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# The inflammatory profiling in a cohort of older patients suffering from cognitive decline and dementia

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ABSTRACT

*Background:* During aging, there is a progressive impairment of immune cell function that triggers the production of pro-inflammatory cytokines causing the so-called "inflammaging". Frailty represents a condition of increased vulnerability to stresses and reduced homeostatic reserve reflecting not only health status but also biological age. In older subjects without dementia, we showed that markers of inflammaging were differently associated with chronological age than with frailty. This study analysed the same markers in older people with cognitive decline and/or dementia.

*Methods:* The cohort consisted of 776 community-dwelling older people: 235 patients with mild cognitive impairment, 63 with Alzheimer's disease (AD), 175 with mixed dementia (MD), and 303 subjects without cognitive decline. Plasma concentrations of inflammatory cytokines and peripheral markers of neuro-inflammation were analysed by next-generation ELISA.

*Results:* After adjustment for age, sex, frailty, education and Apolipoprotein E genotype, only interleukin-10, interleukin-1β, and neurofilament light chain were associated with the risk for AD and MD. Moreover, interleukin-6 showed a weak association only with AD.

*Conclusions:* Our data showed similar associations between AD and MD, supporting the concept that late-onset dementia is a complex outcome of aging, intimately linked to the individual's health status as well as frailty.

## 1. Introduction

Aging and age-related diseases share several common mechanisms identified as "hallmarks of aging" (Schmauck-Medina et al., 2022). Importantly, these hallmarks are finely interconnected, and inflammation represents a kind of biological cap that covers them all (Schmauck-Medina et al., 2022).

Moreover, during aging, there is a progressive impairment of immune cell function resulting in immunosenescence that causes the so-called "inflammaging", which is a state of chronic low-grade inflammation (Calabrese et al., 2018). For a long time, inflammaging was thought to be a harmful process, without thinking that it may be an adaptive mechanism aimed at stimulating an adequate anti-inflammatory response to counterbalance changes associated with aging and to maintain an adequate ability to respond to stresses (Fulop et al., 2020).

Understanding the relationship between inflammation and aging on the one hand, and between inflammation and age-related diseases on the other, can be improved by adopting constructs and models that comprehensively reflect the biological complexity of the organism and the heterogeneity of aging trajectories. In this regard, the concept of frailty can help in unravelling this skein.

Frailty represents a condition of increased vulnerability to stresses and reduced homeostatic reserve (Clegg et al., 2013). This condition is globally driven by the gradual and lifelong accumulation of defects in different organs and systems (Clegg et al., 2013).

There are several models for calculating frailty. The frailty phenotype (Fried et al., 2001) and the Frailty Index (Mitnitski et al., 2001)

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represent the most known operational definitions of frailty in older persons. According to the deficit accumulation approach (Mitnitski et al., 2001), the degree of frailty of an individual is related to the extent of health deficits the individual has accumulated over a lifetime.

In fact, the individual's biological complexity and risk profile can be quantified by combining several variables indicative of the individual's health status into an index called Frailty Index (FI) (Searle et al., 2008), which is a good indicator not only of the individual's health status and degree of frailty, but also of his or her biological age (Arosio et al., 2019).

In this regard, in a cohort of subjects without dementia consisting of old and very old people, we have recently demonstrated that the markers of inflammaging were differently associated with chronological age than frailty measured by FI (Arosio et al., 2023). Indeed, we found that the plasma concentration of interferon-γ (IFN-γ) was positively associated with frailty but not with age, whereas the concentrations of interleukin (IL)-10 and IL-1β were positively associated only with chronological age (Arosio et al., 2023).

Interestingly, FI has been shown to independently predict the onset of dementia among cognitively normal older individuals (Rogers et al., 2017; Song et al., 2011), and increased FI values have been associated with a higher likelihood of conversion to dementia in individuals with mild cognitive impairment (MCI) (Kelaiditi et al., 2016a; 2016b; Kelaiditi et al., 2013; Trebbastoni et al., 2017).

There is also emerging evidence that frailty, quantified as FI, can module the relationships between the neuropathological hallmarks of AD and the clinical presentation of dementia (Wallace et al., 2019) and between the expression of AD biomarkers and cognitive status (Wallace et al., 2020). In addition, FI has been adopted to ascertain the external validity of research protocols enrolling participants with dementia (Canevelli et al., 2017). However, the biological pathways linking frailty to cognitive impairment and dementia are still not well understood.

