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SOCIOECONOMIC BURDEN OF ALZHEIMER'S DISEASE IN ITALY AND DELIRIUM CASELOAD IN AN ACUTE GERIATRIC SETTING: A TWO-STUDY OBSERVATIONAL THESIS.

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Ministero dell'Università e della Ricerca

Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA

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ABSTRACT

Background. Dementia is an acquired syndrome characterised by progressive cognitive decline and loss of independence. Delirium is an acute neuropsychiatric disorder that often occurs during hospitalisation, frequently in the context of dementia. Both conditions carry substantial clinical and socioeconomic burdens. Given rapid population ageing, judicious resources allocation is critical; however, national evidence on the socioeconomic impact of dementia remains limited, and dedicated care pathways for older adults with dementia or delirium are under-implemented.

Aims. To generate policy-relevant evidence to inform sustainable, equitable, and outcomes-oriented care models for Italy's ageing population. This thesis integrates two studies to: (*1*) estimate the socioeconomic burden of Alzheimer's disease (AD) among community-dwelling patients, from both the National Health Service and societal perspectives; and (*2*) quantify delirium prevalence/incidence in an Acute Geriatric Unit (AGU), model daily delirium-probability trajectories and evaluate their prognostic value for 3-month mortality.

Methods. *Study 1* was a cross-sectional study conducted in seven Italian memory clinics, enrolling patients aged ≥50 years with AD across severity stages and their caregivers. A cost-of-illness approach captured health- and social-care resource use over the prior three months (medications, home/community services, caregiver work impact). Multivariable regression identified determinants of total costs. *Study 2* was a prospective cohort study enrolling older adults consecutively admitted to the AGU of the IRCCS Foundation San Gerardo dei Tintori (Monza). Sociodemographic and comprehensive clinical data were collected. In-hospital delirium-probability trajectories were derived using group-based trajectory modelling; associations with 3-month mortality were estimated with Poisson regression adjusted for age, sex, frailty and serum albumin.

Results. *Study 1*: 262 patient-caregiver dyads were enrolled [median patient age 75 years (Q1–Q3: 70–81); 46.9% men; 18.7% Mild Cognitive Impairment, 30.9% mild AD, 30.5% moderate AD, 19.9% severe AD]. Mean monthly per-patient costs rose with severity: from €195 to €304 in the NHS perspective, and from €426 to €1,644 in the societal perspective. Expenditure fell predominantly on families and society via formal paid care, out-of-pocket spending, and especially caregiver productivity losses. Greater neuropsychiatric symptom burden independently increased total costs, whereas better patient instrumental functioning reduced them. Patient health-related quality of life declined with disease severity, with a milder parallel decline among caregivers.

Study 2: 639 patients were enrolled [median age 87 years (Q1–Q3: 84–90); 53.2% women]. Delirium prevalence at admission was 38% (95% CI: 34–42%), and in-hospital incidence 14% (95% CI: 11–18%). Among the 301 patients with delirium, three probability trajectories emerged: High (40.2%), Medium (31.9%), and Medium-to-Low (27.9%). Compared with the Medium-to-Low class, adjusted 3-month mortality risk was higher in the Medium (RR 1.56, 95%CI 1.02–2.36) and High (RR 2.07, 1.41–3.05) trajectories.

Conclusions. AD-related costs escalate with severity and are largely borne by families in the community. In hospital, delirium is common, and certain trajectories are strongly associated with short-term mortality. Together, there findings link the economic and clinical-epidemiological dimensions of older adults' care across the home–hospital continuum, providing practical foundations for targeted, evidence-based investments that may reduce costs while improving outcomes for patients and caregiver in dementia and delirium fields.

CHAPTER 1 - POPULATION AGEING

1.1 GLOBAL TRENDS

According to the United Nations Department of Economic and Social Affairs (UNDESA, 2024), the world population will keep growing for the next 50–60 years, peaking at about 10.3 billion in the mid-2080s (up from 8.2 billion in 2024). Thereafter it is projected to decline slightly, reaching roughly 10.2 billion by 2100 [1]. UNDESA now assigns an 80% probability that the global population will reach its maximum within this century, a major revision from earlier United Nations projections, which placed this likelihood at only 30 percent (**Figure 1**) [1].

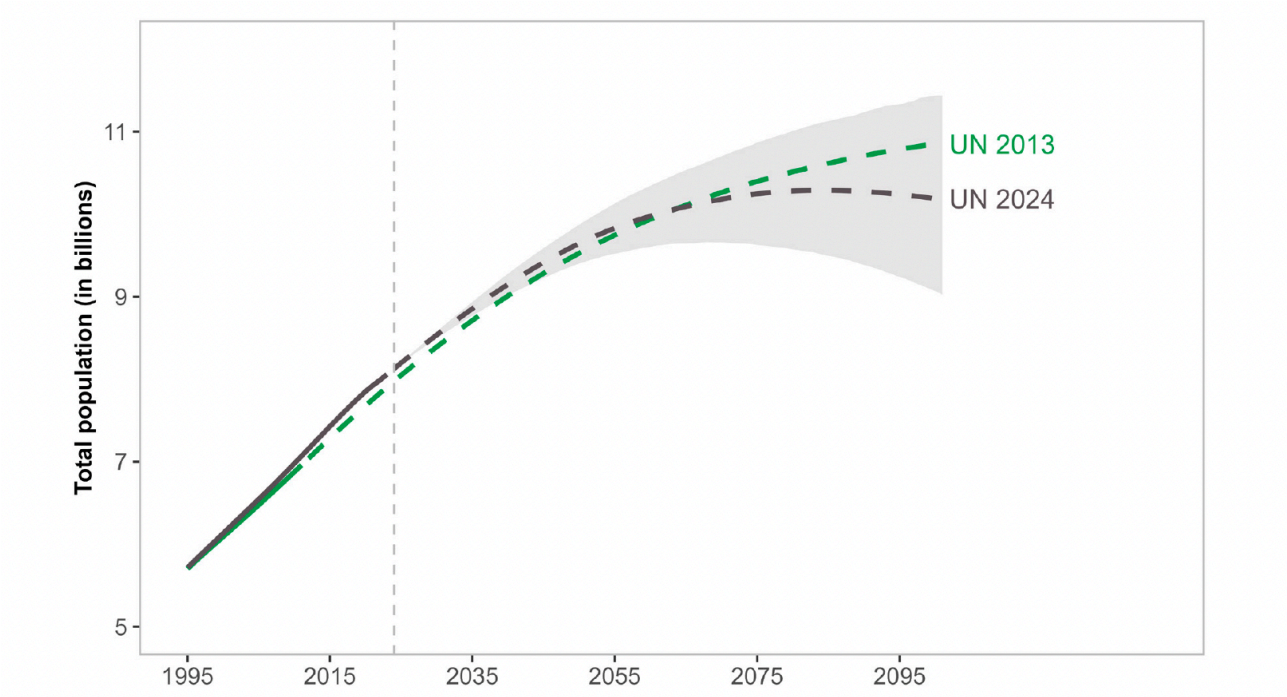


Figure 1. Global population according to the United Nations (UN) World Population Prospects 2013 vs 2024. Estimates cover 1995–2010 (UN 2013) and 1995–2023 (UN 2024); projections cover 2010–2100 (UN 2013) and 2024–2100 (UN 2024), with 95% prediction intervals. [Source: United Nations]

An earlier global peak is consistent with continued fertility decline across much of the world, including China. The total fertility rate fell from 3.3 births per woman in 1990 to 2.25 in 2024; over half of countries are now below the 2.1 replacement level, and 20% of countries have ultra-low fertility (<1.4), including Italy, Spain, China, and the Republic of Korea [1]. A return to replacement fertility within 30 years is therefore unlikely in these settings. Despite falling fertility, demographic momentum keeps populations growing in the near term as large cohorts age into childbearing years; however, working-age populations are already shrinking in regions such as Europe and East Asia [1]. Life expectancy at birth, which has resumed its upward trend after the COVID-19 pandemic, reached 73.3 years in 2024 and is projected to rise to 77.4 by 2054; by the late 2050s, more than half of global deaths are expected at ages ≥80, signalling a shift toward survival at advanced ages [1].

This tendency of populations to expand, reach a peak, and then stabilise or decline reflects the demographic transition, a broad shift tied to social and economic development [2]. Populations typically move from rapid growth (mortality declines while fertility remains high), to a mid-transition phase (fertility falls but growth continues due to excess births over deaths), and finally to low, stable fertility and mortality. When births and deaths balance, growth slows to zero or turns negative, yielding stabilisation or gradual decline after the peak [2]. Notably, about one quarter of the world's population already lives in countries where total population has peaked, including China, Japan, Italy, and several other European nations. In Italy, total fertility has remained well below replacement since 1995 and is projected to stay sub-replacement through 2100, while life expectancy is high and rising (82–84 years today, toward the high 80s by 2100). This combination implies sustained population ageing and downward pressure on population size in absence of substantial net migration (**Figure 2**).

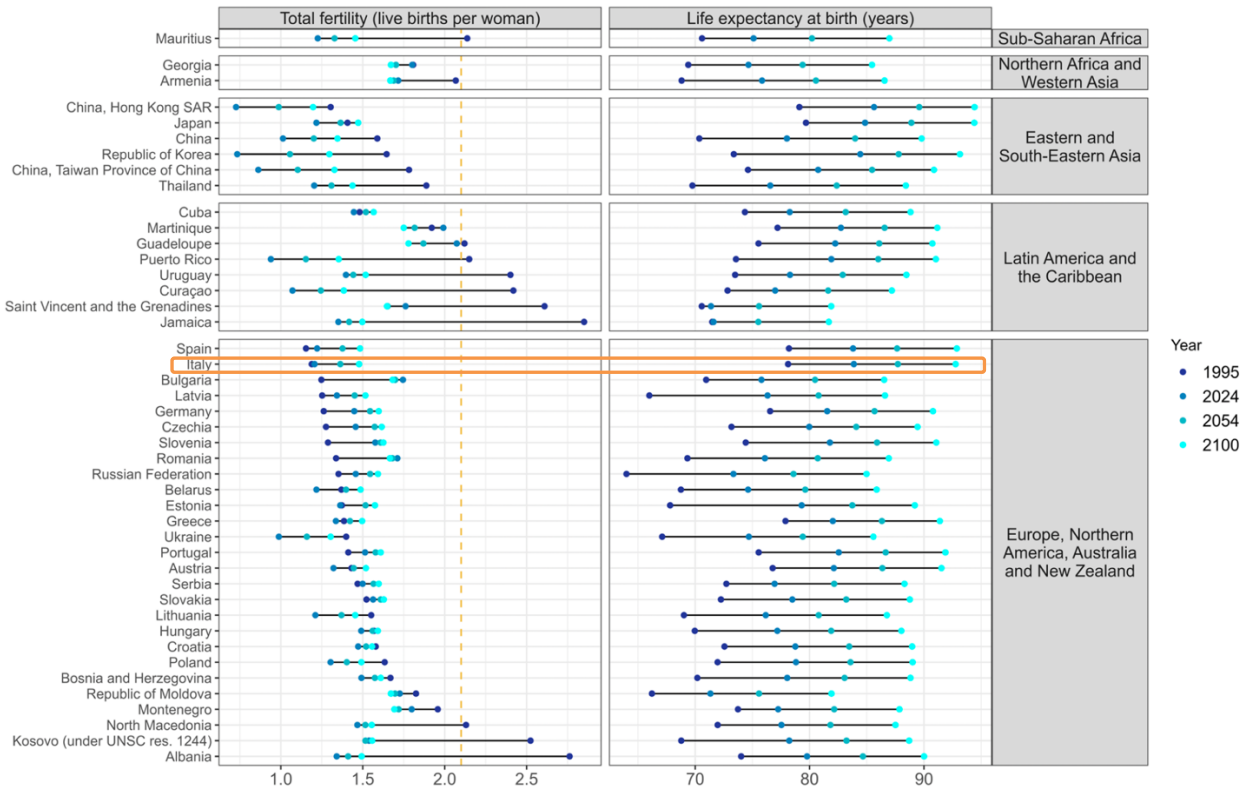


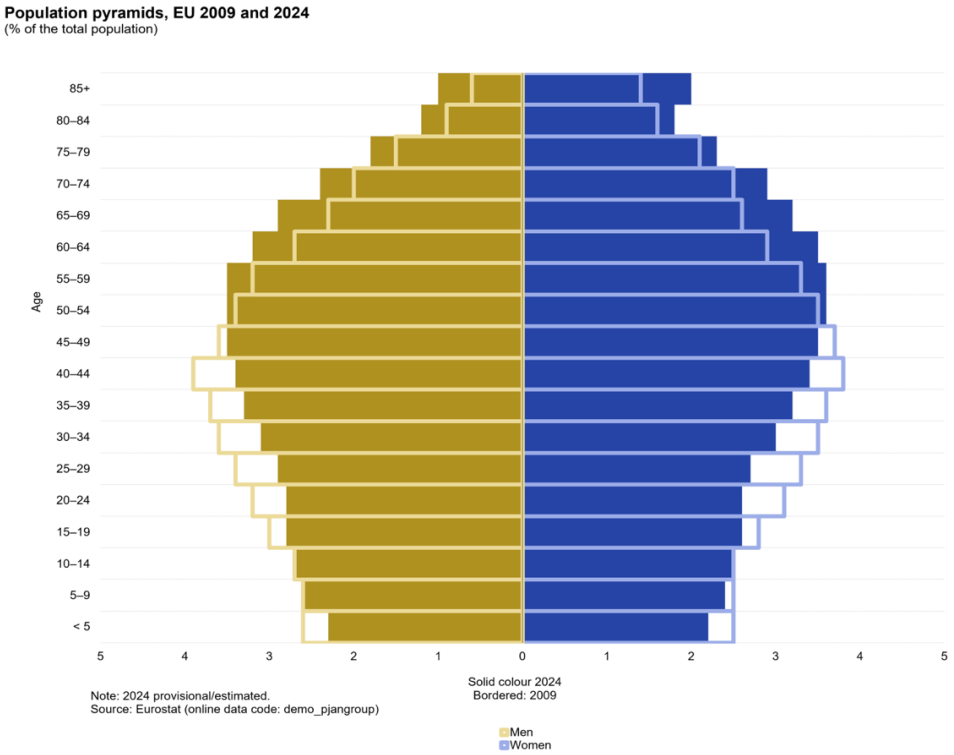
Figure 2. Total fertility and life expectancy at birth in countries whose populations have already peaked. Estimates are shown for 1995 and projections (medium scenario) for 2024, 2054, and 2100 from the United Nations. Countries/areas are ordered by 1995 fertility level within regions. The dashed orange vertical line marks replacement fertility (≈ 2.1 births per woman), whereas the horizontal orange box highlights Italy. [Source: United Nations]

1.2 Demographic Projections in Europe and Italy

Europe is the world's most demographically aged region, characterised by persistently low fertility and high life expectancy. Eurostat's 2024 projections indicate that the EU population will peak at roughly 453 million in 2026 and then decline to about 420 million by 2100 [3]. The share of people aged ≥65 years in the European Union (EU-27) reached 21.5% in 2024 (up 3 percentage points over the past decade) and is projected to approach 29% by 2050, while the working-age population (20–64 years) will shrink, pushing up the old-age dependency ratio and intensifying fiscal and welfare pressures [3].

Population pyramids make this shift visible (**Figure 3**). On January 1st, 2024, the EU pyramid showed a rhomboid profile driven by the baby-boom cohorts - born during the post–World War II period of high fertility - moving into retirement, expanding older age groups and compressing younger and prime-working cohorts. This reflects the combined effects of rising longevity and sustained sub-replacement fertility. By 2100, the projected pyramid resembles a more rectangular "block," signaling the predominance of older ages and the relative contraction of younger and middle-aged groups [3]. Ageing is also occurring within the older population itself: the "very old" (≥80 years) are the fastest-growing segment. Eurostat projects this group to more than double, from 6.1% of the total population in 2024 to 15.3% by 2100, underscoring a pronounced internal ageing process within the older population [3].

A.



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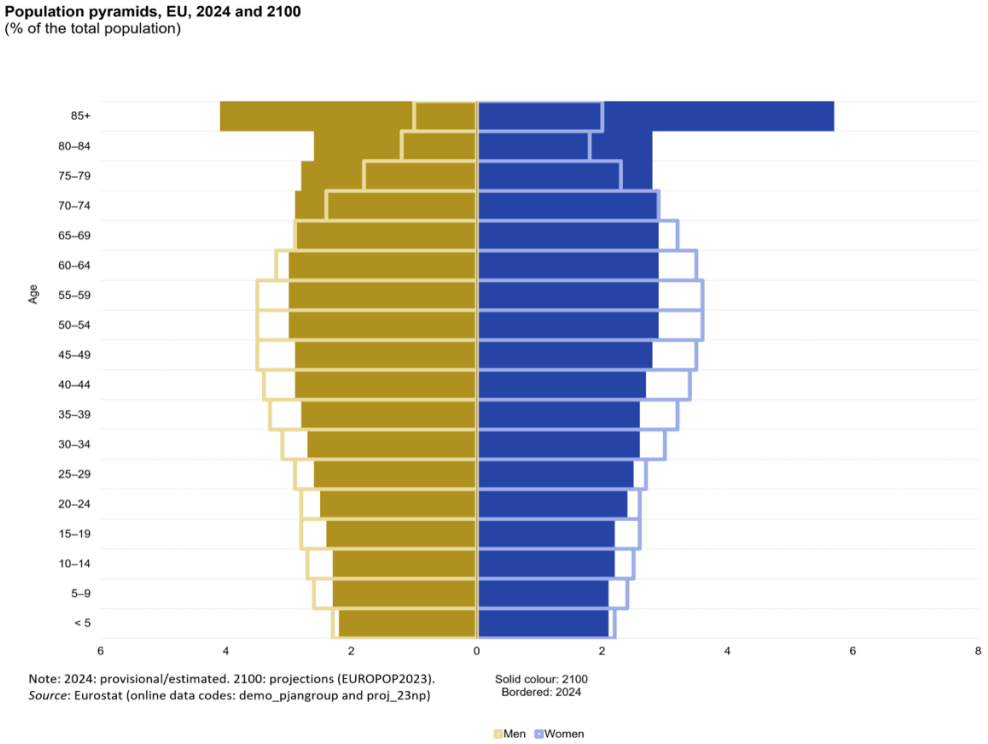


Figure 3. Population pyramids for the EU-27. A) 2009 [bordered colour] vs 2024 [solid colour] (% of the total population). B) 2024 [bordered colour] vs 2100 [solid colour] (projected; (% of the total population). [Source: Eurostat, demo_pjangroup (observed) and proj_23np (projections)]

Countries in Southern and Eastern Europe - Italy in particular - are projected to experience the greatest challenges, given the combined effects of persistently low fertility, modest net migration, and rising longevity. According to ISTAT (2024), Italy's total fertility rate has fallen to a historic low of 1.18 births per woman, while 24.3% of the population is aged ≥65 years. The median age has reached 46.6 years - among the highest globally - and projections indicate that by 2050 nearly 35% of Italians will be 65 or older [4]. Life expectancy remains high at 83.4 years [4].

This longevity gain, however, has been accompanied by a rising prevalence of chronic and neurodegenerative conditions – notably dementia and Alzheimer's disease (AD) - placing growing strain on healthcare and long-term care systems. Consistently, the European Commission's 2024 Ageing Report projects continued increases in age-related public expenditure (pensions, healthcare, and long-term care) across EU Member States through 2070 [5].

1.3 HEALTHY AGEING: BRIDGING THE LIFESPAN-HEALTHSPAN GAP

Despite sustained gains in longevity worldwide, health-adjusted life expectancy (HALE) has risen more slowly than total life expectancy, indicating that older adults are spending a growing share of their later years with morbidity and disability. Analyses from the Global Burden of Disease 2021 confirm the predominance of non-communicable diseases (NCDs) in the overall burden and show that years lived with disability (YLDs) increase as populations age - evidence consistent with a widening gap between lifespan and healthspan [6]. Convergent studies further document a measurable "healthspan–lifespan gap" across world regions (**Figures 4–5**): gains in survival are not uniformly accompanied by equivalent gains in disease-free or functionally independent years, and the magnitude of this gap correlates with NCD burden [7]. These dynamics help explain the growing demand for chronic-disease management and long-term care across European health systems.

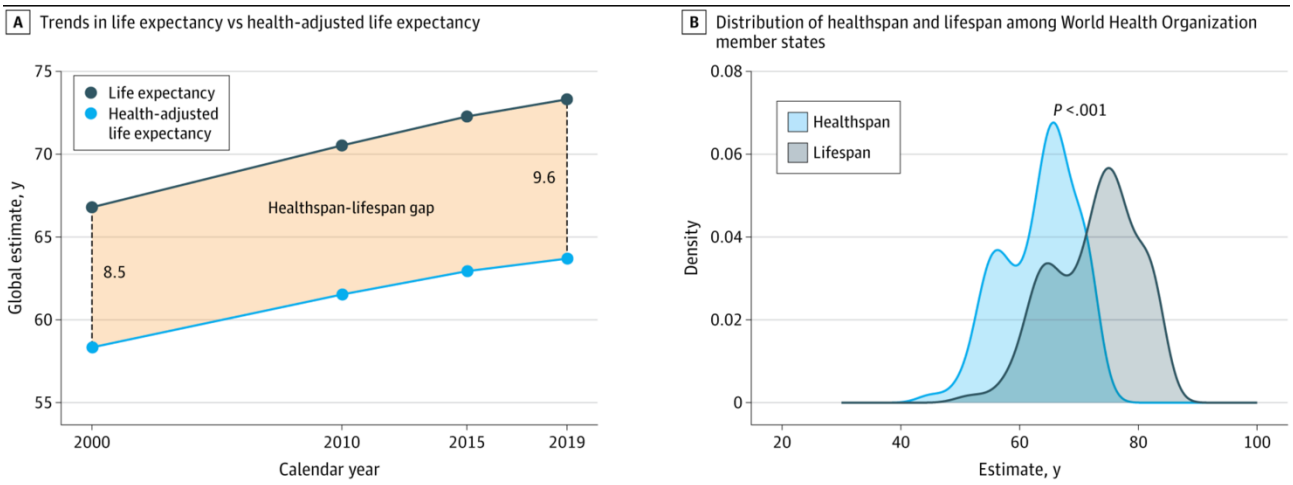


Figure 4. (A). Trends in life expectancy, health-adjusted life expectancy (HALE), and the resulting healthspan–lifespan gap. (B) Cross-national distribution of healthspan and lifespan across 183 WHO Member States. [Source: Global Healthspan–Lifespan Gaps Among 183 World Health Organization Member States. JAMA Network Open. 2024;7(12):e2450241. doi:10.1001/jamanetworkopen.2024.50241]

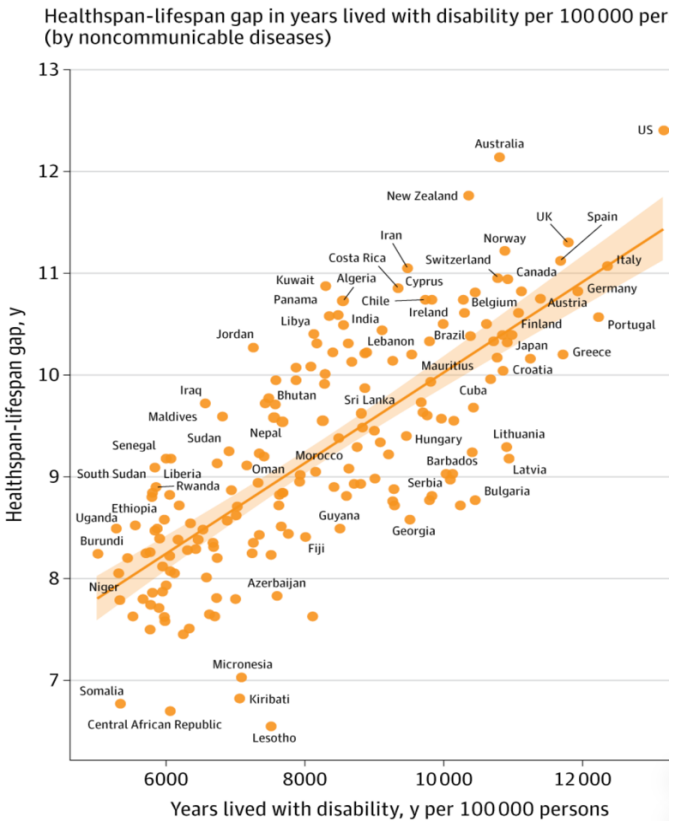


Figure 5. Relationship between the healthspan–lifespan gap and years lived with disability (per 100,000 population) due to non-communicable diseases. The solid line denotes the fitted regression; the shaded ribbon shows the 95% confidence interval [Source: Global Healthspan–Lifespan Gaps Among 183 World Health Organization Member States. JAMA Network Open. 2024;7(12):e2450241. doi:10.1001/jamanetworkopen.2024.50241]

This thesis is situated within the UN Decade of Healthy Ageing (2021–2030), led by the World Health Organization (WHO), which calls for coordinated action to improve the lives of older people, their families, and communities [8]. The Decade's four priority areas (combating ageism; creating age-friendly environments; delivering integrated, person-centred primary and community care; and ensuring access to long-term care) emphasise that added years should be healthy, functional, and dignified [8]. In parallel, WHO has elevated brain and mental health as core pillars of healthy longevity. The Global action plan on the public health response to dementia (2017–2025), recently extended to 2031, sets measurable targets for awareness, risk reduction, timely diagnosis, treatment and care, caregiver support, and research, to align gains in lifespan with gains in healthspan [9].

