# Imaging in Neurodegenerative Disorders



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# CHAPTER 1

# Epidemiology of neurodegenerative diseases

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## Introduction

Neurodegenerative disorders are the main challenge for medicine and public health for healthy living in future years because of demographic changes worldwide. Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) share two main characteristics: (1) the incidence and prevalence increase with age and (2) the majority of cases are sporadic even if some of the cases are familial, including monogenetic forms with early age of onset (under age 50).

In the last two decades the epidemiology of neurodegenerative diseases has focused on descriptive studies and on a wide range of genetic and environmental risk factors. The overall goal of epidemiology is identification of cases and possibly prevention of disease. This chapter therefore focuses on the definition of disease, frequencies, and modifiable risk factors of neurodegenerative diseases (Table 1.1). Unmodifiable risk factors (mainly genetic) are not reviewed here.

## Definition of disease

*Dementia* is a loss of cognitive abilities in multiple domains that results in impairment of the normal activities of daily living and loss of independence. *AD*, the leading cause of dementia and the most common neurodegenerative disorder worldwide, is characterized by a progressive decline in cognitive function, which typically begins with deterioration in memory. The neuropathological hallmarks of the AD brain are diffuse and neuritic extracellular *amyloid plaques*, frequently surrounded by dystrophic neurites, and intracellular *neurofibrillary tangles*. These hallmark pathologies are often accompanied by the presence of reactive microgliosis and the loss of neurons, white matter, and synapses. *Frontotemporal lobar degeneration (FTLD)* is a progressive neurodegenerative disease that affects frontal and temporal regions [1]. It is the second most common form of early-onset dementia. FTLD is used as an umbrella term for three clinical variants that can be distinguished based on the early and predominant symptoms: behavioural-variant frontotemporal dementia (bvFTD), semantic dementia (SD), and progressive non-fluent aphasia (PNFA). The majority of pathologies associated with FTLD clinical syndromes include either *tau-positive* (FTLD-TAU) or *TAR DNA-binding protein 43* (TDP-43)-positive (FTLD-TDP) *inclusion bodies* [2,3]. *Dementia with Lewy bodies (DLB)* is generally considered as the second cause of degenerative dementia after AD [4,5] in older people after age 75, and clinically combines dementia and parkinsonism in most cases [6]. Pathological hallmark of the disease are intracellular accumulation of the protein *α-synuclein* in form of *Lewy bodies* [7]. *Vascular dementia (VaD)* is characterized by a clinical diagnosis of dementia with impairment of executive functioning (subcortical and/or frontal type) and presence of cerebrovascular disease. Progression of the disease could be fluctuating, gradual progressive, and/or stepwise [8] Recent lines of research have shown that neurodegenerative dementia and VaD have additive effects and probably interact, and a clear distinction between AD and VaD cannot be made in most cases [9].

*ALS* is the most common type of adult-onset motor neuron disease. It is typically characterized by degeneration of upper (cortical) (UMN) and lower (brainstem and spinal cord) (LMN) motor neurons to various degrees, even though recent evidences have suggested that the process of degeneration extends beyond motor areas and involves other neuronal and non-neuronal cellular types. The disease is mainly sporadic (sALS); almost 10% of cases are familiar (fALS) in clinical series from referral centres. Neuropathology in ALS is heterogeneous, but typically it is characterized by the presence of ubiquitin-positive neuronal inclusions containing TDP-43 [10].

*PD* is an insidious and slowly progressive neurodegenerative disease, clinically characterized by bradykinesia, resting tremor, rigidity, and postural instability. Symptomatic response to levodopa therapy is used as an additional diagnostic criterion [11]. The pathological hallmark of the disease is progressive loss of dopaminergic neurons in the substantia nigra pars compacta. This is accompanied by microglial activation and intraneural accumulation of Lewy bodies (containing the protein α-synuclein) as the disease spreads from the brainstem to involve a range of other structures, including the cortex.

The aetiological mechanisms underlying the neuropathological changes in these major neurodegenerative diseases remain unclear, but it can be surmised that oxidative/nitrative stress, which is cooperatively influenced by environmental factors, genetic predisposition, and senescence, may be a link between these disorders [12]. Based on advances over the past 30 years, it is now generally accepted that nearly all neurodegenerative disease are diseases of protein homeostasis, or 'proteostasis', caused by the misregulation of protein maintenance. Proteostasis is maintained by the proteostasis network, which comprises pathways that control protein synthesis, folding, trafficking, aggregation, disaggregation, and degradation. The decreased ability of the proteostasis