Under these premises, the present study aims to analyse the cross-sectional association between inflammatory markers and cognitive impairment and dementia, considering the influence of chronological age and frailty. While in our previous study we analysed inflammatory markers in the continuum of aging considering individuals without dementia (Arosio et al., 2023), in this study we intend to analyse the association between the same markers and cognitive decline considering that the degree of frailty (quantified by FI) might influence in a latent way the relationship between these biomarkers and the phenotypic expression of the dementia condition.

For this purpose, in a cohort of older subjects comprising patients with mild cognitive impairment and dementia, we measured markers associated with inflammaging and neuroinflammation already described in the aging continuum (Arosio et al., 2023) and also analysed neurofilament light chain (NfL), a promising marker of frailty as it appears to be associated not only with neurodegeneration and cognitive decline (Delaby et al., 2022; Dutta et al., 2023; Gaetani et al., 2019; Hansson, 2021; Wang et al., 2019), but also with decline in physical (Qaisar et al., 2024) and functional (Grasset et al., 2024) abilities and with sarcopenia (Ladang et al., 2023).

## 2. Materials and methods

### 2.1. Study design

For this study, we considered 776 community-dwelling older adults (65–92 years) who consecutively attended a first geriatric visit to the geriatric unit of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (Milan, Italy) from March 2009 to April 2022. All participants were admitted to the geriatric unit for the investigation of a suspected cognitive decline and their data were recorded in "Registro di Raccolta Dati della Unità di Geriatria" (REGE, protocol number 223248).

Subjects were selected for this study if they had all the information needed to calculate an FI and had sufficient bio-banked biological samples to perform the analyses. At the time of enrolment, all participants underwent a multidimensional geriatric assessment during which information about their medical history and cognitive and functional status (i.e., Mini-Mental State Examination, MMSE; Clinical Dementia Rating Scale, CDR; Clock Drawing Test, CDT; Activity of Daily Living, ADL) were recorded. Finally, the Geriatric Depression Scale (GDS) was used to assess depression.

Only patients with mild to moderate dementia (CDR 0.5–2) were included in this study and all biological samples analysed came from subjects without acute or chronic inflammatory diseases (i.e., Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, lupus, asthma, autoimmune diseases and multiple sclerosis).

This study included 235 patients with mild cognitive impairment (MCI) (Petersen, 2004), 63 with AD (Dubois et al., 2014) and 175 with mixed dementia (MD) (patients characterized by both neurodegenerative and vascular findings) (American Psychiatric Association, 2013; Fierini, 2020). A total of 303 subjects (controls) were diagnosed without cognitive decline (i.e., MMSE score $>$ 24, neuropsychological test negative for dementia, no neurological or psychiatric disorders).

All subjects gave their consent, either personally or through their legal guardian (if the person was mentally incapable of making an independent decision), to use their clinical and biological data for appropriately anonymised research purposes. The study protocol received approval from the local ethics committee (REGE 2.0, protocol number 1696).

### 2.2. Frailty index

An FI was computed as previously described (Arosio et al., 2023). Briefly, for each variable, the presence of a deficit was coded as 1, while the absence as 0. The FI was calculated as the ratio of the number of personal health deficits to the total number of deficits considered for its computation ($n$ = 45) (Arosio et al., 2023) (Supplementary Table 1). Participants with >30 % of variables missing were excluded.

### 2.3. Plasma markers' concentrations

Plasma concentrations of IFN-γ, IL-10, IL-6, tumour necrosis factor (TNF)-α, IL-1β, TNF receptor 1 (TNFR1), soluble TREM1 and TREM2 (sTREM1, sTREM2) and NfL were analysed through Human Simple Plex assays (Protein Simple, CA, USA) on Ella device (Protein Simple, CA, USA) (Arosio et al., 2023).

### 2.4. Apolipoprotein E genotyping

The apolipoprotein E (APOE) genotype was determined using a PCR restriction fragment length polymorphism (PCR-RFLP) as previously described (Ferri et al., 2019). Briefly, the APOE gene was amplified by PCR (step 1: 96 °C for 5 min; step 2 for 30 cycles: 95 °C for 1 min, 60 °C for 1 min 10 s, and 70 °C for 2 min; step 3: 70 °C for 10 min). The primer pairs used were:

Forward: 5′-GATCAAGCTTCCAATCACAGGCAGGAAG-3′;

Reverse: 5′-GATCCGGCCGCACACGTCCTCCATG-3′.

