



**XXXII Corso Nazionale di
Aggiornamento
Dialisi e Tecnologia**

Deficit Cognitivo in Dialisi

**DR. MASSIMILIANO MIGLIORI
VERSILIA**

Declino Cognitivo

- Il declino cognitivo è un termine utilizzato per descrivere il deterioramento delle funzioni cognitive, come la **memoria**, **l'attenzione**, il **ragionamento** e il **linguaggio**, che può verificarsi con l'invecchiamento o in seguito a malattie neurodegenerative.
- Questo fenomeno può manifestarsi in vari gradi, dal **lieve** (come nel caso di un normale invecchiamento) al **grave** (come nelle demenze, inclusa la malattia di Alzheimer)



Sintomi Principali

Difficoltà nel ricordare informazioni recenti

Difficoltà nell'organizzare e pianificare attività

Rallentamento del processo mentale, confusione

Impatto sulla vita quotidiana: le persone con deficit cognitivo possono sperimentare difficoltà nel mantenere l'autosufficienza e la qualità della vita.

Il Declino Cognitivo non è una condizione specifica, ma un sintomo



Invecchiamento normale: Un certo grado di declino cognitivo è comune con l'avanzare dell'età, ma non influisce significativamente sulla vita quotidiana.



Demenza: Condizioni patologiche come l'**Alzheimer**, la **demenza vascolare** o la **demenza frontotemporale** comportano un progressivo deterioramento delle capacità cognitive.



Disturbi legati a malattie neurologiche: Ad esempio, malattie come il morbo di **Parkinson**, la **sclerosi multipla** e altri disturbi neurodegenerativi possono causare declino cognitivo.



Cause reversibili: Alcuni fattori come deficienze nutrizionali, disfunzioni ormonali o effetti collaterali di farmaci possono causare un declino cognitivo temporaneo.

Declino Cognitivo nella Malattia Renale Cronica

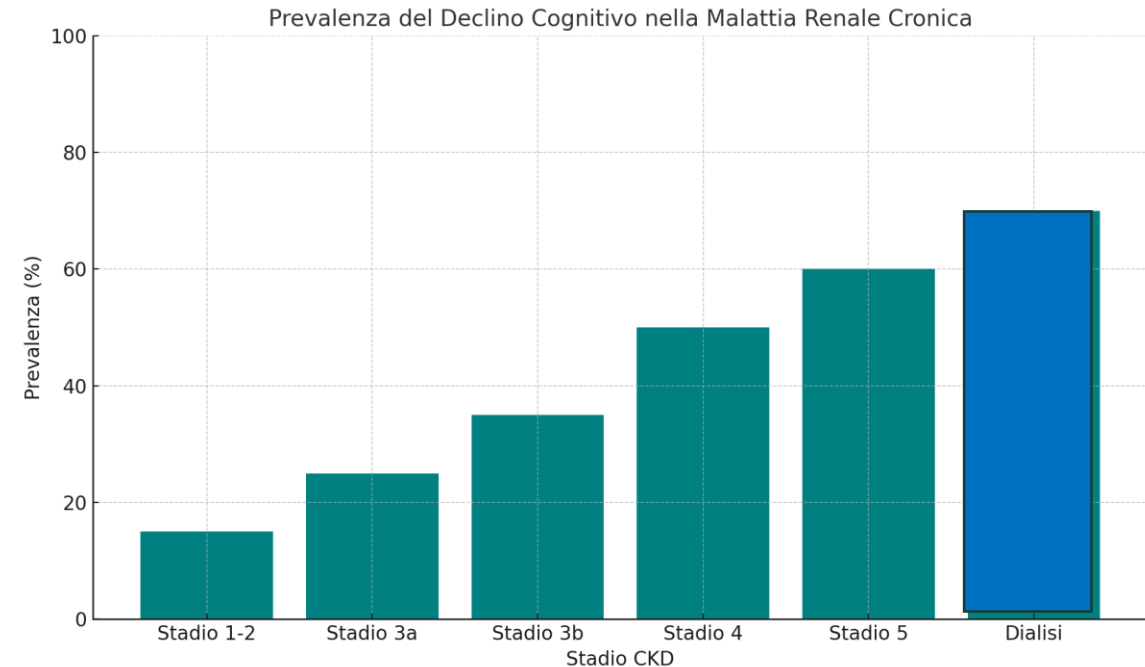
La CKD Colpisce Milioni di Persone Nel Mondo. Si stima che il **10% della popolazione mondiale sia affetto da MRC** (Coresh et al., 2007)

Alta Prevalenza di Compromissione Cognitiva Tra I Pazienti Con CKD (30-70%).

Il Declino Cognitivo nella CKD È Multifattoriale.

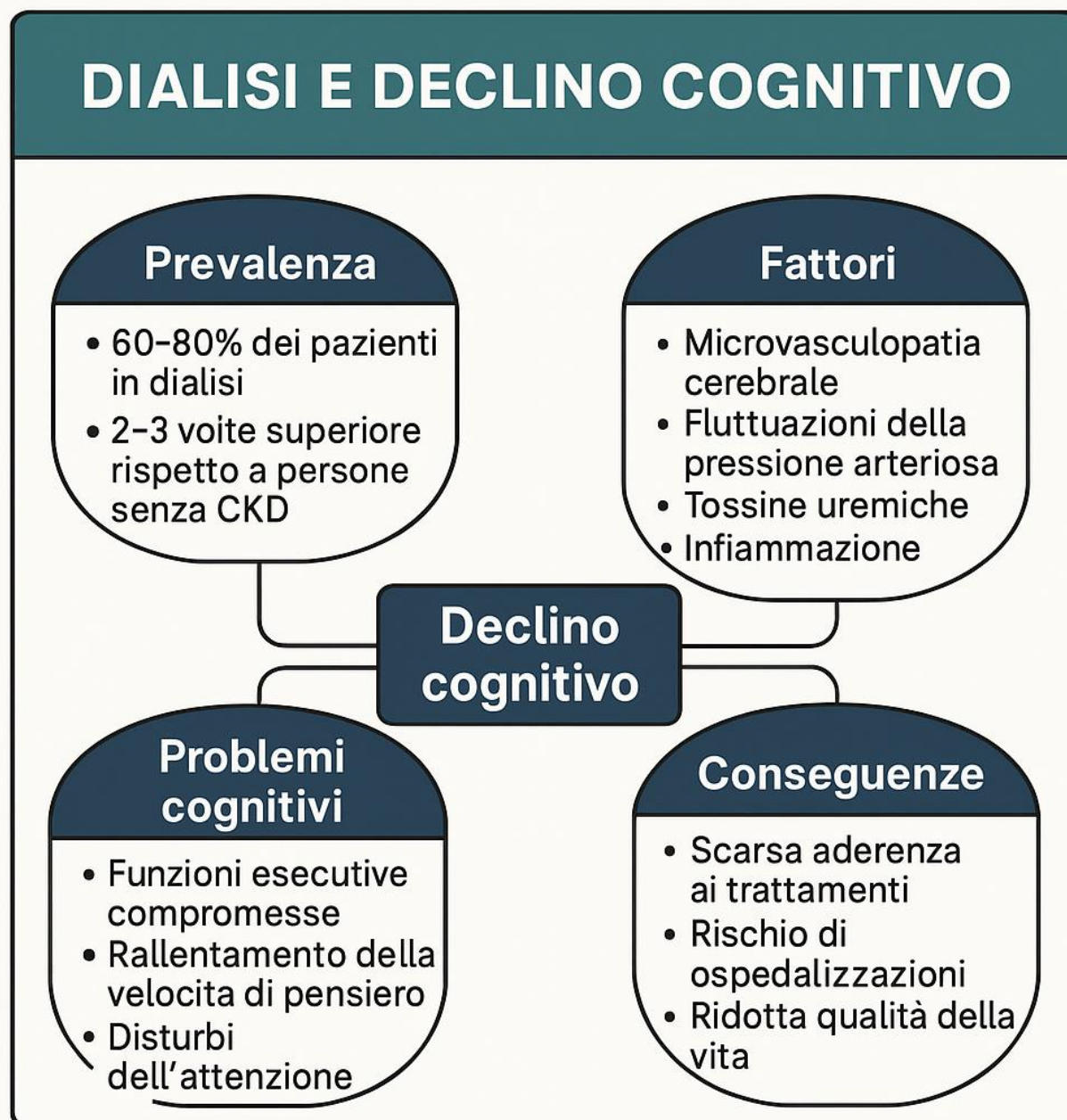
Prevalenza del Declino Cognitivo nella Malattia Renale Cronica

Stadio CKD	Definizione	Prevalenza Declino Cognitivo
Stadio 1-2	GFR \geq 60 ml/min (con danno renale)	10-20%
Stadio 3a	GFR 45-59 ml/min	20-30%
Stadio 3b	GFR 30-44 ml/min	30-40%
Stadio 4	GFR 15-29 ml/min	40-60%
Stadio 5 (pre-dialisi)	GFR $<$ 15 ml/min	50-70%
Dialisi	Pazienti in trattamento dialitico	60-80%

