

2nd International Conference on
Alzheimer's Disease and Dementia

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**METABOLIC SYNDROME,
NEUROINFLAMMATION AND
COGNITIVE IMPAIRMENT: STATE OF
THE ART AND DATA FROM A SECOND
LEVEL OUTPATIENT CLINIC IN ITALY**



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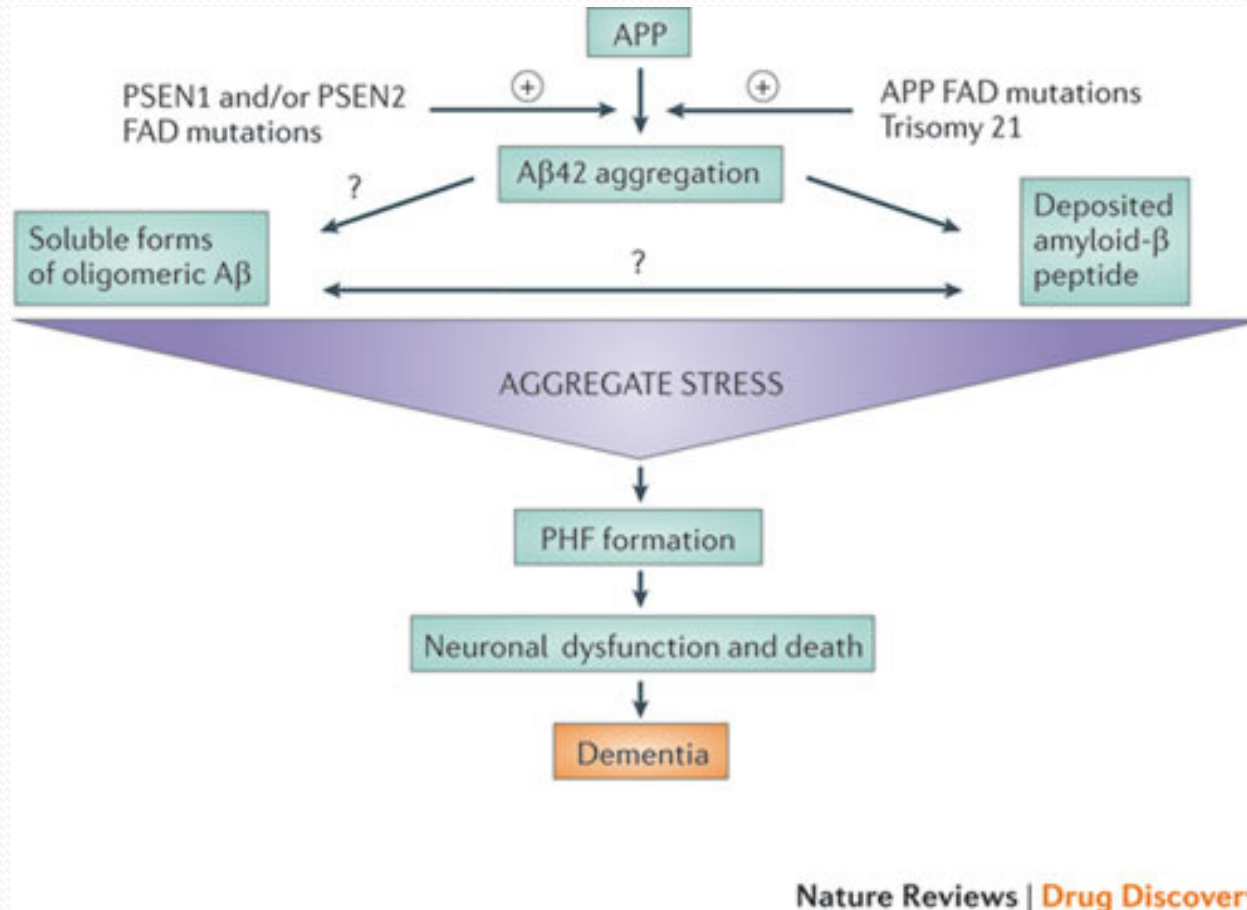


ALZHEIMER'S DISEASE

35.6 million people worldwide living with dementia in 2010, expected to become 65.7 million in 2030 and 115.4 million in 2050

Alzheimer's disease (AD) is the most prevalent type of dementia, comprising about 60%–70% of all dementia cases

AMYLOID CASCADE HYPOTHESIS...