CHAPTER 2 – ALZHEIMER'S DISEASE (AD)

2.1 DEMENTIA: DIAGNOSIS AND EPIDEMIOLOGY

Dementia is an acquired, persistent, and progressive cogntive decline that affects one or more cognitive domains - not attributable to altered level of consciousness – resulting in a significant functional decline that is severe enough to compromise independence in everyday activities, work, or social functioning [10]. According to the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) [11], a Major Neurocognitive Disorder (dementia) is diagnosed when all of the following criteria are met:

A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition), based on:
    1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
    2. A substantial impairment in cognitive performance, preferably documented by standardised neuropsychological testing or, in its absence, another quantified clinical assessment.
B. The cognitive deficits interfere with independence in everyday activities (that is, at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications.
C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depression, schizophrenia).

About 55–57 million people were living with dementia worldwide in 2019–2020, a figure projected to reach 153 million by 2050, largely driven by population ageing [12]. In Europe, the number of people with dementia is expected to nearly double by 2050, rising to 14,298,671 in the EU and 18,846,286 in the wider European region [13]. In Italy, the Istituto Superiore di Sanità estimates 1.1 million people with dementia and 0.9 million with Mild Cognitive Impairment (MCI); recent projections suggest 2.3 million people with dementia by 2050 [14]. Despite this growth in absolute numbers, age-standardised prevalence is forecast to remain broadly stable, indicating that demographic change rather than rising age-specific risk accounts for most of the increase [12]. Globally, dementia is the seventh leading cause of death and a major contributor to disability and dependence in older adults [12].

Overall, AD is the most common cause of dementia worldwide, accounting for 60–70% of cases. Other aetiologies include vascular dementia (VaD), Lewy body disease (LBD), and frontotemporal dementia (FTD). Mixed pathologies are common in older adults, particularly AD plus vascular brain injury, complicating diagnosis and influencing prognosis and management [10].

Age remains one of the strongest risk factor for developing AD dementia; however, emerging evidence indicates that frailty - conceptualised as a diminished physiological reserve and impaired homeostatic compensation which exposes the individual to a greater risk of adverse outcomes [15] - also confers independent, potentially causal vulnerability to incident dementia beyond chronological age [16]. This link underscores the relevance of identifying and modifying frailty to delay or prevent cognitive decline in late life.

2.2 AD PATHOPHYSIOLOGY

Since 2011, the National Institute on Aging and the Alzheimer's Association (NIA–AA) have progressively refined case definitions and diagnostic guidance for AD. The initial consensus statements provided stage-specific criteria for preclinical AD, [17], MCI due to AD [18], and AD dementia [19,20], followed in 2012 by a neuropathology consensus [21] (**Figure 6**). Pathologically, AD is defined by extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau, with progressive synaptic and neuronal loss. Braak staging captures the stereotyped spread of tau from transentorhinal/hippocampal regions to association cortices and correlates with cognitive decline [22].

In 2018, the NIA–AA introduced a unified research framework, the A/T/N system, linking clinical and biological aspects to in-vivo measurement: A (Aβ pathology; Aβ Positron Emission Tomography [PET] or Cerebrospinal fluid [CSF] Aβ42/40), T (tau pathology; CSF p-tau or tau PET), and N (neurodegeneration; Magnetic Resonance Imaging [MRI] atrophy, FDG-PET hypometabolism, or neurofilament light) [23].

The 2024 NIA–AA update operationalises advances in biomarkers and therapeutics across research and clinical practice [24]. It distinguishes "Core 1" early-changing markers - Aβ PET, CSF Aβ42/40 and tau/Aβ ratios, and high-accuracy plasma assays (notably p-tau217) - which are sufficient to diagnose AD across the continuum, including asymptomatic states, and "Core 2" later-changing markers - tau PET and emerging tau fragments – which increase diagnostic confidence, inform prognosis, and support biological staging, though they are not generally stand-alone diagnostics.

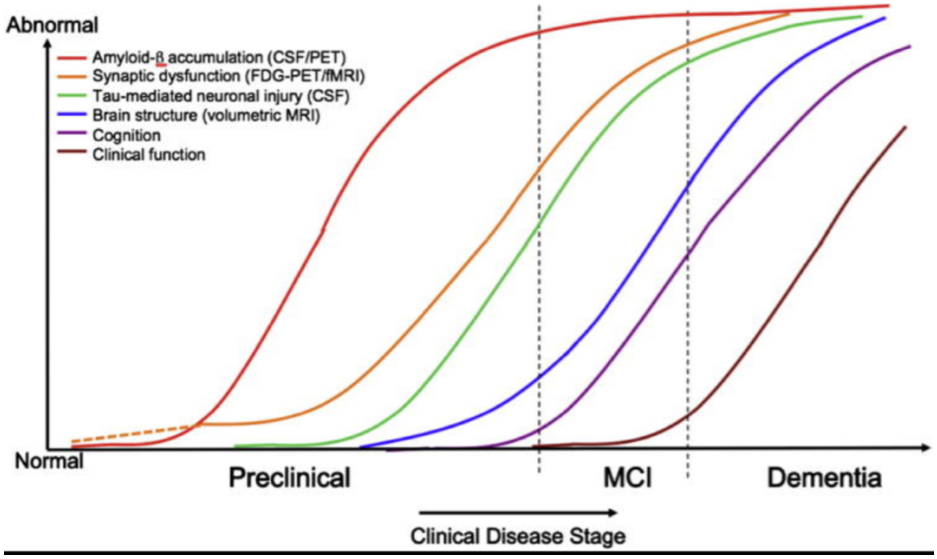


Figure 6. Hypothetical temporal model of AD biomarkers, expanded to delineate the preclinical phase. Curves show the transition from normal to maximally abnormal values (y-axis) across disease stage (x-axis) for core pathophysiologic markers (amyloid, tau/neuronal injury), with superimposed trajectories of cognition/behavior and functional status used in clinical staging. [Source: Sperling RA, et al. Alzheimer's & Dementia. 2011;7(3):280–292. doi:10.1016/j.jalz.2011.03.003]

The framework highlights also expanding access through blood-based biomarkers, and formalises complementary domains: N (neurodegeneration), I (inflammation), and common co-pathologies V (vascular) and S (α-synuclein), to better reflect real-world heterogeneity [24].

In clinical settings, AD is commonly categorised into three stages along a continuous trajectory: a preclinical phase without overt deficits; a prodromal phase marked by MCI; and a dementia phase with objective cognitive decline from prior baseline and significant functional impairment not better explained by delirium or other major psychiatric/neurological conditions, consistent with DSM-5-TR "major neurocognitive disorder due to Alzheimer's disease" [25]. The symptomatic course typically spans 10–12 years, progressing from mild to severe stages [26]. AD often begins with insidious episodic memory impairment and subsequently involves language, visuospatial abilities, executive function, and neuropsychiatric features (e.g., depression, apathy, agitation). Functional losses progress from instrumental to basic activities of daily living, with multi-domain impact on persons,

families, and society, including stigma, barriers to diagnosis, and increased but often unmet care needs [19].

Given the expected rise in cases with population ageing, health systems face sustained growth in demand for diagnosis, long-term care, and informal caregiving. Italy exemplifies this challenges, characterised by high longevity, large numbers of people with dementia, and a care model heavily reliant on families. Policy priorities should therefore include: (i) life-course risk reduction (education, cardio-metabolic control, hearing/vision care, physical activity, air-pollution mitigation), with the Lancet Commission (2024) identifying 14 modifiable factors potentially accounting for up to 45% of preventable or delayable dementia burden [27]; (ii) timely, accurate diagnosis anchored in the updated NIA–AA biological and clinical criteria to enable care planning and access to evolving disease-modifying and symptomatic treatments [24]; and (iii) integrated health-and-social care with robust caregiver support and community-based services to delay institutionalisation and mitigate indirect costs, in line with WHO's global dementia action plan [9].

2.3 Overview of AD Treatment

Standard care for AD combines non-pharmacological and supportive interventions with drug therapy [10]. Non-pharmacological measures remain central across the disease course (structured cognitive and social activities, caregiver education and training, and targeted management of neuropsychiatric symptoms) [27]. Among drugs, acetylcholinesterase inhibitors (Donepezil, Rivastigmine, Galantamine) are recommended to mitigate decline in cognition and daily functioning in mild–moderate AD, while memantine (a non-competitive N-Methyl-D-Aspartate [NMDA]-receptor antagonist) is used from moderate stages onward [10].

In recent years, amyloid-β–targeting monoclonal antibodies (lecanemab and donanemab) have marked a meaningful advance, showing substantial amyloid reduction on PET accompanied by a clinically relevant slowing of decline in early symptomatic AD (MCI due to AD or mild dementia). These agents have obtained regulatory approval by the U.S. Food and Drug Administration (FDA) and the European Medicals Agency (EMA) for early AD (MCI due to AD or mild dementia) with biomarker confirmation, in ApoE ε4 non-carriers or heterozygotes [28–31]. Their use mandates careful safety monitoring for amyloid-related imaging abnormalities (ARIA), for which baseline and serial MRI are recommended; APOE ε4 genotyping is advised to inform ARIA risk and support shared decision-making, particularly in ε4 homozygotes [32,33].

Amyloid-lowering agents introduce a real therapeutic option for a selected subset of patients, supporting the value of a biologically defined diagnosis and staging of AD. Their responsible deployment will depend on appropriate patient selection, risk counselling, MRI and infusion capacity, and integration with ongoing person-centred care, alongside standard symptomatic treatments.

2.4 AD-Related Costs

Cost-of-illness (COI) studies [34] typically classify expenditures into: (i) direct medical costs, including outpatient visits and diagnostics (including neuroimaging and biomarker assays), pharmaceuticals (symptomatic agents and, where available, DMTs), rehabilitation and specialist consultations, hospitalisations, and emergency care; (ii) direct non-medical costs, including formal sociare care such as paid home-care services, day-care and respite services, transport related to care, and institutional or long-term residential/nursing-home care; and (iii) indirect costs, including the economic value of informal caregiving time (estimated via opportunity- or replacement-cost methods, depending on the caregiver's lost time/value pricing or the market cost pricing to substitute that care), productivity losses among patients and working caregivers, costs associated with early retirement or premature mortality, and the "intangible" burden captured as decrements in health-related quality of life for patients and caregivers.

The human and economic burden of Alzheimer's disease (AD) is substantial worldwide. At the global level, mean annual per-person costs were estimated at US$23,796, contributing to societal costs of US$1.313 trillion in 2019; of this total, 16% reflected direct medical care, 34% formal social care (direct non-medical), and 50% informal care, most of it provided by family or friends, who deliver on average 5 hours of daily support [35,36]. The burden is also gendered: women provide 70% of total caregiving hours, and experience also higher dementia-related mortality and disability-adjusted life years [12].

Regarding severity, recent systematic review reported annual per-patient AD costs ranging from US$468 in mild disease to US$171,284 in severe disease, with a non-linear escalation by severity

[37]. Among community-dwelling patients, indirect caregiving typically dominates total costs; once patients transition to institutional settings, the cost profile shifts, with direct non-medical expenditures accounting for as much as two-thirds of the total [37]. In the United States, AD-related spending was US$321 billion, with projections exceeding US$1 trillion by 2050 [38]. Across Europe, the 2019 economic burden was €105.2 billion, with average annual per-person costs €20,000–€25,000 [39,40]. Finaly, Italian estimates place monthly societal costs between €1,552 and €2,728 per person, depending on severity [41] (**Figure 7-8**).

Methodological choices strongly influence COI estimates. Key sources of variation include the analytic perspective (societal vs payer), time frame (prevalence-based costs, which means incurred in a defined period by all existing cases, useful for budgeting and system impact, vs. incidence-based lifetime costs from disease onset, informative for prevention/therapy value and long-range planning), case ascertainment and severity mix, and the evaluation approach for informal care [34]. Because informal care frequently constitutes the largest cost component, its careful measurement has direct implications for policy on caregiver support, respite services, and timing of institutionalisation. Transparent reporting of these parameters is essential to ensure comparability across studies and to guide resource allocation.

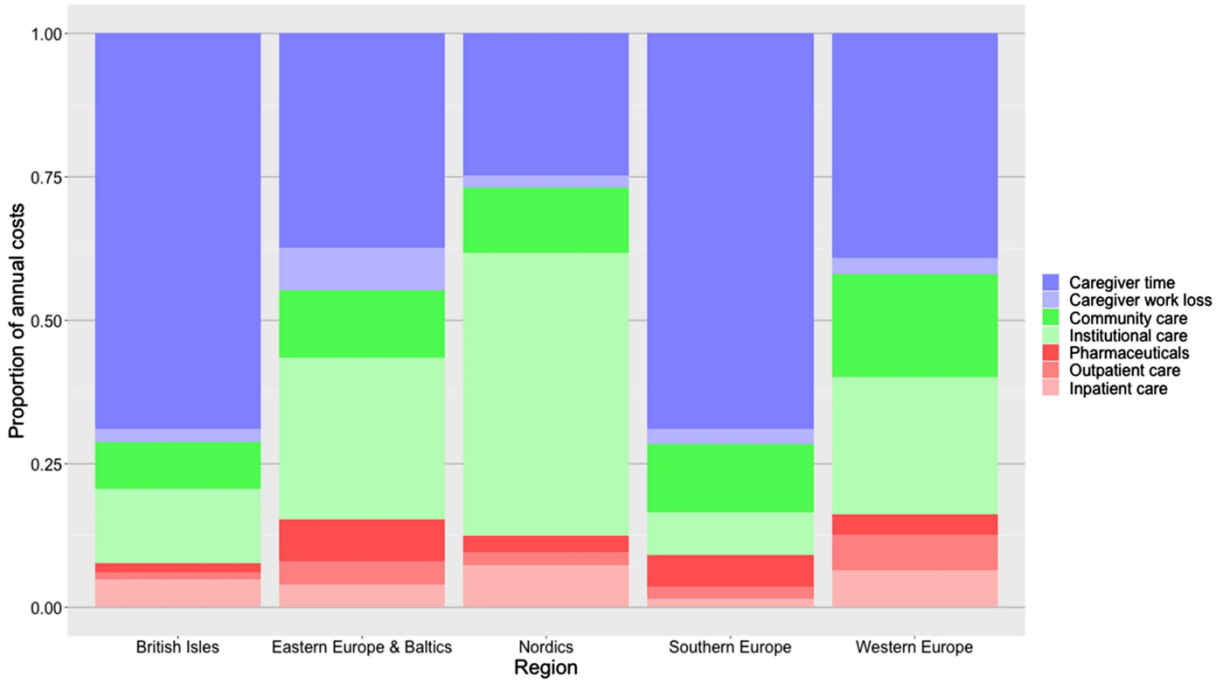


Figure 7. Distribution of dementia costs across components by European region. Bars show the proportion of total societal costs accounted for by direct medical care, direct non-medical care, and informal care in each region. [Source: Jönsson et al. The Costs of Dementia in Europe: An Updated Review and Meta-analysis. PharmacoEconomics 41, 59–75 (2023). https://doi.org/10.1007/s40273-022-01212-z]

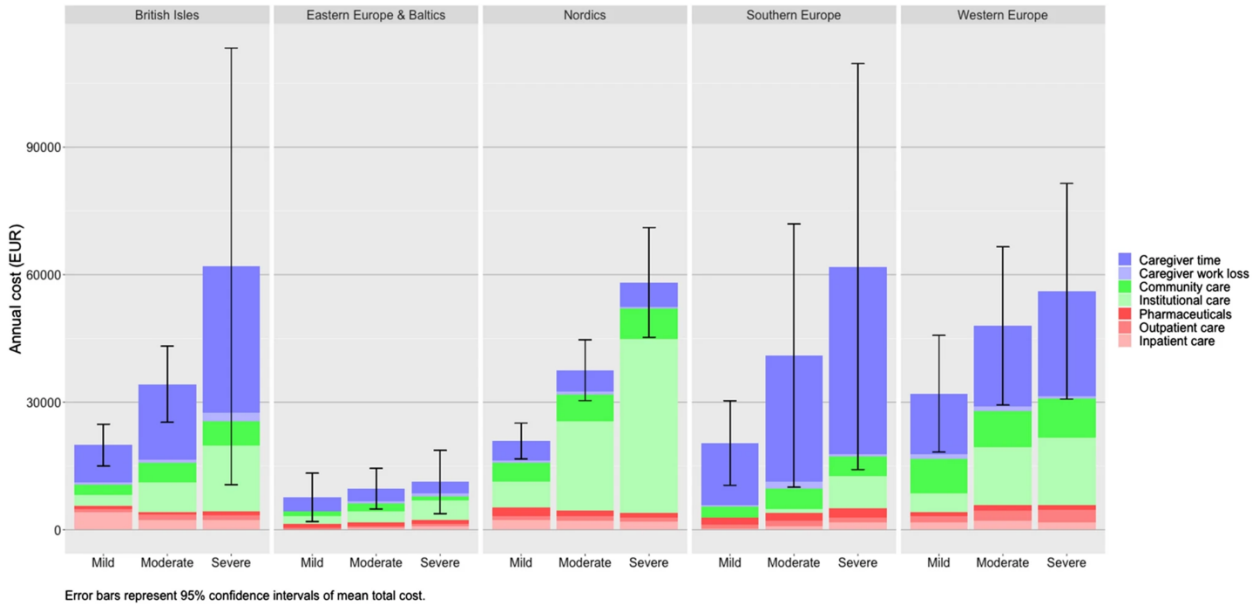


Figure 8. Mean annual per-person costs of dementia by disease severity and European region. Bars indicate average costs stratified by mild, moderate, and severe dementia. [Source: Jönsson et al. The Costs of Dementia in Europe: An Updated Review and Meta-analysis. PharmacoEconomics 41, 59–75 (2023). https://doi.org/10.1007/s40273-022-01212-z]

Given the projected rise in the number of people living with AD, and the associated pressure on families as well as health and social-care systems, country-specific estimates of the socioeconomic burden are essential to inform public-health strategy, research prioritisation, and policy design [36].

To move from measurement to mitigation, COI research should prioritise community-dwelling AD patients, where timely interventions can enhance patient and caregiver quality of life, delay or avert institutionalisation, strengthen the long-term sustainability of care, and facilitate access to emerging DMTs when appropriate.

CHAPTER 3 – DELIRIUM

3.1 DEFINITION AND ETIOPATHOGENESIS

Delirium is an acute neuropsychiatric syndrome characterised by inattention, impaired awareness, and a fluctuating course. Its pooled occurrence is 23% in older medical inpatients [42], with higher rates after major surgery (up to 50%) and in critical illness (as high as 75%) [43–45].

According to the DSM-5-TR criteria, delirium is diagnosed when all of the following are present [25]:

A. A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B. An acute onset (usually hours to a few days), with a change from baseline attention and awareness, and fluctuations in severity during the course of the day
C. An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
D. The disturbances in Criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E. Evidence from history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Delirium can present as hypoactive (characterised by lethargy and reduced motor activity), hyperactive (manifesting as agitation and aggression), mixed (alternating features of both), or as a non-motor subtype, in which cognitive and perceptual disturbances occur without clear changes in motor activity. Hypoactive, mixed, and non-motor forms predominate among frail older adults and are associated with poorer outcomes, including prolonged hospitalisation, increased complications, and higher mortality, compared with purely hyperactive presentations [46–49]. Symptoms typically fluctuate over hours, and may be subtle or easily overlooked in hypoactive or non-motor states, underscoring the importance of systematic routine screening [50].

Despite incomplete understanding of its etiopathogenesis, the vulnerability–precipitant model remains the prevailing explanatory framework (**Figure 9**): predisposing vulnerabilities (advanced age, prior cognitive impairment, frailty, sensory loss) interact with acute precipitating factors (infection, dehydration, metabolic alterations, pain, urinary retention/constipation, hypoxia, new high-risk medications and polypharmacy, immobilisation, catheters, physical restraints, and iatrogenic complications) to trigger delirium. As vulnerability increases, progressively milder insults are sufficient to precipitate delirium [44,51,52].

Among predisposing factors, pre-existing dementia is particularly important, since dementia and delirium are closely interrelated syndromes [53]. Older adults living with dementia are frequently admitted in hopital with delirium: a recent meta-analysis estimated the prevalence of in-hospital delirium superimposed on dementia (DSD) at 49% [54]. Another recent review also highlights the substantial clinical overlap between frailty and delirium, suggesting potential shared biological underpinnings aligned with the hallmarks of ageing (e.g., inflammageing, impaired proteostasis, mitochondrial dysfunction), which may help clarify delirium pathophysiology (**Figure 10**) [55].