The PCR products were visualised on a 4 % agarose gel after digestion with the *Hha*I enzyme.

### 2.5. Statistical analysis

The statistical analyses were conducted using IBM SPSS Statistic software (version 29, IBM Inc., Chicago, IL, USA). The normally distributed variables (age, MMSE, CDT, and ADL scores) were reported as mean and standard deviation (SD), whereas non-normally distributed variables (GDS, FI, and marker concentrations) were expressed as median and interquartile range (IQR: 25–75$^{th}$ percentile). Percentages were used for categorical variables (sex, APOE genotype, and education) and

analysed using Pearson's Chi-squared test. For the comparisons, the normally distributed variables were analysed using the Analysis of Variance (ANOVA) and the Bonferroni post-hoc test, whereas the non-normally distributed were analysed using the Kruskal–Wallis test.

The plasma concentrations of the analytes were non-normally distributed, so the data were log-transformed for regression analyses. Multiple linear regressions were assessed to investigate the association between all the markers' concentrations (dependent variable) and sex, dichotomized FI values (the 0.25 value was used as the discriminator between non-frail and frail subjects), age, education, MMSE score and presence of the APOE ε4 allele (independent variables).

A multinomial logistic regression model adjusted for sex, dichotomized FI, age, education and presence of the APOE ε4 allele was performed to estimate whether marker concentrations were associated with the risk of developing mild cognitive impairment and/or dementia.

An exploratory analysis was conducted to test the interaction between IL-10 and NfL concentrations in further increasing the risk of cognitive impairment (MCI, AD, and MD).

Values of $p < 0.05$ were considered statistically significant.

## 3. Results

In overall cohort, the mean age was 78.5 (SD 5.6) years, 66.6 % were women and the median FI value was 0.24 (IQR 0.16–0.32, from 0.00 to 0.63). The MMSE had a mean score of 25.4 (SD 4.8), the CDT of 3.0 (SD 1.9), and the ADL scale of 5.2 (SD 1.1). The median GDS score was 8.0 (IQR 4.0–14.0, from 0 to 30). The percentage of carriers of at least one ε4 allele of the APOE gene was 25.4 %. Moreover, 28.9 % of subjects received education for 0–5 years, 28.6 % for 6–8 years, 28.2 % for 9–13 years, and 14.3 % for >14 years.

When we classified subjects based on the diagnosis of cognitive impairment and dementia, we observed that MD patients had a significantly higher mean age compared to the other groups (Table 1). Moreover, MD were the most frail (FI), functionally compromised (ADL), and depressed (GDS) (Table 1).

As expected, patients with dementia (AD and MD) showed the lowest MMSE and CDT values and had a lower level of education than the others (Table 1). Confirming the data in the literature, the percentage of carriers of at least one ε4 allele of the APOE gene was the highest among AD patients (Table 1). Interestingly, the MCI patients showed a lower percentage of women compared to the other groups (Table 1).

Table 2 shows the plasmatic concentrations of each marker analysed. In details, the concentrations of IFN-γ were similarly distributed in the four groups. Interestingly, the median concentration of IL-10 and NfL were significantly higher in AD and MD than controls and MCI. A similar trend to that shown by IL-10 was observed for IL-6 and sTREM2, but with MD patients showing the highest concentrations. Concentrations of TNFR1 and sTREM1 were higher in MD than controls, while TNF-α concentration was higher in MD than controls and MCI. Unlike the other markers, the median concentration of IL-1β was significantly lower in AD and MCI compared to controls (Table 2).

Table 3 provides the results obtained from multiple linear regression analysis between plasma concentrations of each marker (dependent variable) and sex, dichotomized FI (non-frail vs. frail), age, education, MMSE score and the presence of the ApoE ε4 allele (independent variables).

All markers' concentrations increased significantly with chronological age, except for IFN-γ and IL-1β. Increased concentrations of IL-10, TNF-α and TNFR1 were associated with men, while higher sTREM2 concentrations were associated with women (Table 3).

In addition, concentrations of IL-6, TNFR1, sTREM1, sTREM2 and NfL were positively associated with FI, and in the case of TNFR1, sTREM1 and NfL also with education. Furthermore, IL-6, IL-1β, TNFR1, sTREM1 and NfL concentrations were significantly associated with the absence of the ApoE ε4 allele (Table 3).