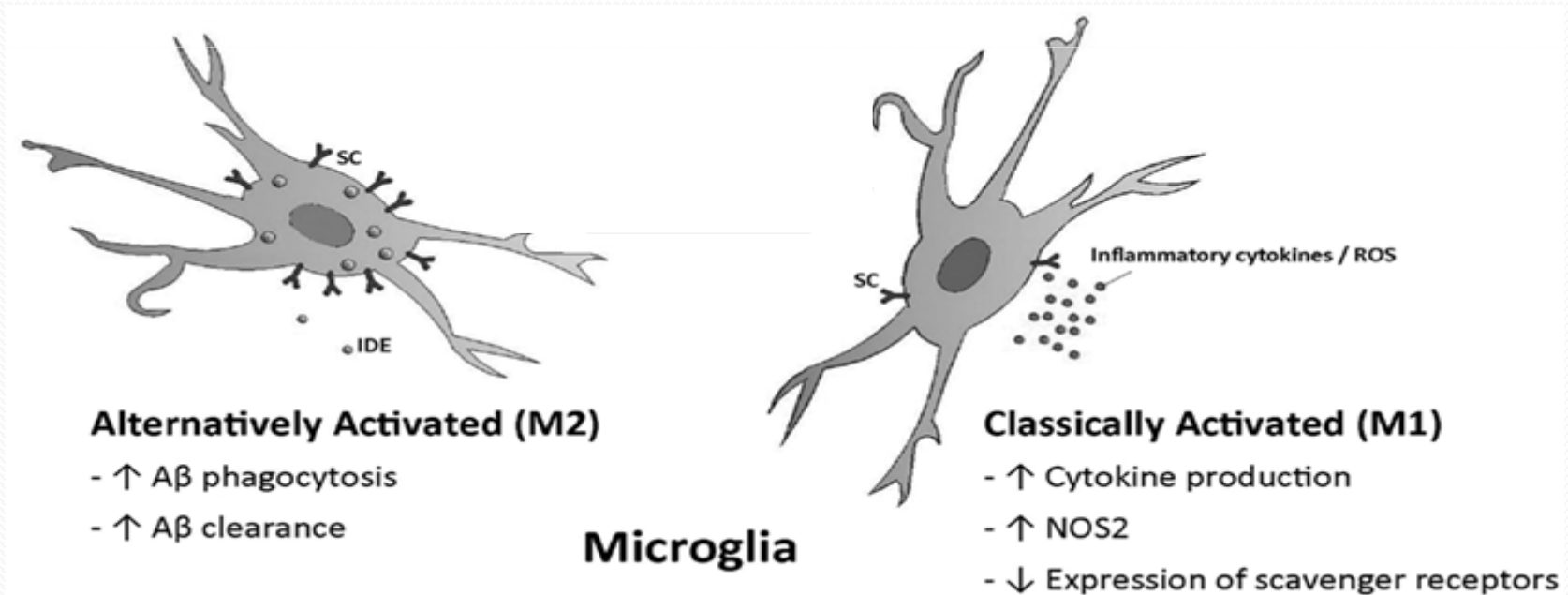
...NOT ENOUGH...