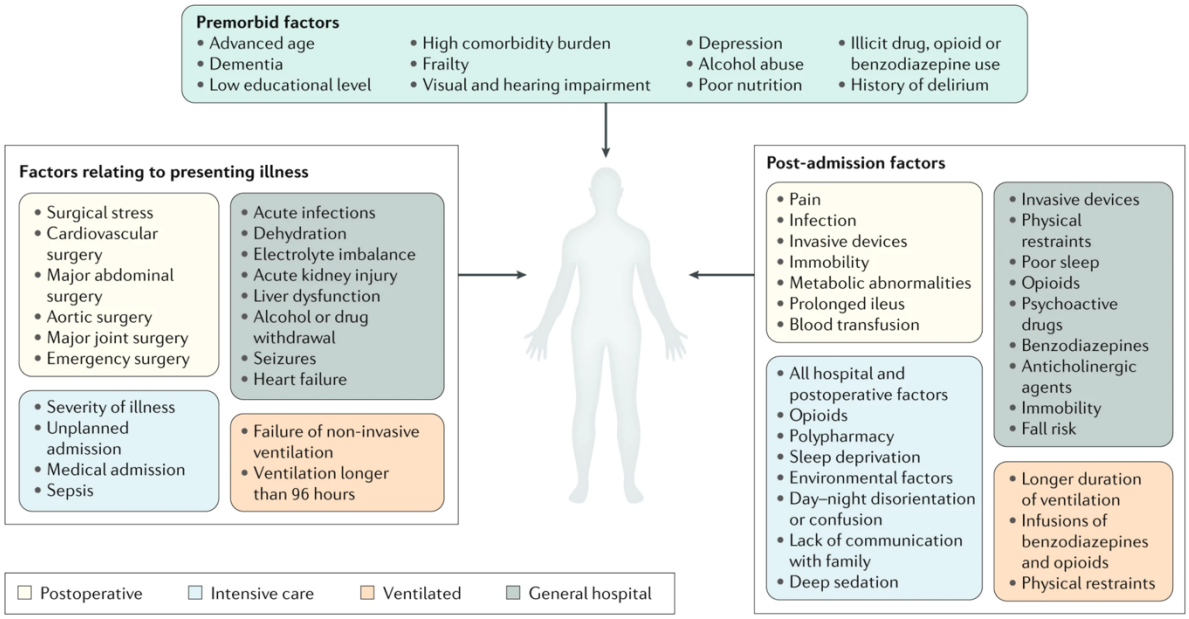


Figure 9. Risk factors for delirium related to predisposing factors and to precipitating factors. [Source: Wilson JE et al. Delirium. Nat Rev Dis Primers. 2020 Nov 12;6(1):90. doi: 10.1038/s41572-020-00223-4]

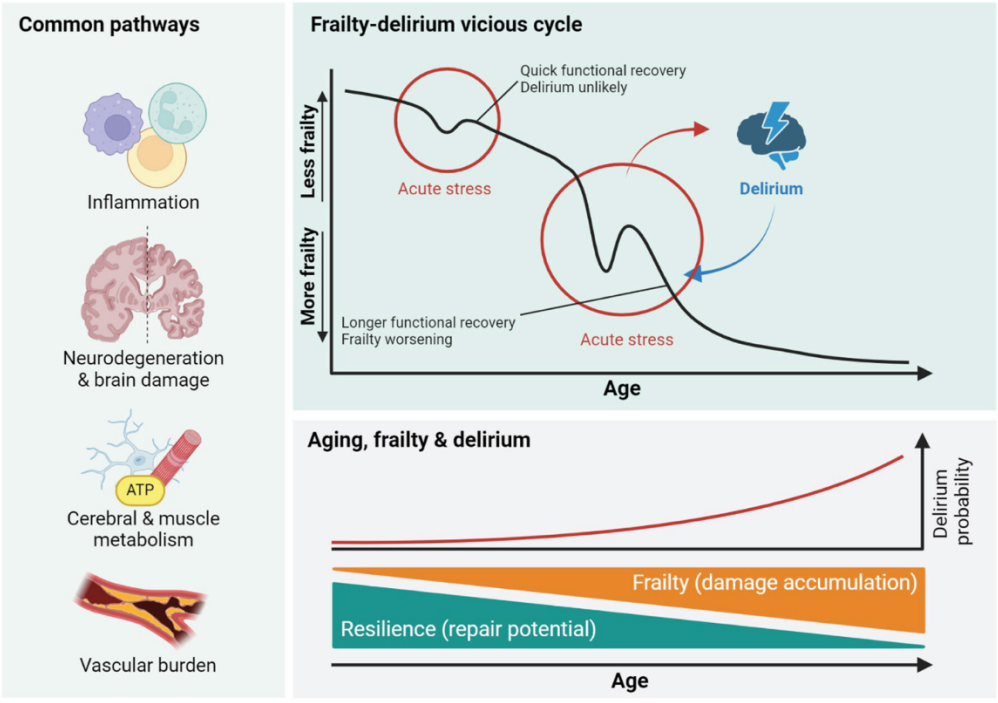


Figure 10. Common pathways and relationship between delirium and frailty [Source: Bellelli G, Triolo F, Ferrara MC et al. Delirium and frailty in older adults: Clinical overlap and biological underpinnings, J Intern Med. 2024 Nov;296(5):382-398. doi: 10.1111/joim.20014].

Despite delirium pathophysiology is largely unknown, it is considered a system-level disorder of brain networks arising from multifactorial converging processes [52] (**Figure 11**). Leading mechanisms include: (i) neurotransmitter imbalance, especially cholinergic deficiency and relative dopaminergic excess; (ii) neuroinflammation, with microglial/astrocytic activation and cytokine signalling across an age-permeable blood–brain barrier; (iii) oxidative stress and neuroendocrine dysregulation; (iv) circadian disruption and sleep–wake inversion; and (v) cerebral bioenergetic insufficiency, whereby reduced ATP production (e.g., in hypoxaemia, shock, or sepsis) impairs neuronal–astrocytic glucose metabolism [52,56,57]. Multiple insults typically co-occur: delirium can therefore be conceptualised as failure of cerebral homeostatic reserve under acute stress [52].

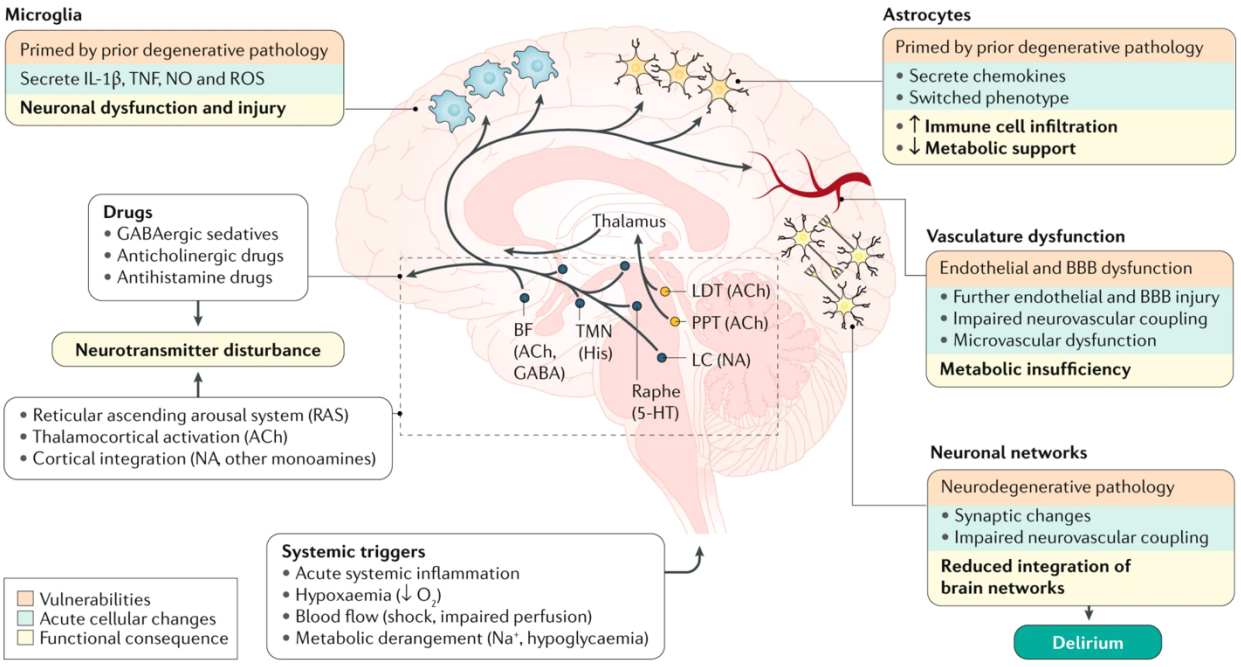
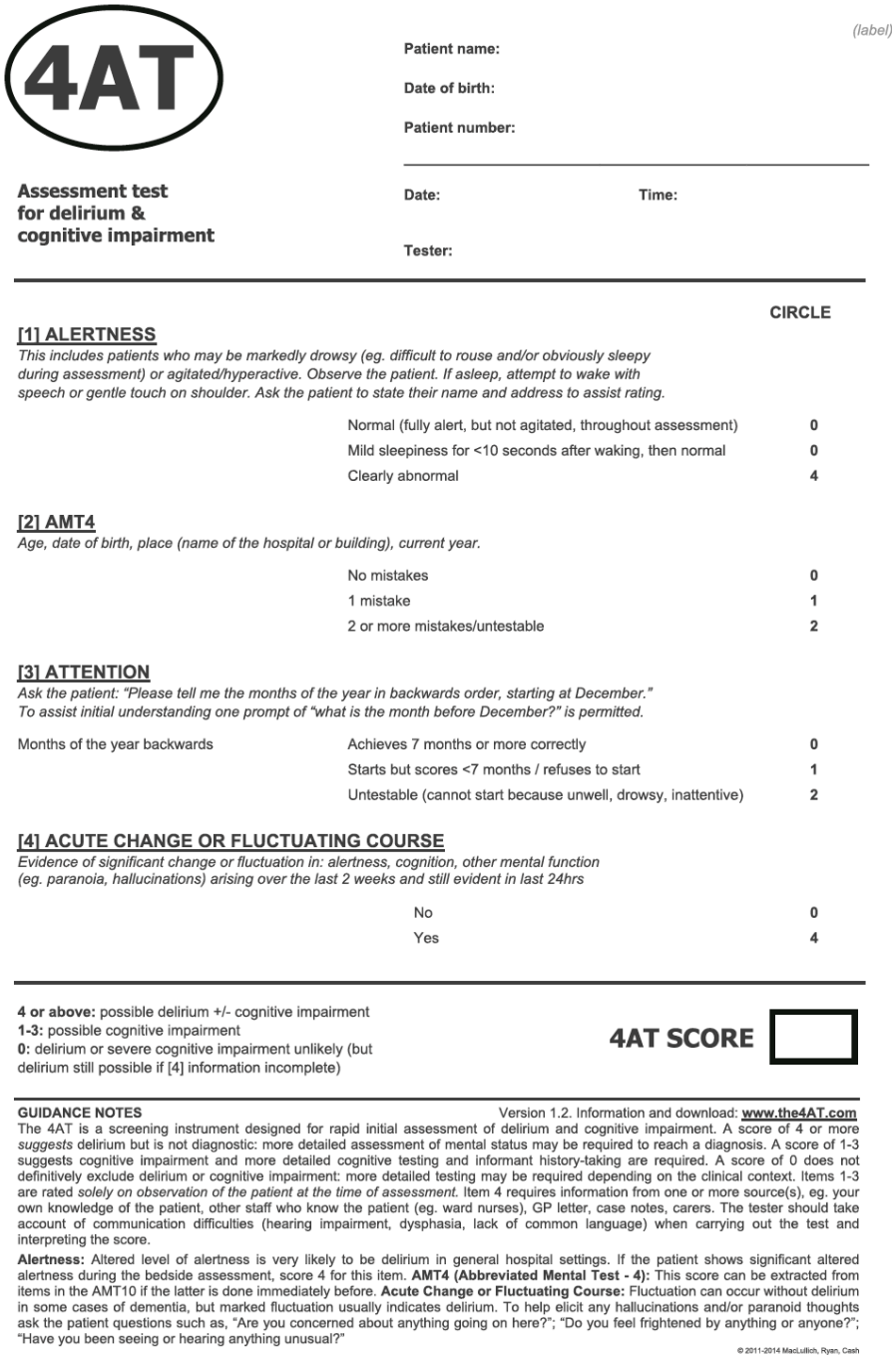


Figure 11. Major mechanisms in delirium pathophysiology. [Source: Wilson JE et al. *Delirium.* Nat Rev Dis Primers. 2020 Nov 12;6(1):90. doi: 10.1038/s41572-020-00223-4]

3.2 Screening and Diagnostic Tools

Recognising delirium promptly is a clinical priority, since it is an acute, time-critical syndrome that demands immediate assessment and management. After establishing the patient's cognitive baseline (through clinical history and informant report), screening should be performed with a brief, standardised tool at first contact and repeated as clinically indicated [52].

The 4A's Test (4AT) measures alertness, cognition (through the Abbreviated Mental Test-4), attention with Months Backwards, and acute change/fluctuation [58,59] (**Figure 12**). It requires no formal training, takes < 2 minutes, and can be used in patients with sensory impairment or who are drowsy or agitated, with good diagnostic performance (sensitivity 88%, specificity 88%) [60]. It compares favourably with the Confusion Assessment Method (CAM) [61] which, while highly specific, typically needs structured training and can be less sensitive, and with the modified Richmond Agitation–Sedation Scale (m-RASS) [62], that is useful to gauge arousal but has low sensitivity for delirium when used alone [59]. Balancing the evidence for accuracy and cost effectiveness with the practicality of implementing the tests, the delirium NICE guidelines (2023) committee agreed that the 4AT was the best option for most settings, especially for acute care, being among the most accurate of the tools, quick and simple to use, and with broader range of diagnostic evidence to support it [63].



4AT

(label)

Patient name:

Date of birth:

Patient number:

Assessment test for delirium & cognitive impairment

Date: Time:

Tester:

CIRCLE

[1] ALERTNESS

This includes patients who may be markedly drowsy (eg. difficult to rouse and/or obviously sleepy during assessment) or agitated/hyperactive. Observe the patient. If asleep, attempt to wake with speech or gentle touch on shoulder. Ask the patient to state their name and address to assist rating.

Normal (fully alert, but not agitated, throughout assessment)	0
Mild sleepiness for <10 seconds after waking, then normal	0
Clearly abnormal	4

[2] AMT4

Age, date of birth, place (name of the hospital or building), current year.

No mistakes	0
1 mistake	1
2 or more mistakes/untestable	2

[3] ATTENTION

Ask the patient: "Please tell me the months of the year in backwards order, starting at December." To assist initial understanding one prompt of "what is the month before December?" is permitted.

Months of the year backwards	Achieves 7 months or more correctly	0
	Starts but scores <7 months / refuses to start	1
	Untestable (cannot start because unwell, drowsy, inattentive)	2

[4] ACUTE CHANGE OR FLUCTUATING COURSE

Evidence of significant change or fluctuation in: alertness, cognition, other mental function (eg. paranoia, hallucinations) arising over the last 2 weeks and still evident in last 24hrs

No	0
Yes	4

4 or above: possible delirium +/- cognitive impairment
1-3: possible cognitive impairment
0: delirium or severe cognitive impairment unlikely (but delirium still possible if [4] information incomplete)

4AT SCORE

GUIDANCE NOTES Version 1.2. Information and download: **www.the4AT.com**

The 4AT is a screening instrument designed for rapid initial assessment of delirium and cognitive impairment. A score of 4 or more *suggests* delirium but is not diagnostic: more detailed assessment of mental status may be required to reach a diagnosis. A score of 1-3 suggests cognitive impairment and more detailed cognitive testing and informant history-taking are required. A score of 0 does not definitively exclude delirium or cognitive impairment: more detailed testing may be required depending on the clinical context. Items 1-3 are rated *solely on observation of the patient at the time of assessment.* Item 4 requires information from one or more source(s), eg. your own knowledge of the patient, other staff who know the patient (eg. ward nurses), GP letter, case notes, carers. The tester should take account of communication difficulties (hearing impairment, dysphasia, lack of common language) when carrying out the test and interpreting the score.

Alertness: Altered level of alertness is very likely to be delirium in general hospital settings. If the patient shows significant altered alertness during the bedside assessment, score 4 for this item. **AMT4 (Abbreviated Mental Test - 4):** This score can be extracted from items in the AMT10 if the latter is done immediately before. **Acute Change or Fluctuating Course:** Fluctuation can occur without delirium in some cases of dementia, but marked fluctuation usually indicates delirium. To help elicit any hallucinations and/or paranoid thoughts ask the patient questions such as, "Are you concerned about anything going on here?"; "Do you feel frightened by anything or anyone?"; "Have you been seeing or hearing anything unusual?"

Figure 12. 4AT score. [Source: https://www.the4at.com/]

3.3 Treatment and Outcomes

Delirium guidelines, including the most recent update from the National Institute for Health and Care Excellence (NICE), converge on a clear principle: delirium is both preventable and treatable when hospitals deliver coordinated, multicomponent, non-pharmacological care early and consistently [63,64]. Core elements, modelled on the Hospital Elder Life Program (HELP), comprise repeated re-orientation and cognitive stimulation; correction of sensory deprivation (ensuring glasses and hearing aids are available and functioning); sleep promotion through quiet nights, appropriate light cues and avoidance of nocturnal interruptions; early mobilisation and physiotherapy with minimisation of bed rest and avoidance of physical restraints; optimisation of hydration and nutrition; prompt relief of pain, constipation and urinary retention; rigorous medication review with deprescribing of deliriogenic psychoactive agents (notably anticholinergics, benzodiazepines, high-dose opioids and corticosteroids when avoidable); and avoidance of unnecessary lines and catheters [65]. Multicomponent non-pharmacological bundles reduce incident delirium by roughly 40–45% versus usual care, whereas pharmacological prophylaxis (e.g., antipsychotics) shows inconsistent benefit and is not recommended for routine prevention [66,67].

When delirium occurs, best practice includes: (i) rapid identification and treatment of precipitating factors; (ii) immediate implementation of the full non-pharmacological bundle; and (iii) cautious, short-term medication only for severe agitation or distress that threatens safety or precludes essential care. In such cases, low-dose antipsychotics (e.g., haloperidol or an atypical) may be considered after ECG/QT assessment and explicit risk–benefit discussion, with frequent review and prompt deprescribing as symptoms abate [63,68].

Delirium is associated with a broad spectrum of adverse outcomes. It is independently associated with prolonged hospitalisation, higher costs, greater risk of institutionalisation, functional decline and accelerated cognitive deterioration, with increased risk of incident dementia or faster progression of pre-existing impairment [52,69–72]. Outcomes are particularly poor when delirium is superimposed on dementia, including longer hospitalisation, greater cognitive and functional decline, higher institutionalisation, and increased mortality compared with dementia alone [54]. These consequences translate into substantial socioeconomic consequences, including higher healthcare utilisation and costs, greater caregiver burden, and worse long-term independence and quality of life for patients [73]. A recent systematic review and meta-analysis estimated wide variation in incremental costs (2019 USD): $806–$24,509 in general inpatient settings, $1,529–$14,462 in ICUs and $1,045–$12,452 in community-dwelling populations, mostly considering only direct medical costs. Notably, delirium costs are 52% higher when downstream dementia consequences are taken into account [72].

Mortality risk is also markedly elevated in the short and long term, and exhibits an exposure–response pattern, with each additional day of delirium conferring greater risk [74]; two-year mortality is approximately doubled even after adjustment for age, comorbidity and dementia [75].

Despite its high prevalence and serious consequences, delirium remains under-recognised in many acute-care settings. Routine, systematic screening coupled with rapid implementation of multicomponent prevention and management bundles should be embedded as core quality-of-care standards for hospitalised older adults. Even partial prevention, or shortening the duration of episodes, is expected to substantially reduce complications, length of stay, costs, and subsequent cognitive-functional decline.

CHAPTER 4 – THESIS RATIONALE

A judicious allocation of health- and social-care resources is a strategic priority for Italy, given rapid population ageing and the consequent growth in expenditure. However, current national evidence on the socioeconomic burden of dementia is limited and fragmented. In parallel, delirium and its complications are frequently under-estimated in routine care, and "delirium-aware"/"dementia-sensitive" hospital pathways remain uncommon. This gap contributes to adverse outcomes and diminished quality of life for patients and caregivers, ultimately inflating societal costs. The overarching goal of this project is to produce policy-relevant evidence that can inform sustainable, equitable, and outcomes-oriented care models for Italy's ageing population.

This thesis comprises two observational studies:

- **Study 1 "Socioeconomic burden of Alzheimer's disease: a multicentre cost-of-illness study",** intended to estimate the current socioeconomic burden of AD in community-dwelling patients in Italy, from both the National Health Service (NHS) and societal perspectives.
- **Study 2 "Delirium prevalence, incidence, and probability trajectories in an acute geriatric setting",** intended to quantify delirium prevalence and incidence in an Acute Geriatric Unit (AGU), while also evaluating the presence of different in-hospital daily delirium-probability trajectories and their potential prognostic value.

Together, Study 1 and 2 link the economic and clinical-epidemiological dimensions of older adults' care across the home–hospital continuum, providing practical foundations for targeted, evidence-based investments that can reduce costs while improving outcomes for both patients and caregivers.

CHAPTER 5 – STUDY 1 Socioeconomic burden of Alzheimer's disease: a multicentre cost-of-illness study.

5.1 AIM

The aim of the study was to assess the socioeconomic burden of AD among community-dwelling patients in Italy, by quantifying healthcare and social-care resource use and estimating mean monthly per-patient incurred costs - overall and by disease severity - from both the National Health Service (NHS) and societal perspectives. Finally, we evaluated the intangible burden through health-related quality of life (HRQoL) in both patients and caregivers.

5.2 MATERIALS AND METHODS

5.2.1 Study design and setting

This multicentre, cross-sectional study captured both costs borne by the NHS and patient- and caregiver-incurred costs (e.g., productivity losses and additional home assistance) from a comprehensive societal perspective. A bottom-up, retrospective approach was applied in this study (data collected with a structured questionnaire, referring to the index outpatient visit and the preceding 3 months) [76].