Finally, IL-10, IL-6, TNF-α and NfL concentrations were negatively associated with MMSE score after all adjustments (Table 3).

The multinomial logistic regression model adjusted for sex, dichotomized FI, age, education and the presence of the ε4 allele of APOE showed that increased IL-10 and NfL concentrations increased the risk of AD and MD (Table 4).

The results of the exploratory analysis that tested the interaction between the concentrations of these two biomarkers did not reveal an additional increase in the risk of cognitive impairment (MCI, AD, and MD) when they were combined (data not shown).

A similar trend to IL-10 and NfL was observed for IL-6, although to a lesser extent. In contrast, increased IL-1β concentration reduced the risk of MCI, AD and MD (Table 4).

## 4. Discussion

The purpose of this study was to extend our previous results

**Table 1**
Characteristics of people categorized in controls, mild cognitive impairment (MCI), Alzheimer's disease (AD), and mixed dementia (MD).

| | | Controls (n 303) | MCI (n 235) | AD (n 63) | MD (n 175) | *p* |
|---|---|---|---|---|---|---|
| Age (years) | | 77.7 (6.1) | 78.2 (5.3) | 77.8 (4.6) | 80.7 (5.0) [a,b] | **<0.001** |
| Sex (% women) | | 71.6 % | 56.2 % [b,c,d] | 77.8 % | 68.0 % | **<0.001** |
| FI | | 0.17 (0.10–0.24) | 0.26 (0.20–0.30) [c] | 0.26 (0.22–0.34) [c] | 0.36 (0.26–0.43) [a,b] | **<0.001** |
| MMSE | | 28.1 (2.7) | 26.9 (2.2) [c] | 20.7 (4.8) [a] | 20.2 (5.1) [a] | **<0.001** |
| CDT | | 3.7 (1.7) | 3.4 (1.7) | 2.1 (1.9) [a] | 1.6 (1.7) [a] | **<0.001** |
| ADL | | 5.5 (0.7) | 5.5 (0.7) | 5.0 (1.4) [a] | 4.4 (1.5) [a,b] | **<0.001** |
| GDS | | 5.5(2.0–10.0) | 10.0 (6.0–14.0) [c] | 8.5 (5.0–12.7) | 16.0 (9.0–18.0) [a,b] | **<0.001** |
| APOE (% ε4+) | | 21.5 % | 23.4 % | 46.0 % [a] | 27.4 % [b] | **<0.001** |
| Education (%) | 0–5 | 18.0 % | 24.2 % | 52.4 % [a] | 45.9 % [a] | **<0.001** |
| | 6–8 | 29.0 % | 28.4 % | 22.2 % [a] | 30.2 % [a] | |
| | 9–13 | 33.3 % | 34.5 % | 12.7 % [a] | 16.3 % [a] | |
| | ≥ 14 | 19.7 % | 12.9 % | 12.7 % [a] | 7.6 % [a] | |

Age, MMSE, CDT and ADL scores were expressed as mean (standard deviation), whereas FI and GDS score as median (interquartile range). Sex distribution was reported as the percentage of women. Genotype distribution of the APOE gene was reported as the percentage of carriers of at least one ε4 allele. Education was indicated as the percentage of subjects who received education for 0–5 years, 6–8 years, 9–13 years, and over 14 years.

MCI, Mild cognitive impairment; AD, Alzheimer's disease; MD, Mixed dementia; FI, Frailty index; MMSE, Mini-mental state examination; CDT, Clock drawing test; ADL, Activities of daily living; GDS, Geriatric depression scale; APOE, apolipoprotein E.

[a] $p < 0.001$ vs Controls and MCI;
[b] **p** $< 0.001$ vs AD;
[c] $p < 0.001$ vs Controls;
[d] $p < 0.05$ vs MD.