- autoptic and imaging studies showed that amyloid deposition, such as neurofibrillary tangles, can be found in cognitively and well-educated normal old subjects
- therapeutics attempt to clear $A\beta$, although efficient in reducing $A\beta$ load both in animal and human models, didn't stop or reduce the progression of AD

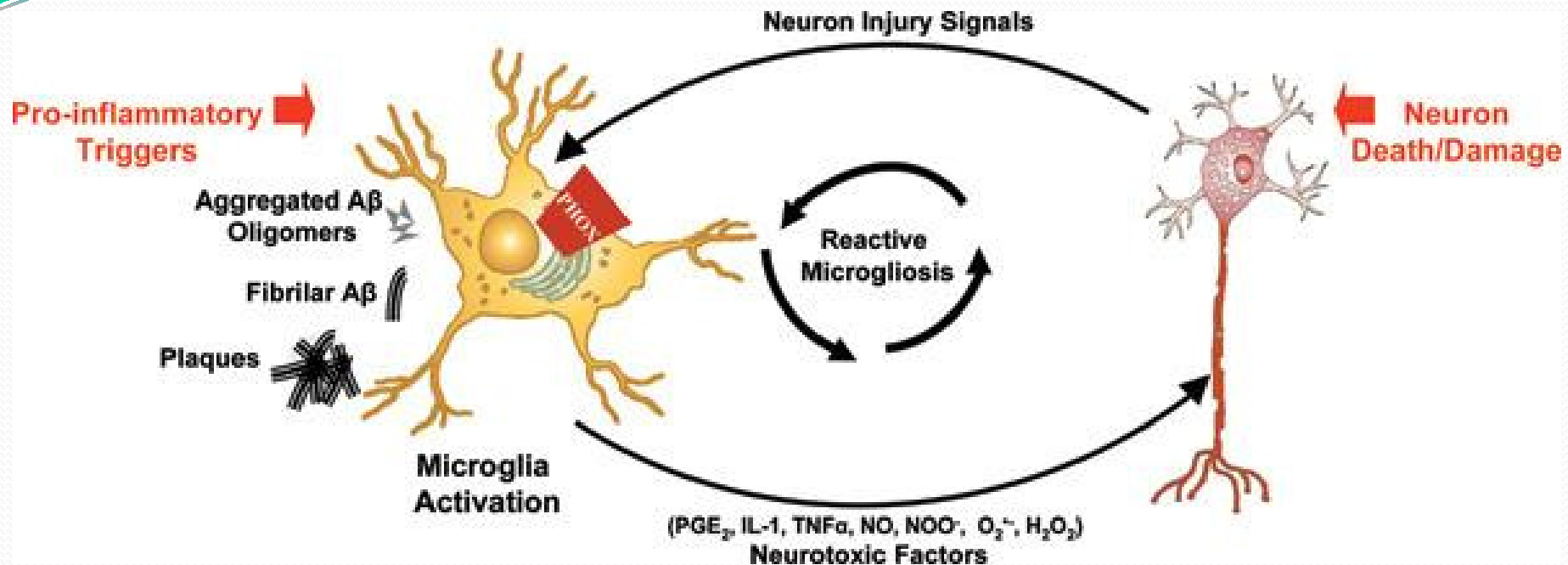


...NEUROINFLAMMATION...

INFLAMMATORY RESPONSE IN THE CENTRAL NERVOUS SYSTEM, DUE TO INJURY; ASTROCYTES AND MICROGLIAL CELLS ARE THE MAIN ACTORS IN THE INFLAMMATORY RESPONSE IN THE CNS



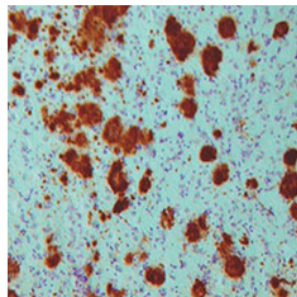
Modified from Microglia function in Alzheimer's disease Egle Solito¹ and Magdalena Sastre



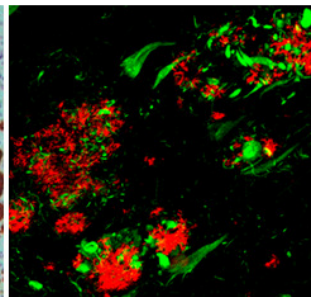
...SELF-PERPETUATING CYCLE OF NEURONAL DAMAGE/DEATH FOLLOWED BY MICROGLIAL ACTIVATION IS COMMONLY REFERRED TO AS REACTIVE MICROGLIOSIS AND MAY BE AN UNDERLYING MECHANISM OF THE PROGRESSIVE NATURE OF DIVERSE NEURODEGENERATIVE DISEASES, INCLUDING ALZHEIMER'S DISEASE...