The study was conducted in seven Italian Centres for Cognitive Disorders and Dementias (CDCDs), specialised in the outpatient management of AD:

1) Geriatric Unit CDCD, IRCCS Foundation San Gerardo dei Tintori (Monza)
2) Neurology Unit CDCD, IRCCS Fuondation San Gerardo dei Tintori (Monza)
3) Neurology Unit, Neurorehabilitation Unit, and Neurophysiology Service, IRCCS San Raffaele Hospital (Milan)
4) Neurology Unit and Brain Health Centre, Spedali Civili (Brescia)
5) Regional Centre for the Aging Brain (CRIC), Azienda Ospedaliera di Padova (Padua)
6) Memory Clinic, Policlinico Gemelli (Rome)
7) Centre for Neurodegenerative Diseases, Pia Fondazione Card. G. Panico (Tricase)

5.2.2 Inclusion and exclusion criteria

Eligible participants were: i) adults ≥50 years; ii) with a confirmed diagnosis of AD-related MCI or dementia of ≥3 months' duration (diagnosis was established at each participating CDCD by specialist clinicians according to local standard practice, based on clinical history and examination, cognitive assessment, neuroimaging and, where clinically indicated, CSF/PET biomarkers); iii) who attended an outpatient visit accompanied by caregiver at one of the participating centres between March 20th, 2023 and December 10th, 2024. The visit date served as the index date (ID). Disease severity was clinically classified by Mini-Mental State Examination (MMSE) score: MCI (>26), mild AD (21–26), moderate AD (10–20), and severe AD (<10) [77, p85].

Patients unable to understand the study information or to provide written informed consent were included only if a legally authorised representative provided consent on their behalf; in all cases, the caregiver also provided written informed consent for their own participation as study partner.

Therefore, exclusion criteria were: (i) incapacity to provide informed consent without a legally authorised representative, (ii) caregiver refusal to provide written informed consent for their own participation, and (iii) failure to meet any prespecified inclusion criterion.

5.2.3 Data collection

Clinical, demographic, quality-of-life, and resource-use data were gathered with a study-specific case report form (CRF) completed by the patient and caregiver, with support from the study physician as needed. The recall window for health-care and social-care resource use was the 3 months preceding the index date (ID), consistent with prior neurodegenerative cost studies and chosen to limit recall bias, particularly for community services and informal care [76]. For caregiver's productivity losses (working time reduced/lost) the recall window was 30 days, in line with the Resource Utilization in Dementia – Lite (RUD-Lite) instrument [78].

At the ID, the following patient's information were recorded:

- Sociodemographic data**:** sex, age, education, employment, marital status, living arrangement (alone / with partner or family / other);

- Clinical data: date of AD diagnosis, current medications, and comorbidity burden summarized with the Charlson Comorbidity Index (CCI) [79];

- Anti-dementia drug (ADD) use: acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and/or memantine;

- Other pharmacological treatments: NHS-reimbursed agents used for AD-related symptoms and Class-C (non-reimbursed) medications/supplements (Appendix 1, §Chapter 5.5);

- Cognitive and behavioral assessment:

- Mini-Mental State Examination (MMSE): 0–30 (higher scores indicate better cognition) [80]. For analysis, severity classes were classified as follows: MCI (>26), mild AD (21–26), moderate AD (10–20), severe AD (<10)
- Neuropsychiatric Inventory – Questionnaire (NPI-Q), investigating behavioral and psychological symptoms of dementia (BPSD) (0-12) through a severity symptom score (0–

36), and caregiver distress score (0–60) (higher scores indicate greater symptom burden/distress) [81]

- Functional assessment:

- Activities of Daily Living (ADL): 0–6 (higher scores reflect greater independence) [82]
- Instrumental Activities of Daily Living (IADL): typical ranges 0–8 (women) and 0–5 (men), but in this study a sex-standardized 0–8 scale was used (higher scores indicating greater independence) [83].

The following data regarding caregiver were also collected: age, sex, education, relationship to the patient, co-residence (yes/no), employment status, weekly working hours (if employed), work hours lost in the last 30 days, sleep hours/day, number of additional formal (paid) caregivers, and time spent on care (hours/month) partitioned into ADL-IADL assistance and supervision/monitoring.

Global resource utilisation over the prior 3 months was captured with the RUD-Lite, covering:

- Hospital care: inpatient admissions, emergency department (ED) visits, day-hospital episodes, and long-stay/rehabilitation.
- Outpatient care: primary-care and specialist visits; laboratory, radiological, and other diagnostics.
- Equipment and services: aids, appliances, medical devices, home adaptations, medical transport, and community services (district nursing, home care, day-care centre, meals-on-wheels, etc.). Aids/appliances were valued separately for the NHS and for out-of-pocket/societal components. Being a community-dwelling cohort, institutional and long-term residential care were recorded if present during the recall window but were not a planned cost component.

- Formal and informal care: declared hours of paid (formal) assistance and unpaid (informal) caregiving by family/friends (reporting any out-of-pocket incurred costs); patient and caregiver productivity losses (30-day window).

Lastly, HRQoL for patients and caregivers was assessed using the EQ-5D-5L (five domains, five levels each) and the EQ-VAS (0–100) [84]. EQ-5D health states were converted to utility indices (0 = death; 1 = full health) using country-specific value sets.

5.2.4 Economic evaluation

Costs were estimated from both the NHS and societal perspectives and reported as mean monthly per-patient costs (€) over the recall horizon; analyses were prevalence-based to inform budgeting and near-term system impact. For each resource, quantities were multiplied by unit costs from:

- Drugs and supplements: Italian Medicines Agency (AIFA) price lists [85,86]
- NHS-funded services (inpatient acute care, day-hospital/rehabilitation, outpatient specialist care): national reimbursement tariffs ("Remunerazione delle prestazioni di assistenza ospedaliera per acuti, riabilitazione e lungodegenza post-acuzie e assistenza specialistica ambulatoriale", 2012, updated with GU Serie Generale n.302 del 27-12-2024 [87]).
- Non-reimbursed services and items (home/community services, devices, home adaptations, out-of-pocket payments): publicly available sources and published literature [40,88].
- Indirect costs included hours of paid (formal) assistance, any out-of-pocket expenses related to informal caregiving, and productivity losses, valued using the human-capital approach [89] (time lost from work due to caregiving was monetised with national average wages reported by ISTAT [90]). The cost of informal (unpaid) caregiving hours was not monetised, as it does not represent an actual/incurred expenditure.

- Intangible burden was captured through EQ-5D utilities and EQ-VAS scores for patients and caregivers.

This specification maps directly onto the cost-of-illness taxonomy: direct medical (hospital/ED, outpatient incl. imaging/biomarkers, pharmaceuticals), direct non-medical (home/community services, transport, aids/appliances; institutional care clarified for this cohort), indirect (productivity and informal care), and intangible (HRQoL).

5.2.5 Ethical and data privacy aspects

The study was conducted in accordance with national regulations, International Conference on Harmonization guidelines for Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki [91]. The coordinating centre and all local Institutional Ethics Committees approved the protocol and informed-consent materials (approval for the coordinating centre was granted on October 6th, 2022). In accordance with regulations for observational research, no tests, treatments, or admissions beyond routine clinical practice were performed for study purposes. Data from site CRFs were entered into a study-specific web application hosted on a dedicated server with a MySQL RDBMS and SSL/TLS encryption. Records were stored in a pseudonymised database compliant with EU GDPR (Reg. 2016/679); each centre kept its own re-identification key locally and inaccessible to the Sponsor (Fondazione CHARTA) or other sites. User access was role-based and centre-restricted, with full audit logs of logins and data changes. Fondazione CHARTA could analyse only pseudonymised data and, if needed, request source verification from the originating centre using the univoque identification number. After data collection and quality checks, the database was locked and the pseudonym replaced with a non-linkable anonymous code.

5.2.5 Sample size and statistical analysis

Resource-use and cost data are typically highly variable and right-skewed, with a small proportion of patients accounting for very high expenditures. To obtain stable estimates across disease severity, we planned to enroll 250-280 patients (50-70 per MMSE-defined category). This target was informed by prior work showing that cost estimates stabilise from about 50 patients per stratum in neurological conditions [76]. With seven sites, an average of nearly 40 participants per centre (10 per severity level) was deemed feasible and ensured geographic balance.

Descriptive characteristics were summarised as median (Q1–Q3) for continuous variables (after assessing the normality assumption using the Shapiro–Wilk test) and n (%) for categorical variables. Between-group differences across ordered MMSE classes (>26, 21–26, 10–20, <10) were tested with Kruskal–Wallis (or Mann–Whitney U for two groups) for continuous/ordinal variables and Pearson's χ^2 (or Fisher's exact) for categorical variables. Given the ordinal nature of severity, trends were evaluated with the Jonckheere–Terpstra test (or weighted median regression) for continuous/ordinal variables, the Cochran–Armitage trend test for binary outcomes, and linear-by-linear association for ordered categorical variables.

Health-care and social-care resource use was expressed as units per patient-month (e.g., inpatient admissions, outpatient visits, diagnostic tests, paid-caregiver days, day-centre days), and costs were reported as mean cost per patient-month with standard deviation (SD).

To identify determinants of total monthly cost (societal perspective), we fitted generalised linear models with gamma distribution and log link (appropriate for right-skewed, non-negative cost data), first univariable and then stepwise multivariable. Candidate covariates, specified *a priori* and guided by model fit, included: patient age, sex, education, marital status, living arrangement, CCI, MMSE class, NPI-Q (items/severity), ADL, IADL, caregiver age, caregiver education, and caregiver

relationship to the patient. We assessed multicollinearity and model adequacy, and reported rate ratios (RR) with 95% Confidence Intervals (95%CI). Two-sided tests were used (p-value < 0.05 was considered statistically significant). Analyses were conducted in SAS 9.4 and R (RStudio 2024.04.0).

5.3 RESULTS

5.3.1 Patient characteristics

A total of 262 dyads [patient and caregiver] were enrolled in the study. Patient distribution by AD severity is shown in the figure below (**Figure 13**).

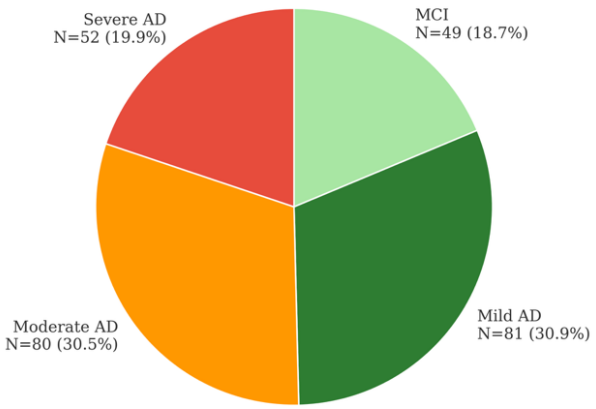


Figure 13. Patient distribution by disease severity (MMSE classes)

Table 1 shows patient characteristics. The median age of the sample was 75 years (Q1–Q3: 70–81), increasing with disease severity (from 74 years in MCI to 78.5 years in severe AD). Men were 46.9% overall, with similar proportions across severity groups. Educational level was broadly comparable, though severe AD patients were more likely to have lower education than those with MCI. Most patients were married or cohabiting (77.5%), without differences by MMSE group. Comorbidity burden was generally low, with higher scores in mild and severe AD. BPSD worsened with severity: NPI-Q positive items, severity scores, and caregiver distress were significantly higher in severe AD.

As expected, functional status also declined with disease severity, with median ADL falling from 6 to 3 and median IADL from 7 to 0, in MCI and severe AD respectively.

Table 1. Patients' characteristics, overall and by disease severity.

	Overall N=262	MCI N=49 (18.7%)	Mild AD N=81 (30.9%)	Moderate AD N=80 (30.5%)	Severe AD N=52 (19.9%)
Age [a*]	75 (70–81)	74 (68–78)	74 (70–79)	76 (69–82)	78.5 (71–85)
Sex (male)	123 (46.9)	17 (34.7)	41 (50.6)	39 (48.8)	26 (50.0)
Education					
None	5 (1.9)	1 (2.0)	0 (0.0)	3 (3.7)	1 (1.9)
Primary school	55 (21.0)	6 (12.2)	16 (19.8)	18 (22.5)	15 (28.8)
Middle school	49 (18.7)	11 (22.5)	13 (16.0)	13 (16.3)	12 (23.2)
High school	90 (34.4)	14 (28.6)	30 (37.0)	32 (40.0)	14 (26.9)
Graduate	59 (22.5)	16 (32.7)	20 (24.7)	14 (17.5)	9 (17.3)
Post-graduate	4 (1.5)	1 (2.0)	2 (2.5)	0 (0.0)	1 (1.9)
Marital status					
Single	11 (4.2)	1 (2.0)	2 (2.5)	4 (5.0)	4 (7.7)
Married/cohabitant	203 (77.5)	40 (81.6)	63 (77.8)	60 (75.0)	40 (76.9)
Separated/divorced	5 (1.9)	0 (0.0)	2 (2.5)	2 (2.5)	1 (1.9)
Widowed	43 (16.4)	8 (16.4)	14 (17.2)	14 (17.5)	7 (13.5)
CCI [a*]	1 (1–2)	1 (1–2)	2 (1–3)	1 (1–2)	2 (1–2)
Years from AD diagnosis [a,b*]	1 (0–3)	0 (0–1)	1 (0–3)	2 (1–4)	3 (1.5–5)
ADL [a*]	6 (4–6)	6 (6–6)	6 (6–6)	5 (4–6)	3 (1–4)
IADL° [a,b*]	4 (1–7)	7 (5–8)	6 (4–8)	3 (1.5–5)	0 (0–1)
NPI-Q (items) [a,b*]	3 (1–5)	1 (0–4)	2 (1–3)	3 (1–5)	4 (3–6)
NPI-Q (Severity) [a*]	5 (2–9)	3 (0–6)	4 (2–6)	5 (2–10)	9 (5.5–13)
NPI-Q (Caregiver stress) [a*]	5 (2–11)	4 (0–7)	4 (1–7)	5 (2–12.5)	10 (6–15)

Notes. Values are n (%) for categorical variables or median (Q1–Q3) for continuous variables. a*p<0.05 for differences among severity levels. b*p<0.05 for trend among severity levels.
Abbreviations: MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; CCI: Charlson Comorbidity Index; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living ° sex-standardized. NPI-Q: Neuropsychiatric Inventory Questionnaire.

Across all severity stages, patients lived at home (rarely attending residential day facilities). Co-residence with a partner/spouse was the most common arrangement (72%). With increasing severity, the proportion of patients living alone declined, while co-residence with a caregiver or other support showed a modest rise (from 10% to 26%) (**Figure 14**).

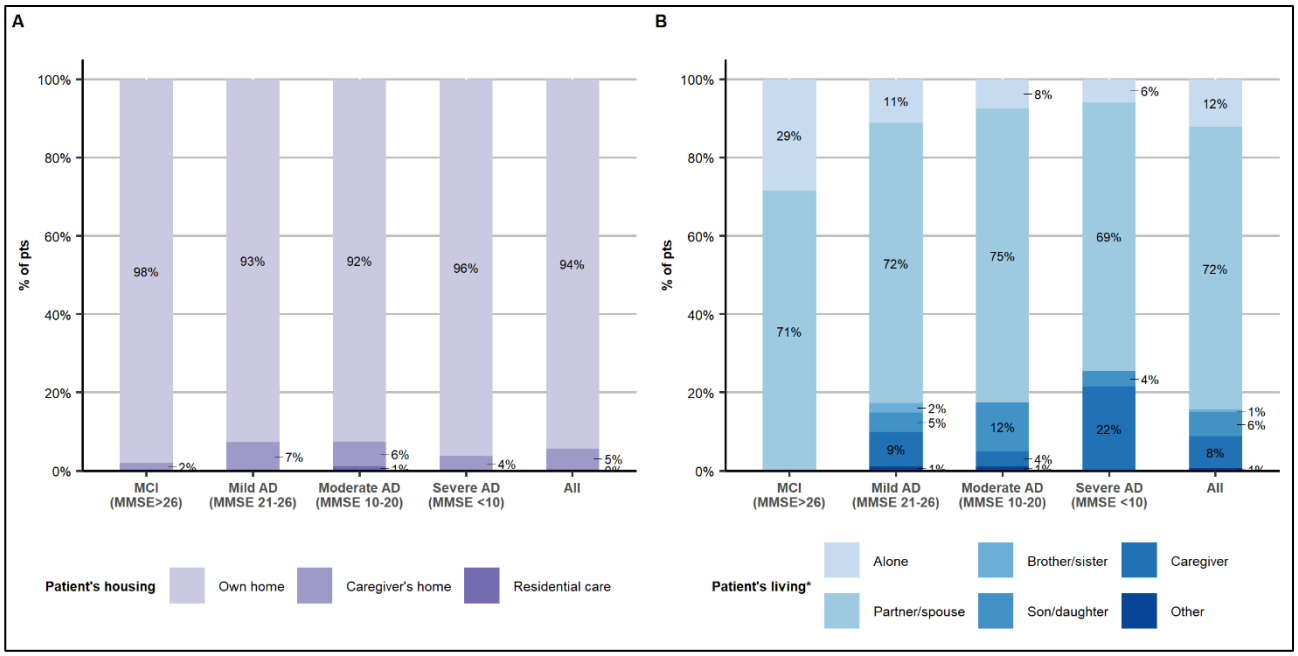
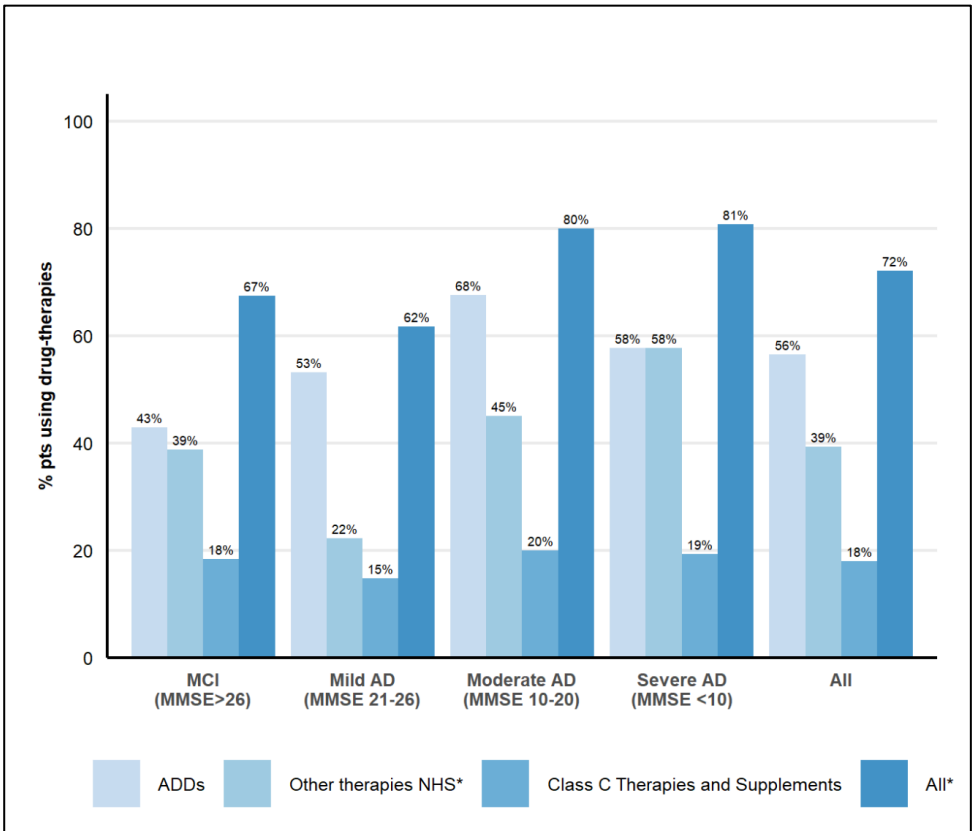


Figure 14. Living condition of AD patients. *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease. *p<0.05 for differences among severity levels.

5.3.2 Treatment use

Overall, 72% of patients received at least one treatment for AD, including ADDs and other symptomatic therapies. The proportion of patients receiving any ADDs increased with disease severity. Coherently with recommended use, Donepezil use peaked in moderate AD (MMSE 10–20: 36.3%), while Memantine use peaked in severe AD (MMSE <10: 38.5%). The use of other NHS-reimbursed symptomatic therapies also rose with severity, although it was frequent in MCI, too. Non-reimbursed Class-C medications and supplements were quite used (roughly 15–20% of patients across all MMSE strata) (**Figure 15**).



ADDs	MCI (MMSE>26)	Mild AD (MMSE 21-26)	Moderate AD (MMSE 10-20)	Severe AD (MMSE <10)	All N=262
Donepezil*	8 (16.3)	19 (23.5)	29 (36.3)	6 (11.5)	62 (23.7)
Rivastigmine	10 (20.4)	16 (19.8)	12 (15)	13 (25)	51 (19.5)
Galantamine	0 (0)	1 (1.2)	0 (0)	0 (0)	1 (0.4)
Memantine*	3 (6.1)	16 (19.8)	24 (30)	20 (38.5)	63 (24.1)

Figure 15. Treatment patterns by disease severity category. ADDs: anti-dementia drugs (AChEIs and/or memantine); "Other therapies NHS": NHS-reimbursed medications used to manage symptoms in AD. "Class C therapies and Supplements": products not reimbursed by the Italian NHS. *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease. *p < 0.05 for differences among severity levels.

5.3.3 Healthcare and resource utilisation

Nearly half of participants underwent at least one AD-related diagnostic tests/examinations in the 3 months before the index date (**Figure 16A**), with no significant differences across MMSE groups. Use of aids/appliances was uncommon overall but rose with severity (**Figure 16B**). Table 2 shows other healthcare use: hospitalisations were rare, whereas geriatric visits increased markedly with severity, from 0.01 (SD 0.05) per patient-month in MCI to 0.10 (SD 0.17) in severe AD. Community

support followed a similar gradient: paid caregiver days rose from 0.05 (SD 0.38) to 8.03 (SD 12.58) per month, and day-care centre attendance from 0.41 (SD 2.86) to 1.15 (SD 4.22), respectively.

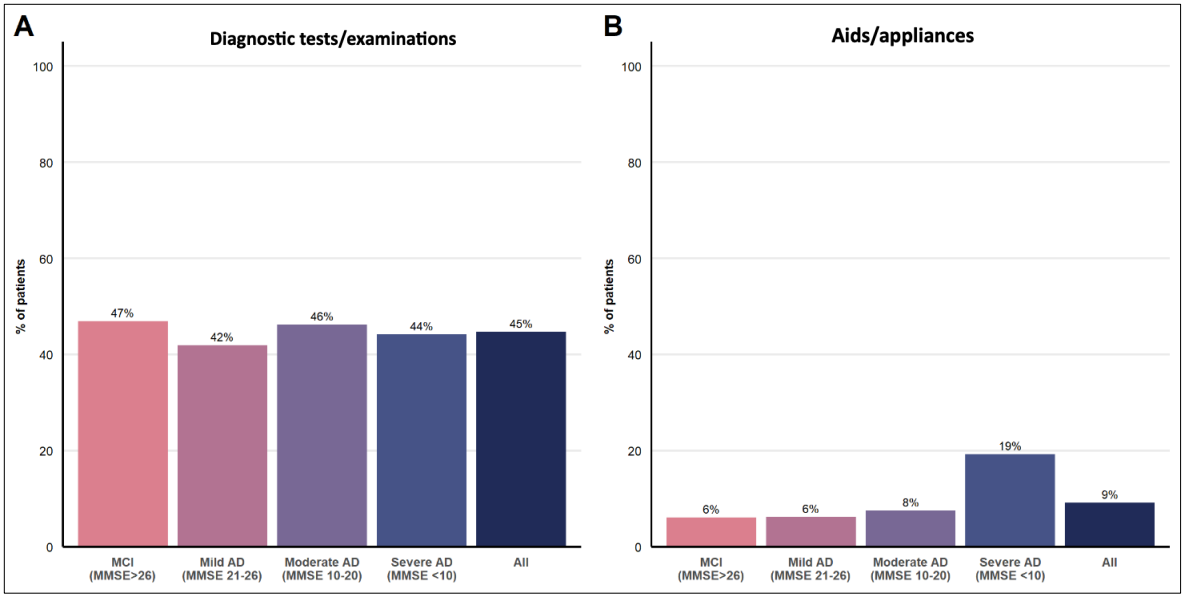


Figure 16. Healthcare resource utilisation (Panel A: diagnostic tests/examinations, including laboratory tests, neuropsychological testing, electroencephalogram, neuroimaging such as Computed Tomography [CT] and MRI, PET; Panel B: aids/appliances, including mobility and transfer devices, continence supplies). *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

Table 2. Healthcare resource utilisation, overall and by disease severity.