**Table 1.1** Frequencies of neurodegenerative diseases in three large population-based studies

| | | Rotterdam study | Kungsholmen study | EURALS |
|---|---|---|---|---|
| Dementia | Prevalence | 6.3% | 12% | – |
| | Incidence | 9.8/1000 per year | 57/1000 per year | – |
| AD | Prevalence | 4.5% | 6.4% | – |
| | Incidence | 7.2/1000 per year | 44/1000 per year | – |
| PD | Prevalence | 1.4% | – | – |
| | Incidence | 1.7/1000 per year | – | – |
| ALS | Prevalence | – | – | 7.9/100 000 |
| | Incidence | – | – | 2.16/100 000 per year |

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease.

network to cope with inherited misfolding-prone proteins, ageing, and/or metabolic/environmental stress appears to trigger or exacerbate proteostasis diseases [13]. These protein misfolding disorders are characterized by pathological central nervous system protein aggregates, alterations in the solubility and metabolism of corresponding disease proteins, and mutations in genes that encode major disease proteins of familial disorders and their sporadic counterparts, including the genes encoding tau, β-amyloid (Aβ), α-synuclein, SOD1, TDP-43, and others.

## Transition phenotypes

The phenotypic features of these diseases are highly variable, but correlations between genetic abnormalities, clinical features and underlying neuropathology are recognized. Furthermore a large amount of overlap presentations and transition phenotypes can be often recognized.

For example, it is now widely demonstrated that ALS, far from being an only motor neuron disease, is characterized by an extreme clinical heterogeneity with numerous fuzzy transition phenotypes, that spans along *three principal axes* (Figure 1.1):

1. *UMN and LMN involvement:* The archetypal phenotypic manifestation of the disease derived from the combined and contemporary presence of UMN (stiffness, hyper-reflexia, Hoffman's and Babinski's signs, corticobulbar reflexes) and LMN (muscular weakness and wasting, hyporeflexia, hypotonia, fasciculations, muscular cramps, dysphagia, dysarthria, dyspnea) signs in one or more body regions. Median survival time of this '*classical ALS*' is 30 months from symptom onset. Besides this phenotypic manifestation that represents approximately 80% of cases, the different degree of involvement of UMN and LMN generates a clinical spectrum that spans from the pure involvement of the UMN (*primary lateral sclerosis—PLS*) to the pure involvement of LMN (*progressive muscular atrophy—PMA*). *PLS* is characterized by the exclusive presence of UMN damage without detectable LMN signs for at least 4 years after onset [14,15]. *PMA* is clinically characterized solely by signs of LMN dysfunction. Patients with LMN signs who at any time later in follow-up develop UMN signs are then considered to have LMN-onset ALS [16]. Also the phenotype UMN-dominant ALS (*UMN-d ALS*) has been clinically defined as the presence of predominantly UMN signs with minor LMN findings at least for 4 years after onset [14]. Epidemiological and pathological studies showed that these nosological entities strictly belong to the ALS phenotype spectrum [17,18] but are distinguished from classical ALS by a more benign course and long survival [14,19–22].
2. *Cognition and behaviour:* Clinical, neuroimaging, and pathological data, especially accumulated in the last decade have been suggested that ALS and frontotemporal dementia (FTD) might form part of a disease continuum, with pure ALS at one extreme and pure FTD at the other. Cognitive impairment occurs in up to 50% of cases, and one in seven patients develops frank FTD.[23]. ALS occurs in up to 15% of patients with FTD, with subtle LMN signs in a larger percentage [24]. Comorbid phenotypes (ALS/FTD and FTD/MND) are characterized by reduced survival [25–27]. Genetics and neuropathology have largely confirm the overlap between ALS and FTD. The existence of families with pure ALS, pure FTD, ALS with comorbid FTD (ALS-FTD). and FTD with comorbid motor neuron impairment (FTD/MND) has been long recognized [28]. In 2006 Manuela Neumann demonstrated that the 43-kDa TAR DNA-binding protein (TDP-43) was a common molecular signature of both the majority of ALS patients and tau protein-negative FTD [3]. In TDP-43-negative cases she added the fused in sarcoma (FUS) protein as a second, but quantitatively less relevant, molecular marker to her discovery [29]. These breakthroughs led to a reclassification of the diseases on the molecular neuropathology level [30]. Pathogenic mutations in the *TARDBP* and *FUS* genes were subsequently described