NEUROINFLAMMATION AND NEURODEGENERATION: SUPPORTING EVIDENCE

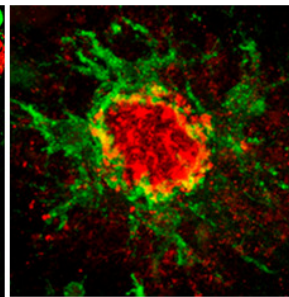
- up-regulated inflammatory mechanisms co-localize in the same region with high level of AD pathology, absent in the region with low AD susceptibility (eg cerebellum)
- microscopical examinations showed that inflammatory mediators are expressed overall closest to the $A\beta$ deposits and neurofibrillary tangles



Amyloid plaques



Amyloid plaques and
tau tangles

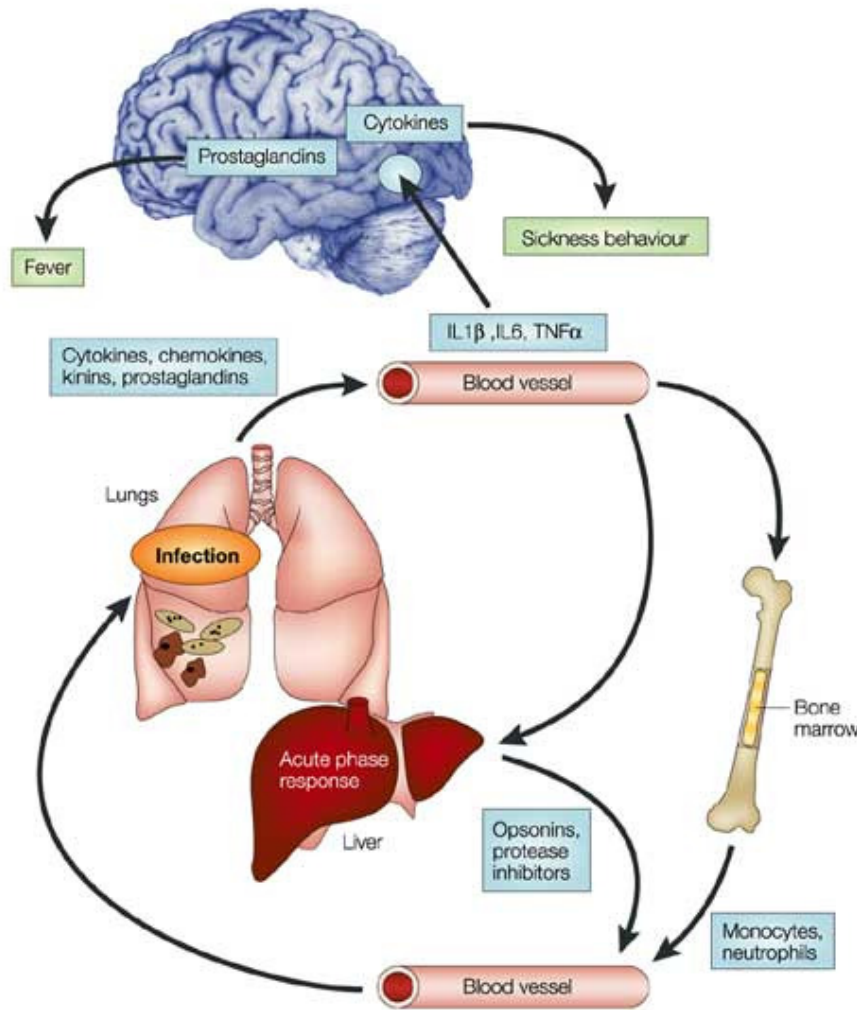


Amyloid plaques and
activated microglia

NEUROINFLAMMATION AND NEURODEGENERATION: SUPPORTING EVIDENCE

- subjects without dementia but with pathologic findings of limbic $A\beta$ and neurofibrillary tangles sufficient to prompt diagnosis of AD show a modest elevation of inflammatory markers, greater than non-demented subjects but less than AD subjects
 - ultrastructural evidence of inflammatory toxicity in AD brain
- potential protective effect of the chronic use of Non-Steroidal Anti-Inflammatories

PERIPHERIC INFLAMMATION AND NEUROINFLAMMATION



Nature Reviews | Neuroscience

inflammatory mediators by cells
local to the insult



liver acute phase response and
immune cell recruitment from the
bone marrow.