**Table 2**
Plasmatic concentrations of the markers analysed in people categorized in controls, mild cognitive impairment (MCI), Alzheimer's disease (AD), and mixed dementia (MD).

| | Controls | MCI | AD | MD | *p* |
|---|---|---|---|---|---|
| IFN-γ (pg/mL) | 0.67 (0.45–1.04) | 0.70 (0.49–1.10) | 0.73 (0.51–0.94) | 0.74 (0.50–1.28) | 0.10 |
| IL-10 (pg/mL) | 2.03 (1.60–2.60) | 2.24 (1.72–2.84) | 2.59 (2.18–3.30) [a,b] | 2.51 (2.04–3.30) [a,b] | **<0.001** |
| IL-6 (pg/mL) | 2.54 (1.72–4.05) | 2.81 (1.95–4.15) | 3.03 (2.04–5.89) [c] | 3.69 (2.49–6.13) [a,b] | **<0.001** |
| IL-1β (pg/mL) | 0.17 (0.10–0.28) | 0.14 (0.08–0.20) [a] | 0.12 (0.05–0.21) [a] | 0.16 (0.08–0.24) | **<0.001** |
| TNF-α (pg/mL) | 9.12 (7.56–11.20) | 9.03 (7.29–11.30) | 9.44 (7.67–11.77) | 9.85 (8.28–12.12) [b,c] | **0.006** |
| TNFR1 (ng/mL) | 1.38 (1.11–1.68) | 1.51 (1.25–1.78) [a] | 1.51 (1.25–1.78) | 1.55 (1.30–1.90) [a] | **<0.001** |
| sTREM1 (ng/mL) | 0.48 (0.39–0.63) | 0.51 (0.42–0.63) | 0.47 (0.39–0.60) | 0.57 (0.46–0.67) [a] | **0.005** |
| sTREM2 (ng/mL) | 35.5 (26.3–47.1) | 36.3 (28.1–46.7) | 39.6 (31.4–51.6) [c] | 42.3 (33.7–58.3) [a,b] | **<0.001** |
| NfL (pg/mL) | 33.4 (26.2–48.0) | 37.2 (28.5–50.2) | 47.3 (36.3–59.5) [a,d] | 48.6 (36.4–70.5) [a,b] | **<0.001** |

Marker concentrations were expressed as median (interquartile range).
MCI, Mild cognitive impairment; AD, Alzheimer's disease; MD, Mixed dementia; IFN-γ, Interferon-γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells; NfL, Neurofilament light chain.
[a] $p < 0.001$ vs Controls;
[b] $p < 0.001$ vs MCI;
[c] $p < 0.05$ vs Controls;
[d] $p < 0.05$ vs MCI.

regarding the different association between inflammation and chronological age versus frailty (Arosio et al., 2023), in this case in the context of older patients with cognitive impairment. The main finding observed in this new cohort is the association of specific biomarkers with cognitive impairment or dementia after the adjustment for chronological age and frailty (measured using the FI).

In fact, after all adjustments, the plasmatic biomarkers found to be significantly associated with the risk of cognitive impairment and/or dementia were IL-10, IL-6, IL-1β, and NfL.

Specifically, IL-10 and NfL were found to be associated with the increased risk of AD and MD, while IL-1β was negatively associated with the risk not only of dementia (AD and MD) but also of MCI. Moreover, IL-6 was weakly and positively associated with the risk of AD.

NfL is the major component of the axonal cytoskeleton and serves to maintain the structure of the neuron by controlling the calibration of axons (Lee and Cleveland, 1996). The blood concentration of NfL increases in several neurological and neurodegenerative diseases, such as traumatic brain injury, multiple sclerosis, frontotemporal lobar degeneration, and AD (Delaby et al., 2022).

Regarding AD, the data in the literature are controversial because both serum and CSF concentrations of NfL have shown moderate to poor ability in discriminating AD from MCI and/or other dementias (Andersson et al., 2020; Bridel et al., 2019; Forgrave et al., 2019; Lewczuk et al., 2018; Mattsson et al., 2019; Sugarman et al., 2020). In addition, NfL concentration does not correlate with typical markers of AD, such as amyloid beta (Aβ) and p-tau (Andersson et al., 2020; Lewczuk et al., 2018; Pereira et al., 2017; Preische et al., 2019), hypothesizing the involvement of other molecules and mechanisms in axonal damage (Kalm et al., 2017).

It is noteworthy that peripheral neuropathy (Mariotto et al., 2018; Sandelius et al., 2018), cardiovascular disease (Polymeris et al., 2020), diabetes and renal failure (Akamine et al., 2020), and aging per se, were all found to be associated with increased plasmatic NfL concentrations (Delaby et al., 2022). Furthermore, NfL levels were inversely correlated with muscle strength and lean mass in a cohort of sarcopenic older adults (Ladang et al., 2023) being a promising marker of frailty since it appears to be associated with decline in physical (Qaisar et al., 2024) and functional (Grasset et al., 2024) abilities.