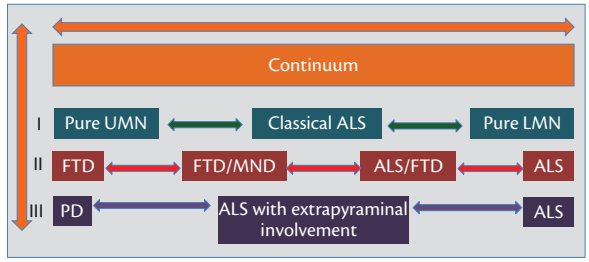


**Fig. 1.1** Three axes of clinical continuum in amyotrophic lateral sclerosis.

in both ALS and FTD cases [31–33]. However, the real turning point was the recent discovery of the genetic abnormality on chromosome 9p21: a GGGGCC repeat expansion within the non-coding region of the *C9ORF72* gene [34,35]. This repeat expansion accounts for 25–60% of familial ALS cases, depending on the population studied, making this the most common genetic cause of ALS and FTD, much more common than the mutations in other identified genes causing familial ALS including *SOD1, TDP43, FUS*, and *VCP*; less than 10% of sporadic ALS and FTD cases test positive for this mutation [34,35]. Neuropathology in both FTD and ALS cases with *C9ORF72* expansions showed TDP-43-positive neuronal and glial inclusions and a higher proportion of nuclear RNA foci in frontal cortex and spinal cord neurons. No unique clinical phenotype was associated with this subtype of ALS or FTD, even though patients with ALS and *C9ORF72* repeat expansion seem to present a recognizable phenotype (earlier disease onset, presence of cognitive and behavioural impairment, specific neuroimaging changes, family history of neurodegeneration with autosomal dominant inheritance, and reduced survival) [36,37].

3. *Extrapyramidal involvement:* Extrapyramidal involvement has been described in ALS. Desai and Swash reported three patients with backward falls and retropulsion at onset [38]. In an epidemiological study in Japan incidence of extrapyramidal signs in ALS was found in 4.8%, more frequent than expected by chance, suggesting that the degeneration of basal ganglia and/or substantia nigra may not be so rare in ALS [39]. The presence of extrapyramidal symptoms seems to be more frequent in ALS cases related to mutations of *TARDBP* [40,41] and if predominant UMN signs are present [42]. Post-mortem analysis of ALS cases shows the diffusion of TDP-43 pathology beyond the motor system to involve the nigrostriatal system, the neocortical and allocortical area, and the cerebellum [10]. Perhaps in the group of TDP-43 proteinopathies besides ALS and FTD an extrapyramidal syndrome may be included.

AD is clinically heterogeneous in presentation and progression, demonstrating variable topographic distributions of atrophy and hypometabolism/hypoperfusion [43]. In addition, AD often keeps company with other conditions that may further nuance clinical expression, such as synucleinopathy exacerbating executive and visuospatial dysfunction and vascular pathologies (particularly small-vessel disease that is increasingly ubiquitous with human ageing) accentuating frontal-dysexecutive symptomatology. PD and dementia often overlap, and co-occur in families. A population-based case–control study reported higher frequency of first-degree relatives with PD among AD patients than among controls, corresponding to a relative risk (RR) of 2.9 [44]; the association was stronger among early-onset PD cases [45,46]. A review including 13 studies with a total of 1767 patients found a prevalence of PD with dementia (PDD) of 31.3% [47], indicating that PD patients have a 4- to 6-fold increased risk of developing dementia compared to the age-matched general population [48]. The prevalence of dementia increased as years of observation rose, up to 83% after 20 years [49]. Cognitive symptoms may be present since the earliest stage of the disease [50]. The presence of cognitive decline or dementia reduces survival in patients with PD [51]. The pathological correlate of PDD could be neocortical synucleinopathy and neocortical synucleinopathy with Aβ deposition. Accumulation of Aβ is associated with lower survival rates in PD patients with dementia [52]. On the other hand extrapyramidal signs (EPS) have been described in a consistent proportion of patients with AD. Portet et al., in a prospective studies on a multiethnic cohort, detected EPS in 12.3% of patients with incident AD at first evaluation and 22.6% for the last evaluation (after a median follow-up of 3.6 years) and described greater rates of cognitive decline in patients with EPS [53].

Over the last 10 years, it became evident that focal onset of AD may not be uncommon. A neuropathological study on 120 patients (100 consecutive cases with focal cortical syndromes and 20 with clinically typical AD) showed that AD is a much commoner cause of focal cortical syndromes than previously recognized, particularly in posterior cortical atrophy, PNFA and corticobasal degeneration, but rarely causes SD or FTDbv [54]. Furthermore the authors found that age at both onset and death was greater in the atypical AD cases than those with non-AD pathology, although survival was equivalent, that the focal syndrome may remain pure for many years, and that patients with atypical AD tend to be older than those with non-AD pathology [54].