The circulating cytokines also
communicate with brain centres
through the cerebral endothelium,
the vagal nerve and the
circumventricular organs to effect
local cytokine and prostaglandin
synthesis and produce sickness
behaviours such as fever and
reduced locomotor activity. IL and
TNF α

PERIPHERIC INFLAMMATION AND NEUROINFLAMMATION

- periodontitis, a clinical condition characterized by chronic periodontal inflammation and systemic release of inflammatory cytokines (Il-1, Il6, TNF)



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Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III

J M Noble^{1,2,3}, L N Borrell⁴, P N Papapanou⁵, M S V Elkind^{3,6}, N Scarmeas^{1,3}, and C B Wright⁷

PERIPHERIC INFLAMMATION AND NEUROINFLAMMATION

METABOLIC SYNDROME:

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic)
- Plasma triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- HDL cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m² and/or waist:hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥ 20 μ g/min or albumin:creatinine ratio ≥ 30 mg/g

*Derived from Alberti et al.^{7,8}

Metabolic Syndrome and Cognitive Decline in Elderly Latinos: Findings from the Sacramento Area Latino Study of Aging Study

Kristine Yaffe, MD, †‡|| Mary Haan, DrPH, MPH, ¶ Terri Blackwell, MA, # Elena Cherkasova, BA, §
Rachel A. Whitmer, PhD, ** and Nancy West, MS ¶*

Longitudinal cohort study, counting 1624 Latinos aged 60 and older who participated.
Conclusions: Metabolic syndrome and inflammation may both contribute to cognitive decline in older people of diverse backgrounds...the composite measure of metabolic syndrome is a greater risk for cognitive decline than its individual components.

The Metabolic Syndrome, Inflammation, and Risk of Cognitive Decline

Kristine Yaffe, MD

Alka Kanaya, MD

Karla Lindquist, MS

Eleanor M. Simonsick, PhD

Tamara Harris, MD

Ronald I. Shorr, MD

Frances A. Tylavsky, PhD

Anne B. Newman, MD, MPH

A 5-year prospective observational study conducted from 1997 to 2002 at community clinics at 2 sites, for a total of 2632 black and white elders (mean age, 74 years).

Conclusions: metabolic syndrome contributes to cognitive impairment in elders, but primarily in those with high level of inflammation



ELSEVIER

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AGING

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Metabolic syndrome, mild
cognitive impairment, and
progression to dementia.
The Italian Longitudinal
Study on Aging

Vincenzo Solfrizzi^{a,*}, Emanuele Scafato^b, Cristiano Capurso^c,
Alessia D’Introno^a, Anna Maria Colacicco^a, Vincenza Frisardi^a, Gianluigi Vendemiale^{c,d},
Marzia Baldereschi^e, Gaetano Crepaldi^f, Antonio Di Carlo^e, Lucia Galluzzo^b,
Claudia Gandin^b, Domenico Inzitari^g, Stefania Maggi^f, Antonio Capurso^a, Francesco Panza^h,
for the Italian Longitudinal Study on Aging Working Group^l

A total of 2097 participants from a sample of 5632 65–84-year-old subjects from the
Italian Longitudinal Study on Aging
Among MCI patients the presence of MetS independently predicted an increased risk of
progression to dementia over 3.5 years of follow-up.

