45)	.002	0.22 (0.05-0.88)	.03
No	369	484 423	0.76	1 [Reference]		1 [Reference]	

Peter et al. JAMA Neurol. 2018

Conclusions

- Our data suggest **a possible link between serum TNF-α and phenoconversion risk in iRBD**.

- **Large-scale studies with a broader range of cytokines** are needed to elucidate the role of peripheral TNF-α in the pathogenesis of neurodegeneration in prodromal α-synucleinopathy and to confirm the usefulness of serum TNF-α in predicting the disease conversion in iRBD.