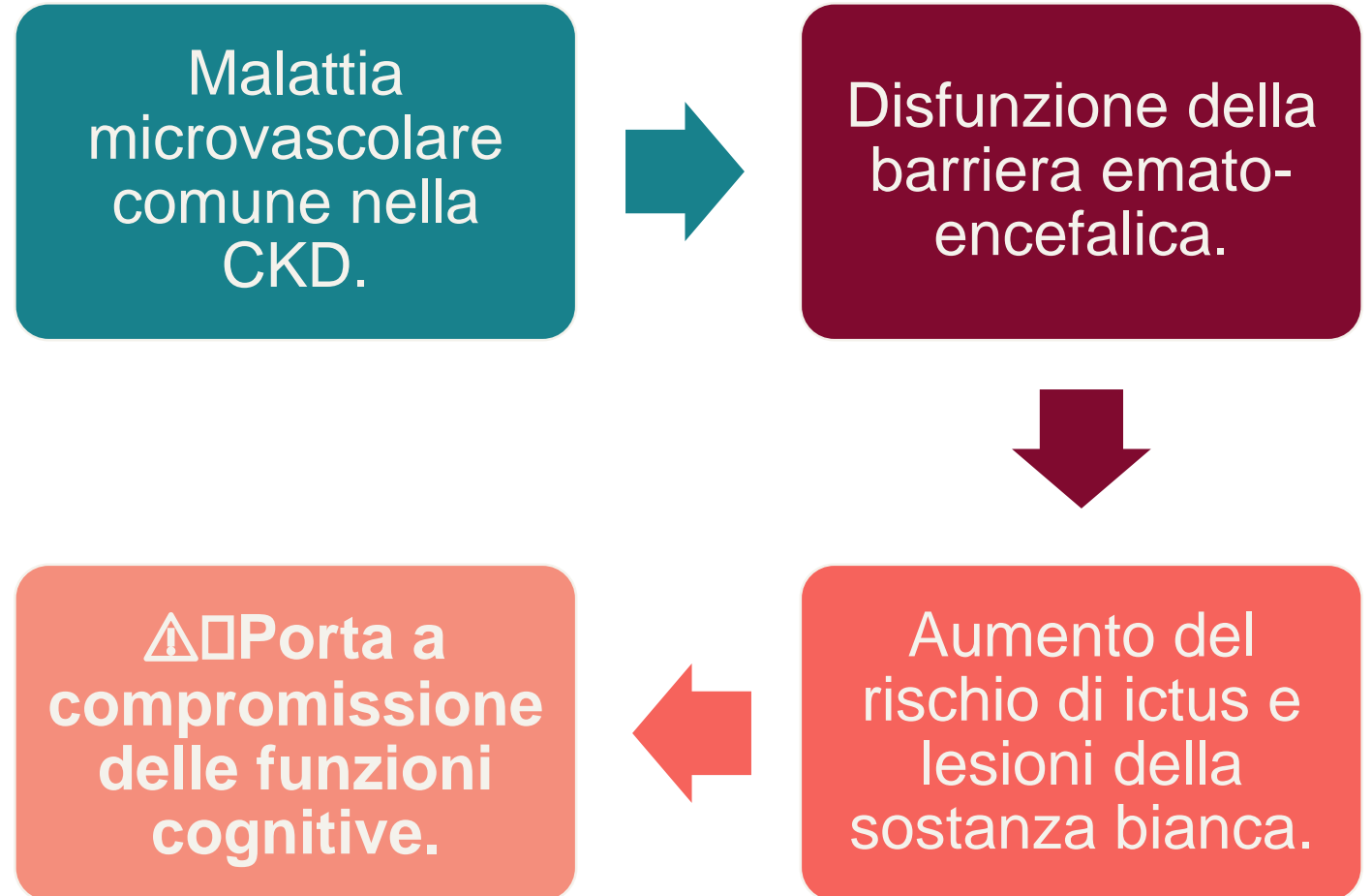


Da: Etgen T, et al. American Journal of Nephrology, 2012. Bugnicourt JM, et al. JASN 2013. Murray AM. Advances in Chronic Kidney Disease, 2008. Sarnak MJ, et al Neurology, 2013.

Fattori che contribuiscono al declino nei dializzati



Danno Cerebrovascolare



Malattia Cerebrovascolare.



I pazienti con CKD hanno una prevalenza elevata di malattie cardiovascolari e dei loro fattori di rischio, come diabete e ipertensione.



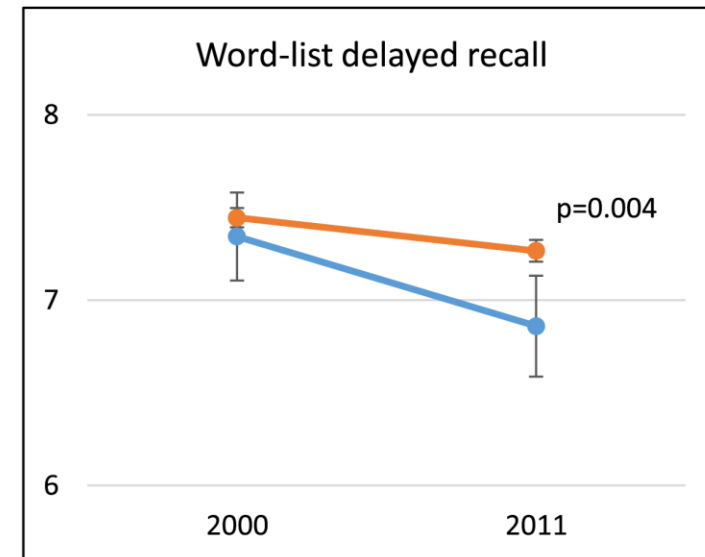
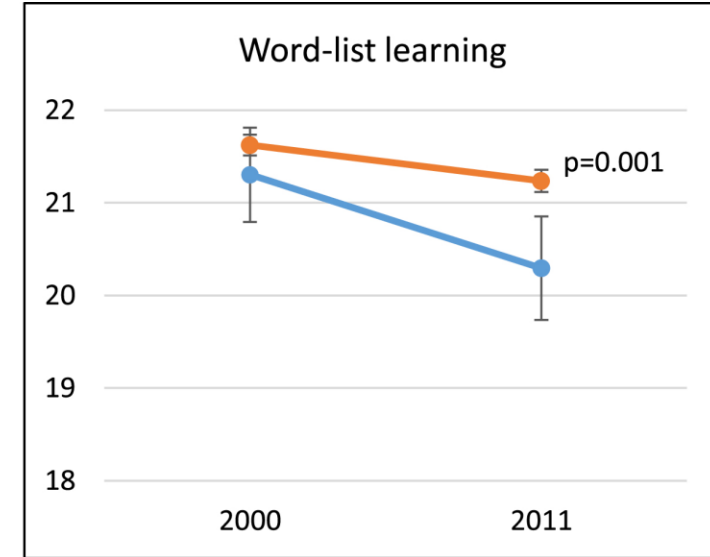
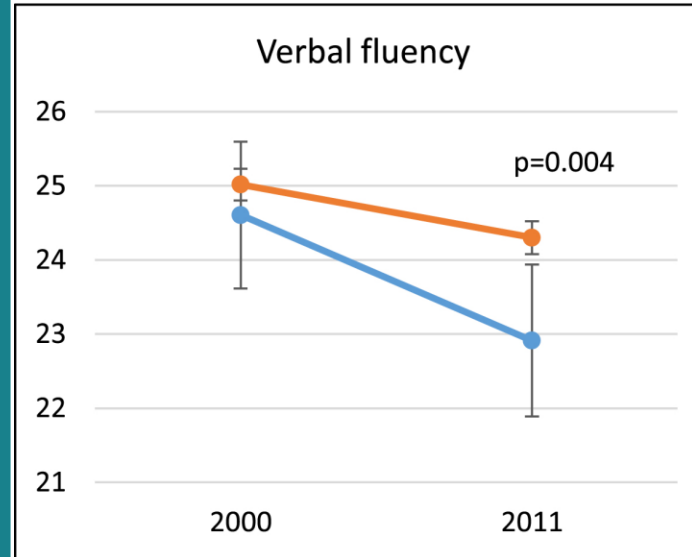
La malattia cerebrovascolare è associata a deficit cognitivi, in particolare nelle funzioni esecutive e di elaborazione.



L'albuminuria è correlata a una funzione esecutiva peggiore e a un aumento del rischio di demenza.

Albuminuria and Microalbuminuria as Predictors of Cognitive Performance in a General Population: An 11-Year Follow-Up Study

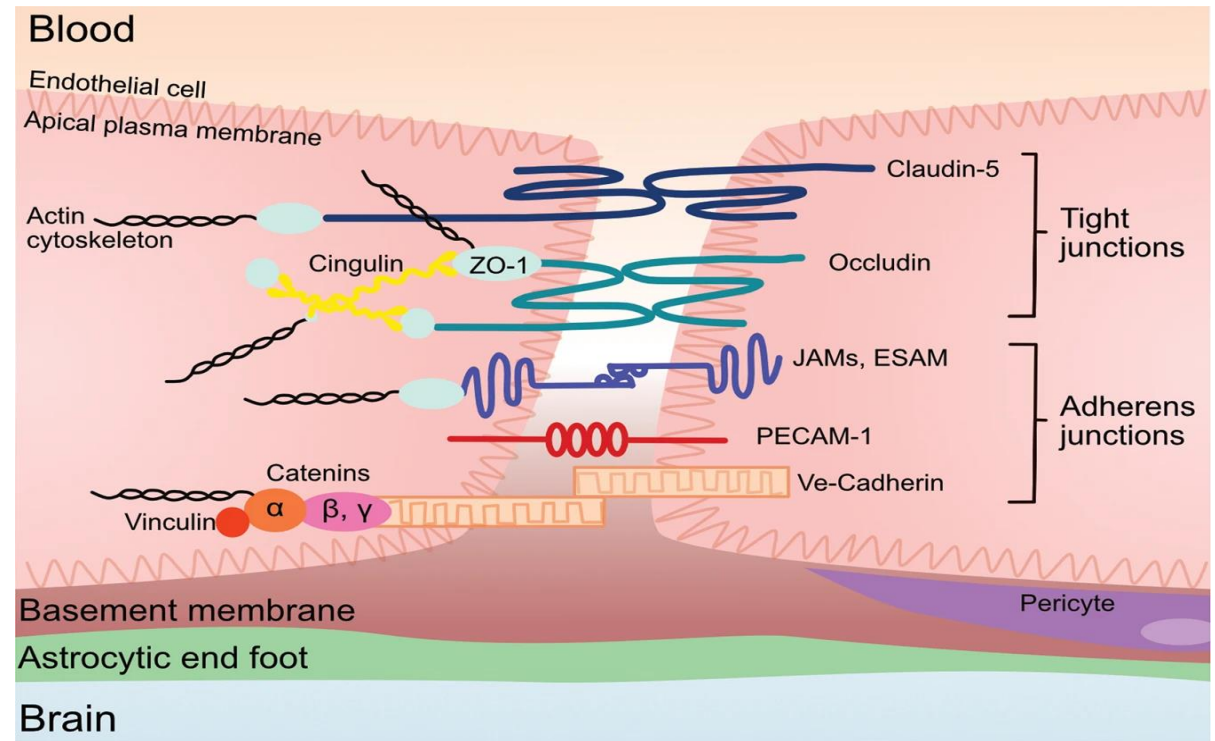
Journal of Alzheimer's Disease 62(2), 2018, 635-648,



No albuminuria **orange** line
Micro- or macroalbuminuria **blue** line.