Healtchare service (monthly per-patient number°)	Overall N=262	MCI N=49 (18.7%)	Mild AD N=81 (30.9%)	Moderate AD N=80 (30.5%)	Severe AD N=52 (19.9%)
Hospitalisations (all causes)	0.01 (0.05)	0.01 (0.05)	0.00 (0.04)	0.01 (0.06)	0.01 (0.05)
Outpatient visits					
General practitioner	0.25 (0.58)	0.20 (0.39)	0.23 (0.57)	0.16 (0.43)	0.44 (0.87)
Geriatric visits [a,b]*	0.05 (0.13)	0.01 (0.05)	0.05 (0.12)	0.05 (0.12)	0.10 (0.17)
Neurology	0.10 (0.19)	0.12 (0.19)	0.09 (0.17)	0.08 (0.20)	0.13 (0.21)
Psychiatry	0.00 (0.04)	0.00 (0.00)	0.01 (0.05)	0.00 (0.04)	0.00 (0.00)
Physiotherapy	0.25 (1.57)	0.12 (0.63)	0.20 (1.08)	0.31 (2.27)	0.37 (1.52)
Occupational therapy	0.12 (1.66)	0.05 (0.38)	0.00 (0.00)	0.00 (0.00)	0.56 (3.71)
Social worker	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
Psychologist	0.14 (0.82)	0.01 (0.10)	0.22 (1.03)	0.22 (1.06)	0.03 (0.11)
Other	0.18 (1.16)	0.09 (0.27)	0.06 (0.20)	0.23 (0.93)	0.39 (2.31)
All	1.11 (3.11)	0.61 (0.93)	0.87 (1.78)	1.05 (3.04)	2.01 (5.29)

Community nurse	0.04 (0.28)	0.01 (0.05)	0.01 (0.11)	0.08 (0.48)	0.03 (0.12)
Home-social care service	0.55 (3.23)	1.10 (4.71)	0.02 (0.22)	1.09 (4.46)	0.02 (0.10)
Home-delivered meals	0.22 (2.53)	0.00 (0.00)	0.35 (3.11)	0.00 (0.00)	0.58 (4.16)
Formal (paid) caregiver days [a,b]*	3.10 (8.48)	0.05 (0.38)	1.88 (6.93)	2.99 (7.95)	8.03 (12.58)
Day-care centre days [a]*	0.60 (3.18)	0.41 (2.86)	0.00 (0.00)	0.95 (4.04)	1.15 (4.22)
Medical transportation	0.02 (0.25)	0.00 (0.00)	0.00 (0.00)	0.05 (0.45)	0.00 (0.00)
Other	0.13 (1.87)	0.00 (0.00)	0.00 (0.00)	0.43 (3.38)	0.00 (0.00)

Note. °Values are all expressed as mean (SD). a*p<0.05 for differences among severity levels. b*p<0.05 for trend among severity levels. *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; ED: Emergency Department.

5.3.4 Caregiver characteristics and burden

Caregiver characteristics are summarised in Table 3. Overall, only 33% of caregivers were men, median age was 65 years (Q1–Q3: 54–73). Educational level was quite high: 41.2% had completed high school and 35.5% held a university or postgraduate degree. Most caregivers were family members, and 62.2% co-resided with the patient. In 40% of cases, the caregiver met ≥80% of the patient's care needs, with similar patterns across MMSE groups. About one half of patients required at least one additional informal caregiver (**Figure 17**). Regarding unpaid caregiver burden (Table 4), time investment significantly increased with dementia severity: from 9.5 (SD 25.9) to 91.3 (SD 121.6) hours/month to help in basic daily activities; from 21.1 (SD 33.1) to 97.9 (SD 115.4) hours/month to help in instrumental tasks; from 10.0 (SD 18.2) to 131.0 (SD 188.4) hours/month to help patient monitoring, and from 40.6 (SD 59.7) to 320.3 (SD 384.7) hours/month for total activities plus monitoring. Accordingly, employment declined with severity (from 55.1% in MCI to 28.8% in severe AD). Among employed caregivers, working time lost significantly rose from 3.0 (SD 7.7) to 5.6 (SD 6.6) hours/week.

Table 3. Caregiver characteristics, overall and by patients' disease severity.

	Overall N=262	MCI N=49 (18.7%)	Mild AD N=81 (30.9%)	Moderate AD N=80 (30.5%)	Severe AD N=52 (19.9%)
Age	65 (54–73)	64 (53–73)	66 (57–72)	62 (52.5–72)	66.5 (56–74)
Sex (male)	86 (33.2)	21 (43.8)	25 (30.9)	25 (31.3)	15 (30.0)
Educational level					
None	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Primary school	19 (7.3)	4 (8.2)	8 (9.9)	5 (6.3)	2 (3.8)
Middle school	41 (15.6)	6 (12.2)	13 (16.0)	13 (16.3)	9 (17.3)
High school	108 (41.2)	18 (36.7)	33 (40.7)	31 (38.8)	26 (50.0)
Graduate	87 (33.2)	20 (40.8)	24 (29.6)	29 (36.3)	14 (26.9)
Post-graduate	6 (2.3)	1 (2.0)	3 (3.7)	2 (2.5)	0 (0.0)
Patient–caregiver relationship					
Spouse/partner	154 (58.8)	31 (63.3)	50 (61.7)	46 (57.5)	27 (51.9)
Brother/sister	6 (2.3)	0 (0.0)	3 (3.7)	1 (1.3)	2 (3.8)
Son/daughter	90 (34.4)	17 (34.7)	24 (29.6)	32 (40.0)	17 (32.7)
Friend	2 (0.8)	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.9)
Other	10 (3.8)	1 (2.0)	3 (3.7)	1 (1.3)	5 (9.6)
Number of children					
0	184 (70.2)	33 (67.3)	57 (70.4)	56 (70.0)	38 (73.1)
1	47 (17.9)	11 (22.4)	15 (18.5)	13 (16.3)	8 (15.4)
2	25 (9.5)	4 (8.2)	7 (8.6)	9 (11.3)	5 (9.6)
3	5 (1.9)	1 (2.0)	2 (2.5)	1 (1.3)	1 (1.9)
Missing	1 (0.4)	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)
Living with patient					
No	96 (36.6)	20 (40.8)	24 (29.6)	27 (33.8)	25 (48.1)
Yes	163 (62.2)	29 (59.2)	56 (69.1)	52 (65.0)	26 (50.0)
Missing	3 (1.1)	0 (0.0)	1 (1.2)	1 (1.3)	1 (1.9)

Notes. Values are n (%) for categorical variables or median (Q1–Q3) for continuous variables. a*p<0.05 for differences among severity levels. b*p<0.05 for trend among severity levels. *Abbreviations*: MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

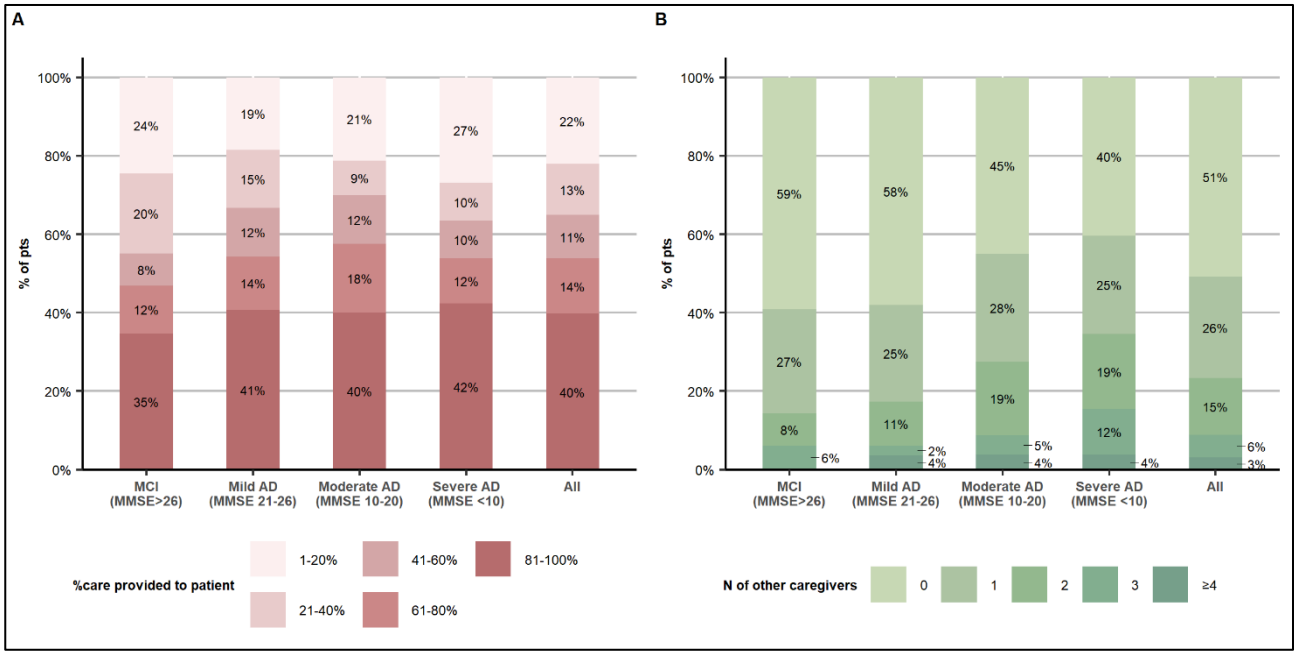


Figure 17. Percentage of time spent in caregiving (Panel A) and number of caregivers (Panel B).
Abbreviations MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

Table 4. Caregivers' working condition and times spent for patient' care.

	Overall N=262	MCI N=49 (18.7%)	Mild AD N=81 (30.9%)	Moderate AD N=80 (30.5%)	Severe AD N=52 (19.9%)
Caregiver's sleeping time, (h/day)	6.5 (1.6)	6.4 (2.0)	6.6 (1.6)	6.6 (1.4)	6.5 (1.5)
Caregiver's time for patient's activities, (h/month)					
Basic activities [a,b*]	46.4 (90.3)	9.5 (25.9)	31.6 (70.6)	54.9 (97.4)	91.3 (121.6)
Instrumental activities [a,b*]	64.2 (87.3)	21.1 (33.1)	49.3 (60.0)	83.6 (98.9)	97.9 (115.4)
Patient monitoring [a,b*]	73.8 (146.6)	10.0 (18.2)	44.8 (99.8)	105.0 (176.8)	131.0 (188.4)
Total [a,b*]	184.1 (285.4)	40.6 (59.7)	125.6 (192.2)	242.8 (319.4)	320.3 (384.7)
Working conditions					
Employed [a*]	113 (43.1)	27 (55.1)	30 (37.0)	41 (51.3)	15 (28.8)
Not employed	149 (56.9)	22 (44.9)	51 (63.0)	39 (48.8)	37 (71.2)

Reason for leaving employment °					
Never worked	6 (2.3)	1 (2.0)	2 (2.5)	1 (1.3)	2 (3.8)
Retired	123 (46.9)	20 (40.8)	44 (54.3)	34 (42.5)	25 (48.1)
Early retirement (not illness-related)	3 (1.1)	1 (2.0)	1 (1.2)	0 (0.0)	1 (1.9)
Fired	2 (0.8)	0 (0.0)	1 (1.2)	1 (1.3)	0 (0.0)
Health-related problems	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.8)
Patient's care	5 (1.9)	0 (0.0)	0 (0.0)	2 (2.5)	3 (5.8)
Other	8 (3.1)	0 (0.0)	3 (3.7)	1 (1.3)	4 (7.7)
Not applicable	113 (43.1)	27 (55.1)	30 (37.0)	41 (51.3)	15 (28.8)
Working time (h/week) °	35.6 (11.8)	39.6 (9.7)	33.2 (12.3)	34.3 (13.0)	36.4 (10.2)
Lost working time in last 30 days (h/week) ° a*	2.9 (5.8)	3.0 (7.7)	0.7 (2.1)	3.6 (5.6)	5.6 (6.6)

Notes. Values are expressed as mean (SD) for continuous variables, and n(%) for categorical variables; a*p<0.05 for differences among severity levels. b*p<0.05 for trend among severity levels. °Only for working caregivers. *Abbreviations*: MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

5.3.5 Economic evaluations, cost drivers and intangible burden

Mean monthly per-patient costs are shown in Table 5. Direct medical costs were generally low. Direct non-medical costs were higher and rose with disease severity—particularly NHS-reimbursed aids/appliances and home/community care services ($p<0.05$). Indirect costs, by contrast, constituted the bulk of total expenditure. Formal (paid) caregiving costs increased from €0.00 (SD 0.00) in MCI to €341.49 (SD 649.04) in severe AD ($p<0.05$). Out-of-pocket expenses reported by informal caregivers were relatively stable across severity, whereas productivity losses among employed informal caregivers rose sharply with severity, from €112.81 (SD 165.91) to €890.35 (SD 1,069.50), displaying a significant upward trend ($p<0.05$).

Table 5. Mean monthly per-patient costs (NHS and societal perspective).

	Overall N=262	MCI N=49 (18.7%)	Mild AD N=81 (30.9%)	Moderate AD N=80 (30.5%)	Severe AD N=52 (19.9%)
Direct medical costs					
Treatments [a*]	30.65 (34.42)	24.68 (31.15)	25.74 (35.44)	34.17 (30.22)	38.48 (40.13)
Test and exams	25.41 (74.17)	26.08 (58.23)	41.95 (112.93)	17.13 (47.02)	12.08 (30.96)
Hospitalisations	14.93 (116.86)	19.39 (135.71)	23.46 (148.34)	0.00 (0.00)	20.41 (132.34)
ED Access	9.57 (36.98)	2.32 (16.07)	11.57 (42.69)	11.14 (41.93)	10.92 (33.45)
Physician Visits	21.51 (54.99)	12.04 (15.36)	18.19 (36.20)	21.75 (56.91)	35.23 (88.81)
Direct non-medical costs					
Aids and appliances (NHS) [a*]	20.70 (112.12)	13.01 (91.05)	1.16 (8.44)	23.95 (119.41)	53.40 (180.45)
Aids and appliances (Society)	3.32 (39.60)	0.84 (4.13)	8.51 (70.83)	0.89 (6.09)	1.29 (4.66)
Accommodation for receiving medical care	1.01 (11.81)	3.33 (23.33)	0.00 (0.00)	0.00 (0.00)	1.92 (13.87)
Home and Community Care services [a*]	112.35 (510.62)	106.86 (584.56)	5.03 (32.31)	204.83 (643.32)	142.43 (580.80)
Indirect costs					
Formal Caregiver [a*]	144.41 (459.12)	0.00 (0.00)	142.03 (465.07)	107.16 (406.83)	341.49 (649.04)
Informal Caregiver	78.61 (256.88)	104.42 (372.64)	17.37 (82.16)	113.53 (274.20)	95.94 (266.73)
Caregiver Work Loss [a,b*]	511.86 (793.48)	112.81 (165.91)	349.22 (534.42)	674.95 (888.04)	890.35 (1,069.50)
Total NHS perspective	226.23 (563.56)	195.29 (611.37)	117.47 (252.08)	304.57 (683.16)	304.29 (644.52)
Total Societal perspective [a,b*]	973.97 (1,103.43)	425.74 (764.96)	643.03 (715.89)	1,209.48 (1,261.48)	1,643.74 (1,185.01)

Note. Values are all expressed as mean (SD). a*p<0.05 for differences among severity levels. b*p<0.05 for trend among severity levels. *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease; ED: Emergency Department; NHS= National Health Service.

Overall, mean monthly per-patient costs from the NHS perspective rose from €195.29 (SD 611.37) in MCI to €304.29 (SD 644.52) in severe AD. From the societal perspective, total incurred costs increased significantly from €425.74 (SD 764.96) to €1,643.74 (SD 1,185.01) across the same severity spectrum. Across all stages, caregiving-related costs - especially productivity losses - represent the largest share and become progressively more dominant with advancing disease. Use of community services and assistive devices also rises with severity, whereas spending on pharmaceuticals and outpatient care remains comparatively modest, and inpatient costs contribute only a minor proportion in every severity group in this sample (**Figure 18**).

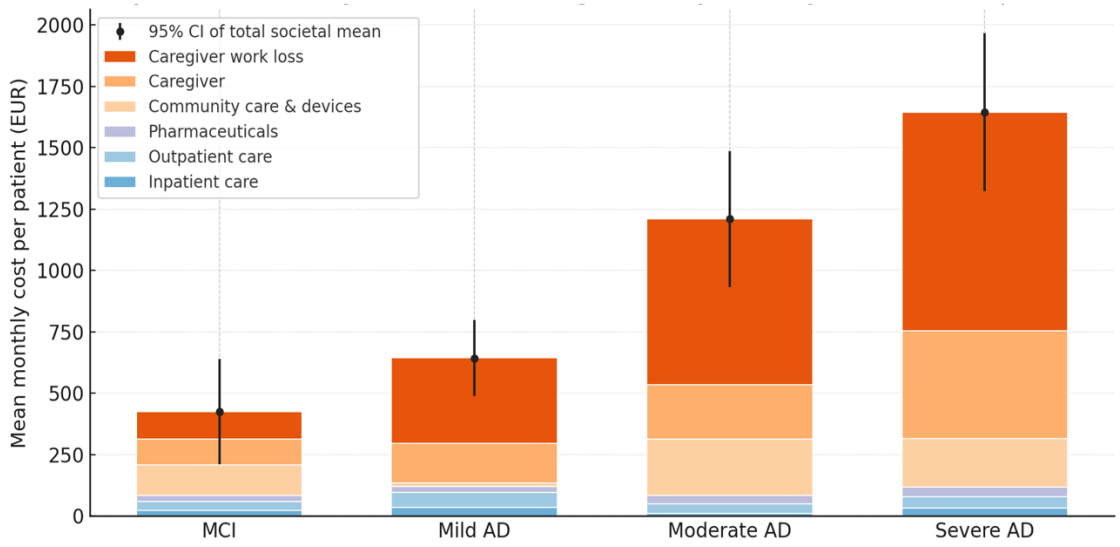


Figure 18. Mean monthly per-person costs by AD severity from societal perspective. Bars indicate average costs stratified by mild, moderate, and severe dementia. *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

Table 6 reports the univariable and multivariable associations for AD–related total costs from societal perspective. In the fully adjusted model, two variables remained independently associated: higher NPI-Q scores were linked to higher expenditure (RR = 1.09; 95% CI 1.00–1.17 per point), while better instrumental functioning on the IADL was associated with lower costs (RR = 0.81; 95% CI 0.76–0.85 per point).

Table 6. Association between participants' characteristics and total costs (univariable and multivariable models).

Univariable		
Variable	**RR (95% CI)**	**p-value**
Age	1.04 (1.02 - 1.06)	0.001
Sex (Ref="Female")	1.12 (0.78 - 1.59)	0.540
Educational degree	0.90 (0.78 - 1.05)	0.183
Marital Status (Ref="Cohabitant")	1.47 (0.96 ; 2.24)	0.074
Patients Living (Ref="Alone")		
Relative/Friend	1.24 (0.73 ; 2.14)	0.426
Formal caregiver	2.83 (1.27 ; 6.29)	0.011
CCI	1.16 (0.96 ; 1.41)	0.126
MMSE class (Ref="MCI")		
Severe AD	3.86 (2.23 - 6.70)	<.0001
Moderate AD	2.84 (1.72 - 4.69)	<.0001
Mild AD	1.51 (0.92 - 2.49)	0.107
NPI-Q (items)	1.19 (1.10 - 1.29)	<.0001
IADL	0.79 (0.75 - 0.83)	<.0001
ADL	0.72 (0.65 - 0.81)	<.0001
Caregiver age	1.00 (0.99 - 1.01)	0.971
Caregiver educational level	0.92 (0.77 - 1.11)	0.393
Partner or spouse caregiver (Ref: "Other")	0.72 (0.50 - 1.03)	0.075

Multivariable		
Variable	**RR (95% CI)**	**p-value**
NPI-Q Score	1.09 (1.00 - 1.17)	0.039
IADL	0.81 (0.76 - 0.85)	<.0001

Abbreviations CCI: Charlson Comorbidity Index; MMSE: Mini-Mental State Examination; NPI-Q: Neuropsychiatric Inventory Questionnaire; IADL: Instrumental Activities of Daily Living; ADL: Activities of Daily Living; RR: rate ratio; 95%CI: 95% Confidence Intervals.

As for the intangible burden, patient-reported HRQoL declined significantly with worsening cognition: both EQ-5D-5L utility and EQ-VAS were lowest in severe AD (**Figure 19**). Caregiver-reported HRQoL showed a similar but attenuated pattern (**Figure 20**).