In our model, we found a significant association between NfL concentration and chronological age, frailty and to a lesser extent with education and the presence/absence of the ε4 allele of the ApoE genotype. Our data disagree with a previous study in which NfL concentration did not correlate with frailty in a cohort of persons older than 70 years (Lu et al., 2022). It is to note that in the study by Lu and colleagues, the frailty status was measured by means of the Fried phenotype (Fried et al., 2001), while in our study the degree of fragilization was calculated by FI as a proxy of the individual's cumulative decline in different physiological systems (Rockwood and Mitnitski, 2007).

Our findings confirmed the hypothesis that the NfL concentration in plasma is unable to discriminate between different types of dementia, having been found to be equally associated with an increased risk of AD and MD, similarly to the IL-10 concentration.

Interestingly, IL-10 concentration was not found to be associated with the degree of frailty in either of our studies. In fact, in our previous study, IL-10 was associated only with chronological age (Arosio et al., 2023), whereas in the present cohort also with cognitive decline by the means of MMSE in addition to age.

It is known that overstimulation of pro-inflammatory components and ineffectiveness of the anti-inflammatory response could be a driving force in the development of age-related diseases (Morrisette-Thomas et al., 2014) and that such alteration in the immune response is a key feature of AD (Town, 2010; Zandman-Goddard and Shoenfeld, 2008). In addition, the peripheral immune system may be a strong contributor to AD pathology, whereby the recirculation of peripheral immune cells and inflammatory mediators such as cytokines, chemokines, and complement across a damaged blood-brain barrier (BBB) establishes a vicious cycle between brain and periphery (Le Page et al., 2018; Schwartz and Deczkowska, 2016).

Interestingly, a dualistic role of inflammation in AD has been hypothesized, either protective or detrimental depending on the biological stage of the disease (Arranz and De Strooper, 2019; De Strooper and Karran, 2016; Edwards, 2019; Heneka et al., 2015; Heppner et al., 2015). In this regard, we have previously shown that peripheral blood mononuclear cells from patients with AD characterized by a rapid disease progression lacking the ability to mount an adequate anti-inflammatory response upon stimulation by Aβ (Asselineau et al., 2015) and thus produced less IL-10 than patients with slow-progressing AD (Tedone et al., 2015).

We confirmed higher plasma concentrations of IL-10 in AD (Baune et al., 2009; King et al., 2018) and described a similar association with MD according to the fact that IL-10 concentration does not appear to be informative to support diagnostic decision-making that distinguishes different types of dementia.

In our cohort, plasma IL-1β concentration was inversely associated with the risk of MCI, AD, and MD. This result might seem counterintuitive, as most studies report a significant positive association between IL-1β concentrations and increased risk of cognitive decline (particularly AD), as summarized in the meta-analysis by Lai and colleagues (Lai et al., 2017). In fact, the studies selected in this meta-analysis did not consider the interaction with disease severity and comorbidities (Lai

**Table 3**
Multiple linear regression model between the log-transformed concentration of each biomarker (dependent variable) and sex, dichotomized frailty index (FI), age, education, MMSE score and presence of the APOE ε4 allele (ε4+) (independent variables).