Endothelial cell tight junctions and adherens junction proteins

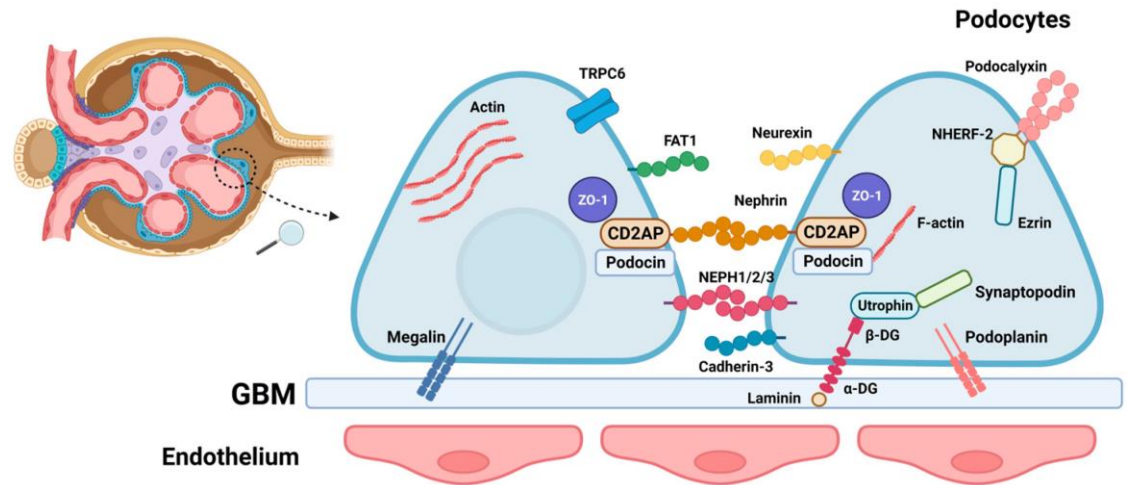
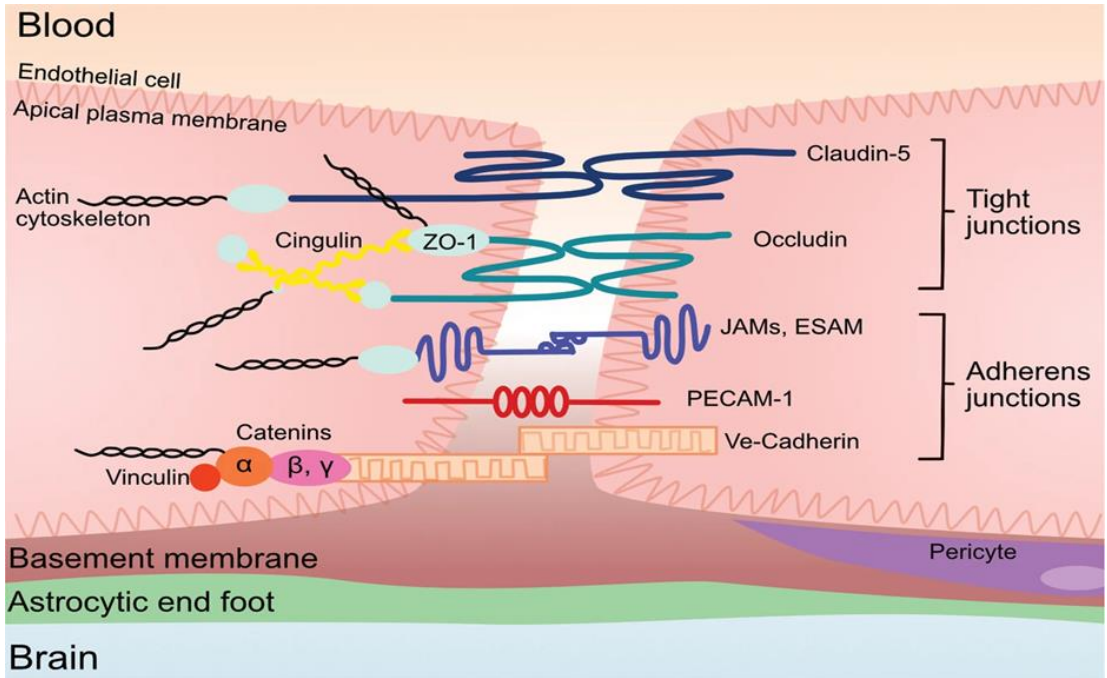
Knox, E.G et al. Mol Psychiatry 27, 2659–2673 (2022).



The tight junction proteins include claudin-5, occludin, and zonula occludins (ZO-1,2,3). Claudin-5 and occludin are both transmembrane proteins while the zonula occludens are intracellular proteins.

The adherens junctions include transcellular components, JAMs, ESAM, PECAM-1, and Ve-cadherin.

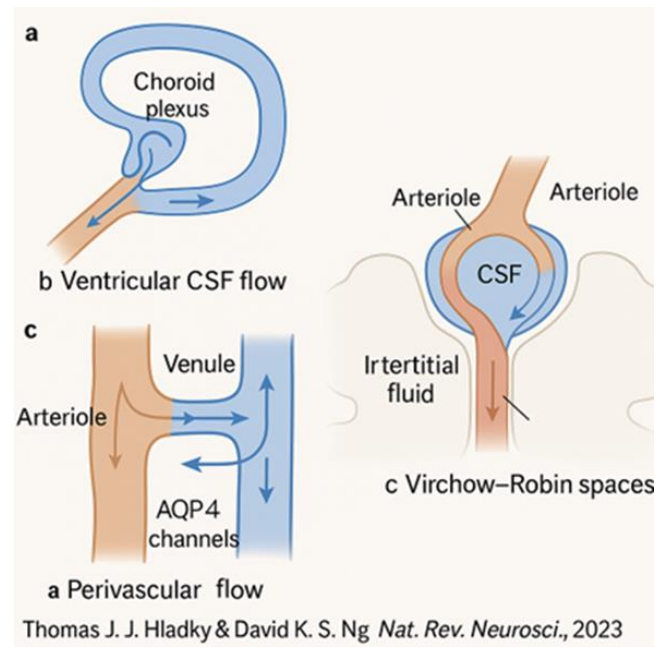
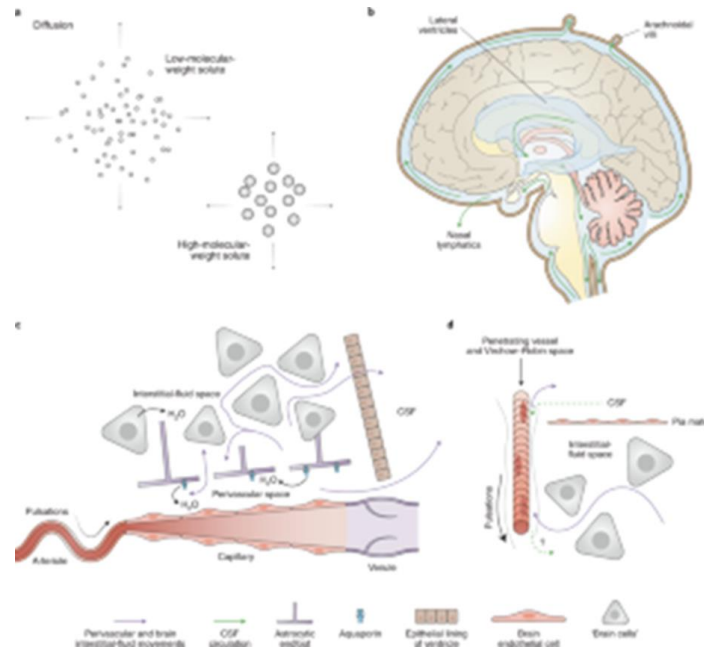
The cytoplasmic catenins form a complex with Ve-cadherin. Actin cytoskeleton helps to anchor the junctional proteins in endothelial cells.



Eppure mi ricorda qualcosa.....



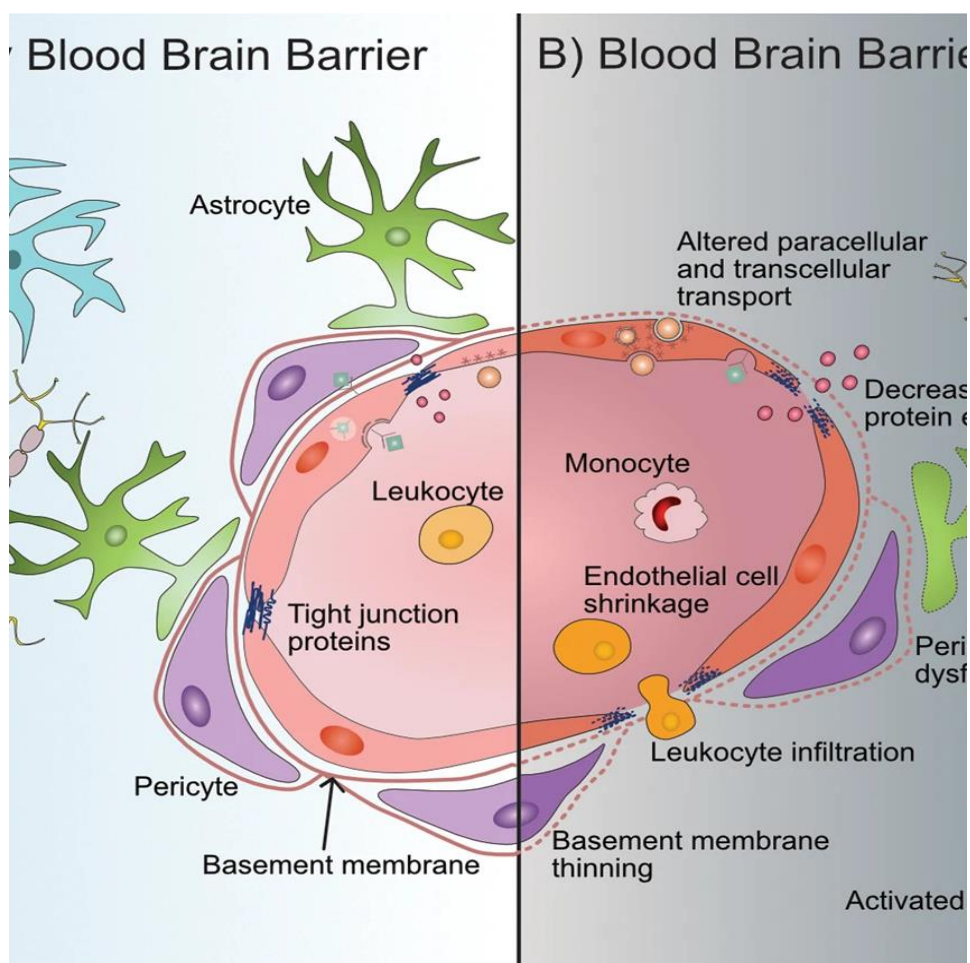
<p>a) Diffusione Motore: moto browniano Dispersione: Simmetrica attorno al punto di origine Più rapida per molecole a basso peso molecolare Effetto dell'invecchiamento: inalterato</p>	<p>c) Convezione negli spazi perivascolari e interstiziali</p> <p>Forze motrici</p> <ul style="list-style-type: none"> • Pulsazioni arteriose • „Acqua libera” tramite canali AQP4 dastróciti • Aumento della pressione oncotifc <p>Percorso del fluido</p> <ul style="list-style-type: none"> • Tra canali turtuosi nel parenchima cerebrale • Spinta verso compartimenti di CSF per gradiente oncotifc
<p>b) Convezione nel liquido cerebrospinale (CSF)</p> <ol style="list-style-type: none"> 1. Produzione Plesso coroideo nei ventricoli 2. Circolazione Flusso all'interno del sistema ventricolare 3. Riassorbimento Granulazioni aracnoidee (villi) Drenaggio verso i linfatici nasali 	<p>d) Scambi CSF–liquido interstiziale tramite spazi di Virchow–Robin</p> <ul style="list-style-type: none"> • Spazi intorno ai vasi penetranti (Virchow-Robin) • Mescolamento facilitato dalle pulsazioni vascolari • Possibile penetrazione profonda del CSF nel



Movement of brain fluids via diffusion and convection.

BANKS, W.A., ET AL. NAT AGING 1, 243–254 (2021).

Schematic representation of the blood-brain barrier (BBB) in a healthy state and during BBB breakdown.