ORIGINAL CONTRIBUTION

Obesity and Vascular Risk Factors at Midlife and the Risk of Dementia and Alzheimer Disease

Miia Kivipelto, MD, PhD; Tiia Ngandu, BM; Laura Fratiglioni, MD, PhD; Matti Viitonen, MD, PhD; Ingemar Kåreholt, PhD; Bengt Winblad, MD, PhD; Eeva-Liisa Helkala, PhD; Jaakko Tuomilehto, MD, MPolSci, PhD; Hilikka Soininen, MD, PhD; Aulikki Nissinen, MD, PhD

High cholesterol and systolic blood pressure were significant predictors of dementia and their risk was additive to that of obesity in this population.

Midlife obesity, high SBP, and high total cholesterol level were all significant risk factors for dementia, each of them increasing the risk around 2 times. Clustering of these vascular risk factors increased the risk of dementia and AD in an additive manner so that persons with all 3 risk factors had around a 6 times higher risk for dementia than persons having no risk factors.



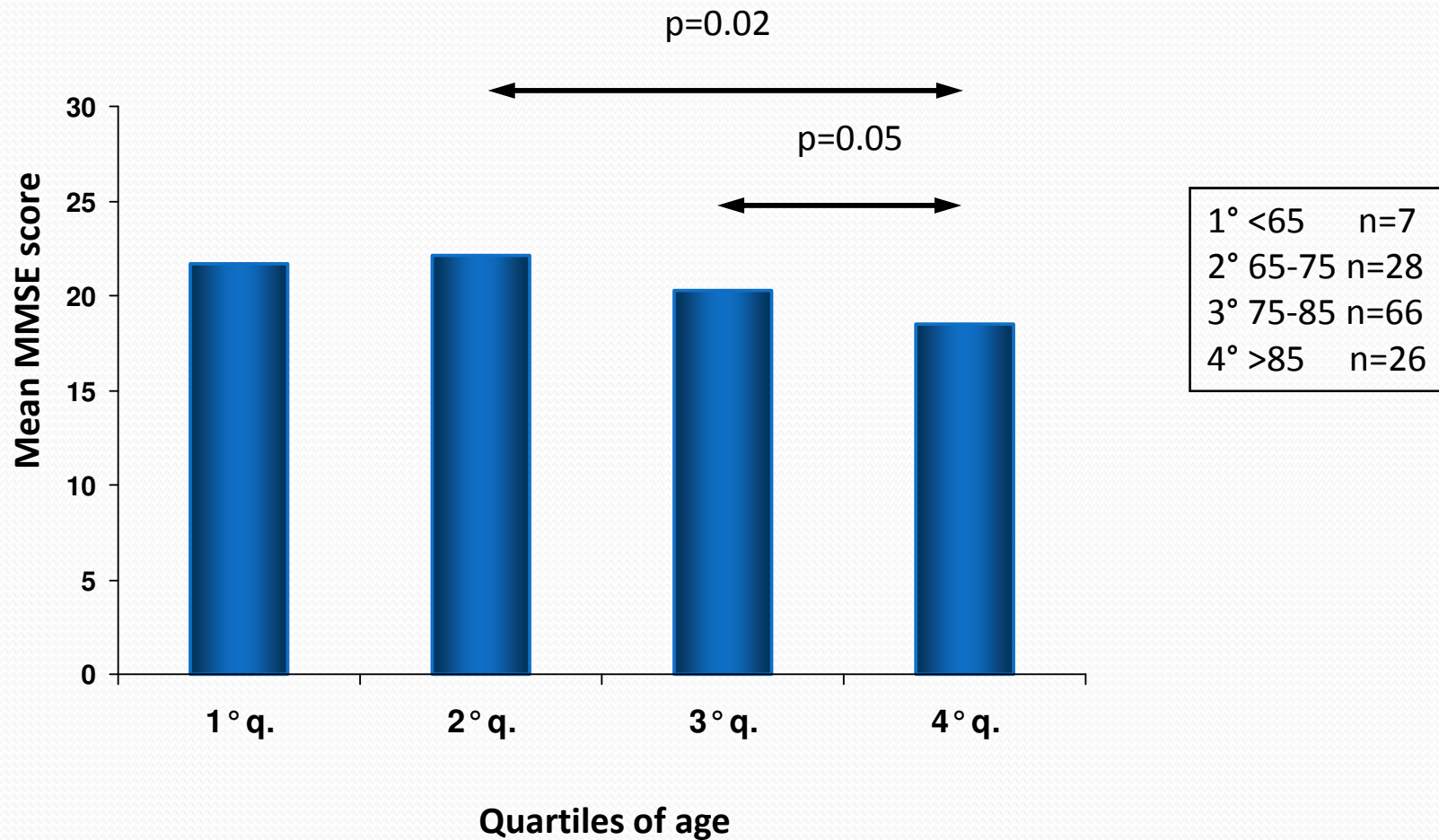
ALZHEIMER'S OUTPATIENT CLINIC LIVORNO HOSPITAL (TUSCANY)