| | Covariates | $R^2$ | B | SE | *p* |
|---|---|---|---|---|---|
| IFN-γ | Sex | 0.02 | −0.051 | 0.059 | 0.39 |
| | FI | | 0.076 | 0.063 | 0.23 |
| | Age | | 0.005 | 0.005 | 0.36 |
| | Education | | −0.005 | 0.028 | 0.85 |
| | MMSE | | −0.012 | 0.007 | 0.06 |
| | APOE (ε4+) | | −0.038 | 0.063 | 0.54 |
| IL-10 | Sex | 0.06 | 0.088 | 0.040 | **0.03** |
| | FI | | 0.034 | 0.042 | 0.42 |
| | Age | | 0.007 | 0.003 | **0.03** |
| | Education | | 0.007 | 0.019 | 0.73 |
| | MMSE | | −0.018 | 0.004 | **<0.001** |
| | APOE (ε4+) | | 0.013 | 0.042 | 0.76 |
| IL-6 | Sex | 0.12 | 0.106 | 0.056 | 0.06 |
| | FI | | 0.293 | 0.060 | **<0.001** |
| | Age | | 0.013 | 0.005 | **0.007** |
| | Education | | −0.009 | 0.027 | 0.74 |
| | MMSE | | −0.021 | 0.006 | **<0.001** |
| | APOE (ε4+) | | −0.114 | 0.060 | **0.05** |
| IL-1β | Sex | 0.02 | 0.022 | 0.082 | 0.79 |
| | FI | | −0.046 | 0.087 | 0.59 |
| | Age | | 0.010 | 0.007 | 0.17 |
| | Education | | −0.029 | 0.039 | 0.46 |
| | MMSE | | 0.012 | 0.009 | 0.19 |
| | APOE (ε4+) | | −0.219 | 0.087 | **0.01** |
| TNF-α | Sex | 0.09 | 0.051 | 0.025 | **0.04** |
| | FI | | 0.048 | 0.027 | 0.07 |
| | Age | | 0.012 | 0.002 | **<0.001** |
| | Education | | 0.010 | 0.012 | 0.41 |
| | MMSE | | −0.008 | 0.003 | **0.006** |
| | APOE (ε4+) | | −0.027 | 0.027 | 0.31 |
| TNFR1 | Sex | 0.23 | 0.057 | 0.023 | **0.01** |
| | FI | | 0.150 | 0.025 | **<0.001** |
| | Age | | 0.017 | 0.002 | **<0.001** |
| | Education | | 0.023 | 0.011 | **0.04** |
| | MMSE | | −0.004 | 0.003 | 0.09 |
| | APOE (ε4+) | | −0.079 | 0.025 | **0.001** |
| sTREM1 | Sex | 0.15 | 0.038 | 0.027 | 0.16 |
| | FI | | 0.104 | 0.029 | **<0.001** |
| | Age | | 0.018 | 0.002 | **<0.001** |
| | Education | | 0.026 | 0.013 | **0.04** |
| | MMSE | | −0.001 | 0.003 | 0.74 |
| | APOE (ε4+) | | −0.067 | 0.028 | **0.02** |
| sTREM2 | Sex | 0.15 | −0.080 | 0.030 | **0.007** |
| | FI | | 0.099 | 0.032 | **0.002** |
| | Age | | 0.020 | 0.003 | **<0.001** |
| | Education | | −0.015 | 0.014 | 0.30 |
| | MMSE | | −0.006 | 0.003 | 0.07 |
| | APOE (ε4+) | | −0.034 | 0.031 | 0.28 |
| NfL | Sex | 0.22 | −0.024 | 0.035 | 0.51 |
| | FI | | 0.145 | 0.038 | **<0.001** |
| | Age | | 0.027 | 0.003 | **<0.001** |
| | Education | | 0.036 | 0.017 | **0.03** |
| | MMSE | | −0.019 | 0.004 | **<0.001** |
| | APOE (ε4+) | | −0.084 | 0.038 | **0.03** |

$R^2$, coefficient of determination; B, unstandardized β coefficient; SE, standard error for the unstandardized β coefficient; FI, Frailty index; MMSE, Mini-mental state examination; APOE, apolipoprotein E; IFN-γ, Interferon-γ; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; TNF-α, Tumour necrosis factor-α; TNFR1, Tumour necrosis factor receptor 1; sTREM, Soluble triggering receptor expressed on myeloid cells; NfL, Neurofilament light chain.

et al., 2017), and this could generate conflicting results, as demonstrated by another study that describes higher concentrations of this cytokine only in patients with MCI and not in those with dementia (King et al., 2018).

Interestingly, also in our model, IL-1β concentration appeared to be associated with mild cognitive decline, as previously described (Galgani et al., 2022). In our cohort, the significant association found not only with the risk of MCI, but also with both types of dementia, indicated that IL-1β concentrations begin to decrease early in cognitive decline and remain at low levels in overt dementia. Furthermore, the distribution of IL-1β concentrations was significantly different in patients with MCI and AD compared with controls, with the lowest median values highlighted in patients with AD.

It is important to note that several cytokines, including IL-1β, promote microglial activation and mediate Aβ clearance (Fu et al., 2016; Shaftel et al., 2007), supporting the dual role of activated microglia in the pathogenesis of AD, namely the beneficial one consisting of phagocytosis and the detrimental one inducing a chronic increase in cytokine levels (Haruwaka et al., 2019; Hong et al., 2016; Schafer and Stevens, 2015). Interestingly, in a transgenic mouse model of sustained overexpression of IL-1β, four weeks of overexpression of this cytokine induced a significant reduction in amyloid pathology through enhancement of microglia-dependent plaque degradation (Schafer and Stevens, 2015).