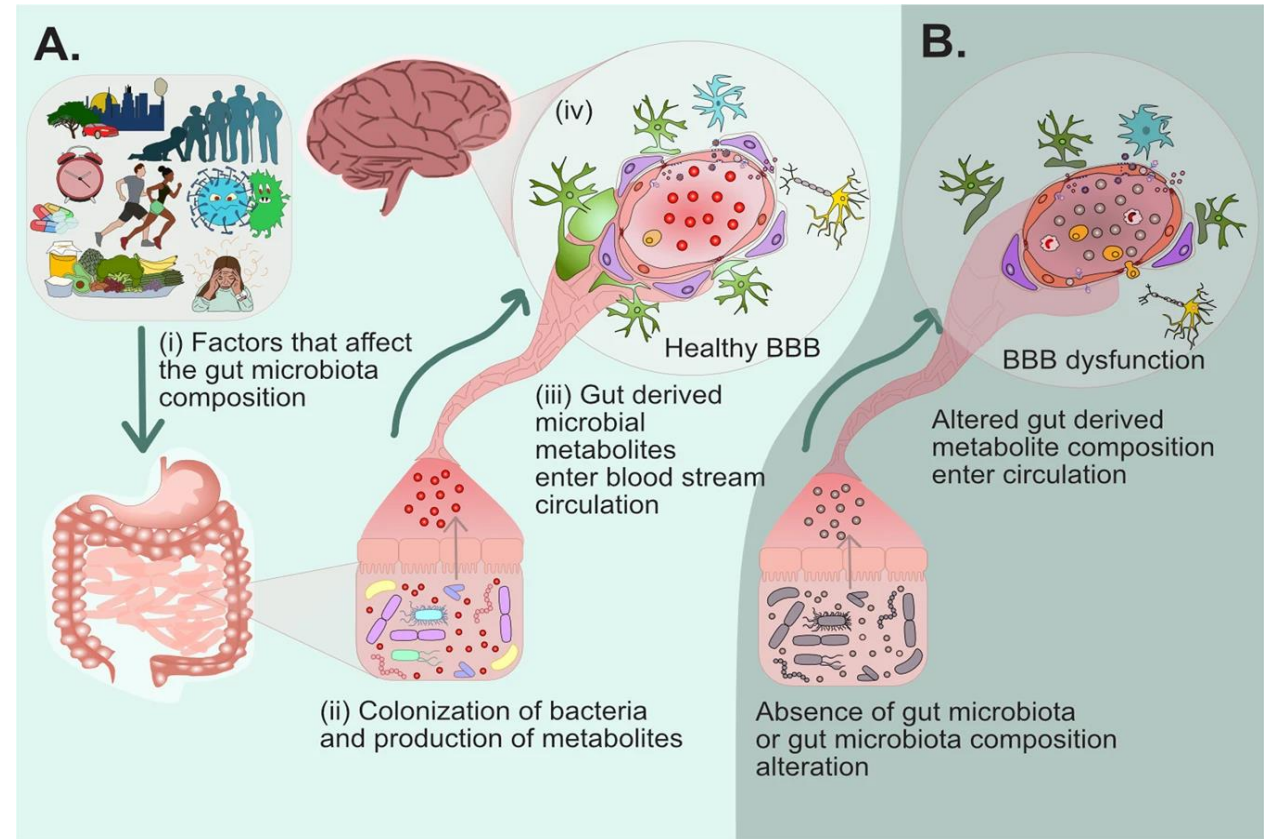


Endothelial cell alterations such as loss of tight junction proteins, endothelial cell shrinkage, changes in molecular transport at the paracellular level, and transcellular level in some cases, and increased leukocyte infiltration.

In some disruption models pericyte dysfunction or loss is apparent as well as astrocyte changes such as swollen or detached end feet.

Microglia can also become activated, and neurons may experience demyelination or become damaged.

Relationship between the gut microbiome and the BBB



In the absence of a gut microbiota (germ-free animals) or where there are compositional alterations in the gut microbiota, microbial metabolites are not produced or are differentially produced that can enter systemic circulation and the lack or increase in microbial-derived metabolites is associated with BBB dysfunction.

Meccanismo di Produzione delle Tossine Uremiche nella CKD

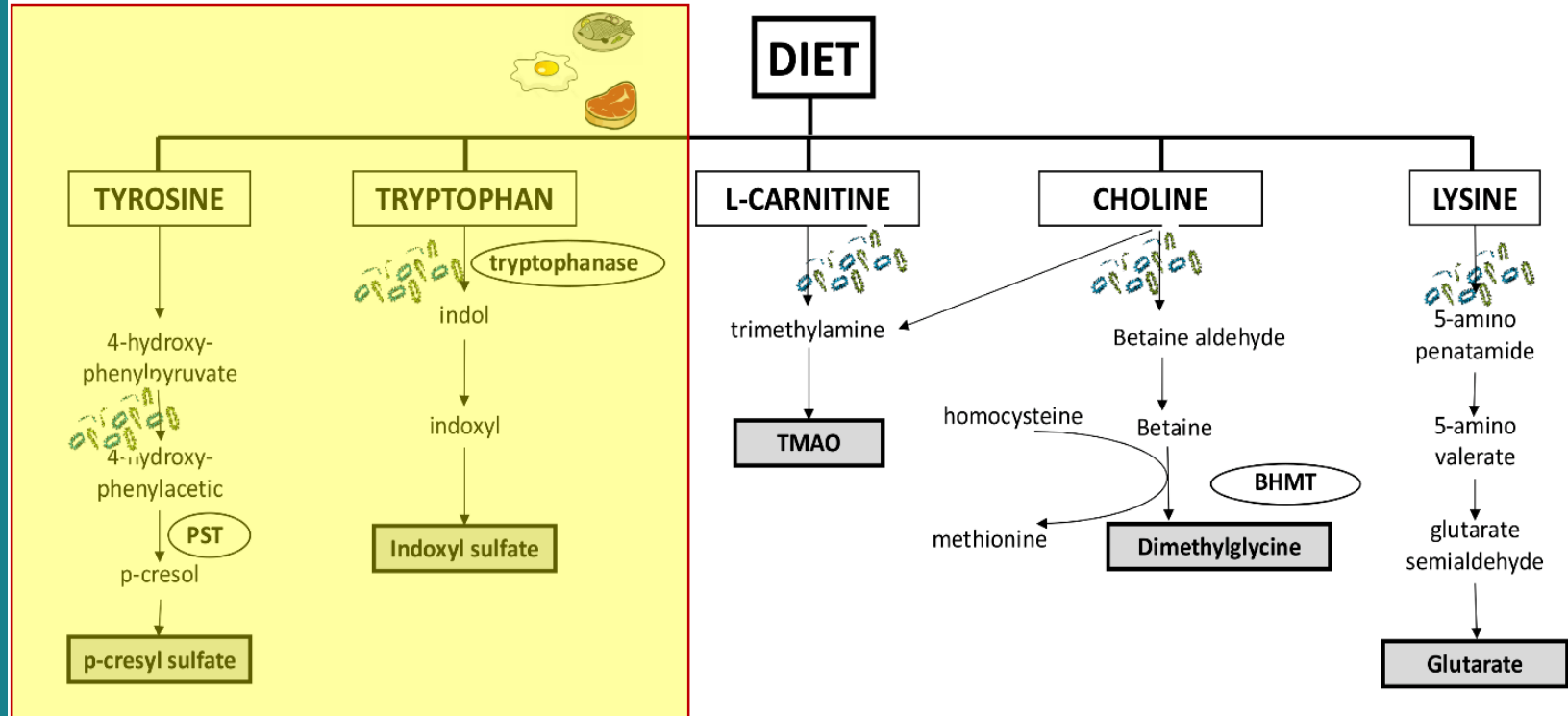
Mishima E., Abe T. (2022). *Toxins*, 14(2), 146.


Graboski A.L., Redinbo M.R. (2020). *Toxins*, 12(9), 590.

Rysz J., et al. (2021). *Toxins*, 13(4), 252

Fase	Dettaglio
Disbiosi intestinale	Riduzione batteri buoni, aumento batteri putrefattivi
	Triptofano → Indolo → Indoxyl sulfate
Metabolismo batterico	Tirosina → p-cresolo → p-cresyl sulfate
	Colina → TMA → TMAO
Assorbimento e trasformazione	Assorbimento intestinale → Conversione epatica
Accumulo	Diminuita escrezione renale in CKD
Tossicità	Infiammazione, stress ossidativo, danno cardiovascolare, prurito, anemia

Meccanismo di Produzione delle Tossine Uremiche nella CKD



 : Intestinal microbiota

Mishima E., Abe T. (2022). *Toxins*, 14(2), 146.
 Graboski A.L., Redinbo M.R. (2020). *Toxins*, 12(9), 590.
 Rysz J., et al. (2021). *Toxins*, 13(4), 252

Tossine Uremiche e Asse Intestino-Cervello

L'accumulo di tossine uremiche compromette le cellule cerebrali.

Alterazioni del microbiota intestinale influenzano la neuroinfiammazione.

Disfunzione neuronale e alterazione della sinapsi.

🔍 **Elementi chiave:**
Indoxylsolfato, P-cresylsolfato.

Experimental Study	Experimental Model		Results
Bobot et al. [7]	Rats	Blood Brain Barrier (BBB)	↑ indoxyl sulfate levels
Jing et al. [9]	Rats	Blood Brain Barrier (BBB)	↓ ZO-1 ↓ occludin ↓ JAM-1
Natale et al. [13]	Rats	Hippocampal CA1 neurons	↑ NMDA currents ↑ AMPA currents
D'Hooge et al. [14]	Mice	Spinal cord neurons	↓ GABAergic transmission ↑ Ca ²⁺ intracellular influx ↑ Na intracellularinflux
Yu et al. [15]	Rats	Hippocampal CA1 neruons	↓ evoked fEPSP following LTP induction
Watanabe et al. [17]	HT-22 cell line and rats	Hippocampal neurons	↓ cell viability ↑ numbers of pyknotic neuronal cells
Lin et al. [20]	Human	Astrocytes	↑ ROS activation ↓ cell-protective factors ↑ MAPK-dependent apoptosis ↑ ERK, MEK, JNK and p38 phosphorylation

Effect of uremic toxins on neuronal and molecular working damage

1	The Uremic Toxicity of Indoxyl Sulfate and p-Cresyl Sulfate: A Systematic Review	Vanholder R, Schepers E, et al.	J Am Soc Nephrol	2014	DOI:10.1681/ASN.2013101062
2	Cognitive dysfunction in chronic kidney disease: state of the art and call to action	Viggiano D, Wagner CA, Martino G, et al.	Nephrol Dial Transplant	2020	DOI:10.1093/ndt/gfz243
3	Cognitive disorders and dementia in CKD: the neglected kidney-brain axis	Bugnicourt JM, Godefroy O, et al.	J Am Soc Nephrol	2013	DOI:10.1681/ASN.2012080866
4	Clinical impact and mechanisms of cognitive dysfunction in CKD	Toyonaga J, Tsuruya K.	Clin Exp Nephrol	2021	DOI:10.1007/s10157-020-01954-7
5	Dementia and cognitive impairment in ESRD: diagnostic and therapeutic strategies	Kurella Tamura M, Yaffe K.	Kidney Int	2011	DOI:10.1038/ki.2011.102
6	Uremic Toxins and BBB Disruption in CKD	(Autori vari)	Eur J Pharm Sci	2023	PubMed
7	Uremic toxins in cerebrovascular disease and cognitive decline	(Autori vari)	PubMed Review	2018	PubMed
8	Neurological complications and uremic toxins in CKD	(Autori vari)	PubMed Review	2021	PubMed
9	CKD and Cognitive Impairment: The Kidney-Brain Axis	(Autori vari)	Kidney Diseases (Karger)	2022	Link
10	Uremic toxins and brain dysfunction: Emerging concepts	(Autori vari)	PubMed Review	2024	PubMed

Uremic Toxins and Brain

Azioni delle Tossine Uremiche

↑ Infiammazione sistemica

```
graph TD; A[↑ Infiammazione sistemica] --> B[↑ Stress ossidativo]; B --> C[↑ Danno endoteliale (vascolare)]; C --> D[↑ Progressione della CKD]; D --> E[↑ Rischio cardiovascolare];
```