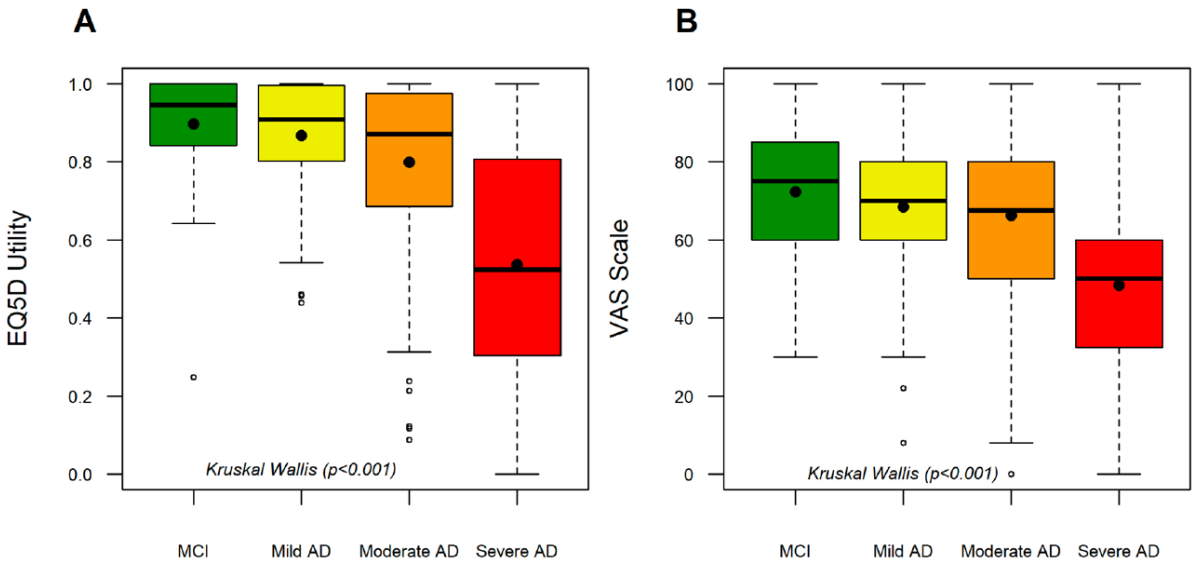


Figure 19. Patient-reported quality of life, measured with EQ-5D utility (Panel A) and EQ-5D VAS (Panel B). *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

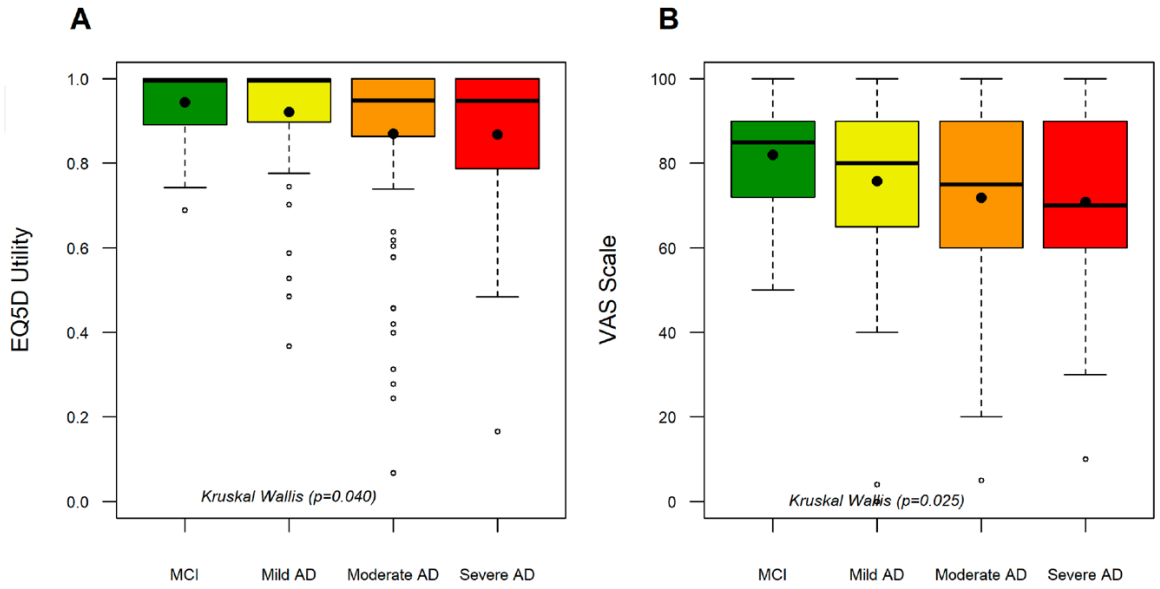


Figure 20. Caregivers' quality of life measured with EQ-5D utility (Panel A) and EQ-5D VAS (Panel B). *Abbreviations* MCI: Mild Cognitive Impairment; AD: Alzheimer's Disease.

5.4 DISCUSSION

In this multicentre, cross-sectional study of 262 community-dwelling AD and their caregivers, we quantified the socioeconomic burden of AD across the disease severity spectrum from both the NHS and societal perspectives. Most patients in our cohort lived at home with informal caregiver relatives, especially retired partners or spouses, but also son and daughters still employed. By quantifying the actual costs borne by the NHS and families/society over the past three months, we found that total costs increased with AD severity, with a much steeper gradient from the societal than from the NHS perspective, driven particularly by caregiving expenditures and informal caregivers' lost work time, while direct medical costs stayed low. Indeed, mean monthly NHS costs increased modestly (from €195 to €304) versus a large societal rise (from €426 to €1,644). Overall, higher NPI-Q predicted higher costs, whereas better IADL predicted lower costs. Patient-reported HRQoL decreased progressively with severity on both EQ-5D utility and EQ-VAS, with wider dispersion in severe AD; caregivers showed a similar, albeit attenuated, decline.

Our findings align with international evidence that the average annual per-person costs in Europe are €20,000–€25,000 [39,40], and that total costs escalate with advancing AD [35,40,41]. COI studies consistently show that, for community-dwelling patients, informal and productivity-related costs dominate and rise with functional decline, often comprising 50–90% of total expenditures as disability accrues [35,40,41,92]. In the community, indirect caregiving typically dominates, while the cost profile shifts after institutionalisation with direct non-medical expenditures accounting for up to two-thirds of total costs [37]. Aligning with current literature, family members were the primary caregivers [40]. Caregivers profiles (predominantly women, mean age 65 years, generally well educated) echo Alzheimer's Association and NAC/AARP reports, which describe caregivers as

mostly female and ≥55 years old [12,93–96]. Although spousal caregiving did not differ significantly across MMSE strata, spouses were relatively more common in less severe disease than in severe AD, a pattern consistent with prior European burden studies [41,97,98]. In our sample, 56% of caregivers were not employed (46% retired), but it should be noted that a crucial component of social burden is the very high number of hours devoted by these informal cargivers to patient care, helping in ADLs and IADLs functioning and supervising the patient, which increased with severity. These informal caregiving hours were not monetised in our study, since they did not constitute incurred expenditures, but they would translate into substantial costs if valued. A recent Italian study on the socio-economic costs of AD (2018) [41] adopted a societal perspective but additionally monetised the informal caregiving by valuing the hours spent supervising or assisting the patient as if they were paid to a formal caregiver. Using a case mix similar to ours, it valued roughly the same caregiving time we observed (about 200 hours/month in mild AD and 300 hours/month in severe AD) at €1,300-€2,200/month. Adding this component to our estimates, the monthly per-patient total costs would be substantially higher (from nearly €1,700 in mild AD to €3,900 in severe AD). Moreover, as highlighted by Richardson and colleagues, caregiving is physically and emotionally demanding, with significant implications for caregiver health and well-being [96]. Together, these data underscore the substantial impact of AD on caregiver well-being and the need for public health interventions that both improve patient care and alleviate caregiver strain.

On the other hand, the hospital costs observed were quite low, yet consistent with those reported in a recent Italian study by Mennini et al. [88], which estimated costs from administrative data, finding a total of nearly €200/month for hospitalisations and annual NHS-reimbursed costs of €4,359 per patient with AD [88]. However, since it excluded all non-reimbursed items, the true societal costs are plausibly higher than their estimates.

Treatment patterns in our population were coherent with European memory-clinic practice, where symptomatic therapy is commonly started in prodromal/mild stages and combined with adjunctive measures to manage related symptoms [27]. No DMTs were administered in our population, since they were not yet authorized in Italy during the data collection for the study.

As for the major cost drivers, it is expected that BPSD increase monitoring needs, drive additional visits and treatments, and often precipitate paid support; BPSD independent association with higher costs in our models mirrors evidence linking BPSD to greater service use, heavier caregiver burden, and earlier institutionalisation [99]. Loss of IADL is another early, powerful driver of dependence in community settings; preserving instrumental abilities plausibly delays transition to high-intensity care, consistent with the protective association we observed.

This study has several implications: because the bulk of costs falls outside the NHS ledger - caregiver time, productivity loss, and social care - the greatest societal returns are likely from strategies that promote early diagnosis, proactive BPSD management, and preservation of instrumental function (cognitive and occupational rehabilitation, physical exercise, nutrition, sensory optimisation). In the context of emerging DMTs, earlier diagnosis and timely pharmacological treatment, together with the non-pharmacological multidimensional approach, could slow progression and reduce downstream costs, with long-term savings for health systems and society [100–106].

Study strengths include that: it provides updated real-world data from Italian CDCDs, focusing on patients who are still managed at home and who are often under-represented in AD COI literature; it employs validated instruments to assess the resource utilisation, thereby supporting international comparability; and it applies adequate statistical methods suited to cost distributions.

This work also has limitations. Resource use over the prior three months was caregiver-reported and thus vulnerable to recall or interpretation bias, although this is a standard approach in dementia burden and COI studies, and was mitigated by a shorter (30-day) window for productivity loss [107].

Caregiver time showed wide variability, which warrants further investigation in dedicated, more granular studies. The cross-sectional design precludes causal inference, and future studies should test interactions between dementia severity and disability/BPSD, as dementia severity may plausibly act as an effect modifier between disability/BPSD and costs. Recruitment from memory-clinics may limit generalisability to extremely severe AD cases who are more often residents in long-term care, likely yielding conservative societal cost estimates. Finally, participating CDCDs were mostly located in Northern Italy, despite being in line with the current national distribution of dementia services [108], which may have limited the generalisability of our estimates given potential regional differences. Exploring regional variability in costs and models of care could therefore represent a valuable sub-study in future work.

In conclusion, AD in Italy imposes a substantial and escalating societal burden that falls predominantly on families as severity advances. The pattern we document in our outpatient cohort - higher costs with worsening cognition and function, amplificated by BPSD, and strong dependence on caregiver time - converges with international evidence and highlights where practical actions are most urgent. Policies enabling earlier diagnosis, targeted BPSD management, preservation of IADL, and structured supports for caregivers (at home and at a community-level) are well justified. These real-world estimates provide an important pre-DMTs baseline for Italy, directly relevant to future budget impact and cost-effectiveness evaluations of monoclonal antibodies for AD, including potential shifts from informal-care and productivity costs to diagnostic and treatment-related resource use. Tracking how disease severity, HRQoL, and the composition of costs evolve will be crucial to optimise dementia care pathways and support NHS sustainability.

5.5 APPENDIX 1

Drugs/supplements for AD symptoms management.

ATC	Substance name	Classification
N02BF01	GABAPENTIN	Drug reimbursed by NHS
N02BF02	PREGABALIN	Drug reimbursed by NHS
N03AE01	CLONAZEPAM	Drug reimbursed by NHS
N03AG01	VALPROIC ACID	Drug reimbursed by NHS
N03AX09	LAMOTRIGINE	Drug reimbursed by NHS
N03AX14	LEVETIRACETAM	Drug reimbursed by NHS
N04BC05	PRAMIPEXOLE	Drug reimbursed by NHS
N04BD01	SELEGILINE	Drug reimbursed by NHS
N05AC01	PERICIAZINE	Drug reimbursed by NHS
N05AD01	HALOPERIDOL	Drug reimbursed by NHS
N05AH03	OLANZAPINE	Drug reimbursed by NHS
N05AH04	QUETIAPINE	Drug reimbursed by NHS
N06AA09	AMITRIPTYLINE	Drug reimbursed by NHS
N06AB04	CITALOPRAM	Drug reimbursed by NHS
N06AB05	PAROXETINE	Drug reimbursed by NHS
N06AB06	SERTRALINE	Drug reimbursed by NHS
N06AB08	FLUVOXAMINE	Drug reimbursed by NHS
N06AB10	ESCITALOPRAM	Drug reimbursed by NHS
N06AX05	TRAZODONE	Drug reimbursed by NHS
N06AX11	MIRTAZAPINE	Drug reimbursed by NHS
N06AX16	VENLAFAXINE	Drug reimbursed by NHS
N06AX21	DULOXETINE	Drug reimbursed by NHS
N06AX26	VORTIOXETINA	Drug reimbursed by NHS
N06DA02	DONEPEZIL	Drug reimbursed by NHS
N06DA03	RIVASTIGMINE	Drug reimbursed by NHS
N06DA04	GALANTAMINE	Drug reimbursed by NHS
N06DX01	MEMANTINE	Drug reimbursed by NHS
N05AA03	PROMAZINE	Drug not reimbursed by NHS
N05BA06	LORAZEPAM	Drug not reimbursed by NHS
N05BA12	ALPRAZOLAM	Drug not reimbursed by NHS
N05CD09	BROTIZOLAM	Drug not reimbursed by NHS
N05CF02	ZOLPIDEM	Drug not reimbursed by NHS
N05CH01	MELATONIN	Drug not reimbursed by NHS
N07AX02	CHOLINE ALFOSCERATE	Drug not reimbursed by NHS
N05BA49	DELORAZEPAM	Drug not reimbursed by NHS

SUPPLEMENT BASED ON HERBAL EXTRACTS	Supplements
GLYCEROPHOSPHORYLETHANOLAMINE MONOHYDRATEMONOIDRATA MICRONIZED	Supplements
PALMITOYLETHANOLAMIDE	Supplements
SODIUM CITICOLINE	Supplements

CHAPTER 6 – STUDY 2 Delirium prevalence, incidence, and probability trajectories in an acute geriatric setting.

6.1 AIM

Delirium is common among hospitalised older adults and is associated with adverse outcomes. However, it remains unclear whether mortality risk varies with different daily patterns of delirium probability over the course of hospitalisation.

The study aimed to: (i) quantify delirium prevalence at ward admission and its incidence during hospitalisation in an Acute Geriatric Unit (AGU); and (ii) model daily in-hospital delirium-probability trajectories, assessing their prognostic value for 3-month mortality.

6.2 MATERIALS AND METHODS

6.2.1 Study design and setting

We conducted a prospective, single-centre cohort study of adults aged ≥65 years consecutively admitted for acute medical conditions to the AGU of a high-volume tertiary-care hospital (IRCCS Foundation San Gerardo dei Tintori, Monza, Italy) between February 12th and December 31st, 2024.

The study was embedded within the ReGeMa observational registry of geriatric inpatients, with the addition of a dedicated module that systematically recorded anamnestic or previously unrecognised dementia and the day-by-day presence of delirium during hospitalisation.

6.2.2 Inclusion and exclusion criteria

Inclusion criteria were: (i) age ≥65 years; (ii) first admission to the AGU during the study period; (iii) written informed consent for ReGeMa data collection from the patient or a legally authorised representative. No additional exclusion criteria were applied.

6.2.3 Data collection

A study CRF was completed by clinicans involved in the study at baseline and updated daily until discharge. Sources included patient examination, medical/nursing notes, medication lists, laboratory reports, and caregiver/next-of-kin interviews. Collected data are listed below.

- Sociodemographic data: Age, sex, marital status, pre-admission living arrangement (home alone; home with partner/spouse; home with caregiver; residential setting), and deambulation (autonomous; with help; with aid; not possible)
- Comorbidity and medications: CCI (calculated without age-derived score) [79] and number of home drugs at admission
- Symptoms at ED presentation and laboratory tests at admission
- Functional status and frailty:
    - Deambulation impairment; ADL, ranging from 0 to 6 (6 = independent) [82]; IADL, using sex-specific ranges (women 0–8; men 0–5) [83]
    - Clinical Frailty Scale (CFS), ranging from 1 (fit) to 9 (terminally ill), with a score of 5 or more representing mild-to-severe frailty [109] (**Figure 21**)
    - Primary Care Frailty Index (PC-FI), ranging continuously from 0 to 1 (cut-offs indicate mild frailty for 0.07–0.14 scores, moderate frailty for 0.15–0.21, and severe frailty for >0.21 severe frailty)[110] (**Figure 22**)

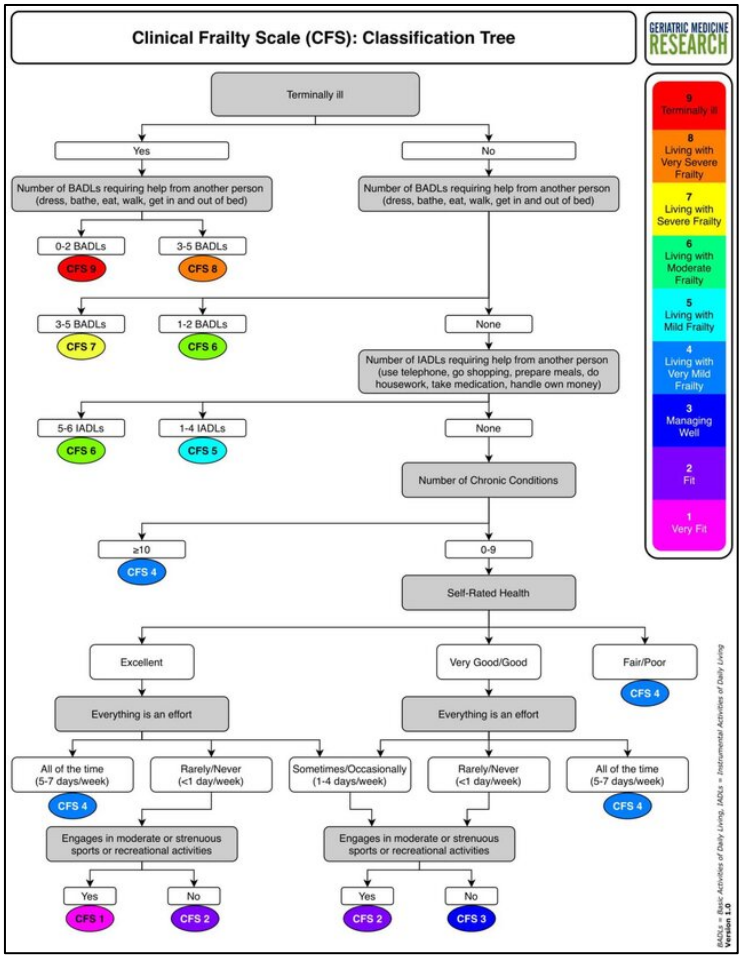


Figure 21. Clinical Frailty Scale (CFS) Classification Tree to identify frailty level. [Source: Theou O et al. A classification tree to assist with routine scoring of the Clinical Frailty Scale. Age Ageing. 2021 Jun 28;50(4):1406-1411. doi: 10.1093/ageing/afab006].

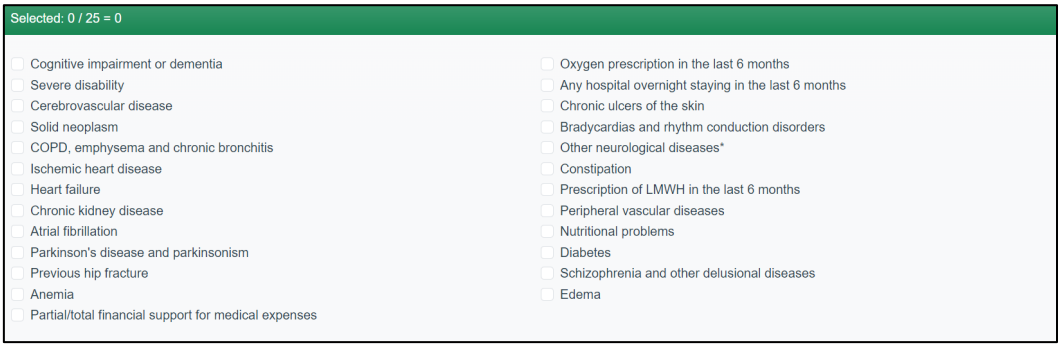


Figure 22. Primary Care Frailty Index [Source: Vetrano DL et al. Frailty detection among primary care older patients through the Primary Care Frailty Index (PC-FI). Sci Rep. 2023 Mar 2;13(1):3543. doi: 10.1038/s41598-023-30350-3].

- Delirium ascertainment and severity
    - Screening/diagnosis: daily assessment using the Italian version of 4AT (score 0–12; ≥4 suggests delirium; 1–3 possible cognitive impairment) [58], with a final diagnosis made by a senior geriatrician according to DSM-5 criteria
    - Severity and motor subtype (measured on the first day of delirium) using the DEL-S Short Form [111] (0–12; higher = more severe)
    - Putative precipitating factors on the first day of delirium [51]
    - Overall motor subtype during hospitalisation
    - Delirium duration (days)
- Dementia and cognition
    - Documented history of dementia and aetiology (AD, VaD, LBD, FTD, Parkinson's disease dementia, mixed/unknown)
    - Screening for previously unrecognised dementia: in the absence of an anamnestic diagnosis, the Ascertain Dementia 8 (AD8) caregiver questionnaire was administered (score 0–8; >2 indicates a positive screen for possible dementia) [112–114]
    - Global Deterioration Scale (GDS) for cognitive staging from 1 to 7 [115] (**Figure 23**)
- Macro-diagnoses at discharge, length of stay (days), discharge setting
- All-cause 3-month mortality after admission (including in-hospital mortality).

Level	Clinical Characteristics
1 No cognitive decline	No subjective complaints of memory deficit. No memory deficit evident on clinical interview.
2 Very mild cognitive decline **(Age Associated Memory Impairment)**	Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects; (b) forgetting names one formerly knew well. No objective evidence of memory deficit on clinical interview. No objective deficits in employment or social situations. Appropriate concern with respect to symptomatology.
3 Mild cognitive decline **(Mild Cognitive Impairment)**	Earliest clear-cut deficits. Manifestations in more than one of the following areas: (a) patient may have gotten lost when traveling to an unfamiliar location; (b) co-workers become aware of patient's relatively poor performance; (c) word and name finding deficit becomes evident to intimates; (d) patient may read a passage or a book and retain relatively little material; (e) patient may demonstrate decreased facility in remembering names upon introduction to new people; (f) patient may have lost or misplaced an object of value; (g) concentration deficit may be evident on clinical testing. Objective evidence of memory deficit obtained only with an intensive interview. Decreased performance in demanding employment and social settings. Denial begins to become manifest in patient. Mild to moderate anxiety accompanies symptoms.
4 Moderate cognitive decline **(Mild Dementia)**	Clear-cut deficit on careful clinical interview. Deficit manifest in following areas: (a) decreased knowledge of current and recent events; (b) may exhibit some deficit in memory of ones personal history; (c) concentration deficit elicited on serial subtractions; (d) decreased ability to travel, handle finances, etc. Frequently no deficit in following areas: (a) orientation to time and place; (b) recognition of familiar persons and faces; (c) ability to travel to familiar locations. Inability to perform complex tasks. Denial is dominant defense mechanism. Flattening of affect and withdrawal from challenging situations frequently occur.
5 Moderately severe cognitive decline **(Moderate Dementia)**	Patient can no longer survive without some assistance. Patient is unable during interview to recall a major relevant aspect of their current lives, e.g., an address or telephone number of many years, the names of close family members (such as grandchildren), the name of the high school or college from which they graduated. Frequently some disorientation to time (date, day of week, season, etc.) or to place. An educated person may have difficulty counting back from 40 by 4s or from 20 by 2s. Persons at this stage retain knowledge of many major facts regarding themselves and others. They invariably know their own names and generally know their spouses' and children's names. They require no assistance with toileting and eating, but may have some difficulty choosing the proper clothing to wear.
6 Severe cognitive decline **(Moderately Severe Dementia)**	May occasionally forget the name of the spouse upon whom they are entirely dependent for survival. Will be largely unaware of all recent events and experiences in their lives. Retain some knowledge of their past lives but this is very sketchy. Generally unaware of their surroundings, the year, the season, etc. May have difficulty counting from 10, both backward and, sometimes, forward. Will require some assistance with activities of daily living, e.g., may become incontinent, will require travel assistance but occasionally will be able to travel to familiar locations. Diurnal rhythm frequently disturbed. Almost always recall their own name. Frequently continue to be able to distinguish familiar from unfamiliar persons in their environment. Personality and emotional changes occur. These are quite variable and include: (a) delusional behavior, e.g., patients may accuse their spouse of being an impostor, may talk to imaginary figures in the environment, or to their own reflection in the mirror; (b) obsessive symptoms, e.g., person may continually repeat simple cleaning activities; (c) anxiety symptoms, agitation, and even previously nonexistent violent behavior may occur; (d) cognitive abulla, i.e., loss of willpower because an individual cannot carry a thought long enough to determine a purposeful course of action.
7 Very severe cognitive decline **(Severe Dementia)**	All verbal abilities are lost over the course of this stage. Frequently there is no speech at all -only unintelligible utterances and rare emergence of seemingly forgotten words and phrases. Incontinent of urine, requires assistance toileting and feeding. Basic psychomotor skills, e.g., ability to walk, are lost with the progression of this stage. The brain appears to no longer be able to tell the body what to do. Generalized rigidity and developmental neurologic reflexes are frequently present.