## Frequency (prevalence and incidence)

### Alzheimer's disease

The number of people affected by AD was 26.6 million worldwide in 2006 [55] and, due to dramatic increase of life expectancy over the past century across the globe, the prevalence is expected to quadruple by 2050, so that 1 in 85 persons will be living with the disease [56], and 43.0% of them are expected to need a high level of care (e.g. a nursing home). In developed countries, approximately 1 in 10 persons over 65 years of age suffers from a form of dementia compared with more than one-third of those older than 85 years [57]. The global *prevalence* of AD is estimated at 3.9% in people older than 60 years, with regional variations in individual continents [58]. Among regional populations of individuals aged 60 years or more, those from North America and western Europe exhibited the highest prevalence of dementia (6.4% and 5.4%, respectively), followed by those from Latin America (4.9%) and China and its western Pacific neighbours (4.0%) [58]. Almost 70% of these cases were attributed to AD. Two US studies of persons aged 65 or more reported an AD *incidence* of 15.0 per 1000 person-years. The incidence rates for males and females were 13.0 and 16.9 per 1000 person-years, respectively [59,60]. The prevalence and incidence rates for AD increase exponentially with age [61]. Although a consensus does not yet exist, a growing body of evidence suggests that both the prevalence and the incidence of AD may vary substantially between different ethnoracial groups. The Alzheimer's Association estimates that the prevalence of AD and other dementias in African Americans above the age of 65 years is about twice the rate among elderly whites, while the prevalence in Hispanics is approximately one and a half times greater than in whites [62].

### Amyotrophic lateral sclerosis

The *point prevalence* in the 1990s ranged from 2.7 to 7.4 per 100 000 (average 5.2 per 100 000) in Western countries [63]. The *incidence*

*rate* of ALS varies from approximately 0.3 to 2.5 cases per year per 100 000 persons worldwide [64]. Five per cent or more of all cases run in families (FALS) [65], with a range from 2%–15% in different populations [66], although regional and/or ethnic variations in incidence and penetrance complicate the estimation [67], as does the organization of the studies themselves, being either population- or clinic-based. Typically, in sporadic ALS (SALS) cases, but not always in FALS, males appear to predominate [68], but this may vary among ethnic backgrounds and may be trending toward equality with time [63]. Prospective population-based registries in three European countries (Italy, UK, and Ireland) show a crude annual incidence rate of ALS in the general European population of 2.16 per 100 000 person-years and an age-adjusted incidence of 2.1 per 100 000 [69]. In northern Italy during the 10-year period of observation, the Piemonte and Valle d'Aosta Register for ALS (PARALS) reported a mean annual crude incidence rate of 2.90/100 000 population, without any relevant variation during the 10-year period of the study and with a constantly higher rate among men, and a crude prevalence rate (31 December 2004) of 7.89/100 000 population [70]. A population-based study in Netherlands using capture–recapture methodology reported incidence rate of 2.77 per 100 000 person-years and a prevalence rate (2004–2009) of 10.32 per 100 000 individuals. Incidence and prevalence peaked in the 70–74 year age group followed by a rapid decline in older age. The male:female ratio in the premenopausal age group was 1.91 and in the postmenopausal age group was 1.50 [71]. Low crude and age-adjusted incidence and prevalence rates have been reported for specific ethnic groups, such as American Indians and Alaska natives [72], Africans [73], and Hispanic and 'mixed' ethnicity in the USA and Cuba [74,75]. In Cuba lower incidence has been reported in mixed-race populations compared to whites and blacks, suggesting variable genetic and/or environmental susceptibilities in different ethnicities and/or ancestral populations.