↑ Stress ossidativo

↑ Danno endoteliale (vascolare)

↑ Progressione della CKD

↑ Rischio cardiovascolare

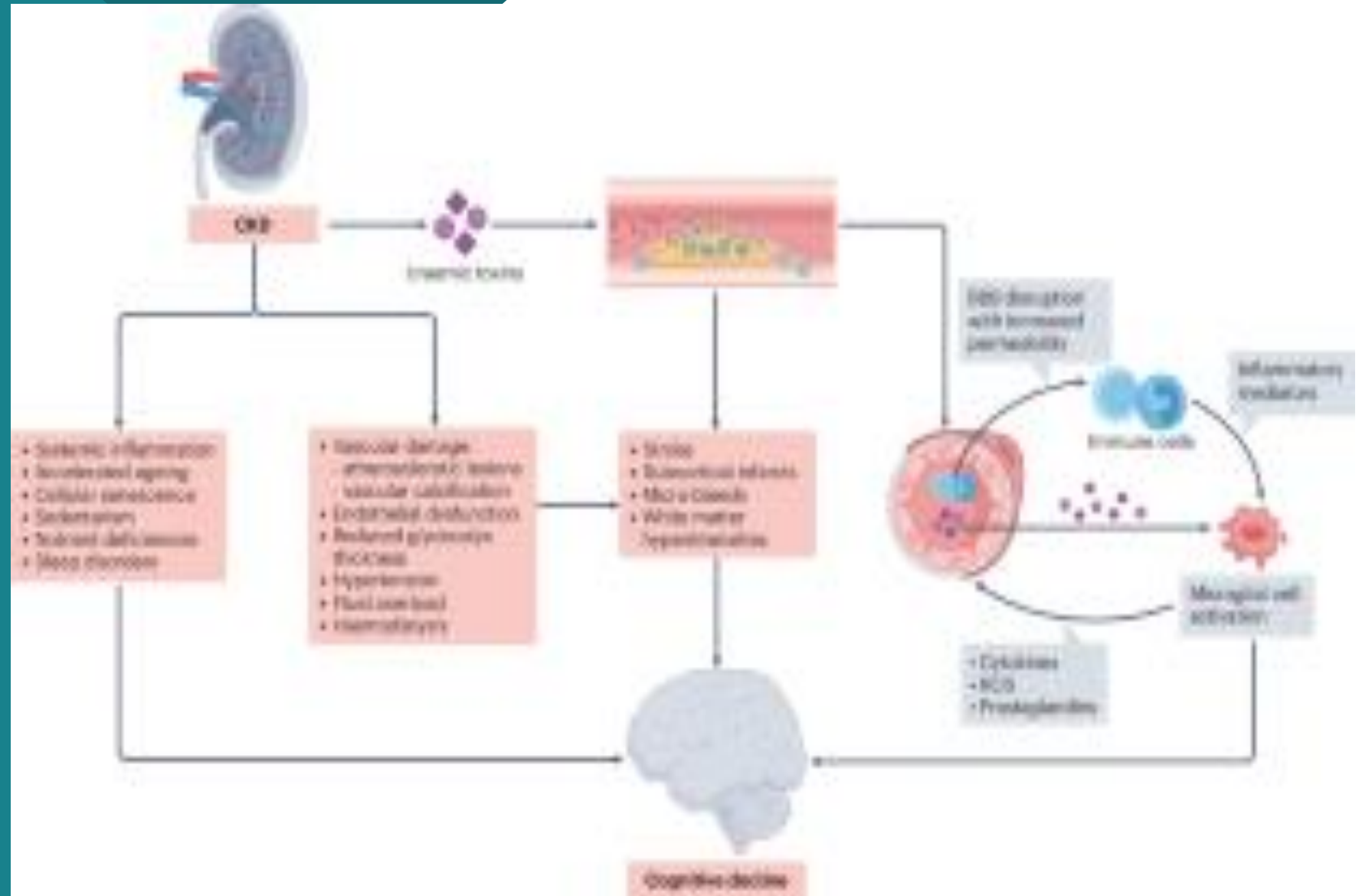
Infiammazione e Disfunzione Metabolica

- **L'infiammazione Cronica Favorisce l'Invecchiamento Cellulare.**
- **Lo Stress Ossidativo Danneggia le Strutture Neuronal.**
- **Collegamenti con Patologie Simili all'Alzheimer.**

‡ I Pazienti con CKD Sperimentano un "Invecchiamento Cerebrale Precoce".



CKD-associated factors with potential to accelerate cognitive decline.



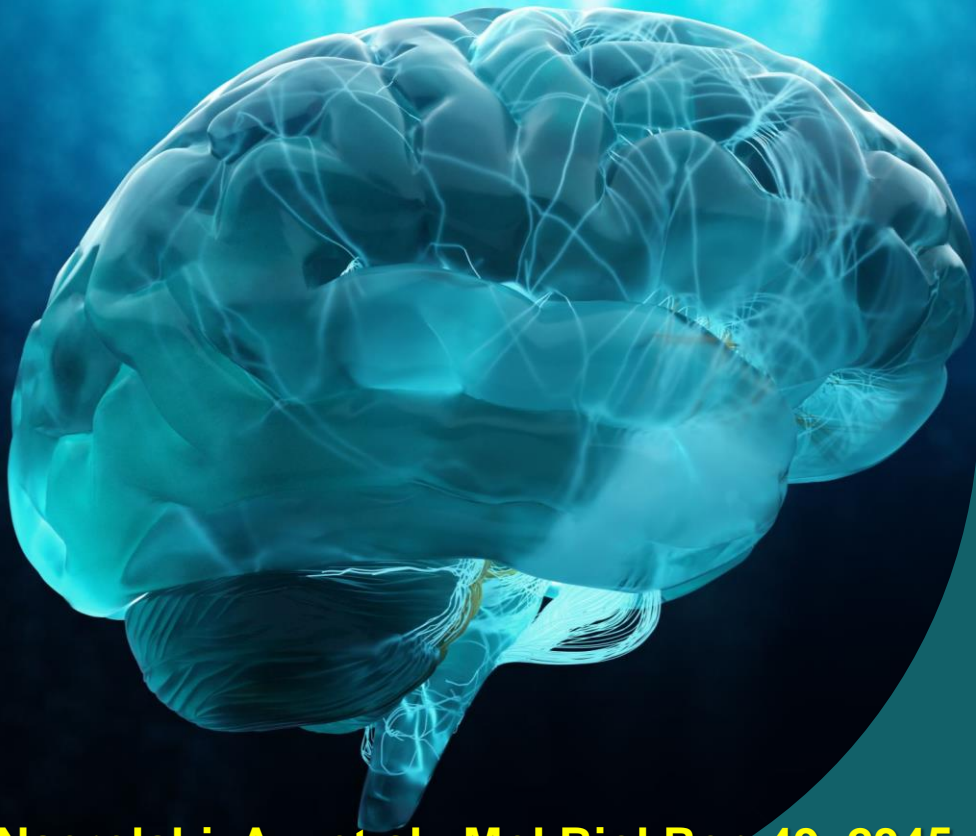
Classificazione e funzioni dei Fattori Neurotrofici



- I NTFs sono piccole proteine suddivise in quattro famiglie:
- **Neurotrofine** (es. BDNF, NGF, NT-3, NT-4/5)
- **Neurochine**
- **Ligandi della famiglia GDNF** (Glial cell line-derived neurotrophic factor)
- **CDAF/MANF** (Cerebral dopamine neurotrophic factor/mesencephalic astrocyte-derived neurotrophic factor)

Questi fattori possono prevenire la morte cellulare e promuovere la crescita e la funzionalità neuronale in condizioni degenerative.

Neurotrofine



- Le **neurotrofine** sono proteine secrete che sostengono la sopravvivenza, la crescita e la differenziazione dei neuroni, nonché la plasticità sinaptica. Le più studiate in relazione alla funzione cognitiva sono:

- **NGF** (Nerve Growth Factor)
- **BDNF** (Brain-Derived Neurotrophic Factor)
- **NT-3** (Neurotrophin-3)
- **NT-4/5** (Neurotrophin-4/5)
- **GDNF** (Glial cell line-Derived Neurotrophic Factor)

Diminuzione dei livelli di neurotrofine con l'invecchiamento

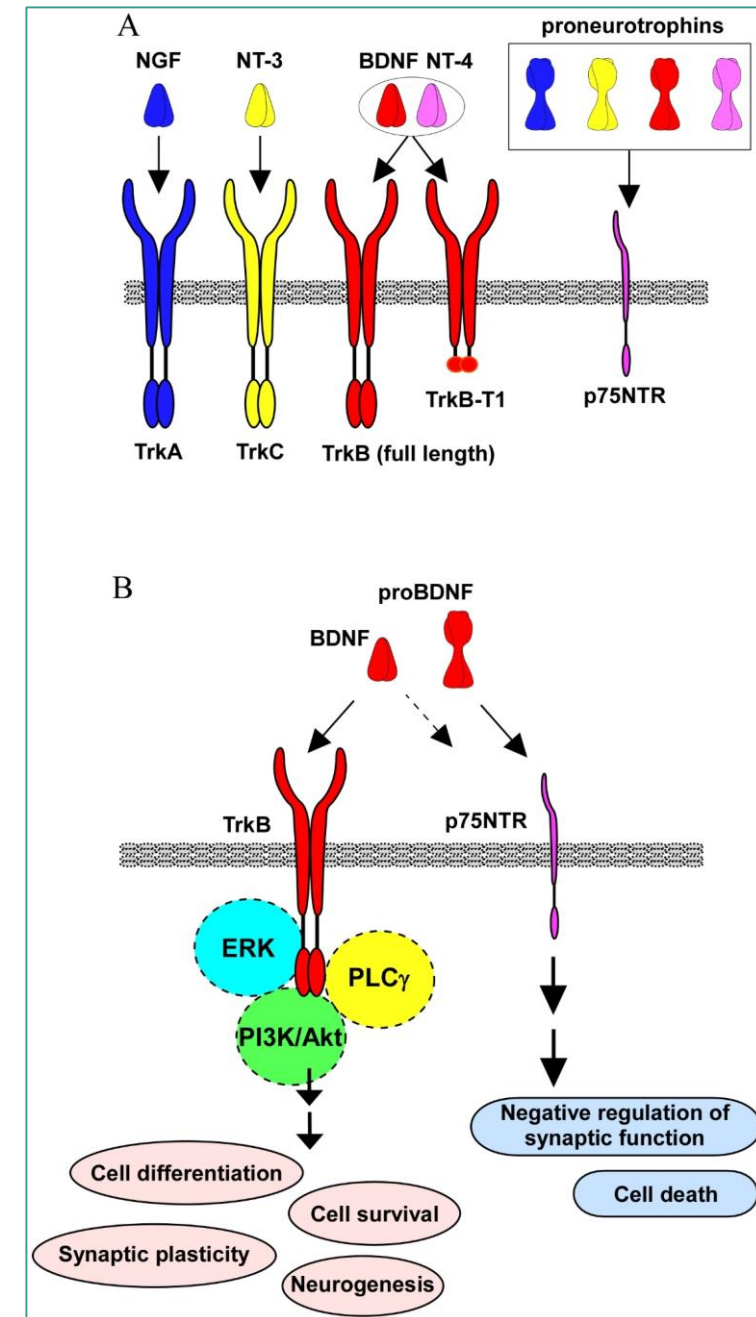
- **BDNF/TrkB**: con l'avanzare dell'età e in patologie neurodegenerative si osserva una **riduzione dell'attività del recettore TrkB e dei livelli di BDNF nell'ippocampo e nella corteccia**, aree chiave per memoria e apprendimento
- **NGF** e **GDNF**: analoghe flessioni sono state documentate nei cervelli di modelli animali e in campioni umani, contribuendo a sinaptopatie e perdite neuronali



Gao, L.. et al. Transl Neurodegener 11, 4 (2022).