	subjects (n=127)	female (n=76)	male (n=51)	p (F vs M)
Age	78,2±7,1	78,5±7,1	77,6±7,2	0,5
MMSE	20,6±5,1	20,2±4,9	21,0±5,4	0,4
HBP	53,1%	54,2%	51,4%	0,8
DM	34,7%	35,6%	33,3%	0,6
IFG	7,9%	10,2%	4,8%	0,6
Dyslipidemia	79,1%	88,5%	64,7%	0,08
CVI	53,1%	48,8%	57,9%	0,4
CRI	24,0%	48,6%	30,9%	0,4
↑ Inflammation indexes	41,7%	48,6%	30,4%	0,2

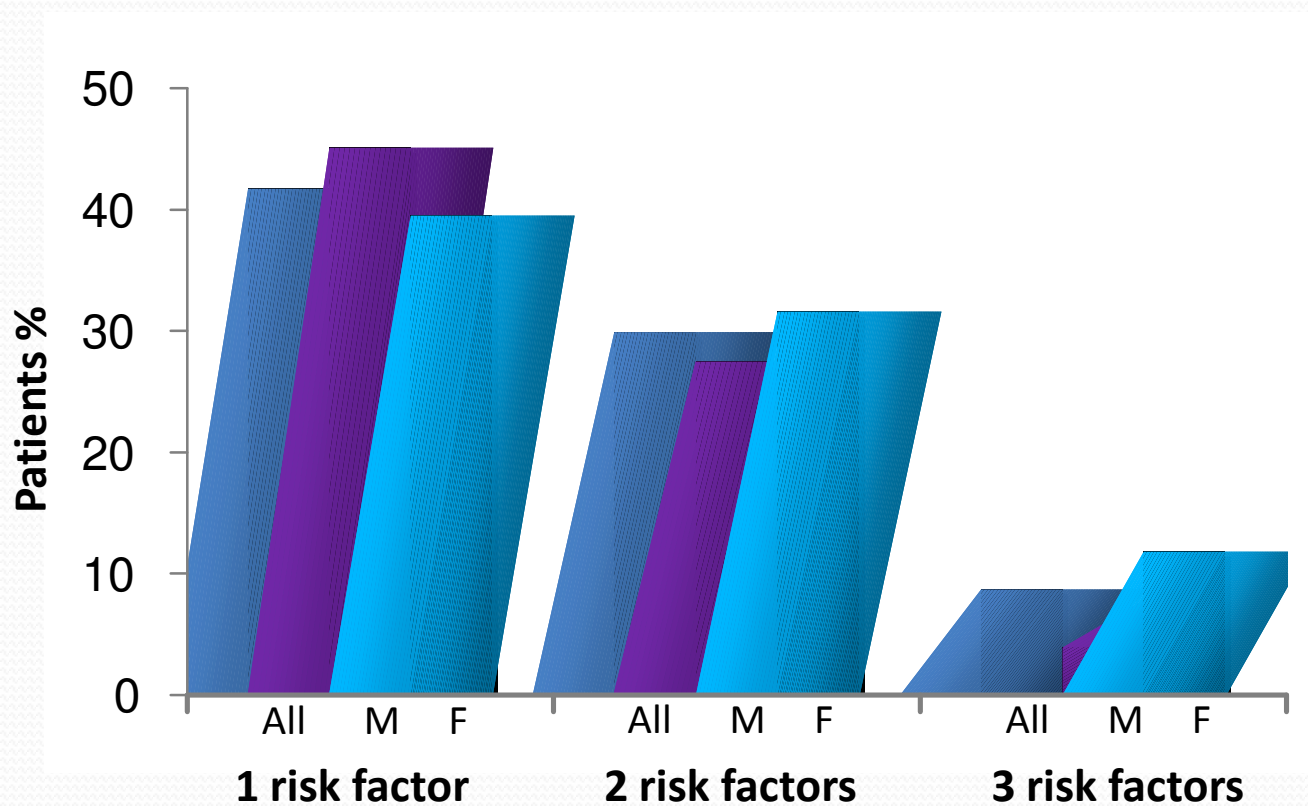
With contribution of Cassa di Risparmio di Livorno