Figure 23. Global Deterioration Scale (GDS) [Source: Reisberg et al. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982 Sep;139(9):1136-9. doi: 10.1176/ajp.139.9.1136]

6.2.4 Ethical and data privacy aspects

All participants (or their legally authorised representatives) provided written consent for inclusion in ReGeMa. The study complied with the Declaration of Helsinki [91] and GDPR, and was approved by the Brianza Ethics Committee (protocol 001421). Data were entered into a dedicated REDCap electronic CRF hosted on secure servers. Each participant was assigned a unique study identifier; direct personal identifiers were stored separately from clinical data and were accessible only to the authorised staff, with role-based permissions and encrypted connections.

6.2.5 Statistical analysis

Continuous variables were summarised as median (Q1–Q3), after assessing distributional assumptions with the Shapiro–Wilk test and visual inspection of Q–Q plots; categorical variables were reported as n (%). Between-group differences were tested using Mann–Whitney U or Kruskal–Wallis tests for continuous variables and Pearson's χ^2 or Fisher's exact tests for categorical variables, as appropriate. When global tests were significant, we performed post-hoc pairwise comparisons with Bonferroni adjustment of p-values.

For each inpatient day, delirium status (yes/no) was derived from the clinical assessment. Delirium prevalence was defined as the proportion of patients with delirium at ward admission or within the first 24 hours (with 95% Cis estimations). Incident delirium was defined among patients without delirium in the first 24 hours as any subsequent delirium episode during the hospital stay; corresponding incidence proportions with 95% CIs were likewise estimated.

In-hospital delirium-probability trajectories were identified using daily delirium status over the first 10 inpatient days (median length of stay) through group-based trajectory modelling (GBTM),

conceptualised as a finite mixture of longitudinal patterns over time. The 10-day window was chosen a priori to balance clinical relevance and data completeness, as the early-to-mid hospital phase is the most clinically actionable period and a fixed horizon improves comparability across patients while avoiding unstable estimates due to long, heterogeneous stays (data from additional days among patients with longer stays were not included in the trajectory modelling).

Candidate models with 2–4 classes and linear/quadratic terms for day were compared using Bayesian Information Criterion (BIC), parsimony, minimum class size, and clinical interpretability; a three-class solution provided the best fit. Individuals were assigned to the class with the highest posterior probability. Model adequacy was evaluated using average posterior probabilities, relative entropy, and observed-versus-predicted plots with 95% CIs.

We next examined the association between trajectory class and 3-month all-cause mortality using Poisson regression with a log link and robust variance to estimate relative risks (RRs). Multivariable models were adjusted for age, sex, frailty (CFS) and serum albumin at admission (variables selected a priori as clinically plausible confounders of the relationship between delirium trajectories and prognosis, avoiding multicollinearity). We also conducted sensitivity analyses: incorporating delirium motor subtype on day 1 and delirium severity (DEL-S) on day 1 in the model, and evaluating the potential mediating role of other specific delirium features referred to the whole period (duration, motor subtype during hospital course). Lastly, to characterise baseline risk of assignment to unfavourable trajectories, we fitted a logistic model with two simple baseline stratifiers (CFS and GDS) as potential predictors. Predicted probabilities were displayed as a heatmap to aid clinical interpretation.

Two-sided tests were used for all analyses, considering statistically significant a p-value < 0.05. Analyses were performed in SAS 9.4 and Stata 18.0 (with GBTM packages as appropriate).

6.3 RESULTS

6.3.1 Population characteristics

A total of 639 patients were enrolled. Table 7 shows the main characteristics of the population. Median age was 87 years (Q1–Q3: 84–90), and 53.2% were women. Overall functional status was poor, with low median ADL and IADL scores [3 (Q1-Q3: 1-6), and 1(Q1-Q3: 0-4) for both sexes, respectively]. Comorbidity burden was modest [median CCI 3 (Q1-Q3: 2–4)], while polypharmacy was common [median number of home drugs 7 (Q1-Q3: 5-10)]. Anamnestic dementia was present in 266 (41.6%) patients; among those without a prior diagnosis, 192 (30% of the total population) screened positive for possible dementia on the AD8. Among patients with anamnestic dementia, etiologies were predominantly mixed/uncertain (58%), followed by VaD (21%), AD (11%), Parkinson's disease dementia (7%), and FTD/LBD (3%) (**Figure 24**). Cognitive staging on the GDS provided a more granular distribution of cognitive impairment. Frailty was high overall [CFS: 6 (Q1-Q3: 5–7); PC-FI: 0.20 (Q1-Q3: 0.16–0.28)].

Delirium occurred in 301 patients (at least 1 day from admission to discharge). Compared with those without delirium, affected patients were less likely to live alone (17.9% vs 31.1%, p<0.001) and had worse baseline function, in terms of greater mobility impairment (64.1% vs 53.3%), lower ADL [2 (1–5) vs 5 (2–6)], and lower IADL [0 (0–2) vs 2 (1–5)] (all p<0.001). Charlson index and number of home drugs did not differ significantly. Prior dementia was markedly more frequent in the delirium group (62.1% vs 23.4%, p<0.001), as was a positive AD8 screen (33.4% vs 26.2%, p<0.001), aligning with more advanced GDS stages (p<0.001). Both frailty measures were higher among patients with delirium [median CFS 7 (Q1-Q3: 6-7) vs 6 (Q1-Q3: 5-7) and median PC-FI 0.2 (Q1-Q3: 0.16-0.28) vs 0.2 (Q1-Q3: 0.12-0.24, each p<0.001].

Table 7. Population characteristics (overall and by delirium status)

	Overall (N=639)	Delirium° (N=301)	No Delirium (N=338)	p-value
Age	87 (84-90)	87 (84–91)	87 (84–90)	0.068
Sex (female)	340 (53.2%)	151 (50.2%)	189 (55.9%)	0.146
Marital status				0.209
Married/Cohabitant	269 (42.1%)	130 (43.2%)	139 (41.1%)	
Widowed	348 (54.5%)	157 (52.2%)	191 (56.5%)	
Other	22 (3.4%)	14 (4.7%)	8 (2.4%)	
Domiciliation				< 0.001
At home alone	159 (24.9%)	54 (17.9%)	105 (31.1%)	
At home with partner/spouse	261 (40.8%)	125 (41.5%)	136 (40.2%)	
At home with caregiver	199 (31.1%)	108 (35.9%)	91 (26.9%)	
Residential setting	20 (3.1%)	14 (4.7%)	6 (1.8%)	
Deambulation				< 0.001
Autonomous	266 (41.6%)	108 (35.9%)	158 (46.7%)	
With help	55 (8.6%)	35 (11.6%)	20 (5.9%)	
With aid	226 (35.4%)	98 (32.6%)	128 (37.9%)	
Not possible	92 (14.4%)	60 (19.9%)	32 (9.5%)	
ADL	3 (1-6)	2 (1–5)	5 (2–6)	<0.001
IADL (female)	1 (0-4)	0 (0–2)	2 (1–5)	<0.001
IADL (male)	1 (0-4)	0 (0–2)	2 (1–5)	<0.001
Charlson Comorbidity Index	3 (2-4)	3 (2–4)	3 (2–4)	0.357
N° of drugs at admission	7 (5-10)	7 (5–10)	7 (5–10)	0.083
Anamnestic dementia	266 (41.6%)	187 (62.1%)	79 (23.4%)	< 0.001
Possible dementia (AD8 ≥ 2)	192 (30%)	79 (26.2%)	113 (33.4%)	< 0.001
Global Deterioration Scale				< 0.001
1 (No cognitive decline)	193 (30.2%)	41 (13.6%)	152 (45.0%)	
2 (Age associated memory impairment)	73 (11.4%)	27 (9.0%)	46 (13.6%)	
3 (MCI)	70 (11.0%)	26 (8.6%)	44 (13.0%)	
4 (Mild dementia)	105 (16.4%)	54 (17.9%)	51 (15.1%)	
5 (Moderate dementia)	115 (18.0%)	81 (26.9%)	34 (10.1%)	
6 (Moderately severe)	54 (8.5%)	45 (15.0%)	9 (2.7%)	
7 (Severe dementia)	29 (4.5%)	27 (9.0%)	2 (0.6%)	
Clinical Frailty Scale	6 (5-7)	7 (6–7)	6 (5–7)	<0.001
Primary Care - Frailty Index	0.2 (0.12-0.28)	0.2 (0.16–0.28)	0.2 (0.12–0.24)	<0.001

Notes Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables;
° At least one day during hospitalisation (4AT positive and confirmed diagnosis). *Abbreviations*: Activities of Daily Living; Instrumental Activities of Daily Living; AD8: Ascertain Dementia 8; MCI: Mild Cognitive Impairment.

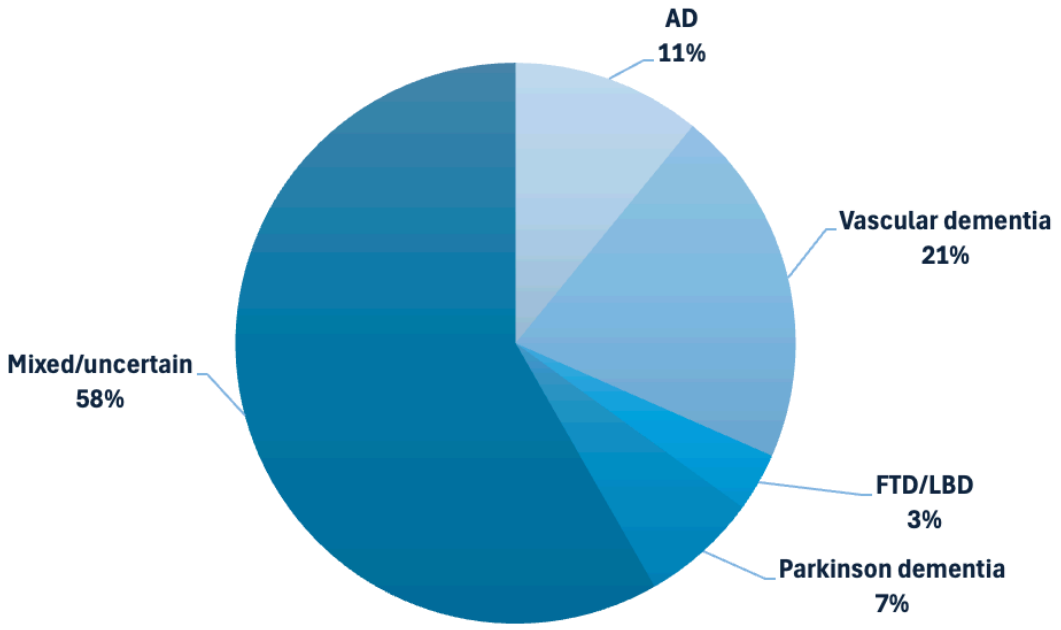


Figure 24. Etiologic subtypes of anamnestic dementia. *Notes.* AD: Alzheimer's disease; VaD: Vascular dementia; FTD/LBD: Frontotemporal/Lewy body dementia.

Table 8 summarises additional clinical features at ED presentation and during hospitalisation. Patients who developed delirium at any time were more likely to present with neurological symptoms and with a fall as the index complaint (both $p<0.001$). On admission they showed higher leukocyte counts and C-reactive protein ($p\leq0.01$), with no meaningful differences in creatinine or albumin values. Overall median length of stay was 10 days (Q1–Q3: 8–14) and did not differ between groups. Major diagnostic categories also differed: gastrointestinal and neurological conditions were more frequent among patients with delirium (each $p\leq0.001$), whereas cardiovascular and onco-haematological diseases were more common in those without delirium.

Table 8. Additional in-hospital population characteristics (overall and by delirium status)

	Overall (N=639)	Delirium° (N=301)	No Delirium (N=338)	p-value
Symptoms at ED*				
Fever	146 (22.8%)	59 (19.6%)	87 (25.7%)	0.065
Respiratory	172 (26.9%)	75 (24.9%)	97 (28.7%)	0.282
Gastro-intestinal	115 (18.0%)	33 (11.0%)	82 (24.3%)	<0.001
Fall	103 (16.1%)	66 (21.9%)	37 (10.9%)	<0.001
Neurological	155 (24.3%)	106 (35.2%)	49 (14.5%)	<0.001
Leucocytes (µL/mmc)	8,800 (6,440-11,480)	9,360 (6,770–12,630)	8,180 (6,100–10,610)	<0.001
Creatinine (mg/dL)	1.2 (0.9-1.7)	1.2 (0.9–1.7)	1.2 (0.9–1.6)	0.585
Albumin (g/dL)	3.33 (3-3.6)	3.30 (2.90–3.70)	3.40 (3.00–3.60)	0.468
C-Reactive Protein (mg/dL)	5.7 (1.7-11.9)	6.4 (2.6–12.5)	5.10 (1.2–11)	0.005
Hospital stay (days)	10 (8-14)	11 (8–14)	10 (8–14)	0.479
Macro-diagnoses at discharge*				
Cardiovascular	265 (41.5%)	112 (37.2%)	153 (45.3%)	0.039
Respiratory	247 (38.7%)	120 (39.9%)	127 (37.6%)	0.552
Gastro-intestinal	115 (18.0%)	32 (10.6%)	83 (24.6%)	<0.001
Nephro/urological	200 (31.3%)	100 (33.2%)	100 (29.6%)	0.322
Neurological	113 (17.7%)	75 (24.9%)	38 (11.2%)	<0.001
Infectious	224 (35.1%)	113 (37.5%)	111 (32.8%)	0.214
Hematological	133 (20.8%)	49 (16.3%)	84 (24.9%)	0.008
Oncological	89 (13.9%)	30 (10.0%)	59 (17.5%)	0.006

Notes. Values are expressed as mean (SD) for continuous variables, and n(%) for categorical variables; ° At least one day during hospitalisation (4AT positive and confirmed diagnosis). *More than one allowed. *Abbreviations.* ED: Emergency Department.

Table 9 shows downstream outcomes. In-hospital mortality was nearly 10% overall, but was markedly higher among patients with delirium (18.6% vs 2.1%; p<0.001). Most patients were discharged home; however, those with delirium were disproportionately discharged to residential facilities, hospice, or home-based palliative care compared to those without it (p<0.001).

By 3 months from admission, 206 patients (32.2%) had died. Three-month mortality was substantially greater in the delirium group than in those without delirium (68.9% vs 31.1%; p<0.001), and time-to-death was also shorter [median 17 days (Q1–Q3: 9–32) vs 39.5 days (Q1–Q3: 19.5–59.5); p<0.001].

Table 9. Discharge setting and mortality (overall and by delirium status)

	Overall (N=639)	**Delirium° (N=301)**	**No Delirium (N=338)**	**p-value**
In-hospital mortality	63 (9.9%)	56 (18.6%)	7 (2.1%)	< 0.001
Discharge setting	**N=576**	**N=245**	**N=331**	
Home	397 (68.9%)	134 (54.7%)	263 (79.4%)	<0.001
Nursing home	49 (8.5%)	31 (12.6%)	18 (5.4%)	
Home with Palliative Care	54 (9.3%)	29 (11.8%)	25 (7.5%)	
Hospice	40 (6.9%)	29 (11.8%)	11 (3.3%)	
Other	36 (6.2%)	22 (9%)	14 (4.2%)	

	Overall (N=639)	**Delirium° (N=301)**	**No Delirium (N=338)**	**p-value**
3-month mortality (including in-hospital mortality)	206 (32.2%)	142(47.2%)	64 (18.9%)	< 0.001
Time-to-death (days)	20.5 (10-45)	17 (9–32)	39.5 (19.5–59.5)	<0.001

Notes. Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables.
° At least one day during hospitalisation (4AT positive and confirmed diagnosis).

6.3.2 Delirium prevalence at ward admission and in-hospital incidence

Delirium prevalence (defined as delirium present within the first 24 hours of ward admission) was 38% (95% CI: 34–42%). Among patients free of delirium during the first 24 hours, the incidence of new-onset delirium over the hospital stay was 14% (95% CI: 11–18%).

6.3.3 Delirium trajectories

Among the 301 patients who experienced delirium during hospital admission, GBTM identified three different delirium-probability trajectories (**Figure 25**): a High trajectory (n=121; 40.2%) with a daily probability of delirium close to 1 throughout the whole stay; a Medium trajectory (n=96; 31.9%) starting around 0.6 and declining gradually; and a Medium-to-Low trajectory (n=84; 27.9%) with a steep drop by day 3, approaching zero by day 6.

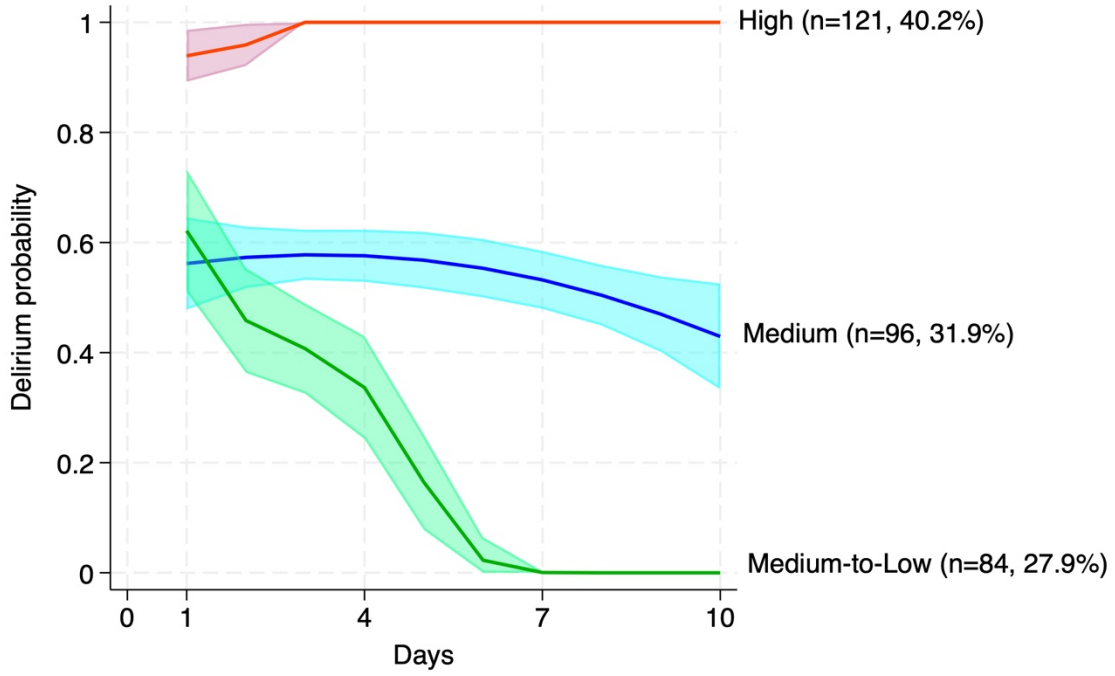


Figure 25. Estimated group-based trajectories of in-hospital delirium probability over the first 10 days. Solid lines show model-based mean probabilities; shaded ribbons are 95% CIs.

As shown in Table 10, baseline sociodemographic profiles among patients who experienced delirium were broadly similar across trajectory classes (age, sex, marital status, domiciliation). By contrast, functional status showed clear gradients. Mobility impairment was most pronounced in the High trajectory (32.2% non-ambulant vs 8.3% in Medium-to-Low; p<0.001), while ADL and IADL were consistently lowest in the High class. Known dementia increased stepwise across classes (from 45.2% to 76.0%; p<0.001), paralleled by more advanced GDS stages (p<0.001). Frailty was also higher with worsening trajectories: CFS clustered at 7 in the High group (p<0.001), and median PC-FI was 0.24 in the High group (0.16–0.28) vs 0.20 in the others (p=0.006). Comorbidity burden (CCI) and number of home drugs did not differ meaningfully.

Table 10. Characteristics of patients with delirium (overall and by trajectories)

	Overall (N=301)	**Medium-to-Low (N=84)**	**Medium (N=96)**	**High (N=121)**	**p-value**
Age	87 (84-81)	86.5 (84-90)	87 (83-90)	88 (85-91)	0.100
Sex (female)	151 (50.2%)	46 (54.8%)	43 (44.8%)	62 (51.2%)	0.392
Marital status					0.083
Married/Cohabitant	130 (43.2%)	31 (36.9%)	44 (45.8%)	55 (45.5%)	
Widowed	157 (52.2%)	47 (56.0%)	45 (46.9%)	65 (53.7%)	
Other	14 (4.7%)	6 (7.1%)	7 (7.3%)	1 (0.8%)	
Domiciliation					0.173
At home alone	54 (17.9%)	23 (27.4%)	16 (16.7%)	15 (12.4%)	
At home with partner/spouse	125 (41.5%)	31 (36.9%)	44 (45.8%)	50 (41.3%)	
At home with caregiver	108 (35.9%)	27 (32.1%)	32 (33.3%)	49 (40.5%)	
Residential setting	14 (4.7%)	3 (3.6%)	4 (4.2%)	7 (5.8%)	
Deambulation					<0.001°
Autonomous	108 (35.9%)	36 (42.9%)	41 (42.7%)	31 (25.6%)	
With help	35 (11.6%)	8 (9.5%)	7 (7.3%)	20 (16.5%)	
With aid	98 (32.6%)	33 (39.3%)	34 (35.4%)	31 (25.6%)	
Not possible	60 (19.9%)	7 (8.3%)	14 (14.6%)	39 (32.2%)	
ADL	2 (1-5)	3 (1-5)	2.5 (1-5)	1 (0-3)	<0.001°
IADL (female)	0 (0-2)	0.5 (0-3)	0 (0-2)	0 (0-0)	0.012§
IADL (male)	0 (0-2)	1 (0-3)	0 (0-1)	0 (0-1)	<0.001§
Charlson Comorbidity Index	3 (2-4)	3 (1.5-4)	3 (2-5)	3 (2-4)	0.098

N° of drugs at admission	7 (5-10)	6.5 (5-10)	7 (5-10)	6 (4-9)	0.360
Anamnestic dementia	187 (62.1%)	38 (45.2%)	57 (59.4%)°	92 (76.0%)	<0.001
Possible dementia (AD8 ≥ 2)	79 (26.2%)	37 (44%)	24 (25%)	18 (14.9%)	0.106
Global Deterioration Scale					<0.001°
1 (No cognitive decline)	41 (13.6%)	14 (16.7%)	14 (14.6%)	13 (10.7%)	
2 (Age associated memory impairment)	27 (9.0%)	8 (9.5%)	16 (16.7%)	3 (2.5%)	
3 (MCI)	26 (8.6%)	15 (17.9%)	4 (4.2%)	7 (5.8%)	
4 (Mild dementia)	54 (17.9%)	22 (26.2%)	23 (24.0%)	9 (7.4%)	
5 (Moderate dementia)	81 (26.9%)	16 (19.0%)	25 (26.0%)	40 (33.1%)	
6 (Moderately severe)	45 (15.0%)	8 (9.5%)°	12 (12.5%)	25 (20.7%)	
7 (Severe dementia)	27 (9.0%)	1 (1.2%)	2 (2.1%)	24 (19.8%)	
Clinical Frailty Scale	7 (6-7)	7 (6-7)	7 (6-7)	7 (7-7)	<0.001°
Primary Care - Frailty Index	0.20 (0.16-0.28)	0.20 (0.12-0.24)	0.20 (0.16-0.28)	0.24 (0.16-0.28)	0.006§

Notes. Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables. *Abbreviations*: Activities of Daily Living; Instrumental Activities of Daily Living; MCI: Mild Cognitive Impairment; AD8: Ascertain Dementia 8. Significant post-hoc pairwise comparisons (after Bonferroni correction): § only Medium-to-Low vs High; # only Medium vs High; ° Medium-to-Low vs High and Medium vs High.