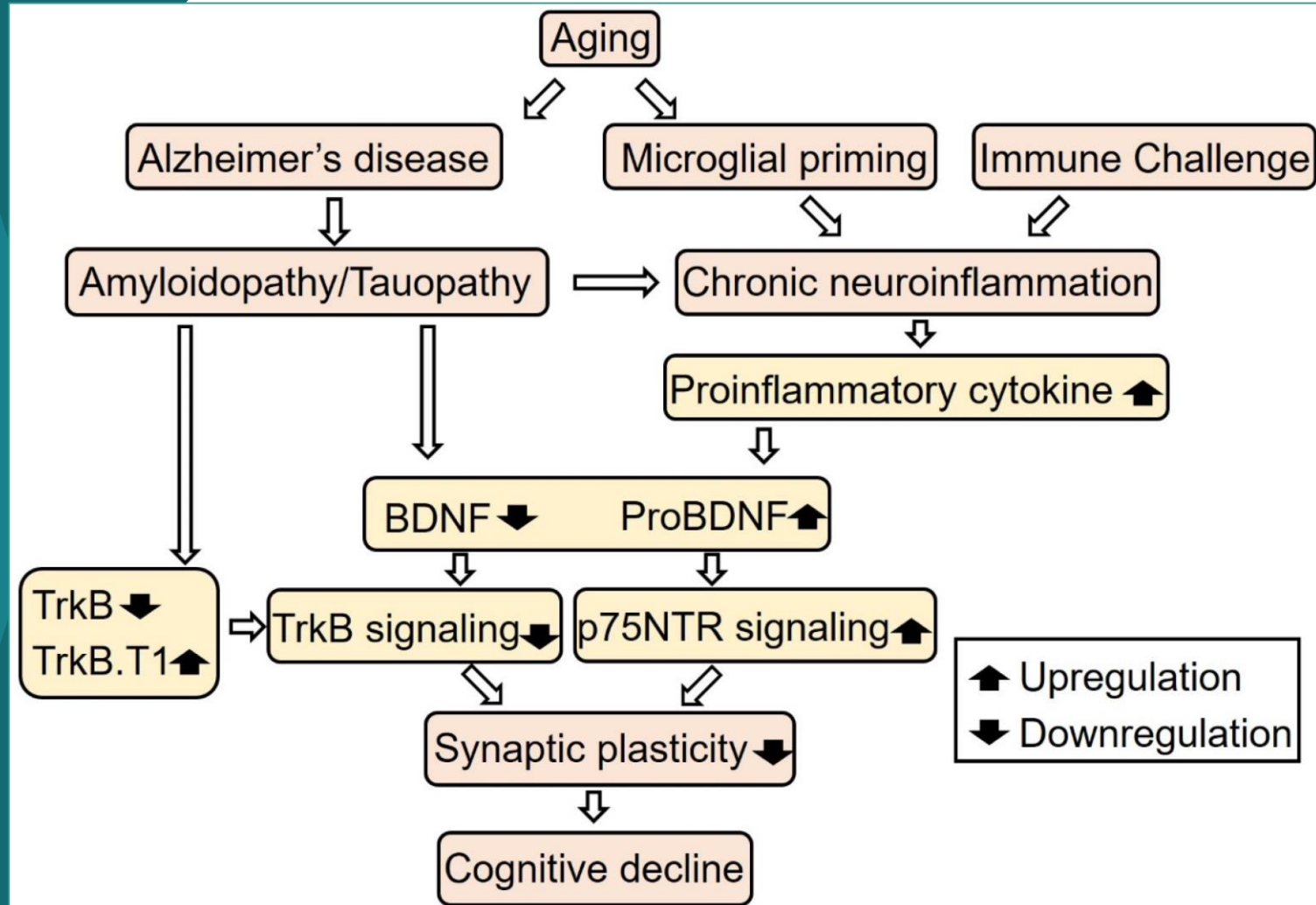
The Role of Neurotrophin Signaling in Age-Related Cognitive Decline and Cognitive Diseases

INT. J. MOL. SCI. 2022,
23(14), 7726



Aging increases the risk of Alzheimer's disease and neuroinflammation via microglial priming, resulting in the **disbalance of BDNF/ProBDNF and/or TrkB/TrkB.T1, an impairment of synaptic plasticity, and a decline in cognitive function.**

Int. J. Mol. Sci. 2022, 23(14), 7726



Neurotrofine nel Declino Cognitivo

It has been reported that **patients with AD have significantly lower peripheral blood BDNF levels** than healthy controls [Mol Psychiatr. 2016;22:312.].

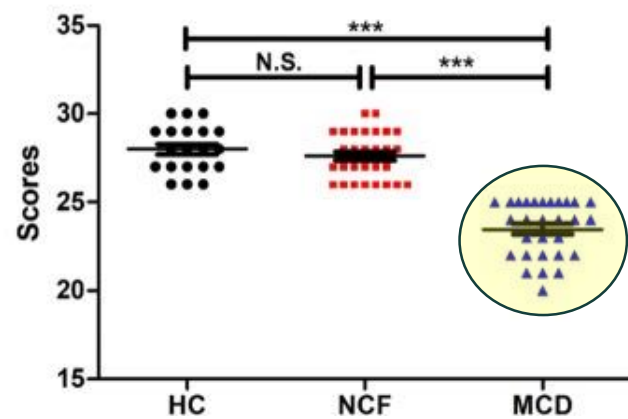
A **higher serum BDNF** level has also been linked to a **reduced risk** of dementia [JAMA Neurol. 2014;71(1):55–61.].

When compared with the age- and sex-matched healthy controls, blood BDNF levels initially increase during the early stages of AD and then **reduce in patients with moderate or severe AD** [Mol Neurobiol. 2017;54(9):7297–311].

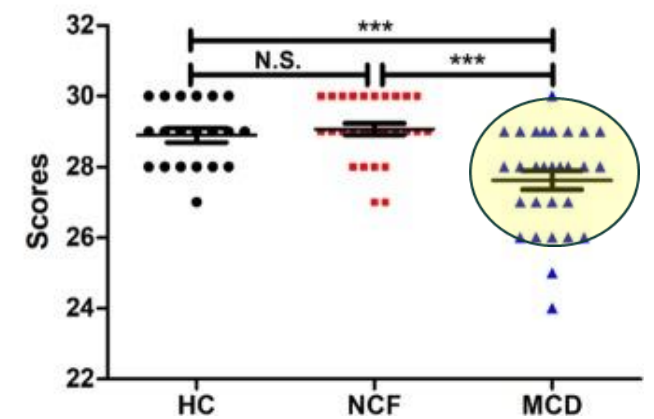
Assessment of cognitive function by MoCA and MMSE in HD.

Sci Rep. 2018 16;8:12250

A Montreal Cognitive Assessment MoCA



B Mini-Mental State Examination MMSE

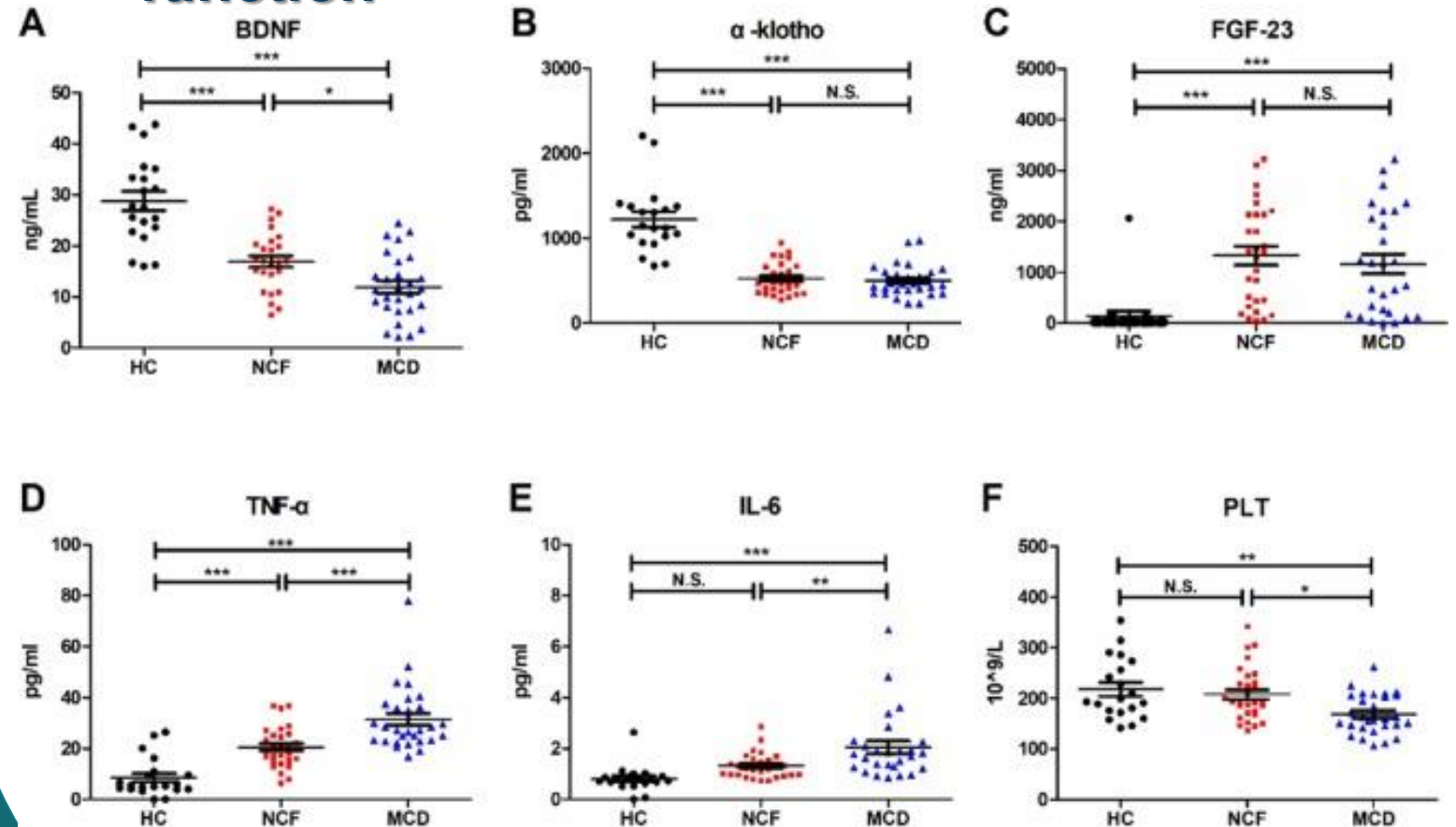


- (A) MoCA scores among the three study groups ($F_{2,75} = 83.21$, $p < 0.0001$).
- (B) MMSE scores among the groups ($F_{2,75} = 13.89$, $p < 0.0001$). Data are shown as means \pm standard error of means ($n = 20-29$); *** $p < 0.001$.
- HC: healthy control; MCD: mild cognitive decline; MMSE: Mini-Mental State Examination; MoCA; NCF: normal cognitive function; N.S.: not significant.