ALZHEIMER'S OUTPATIENT CLINIC LIVORNO HOSPITAL (TUSCANY)

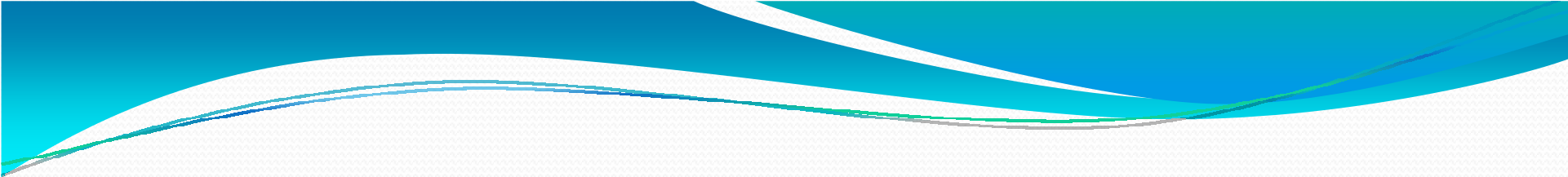


With contribution of Cassa di Risparmio di Livorno

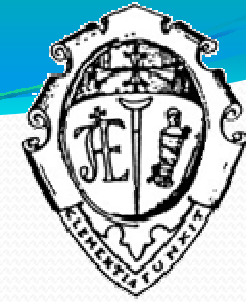
ALZHEIMER'S OUTPATIENT CLINIC LIVORNO HOSPITAL (TUSCANY) PREVALENCE OF CARDIOVASCULAR RISK FACTORS



With contribution of Cassa di Risparmio di Livorno



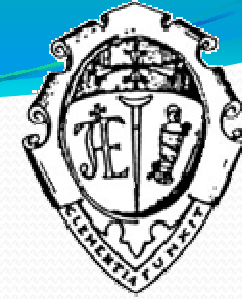
**INTERESTINGLY, ALTHOUGH THE ASSOCIATION
BETWEEN PERIPHERAL INFLAMMATION AND
COGNITIVE IMPAIRMENT IS GENERALLY
RECOGNIZED, RHEUMATOID ARTHRITIS, A
TYPICAL SYSTEMIC AUTOIMMUNE DISORDER,
SEEMS NEGATIVELY ASSOCIATED TO
ALZHEIMER'S DISEASE DEVELOPMENT**



On this basis, we propose a translational research project

Relationship between cognitive function and inflammation in animal models and in patients with morbid obesity, rheumatoid arthritis, osteoarthritis and periodontitis

to evaluate the effect of peripheral chronic inflammation on neuro-inflammation and cognitive function as well as AD pathophysiology,



GOALS:

Demonstrate that peripheral chronic inflammation, depending on the cytokine pattern, specific for **MORBID OBESE, REUMATHOID ARTHRITIS AND PERIODONTITIS PATIENTS**, could act at CNS level and favor or prevent negative inflammation and consequent oxidative stress on the ad developing process.

Pisa University Hospital:

- Geriatrics Unit (PI)
- Rheumatology Unit
- Odontostomatholgy Unit
 - Neurology Unit
 - Endocrinology Unit

Imperial College, London:

Neuro-Imaging Unit, Hammersmith Hospital

THANK YOU