Presenting symptoms in the ED did not differ significantly across classes, as well as laboratory profiles at admission, distribution of macro-diagnoses, and median length of stay (Table 11).

Table 11. Additional in-hospital characteristics of delirious patients (overall and by trajectories)

	Overall (N=301)	**Medium-to-Low (N=84)**	**Medium (N=96)**	**High (N=121)**	**p-value**
Symptoms at ED admission*					
Fever	59 (19.6%)	14 (16.7%)	17 (17.7%)	28 (23.1%)	0.441
Respiratory	75 (24.9%)	17 (20.2%)	21 (21.9%)	37 (30.6%)	0.171
Gastro-intestinal	33 (11.0%)	12 (14.3%)	11 (11.5%)	10 (8.3%)	0.391
Fall	66 (21.9%)	24 (28.6%)	23 (24.0%)	19 (15.7%)	0.077
Neurological	106 (35.2%)	26 (31.0%)	34 (35.4%)	46 (38.0%)	0.581
Leucocytes (µL/mmc)	9360 (6770–12630)	8350 (6245–11185)	9460 (6825–11795)	9830 (7160–14470)	0.062
Creatinine (mg/dL)	1.2 (0.9–1.7)	1.1 (0.8–1.4)	1.2 (0.9–1.7)	1.2 (0.9–2.1)	0.180
Albumin (g/dL)	3.3 (2.9–3.7)	3.4 (3.0–3.6)	3.4 (2.9–3.7)	3.2 (2.8–3.7)	0.450
C-Reactive Protein (mg/dL)	6.40 (2.6–12.5)	6.4 (1.9–13.2)	6.4 (2.7–12.7)	5.9 (2.9–12.2)	0.980
Hospital stay (days)	11 (8-14)	10 (8-14)	11 (9-15)	10 (7-14)	0.076

Macro-diagnosis at discharge*					
Cardiovascular	112 (37.2%)	32 (38.1%)	42 (43.7%)	38 (31.4%)	0.171
Respiratory	120 (39.9%)	32 (38.1%)	48 (39.7%)	40 (41.7%)	0.886
Gastro-intestinal	32 (10.6%)	8 (9.52%)	13 (13.5%)	11 (9.1%)	0.531
Nephro/urological	100 (33.2%)	26 (30.9%)	31 (32.3%)	43 (35.5%)	0.769
Neurological	75 (24.9%)	20 (23.8%)	23 (23.9%)	32 (26.4%)	0.881
Infectious	113 (37.5%)	36 (42.9%)	34 (35.4%)	43 (35.5%)	0.495
Hematological	49 (16.3%)	19 (22.6%)	17 (17.7%)	13 (10.7%)	0.069
Oncological	30 (10%)	7 (8.3%)	11 (11.5%)	12 (10%)	0.783

Notes. Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables
*More than one allowed. *Abbreviations.* ED: Emergency Department.

Looking at delirium features (Table 12), severity on the first delirium day (DEL-S) increased across classes [median from 4 to 6; $p<0.001$, with Medium-to-Low vs High and Medium vs High significant pairwise comparisons]. Motor phenotype differed both at onset ($p<0.001$) and over the entire stay ($p=0.002$): the High trajectory showed a predominance of hypoactive and mixed forms, whereas the Medium-to-Low class more often had hyperactive or non-motor presentations. Delirium duration lengthened with trajectory level [2 (Q1-Q3: 1–3) vs 6 (Q1-Q3: 4–8) vs 11 (Q1-Q3: 7–14) days; $p<0.001$; all significant pairwise comparisons]. The number of precipitating factors rose in parallel [median from 4 to 6; $p<0.001$; Medium-to-Low vs High and Medium vs High significant]. Specific precipitating factors that were more frequent in the High class included underhydration ($p=0.033$; Medium vs High significant), electrolyte imbalance ($p=0.030$), exposure to psychoactive drugs ($p=0.014$; Medium vs High significant), fluid therapy ($p=0.028$), and prolonged bedrest ($p<0.001$; Medium-to-Low vs High and Medium vs High significant).

Table 12. Delirium features (overall and by trajectories)

	Overall (N=301)	Medium-to-Low (N=84)	Medium (N=96)	High (N=121)	p-value
DEL-S (first day)	5 (4-7)	4 (3-5)	5 (3-7)	6 (5-8)	<0.001°
Motor subtype (first day of delirium)					<0.001°
Hyperactive	113 (37.5%)	34 (40.5%)	43 (44.8%)	36 (29.8%)	
Hypoactive	123 (40.9%)	25 (29.8%)	34 (35.4%)	64 (52.9%)	
Mixed	17 (5.6%)	2 (2.4%)	4 (4.2%)	11 (9.1%)	
Non-motor	48 (15.9%)	23 (27.4%)	15 (15.6%)	10 (8.3%)	
Motor subtype (during hospital course)					0.002§
Hyperactive	82 (27.2%)	30 (35.7%)	32 (33.3%)	20 (16.5%)	
Hypoactive	91 (30.2%)	25 (29.8%)	22 (22.9%)	44 (36.4%)	
Mixed	115 (38.2%)	22 (26.2%)	39 (40.6%)	54 (44.6%)	
Non-motor	13 (4.3%)	7 (8.3%)	3 (3.1%)	3 (2.5%)	
Delirium duration (days)	6 (3-10)	2 (1-3)	6 (4-8)	11 (7-14)	<0.001°°
Precipitating factors (N°)	5 (4-6)	4 (3-6)	5 (3-6)	6 (4-8)	<0.001°
Infection/fever	220 (73.1%)	63 (75.0%)	68 (70.8%)	89 (73.6%)	0.812
Pain	117 (38.9%)	24 (28.6%)	39 (40.6%)	54 (44.6%)	0.062
Underhydration	118 (39.2%)	30 (35.7%)	30 (31.2%)	58 (47.9%)	0.033#
Electrolyte imbalance	117 (38.9%)	27 (32.1%)	32 (33.3%)	58 (47.9%)	0.030
Constipation	93 (31.0%)	26 (31.3%)	27 (28.1%)	40 (33.1%)	0.735
Urinary retention	48 (15.9%)	7 (8.3%)	16 (16.7%)	25 (20.7%)	0.059
Psychoactive drugs	61 (20.3%)	15 (17.9%)	12 (12.5%)	34 (28.1%)	0.014#
Severe hypotension	36 (12.0%)	6 (7.1%)	9 (9.4%)	21 (17.4%)	0.055
Oxygen therapy	125 (41.5%)	33 (39.3%)	36 (37.5%)	56 (46.3%)	0.379
Urinary catheter	138 (45.8%)	34 (40.5%)	42 (43.8%)	62 (51.2%)	0.278
Fluid therapy	91 (30.2%)	20 (23.8%)	24 (25.0%)	47 (38.8%)	0.028
Nasogastric tube	8 (2.7%)	1 (1.2%)	4 (4.2%)	3 (2.5%)	0.459
Prolonged bedrest	70 (23.3%)	11 (13.1%)	13 (13.5%)	46 (38.0%)	<0.001°
Physical restraints	55 (18.3%)	15 (17.9%)	17 (17.7%)	23 (19.0%)	0.964
Neurological event	62 (20.6%)	13 (15.5%)	18 (18.8%)	31 (25.6%)	0.181
Cardiac Ischemia	10 (3.3%)	1 (1.2%)	5 (5.2%)	4 (3.3%)	0.324
Other (drains, hypoglycemia, etc.)	36 (12.0%)	12 (14.3%)	12 (12.5%)	12 (9.9%)	0.626

Notes. Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables. Significant post-hoc pairwise comparisons (after Bonferroni correction): § only Medium-to-Low vs High; # only Medium vs High; ° Medium-to-Low vs High and Medium vs High; °° Medium-to-Low vs High, Medium vs High and Medium-to-Low vs Medium.

As for the outcomes (Table 13), in-hospital mortality significantly increased from 4.8% (Medium-to-Low) to 16.7% (Medium) and 29.8% (High) (p<0.001), while discharge home became progressively less likely (from 67.5% in the Medium-to-Low to 41.2% in the High; p=0.003), with corresponding increases in hospice and palliative-care referrals. Three-month all-cause mortality (including in-hospital deaths) rose sharply across classes (from 26.2% in Medium-to-Low up to 65.3% in High; p<0.001), and time-to-death significantly shortened [30 (Q1-Q3: 15–75) to 12 (Q1-Q3: 7–24) days; p<0.001].

Table 13. Discharge setting and mortality (overall and by trajectories)

	Overall (N=301)	**Medium-to-Low (N=84)**	**Medium (N=96)**	**High (N=121)**	**p-value**
In-hospital mortality	56 (18.6%)	4 (4.8%)	16 (16.7%)	36 (29.8%)	<0.001§§
Discharge setting	**N=245**	**N=80**	**N=80**	**N=85**	0.003§
Home	134 (54.7%)	54 (67.5%)	45 (56.2%)	35 (41.2%)	
Nursing home	31 (12.7%)	10 (12.5%)	13 (16.2%)	8 (9.4%)	
Home with Palliative Care	29 (11.8%)	6 (7.5%)	7 (8.8%)	16 (18.8%)	
Hospice	29 (11.8%)	3 (3.8%)	8 (10.0%)	18 (21.2%)	
Other	22 (9.0%)	7 (8.8%)	7 (8.8%)	8 (9.4%)	
3-month mortality (including in-hospital mortality)	142 (47.2%)	22 (26.2%)	41 (42.7%)	79 (65.3%)	<0.001°
Time-to-death (days)	17 (9-32)	30 (15-75)	22 (9-44)	12 (7-24)	<0.001§

Notes. Values are expressed as median (Q1-Q3) for continuous variables, and n(%) for categorical variables. Significant post-hoc pairwise comparisons (after Bonferroni correction): §§ only Medium-to-Low vs Medium; § only Medium-to-Low vs High; ° Medium-to-Low vs High and Medium vs High.

On post-hoc pairwise comparisons with Bonferroni correction, differences were consistently significant only when contrasting the High trajectory with either the Medium-to-Low or the Medium class. By contrast, the Medium-to-Low and Medium trajectories did not differ significantly from each other across characteristics, with the exceptions of in-hospital mortality and delirium duration, for which pairwise differences were significant.

6.3.4 Association between delirium trajectories and 3-month mortality

In the multivariable Poisson regression, delirium trajectories resulted independently associated to 3-month all-cause mortality (Table 14). Compared with the Medium-to-Low trajectory, risk was significantly higher in the Medium trajectory (RR = 1.56, 95% CI 1.02–2.36; p = 0.038) and more than doubled in the High trajectory (RR = 2.07, 95% CI 1.41–3.05; p < 0.001). Among covariates, higher frailty was significantly associated with increased mortality, whereas higher serum albumin at admission was protective. Age and sex were not significant.

Table 14. Association between delirium trajectories and 3-month all-causes mortality

	RR	**IC 95%**	**p-value**
Delirium trajectory			
Medium°	1.56	1.02 – 2.36	0.038
High°	2.07	1.41 – 3.05	<0.001
Clinical Frailty Scale *(per one-level increase)*	1.23	1.06 – 1.43	0.008
Albumin *(per one decimal increase)*	0.70	0.57-0.86	0.001
Age	1.02	1.00 – 1.04	0.112
Female sex (vs male)	0.93	0.75 – 1.15	0.505

Note. ° Reference: Medium-to-Low.
Abbreviations. RR: Relative Risk; 95%CI: 95% Confidence Interval

In sensitivity analyses (data not shown), day-1 motor subtype and day-1 delirium severity were not associated to the outcome, and did not modify the association between trajectories and mortality. Adding delirium duration likewise did not attenuate the trajectory–mortality association, which does not support a possible mediating role for duration. By contrast, the motor subtype observed over the hospital course sligthly reduced the excess risk trajectory-related in the Medium one, suggesting a possible mediating effect of hypoactive and mixed phenotypes in the relationship.

Finally, regarding the baseline risk of unfavourable trajectories (Medium and High), **Figure 26** shows the heatmap with a graded pattern based on frailty and cognition: patients with GDS 6–7 and CFS 7–9 are most likely to follow the High trajectory, whereas those with GDS 1–3 and CFS 3–4 are most likely to follow the Medium-to-Low trajectory.

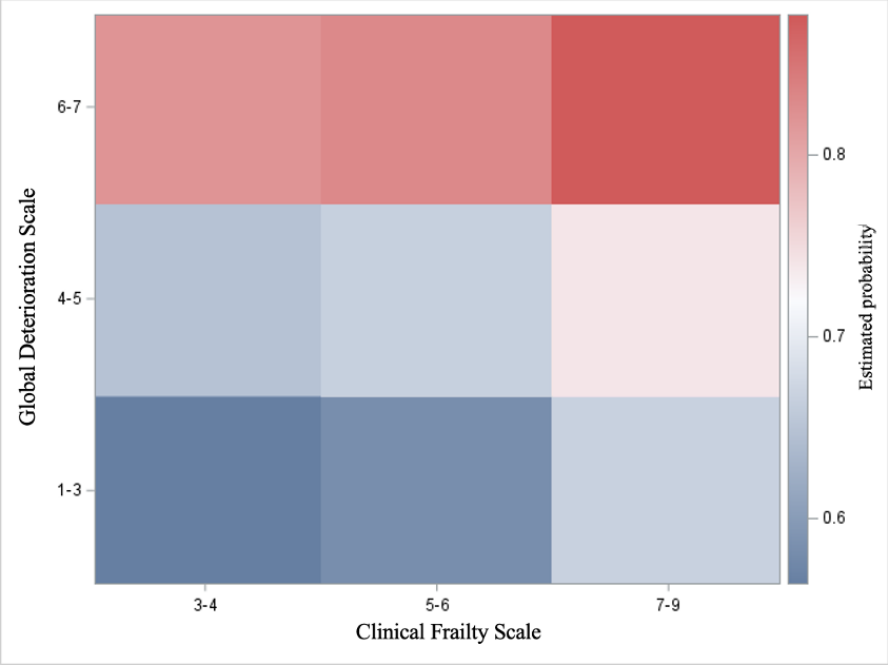


Figure 26. Heatmap of the estimated probability of following unfavourable trajectories (Medium or High) among patients with delirium. Rows show Global Deterioration Scale strata (1–3, 4–5, 6–7); columns show Clinical Frailty Scale strata (3–4, 5–6, 7–9). Colour scale: blue = lower probability; red = higher probability (legend at right). Probabilities are derived from a logistic model with trajectory class as outcome and predictors GDS and CFS.
Note: because the analysis is conditional on having delirium, and Medium/High classes were common in the cohort (≈72% overall), even the most favourable cell exceeds 0.50.

6.4 DISCUSSION

In this prospective study of 639 older adults consecutively admitted to a tertiary-care AGU for acute medical conditions, delirium was frequent. Prevalence at admission was 38% (95% CI 34–42%), and in-hospital incidence was 14% (95% CI 11–18%). Among patients with delirium, three daily probability trajectories were identified: High (n=121; 40.2%), with persistently high probability; Medium (n=96; 31.9%), with a gradual declining course; and Medium-to-Low (n=84; 27.9%), with a rapid decrease after day 3. Three-month all-cause mortality was more than doubled in the High trajectory compared to the the Medium-to-Low, and was 56% higher in the Medium vs. Medium-to-Low, independent of age, sex, frailty, and serum albumin.

The burden of delirium in our cohort exceeded pooled estimates for general older medical inpatients reported by Gibb et al. (prevalence 15% [95% CI 14–16%] and incidence 9% [95% CI 7–10%] over two weeks; overall occurrence 23%) [42]. This discrepancy with our data is plausible, given our very old age distribution, high frailty burden, and complex case-mix of a dedicated geriatric unit, and it is consistent with single-center studies with similar age and dementia profiles [116,117].

Consistent with prior literature, patients who had delirium had also greater cognitive impairment burden and higher frailty [55,68], and were exposed to worse outcomes in terms of short-term mortality [70,118,119]. To our knowledge, no study has examined whether distinct trajectories of delirium probability during hospitalisation can be differently associated to mortality. The only similar study is a recent large retrospective ICU study (>20,000 patients; median age 59 years) which modeled trajectories of delirium severity, finding five temporal patterns - characterised by increasing baseline functional and cognitive impairment - but that were not associated with 30-day mortality [120]. Clinical correlates were coherent with trajectory membership also in our cohort. The High trajectory was associated with poorer baseline function, more advanced cognitive impairment, higher

frailty, higher initial delirium severity, a larger burden of precipitating factors, and longer delirium duration. In contrast, the Medium-to-Low trajectory included less frail patients with lower dementia burden, and the Medium trajectory appeared to be intermediate. Notably, comorbidity burden and the macro-diagnoses at discharge were not associated with any trajectory membership, being similar in all groups. Pairwise comparisons confirmed different baseline clinical and functional differences between groups, although no differences were found between the Medium-to-Low and Medium trajectories, except for delirium duration itself.

The association between persistent high delirium probability and mortality is definitely plausible and aligns with evidence linking longer delirium duration to 6-month mortality [74]. However, in our sensitivity analyses, duration was not independently associated with 3-month mortality and did not attenuate the trajectory–mortality association. This finding suggests that duration may be a manifestation of the underlying temporal pattern captured by the trajectories rather than its driver.

Unmeasured dynamic factors, such as biological markers of stress or resilience, may contribute to trajectory assignment and consequently to mortality, beyond age, sex, frailty, and nutritional status. Frailty and low serum albumin also resulted independently associated with mortality, as expected, and are likely to act jointly with delirium to worsen prognosis [121,122]. The absence of an independent effect of admission-day motor subtype and delirium severity indicates that single-day features may be less informative prognostically than the evolving pattern over time. This interpretation aligns with the modest attenuation observed when accounting for hypoactive/mixed motor subtypes during the whole stay in the Medium trajectory.

Future studies should evaluate whether risk stratification for trajectory class can be improved by combining baseline frailty and cognition with dynamic markers, such as systemic inflammation and neuroinflammation, time-varying delirium severity, vital-sign instability, and complications. These

factors may sustain delirium, helping explain differences in mortality between the Medium trajectory vs. the Medium-to-Low one.

The study has important clinical implications: since choices between intensive and palliative approaches are crucial in geriatric acute hospital settings, early recognition of a high probability of unfavorable prognostic trajectories could inform evidence-based discussions about goals of care. Although very high CFS and high GDS strongly predict membership worst trajectories, being able to distinguish better the Medium-to-Low from the Medium trajectory would be even more clinically relevant, as it may represent a potentially modifiable medium-risk window for intensified prevention and management.

Strengths of the study include consecutive enrollment, delirium daily assessments using systematic tools enabling trajectory modeling, and adjustment for key confounders (age, sex, frailty, albumin) with sensitivity analyses for duration and motor subtypes. Limitations are related to the single-center and the observational design with possible residual confounding (e.g., complications, dynamic illness severity). In addition, delirium trajectories were modelled over the first 10 inpatient days - a pragmatic compromise between clinical relevance and methodological stability - which may not fully reflect the entire delirium course until discharge, especially among patients with longer-than-median hospital stays. Moreover, the restricted outcome scope (all-cause 3-month mortality), and the lack of serial plasma biomarkers should be acknowledged as additional limitations.

Overall, our findings suggest that routine daily delirium assessment and proactive management are warranted in acute geriatric care, where over one in three patients present with delirium on admission and one in eleven develop it during hospitalisation. In addition, modelling the temporal pattern of delirium probability better captures 3-month mortality risk than static measures. From a practical standpoint, a trajectory-informed perspective reinforces the value of systematic daily monitoring to distinguish sustained delirium from early resolution, which can guide intensified multicomponent

management, closer surveillance for complications, and tailored discharge and goals-of-care planning. Taken together, these findings offer a novel, time-sensitive risk stratification approach that may inform the development of pragmatic delirium-aware and dementia-sensitive hospital care pathways.

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CHAPTER 7 – CONCLUSION AND IMPLICATIONS

This thesis presents two complementary findings that warrant consideration in the WHO Decade of Healthy Ageing. First, the socioeconomic burden of AD rises with severity and is borne largely by families in the community, mainly through unpaid caregiving time and productivity losses. Second, in-hospital delirium is frequent, especially among frail older adults with dementia, and daily delirium-probability trajectories can help explain short-term mortality risk. Together, these results argue for stronger community support and delirium-aware practice in acute care, and they can inform better health and social-care planning for patients with dementia or delirium.

Future implications include:

- Strengthen home and community services, through expanding hospital-at-home, rapid response teams, community geriatrics, rehabilitation, and occupational therapy for structured BPSD management, to relieve families and provide patients better care.
- Improve caregiver-centred policies (systematic assessment of strain, training, respite, and protection against income loss), since today's caregivers are the next cohort of older adults.
- Adopt dementia-sensitive, delirium-aware hospital care: routine daily screening, multicomponent prevention (mobilisation, hydration/nutrition, sleep hygiene, medication review), prompt management of precipitating factors, and early, structured goals-of-care discussions. If validated in further studies, delirium-probability trajectories could provide pragmatic risk stratification to guide discharge planning and palliative transitions, too.

An integrated model across the home–hospital continuum may offer innovative and feasible path to better outcomes in dementia and delirium fields, together with lower societal costs and more dignified ageing for both patients and caregivers.

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