Serum levels of biomarkers among the three study groups.

Sci Rep. 2018 16;8:12250

HC: healthy control; MCD: mild cognitive decline; NCF: normal cognitive function



Declino Cognitivo, Dialisi, BDNF

Livelli ↓ di BDNF nel gruppo
HD associati a
peggioramento cognitivo
(MoCA/MMSE)

Piastrine: principali depositi
di BDNF; variazioni PLT
influenzano livelli plasmatici

BDNF come biomarcatore
per monitoraggio cognitivo e
stato infiammatorio

Interventi: esercizio e
training cognitivo
intradialitico, modulazione
infiammazione

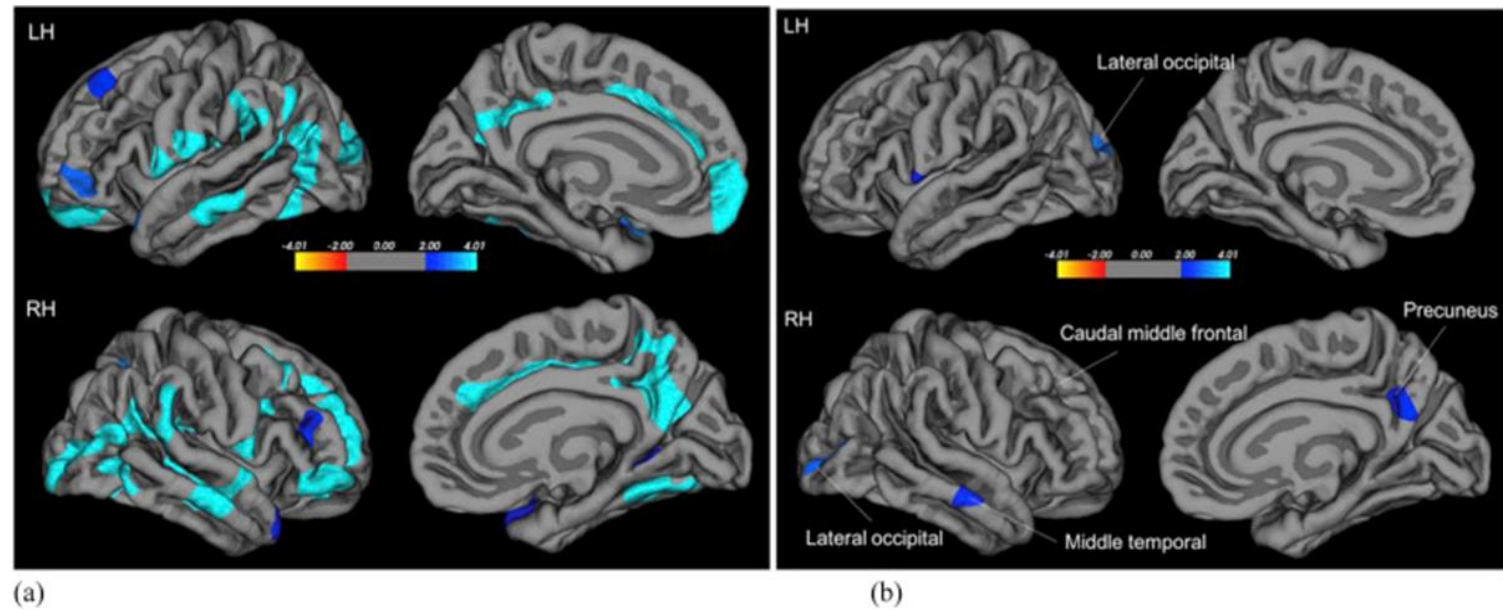


Original Article

Cognitive impairment in patients with end-stage renal disease: Accelerated brain aging?

Yen-Ling Chiu Hsiu-Hui Tsaid Yen-Jun Laid Hsin-Yi Tsenge Yen-Wen Wuf Yu-Sen Pengag Cheng-Ming Chiu Yi-Fang Chuangij

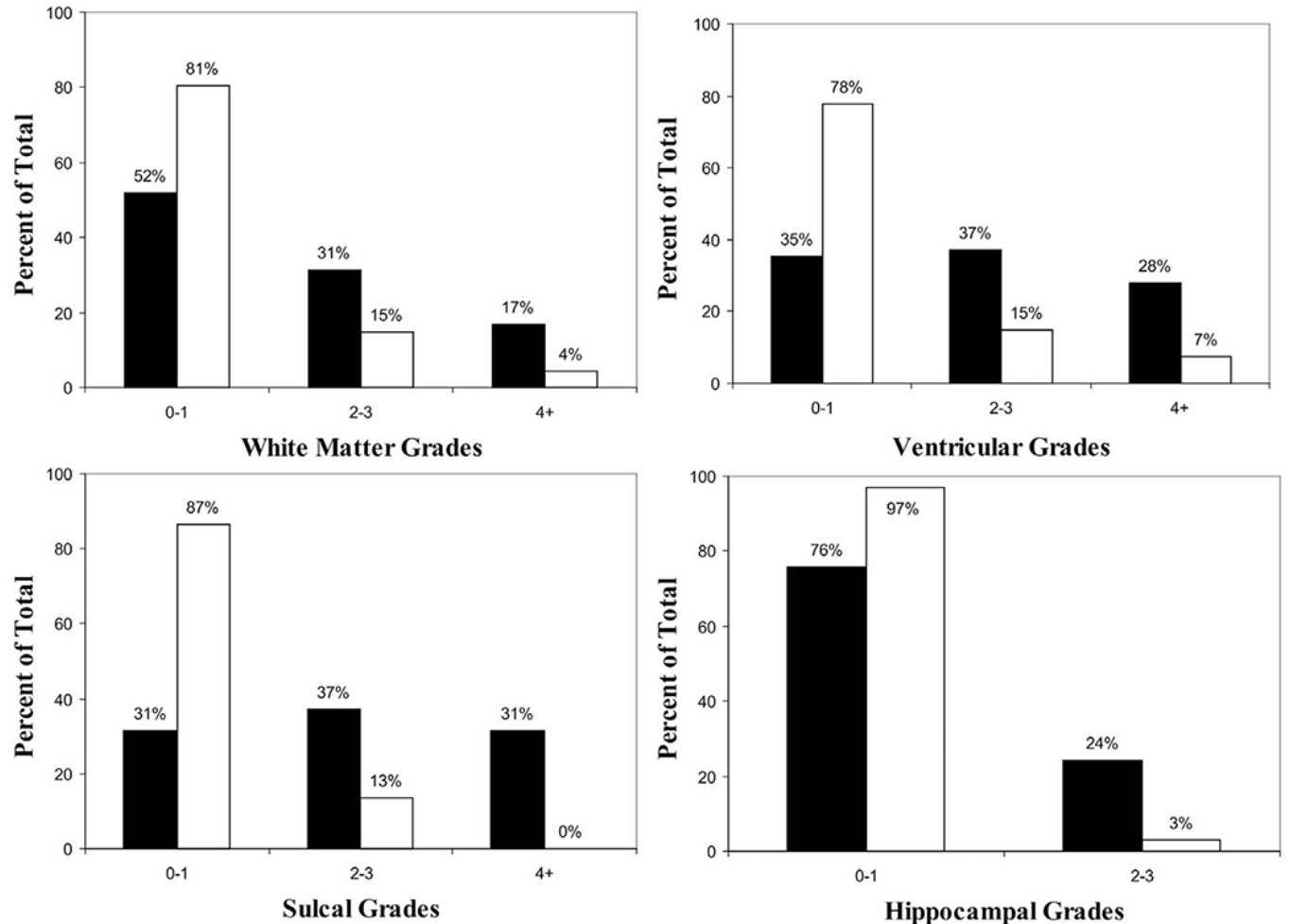
Non-demented, independently living dialysis patients present an accelerated brain aging phenotype even after taking into account effects of age, diabetes and depression.



Distribution of brain magnetic resonance imaging (MRI) white matter disease and cerebral atrophy grades for individuals receiving maintenance hemodialysis versus individuals without known chronic kidney disease.

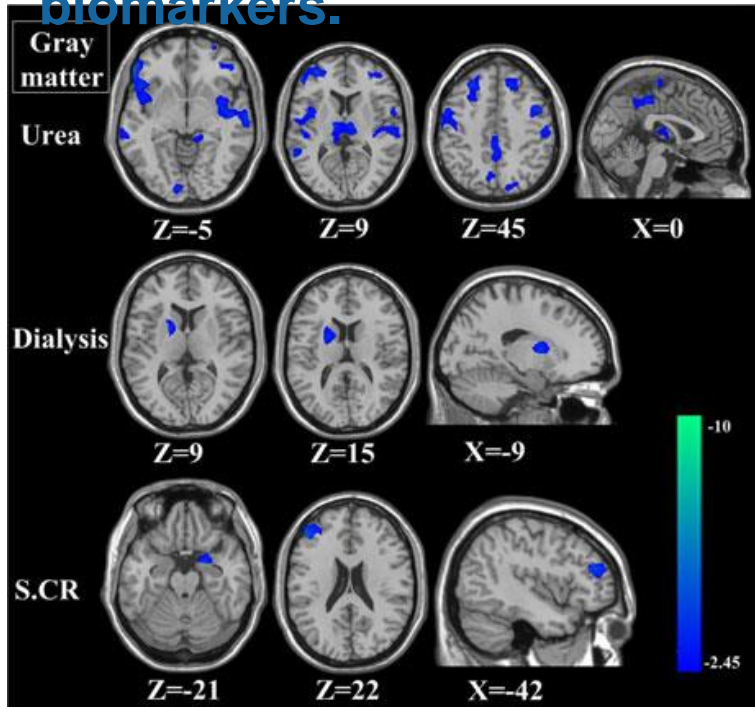
Am J Kidney Dis. 2019 December ; 74(6): 782–790

Hemodialysis patients consistently displayed more severe white matter damage and more cerebral atrophy than controls.



Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study

Correlation of gray matter volume changes with clinical biomarkers.



Serum urea is negatively correlated with cerebellum anterior lobe and culmen

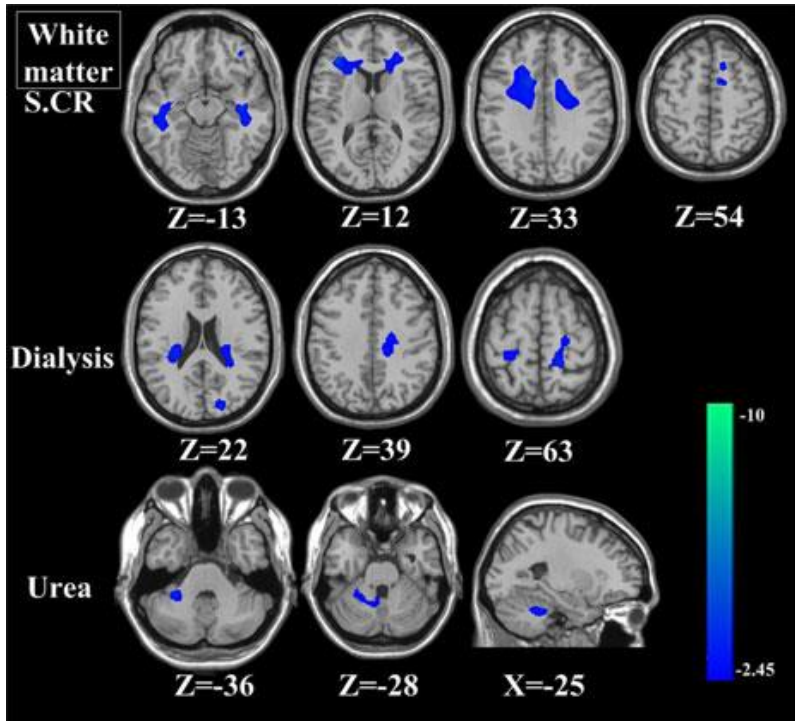
Serum creatinine is negatively correlated with bilateral frontal lobes and bilateral temporal lobes,

Dialysis duration is negatively correlated with bilateral frontal lobes, bilateral parietal lobes, left occipital lobe, left cuneus, and right extra-nuclear.