In addition, in our linear regression model, IL-1β concentrations showed an association with the presence/absence of the ε4 allele of the APOE gene, suggesting their interaction in the clearance mechanisms (Rodriguez et al., 2014) and supporting the notion that some inflammatory markers may play a different role in the AD onset in ε4 carriers than in non-carriers (Tao et al., 2018). These results seem to suggest an involvement of IL-1β primarily in the onset of neurodegenerative dementia, although the plasma concentration of this cytokine cannot be used to distinguish AD from MD.

Lastly, IL-6 concentration showed a weak association with the risk of AD and only a trend with the risk of MD, in contrast it was significantly associated with frailty, age and cognitive decline.

Albeit the other biomarkers showed no association with dementia, the highest concentrations of all were generally observed in the MD group. It should be noted that the MD patients were significantly older and more frail than the others, which would account for the higher concentration found of the other markers in this group.

The first limitation of our study lies in its cross-sectional nature, with the possibility that our results reflect lifestyle factors other than the described and analysed determinants of health. Moreover, although the influence of some of the main potential confounding factors, such as age, sex, and frailty status, has been considered, the possibility of residual confounding remains possible. Finally, the main weakness is the exclusion of all individuals characterized by the presence of known pathological conditions involving altered markers of inflammation. The exclusion was necessary from a mechanistic point of view, leading to the exclusion of a large portion of older people, and thus distancing the results from real life and limiting the translation of these measures into clinical practice.

In conclusion, our data showed similar associations between AD and MD, supporting the concept that late-onset dementia is a complex outcome of aging, intimately linked to the individual's health status and biological risk factors as well as the individual's frailty status. Data from the snapshot of our cohort at the moment of first geriatric visit indicate that considering the degree of frailty in older people can improve our understanding of the biological changes that realistically contribute to dementia. Furthermore, the ability to monitor over time in the same individuals the association between disease progression and changes in these biomarkers may provide valuable input to diagnostic procedures in the future.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2025.112692.

## CRediT authorship contribution statement

**Beatrice Arosio:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Paolo Dionigi Rossi:** Writing – review & editing, Conceptualization. **Evelyn Ferri:** Writing – review & editing, Methodology, Formal analysis. **Ernesto Consorti:** Writing – review & editing. **Simona Ciccone:**

**Table 4**
Multinomial logistic regression model for mild cognitive impairment (MCI), Alzheimer's disease (AD), and mixed dementia (MD) per the log-transformed concentration of each biomarker, adjusted for sex, dichotomized frailty index (FI), age, education and presence of the Apolipoprotein E ε4 allele (APOE ε4+) (only significant results).

| | MCI | | AD | | MD | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | ***p*** | OR (95% CI) | *p* | OR (95% CI) | *p* |
| IL-10 (pg/mL) | 1.41 (0.95–2.09) | 0.08 | 2.72 (1.57–4.70) | **<0.001** | 2.42 (1.56–3.74) | **<0.001** |
| IL-6 (pg/mL) | 0.95 (0.73–1.25) | 0.72 | 1.51 (1.04–2.19) | **0.03** | 1.34 (1.00–1.80) | **0.05** |
| IL-1β (pg/mL) | 0.70 (0.58–0.86) | **<0.001** | 0.63 (0.47–0.84) | **0.002** | 0.71 (0.56–0.90) | **0.004** |
| NfL (pg/mL) | 1.25 (0.81–1.94) | 0.31 | 3.51 (1.87–6.57) | **<0.001** | 2.94 (1.78–4.84) | **<0.001** |

Controls were the reference group.
MCI, Mild cognitive impairment; AD, Alzheimer's disease; MD, Mixed dementia; OR, Odds ratio (adjusted for age, sex and dichotomized frailty index); 95 % CI, 95 % confidence interval; IL-10, Interleukin-10; IL-6, Interleukin-6; IL-1β, Interleukin-1β; NfL, Neurofilament light chain.

Writing – review & editing. **Tiziano Angelo Lucchi:** Writing – review & editing. **Nicola Montano:** Writing – review & editing, Supervision, Funding acquisition.

## Ethics approval and consent to participate

The study was approved by the ethics committee of the Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico of Milan (REGE, protocol number 223248; REGE 2.0, protocol number 1696).

## Consent for publication

Not applicable.

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## Declaration of competing interest

The authors declare no competing interests.

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## Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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