All $P < 0.05$, corrected for multiple comparisons using AlphaSim program
Metab Brain Dis (2013) 28:647–654

Predominant gray matter volume loss in patients with end-stage renal disease: a voxel-based morphometry study

Correlation of whiter matter volume changes with clinical biomarkers.



Serum urea is negatively correlated with bilateral parietal lobes, bilateral frontal lobes, bilateral temporal lobes, bilateral insula, bilateral thalamus

Serum creatinine is negatively correlated with right frontal lobe, left uncus, and left temporal pole

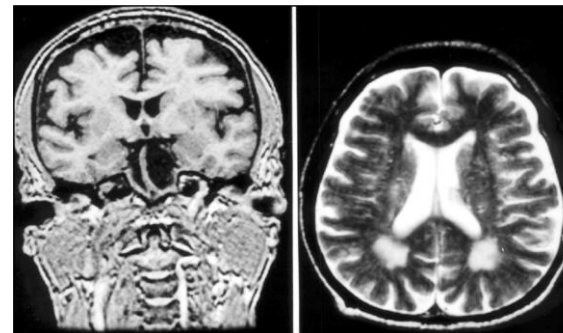
Dialysis duration is negatively correlated with the right caudate and right extra-nuclear.

All P < 0.05, corrected for multiple comparisons using AlphaSim program
Metab Brain Dis (2013) 28:647–654

□ Declino Cognitivo in Dialisi - Evidenze di Neuroimaging

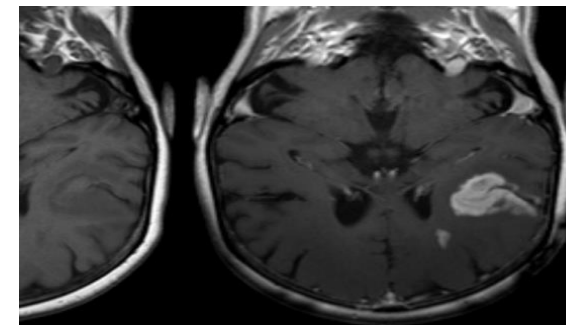
1. Atrofia Cerebrale

Atrofia con ampliamento dei solchi corticali e ventricoli laterali.



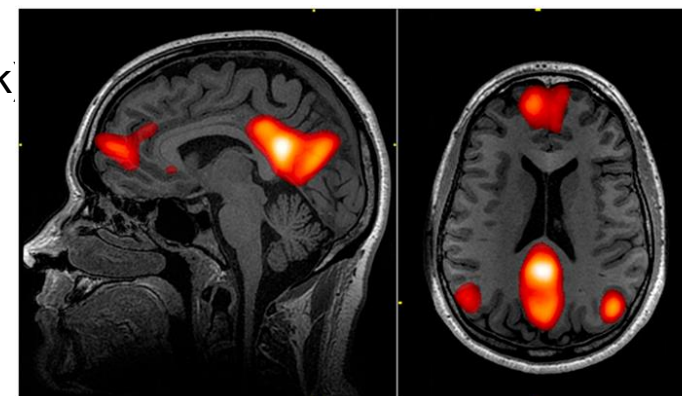
2. Microinfarti Cerebrali

Microinfarti subcorticali visibili come piccole lesioni iperintense.



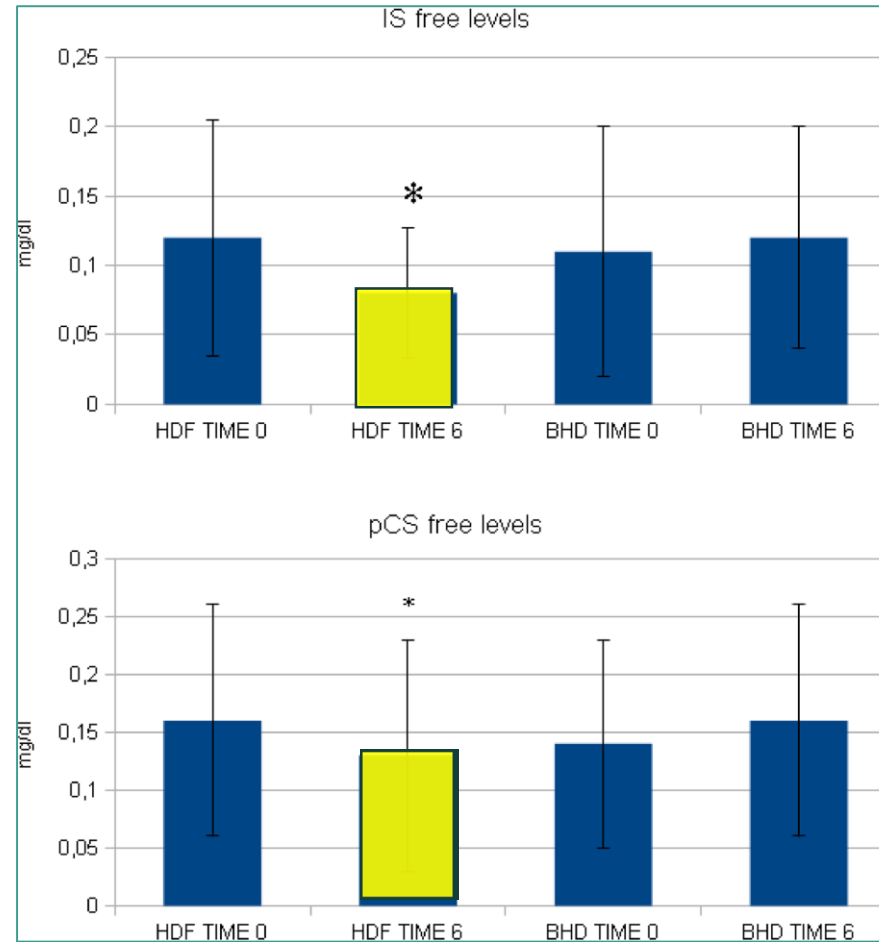
3. Ridotta Connettività Funzionale (fMRI)

Riduzione della connettività neuronale nelle reti cognitive (default mode network).



Long term variation of serum levels of uremic toxins in patients treated by post-dilution high volume on-line hemodiafiltration in comparison to standard low-flux bicarbonate dialysis: results from the REDERT study

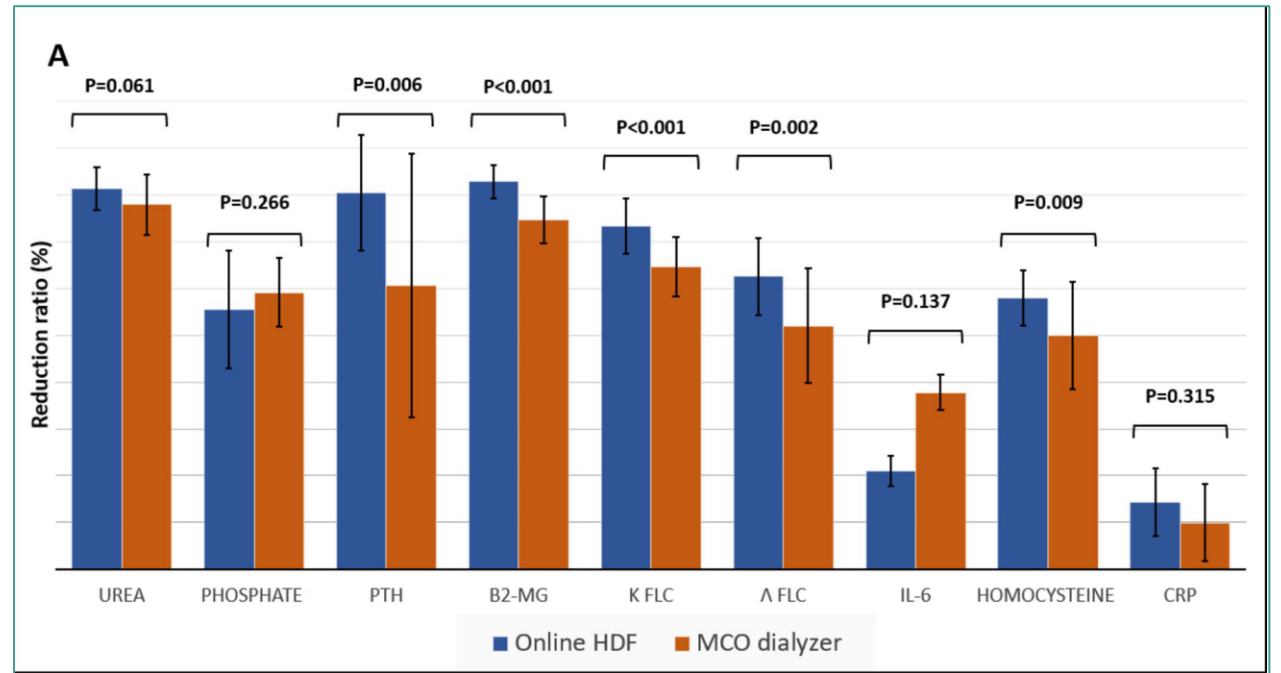
J Nephrol . 2017; 30(4): 583-591



Pre-dialysis IS and pCS free levels in hv-OL-HDF and BHD (time 0 and 6 months); *p < 0.001. # p< 0.01. Data are expressed as mg/dl

Pre- to post-dialysis reduction ratios of small-molecule, middle-molecule, and protein-bound uremic toxins, (A) compared between online-HDF and HDx with medium cut-off dialyzers

**Scientific Reports (2025)
15:5467**



High convection volume post-dilutional OI-HDF demonstrated superior removal of various uremic toxins compared to HDx with MCO dialyzers. However, HDx maintained pre-dialysis levels of middle molecules and inflammatory cytokines similarly to OI-HDF throughout the 8-week study period.

Both MCO dialyzers showed similar effectiveness in removing uremic toxins, making HDx a viable alternative for patients unable to undergo high convective volume OI-HDF.

Declino Cognitivo in Dialisi: Strategie di Prevenzione e Gestione



- **Controllo ottimale della pressione arteriosa e del diabete**
- **Minimizzazione dell'ipotensione intradialitica**
- **Screening cognitivo periodico**
- **Attività fisica e stimolazione cognitiva**
- **Rimozione delle tossine uremiche**

Grazie a tutti per l'attenzione