### Parkinson's disease

PD is the second most common neurodegenerative disorder worldwide, after AD. It affects 1–2% of the population over the age of 60 years, although the disease is seen in younger individuals as well [76]. The *prevalence* of PD varies among different ethnic and geographic regions around the world. Approximately 1–2% of the population over 65 years suffers from PD. Overall prevalence in door-to-door studies ranged from 167 to 5 703 per 100 000, with those studying an elderly population (>60 or 65 years) reporting the highest statistics [77–82]. Early onset of sporadic PD is rare, with about 4% of patients developing clinical signs of the disease before the age of 50 years [83]. Several studies reported lower prevalence of PD in Africa [84,85], Asia [86–88], and South America [89,90] compared to Europe [91–96]. It is still questioned if this extreme variation in the reported prevalence may be due to differences in methodology, diagnostic criteria, and case-finding strategies. Some population-based studies conducted in China and South America reported prevalence rates similar to European countries [80,81,97]. Part of the variation may be explained by geographical difference in the same countries, with rural and undeveloped areas reporting lower frequencies. The age-specific prevalence of PD has been found to be 5–10-fold lower in mainland China compared with Europe in the past epidemiological studies [88], with higher frequencies in highly developed regions in China and Singapore [87,88,98] and lower rates in rural areas [99]. The low prevalence in Africa may be due in part to population structure (shorter life expectancy compared to developed countries) [100], with rates in northern Africa similar to those in developed countries [101], and in part to ethnic differences, with lower prevalence rates reported in African Americans as compared with whites [85,102]. Overall, *incidence rates* for PD in studies that reported results for all age groups ranged between 1.5 and 22 per 100 000 person-years [103]. Studies restricted to older populations (>55 or 65 years) reported overall incidence rates between 410 and 529 per 100 000 person-years [104,105]. A meta-analysis of eight high-quality studies estimated the median standardized incidence rate in developed countries at 14 per 100 000 person-years [106]. There are no cases, or very few, occurring before 40 years. Also, the incidence of PD clearly increases with age steeply after age 60. However, several studies reported that incidence rates dropped in older age groups [86,107–112]. It is still a matter of debate whether this decline is real or due to underdiagnosis. In fact several studies reported increasing incidence rates up to 85 years [83,104,105,109]. Comparison among incidence studies of PD is hampered by differences in methodology and reporting. Although incidence data for PD are limited for populations other than whites, there are indications of ethnic differences. In a male North American population, incidence of PD was higher among African Americans [85]. In a multiethnic population in California, incidence of PD was highest among Hispanics, followed by non-Hispanic whites, Asians and African Americans [83]. The incidence of PD seems to be higher in men than in women. A meta-analysis based on 17 incidence studies of PD reported a pooled age-adjusted male to female ratio of 1.46 (95% CI 1.24–1.72) with significant heterogeneity between studies [113]. Neuroprotective properties of female steroid hormones, or alternatively differences in exposure to environmental and occupational risk factors or gender-specific genetic influences, have been discussed as possible underlying causes of this gender difference [113,114]. However, gender differences in incidence of PD appear to differ by ethnicity. In Asian populations gender distribution was almost equal (M:F ratio 0.95–1.2) [113,115]. In rural areas a lower incidence of PD has been reported [116].



## Modifiable risk and protective factors

It is now largely accepted that most cases of neurodegenerative diseases are caused by the interaction between genetic and environmental factors that may have a beneficial or detrimental effect over the whole lifetime (Figure 1.2). The principal modifiable risk and protective factors for neurodegenerative diseases are discussed in the following sections and summarized in Table 1.2.

### Cigarette-smoking

Smoking is one of the most extensively studied lifestyle exposures in relation to neurodegenerative diseases. Numerous analytical studies have found a significantly increased risk of AD associated with cigarette-smoking, especially in *apoE4* allele non-carriers [117,118]. Meta-analyses concluded that current smoking was

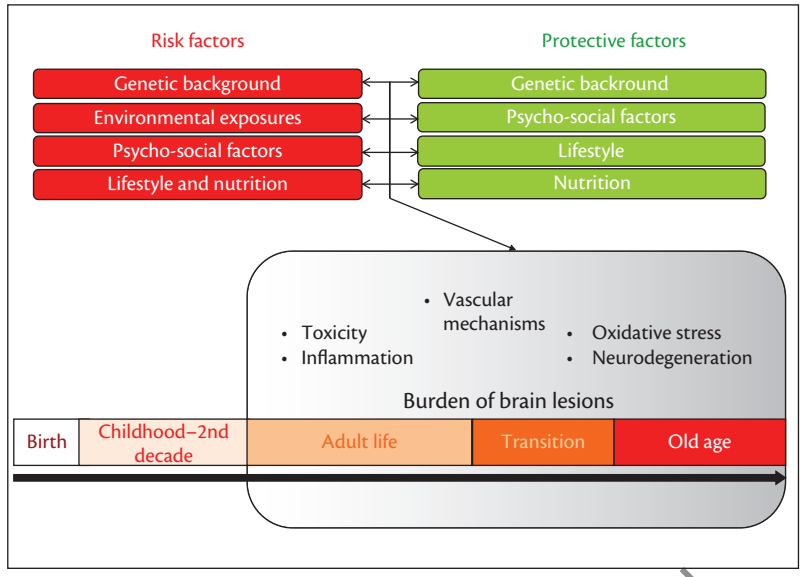


**Fig. 1.2** Multiple interactions in the process of neurodegeneration over life course.



associated with an increased risk of the development of AD, with RR = 1.79 [119,120]. The majority of case–control studies and all the prospective studies reported an inverse relationship of smoking with PD, without gender differences. In the large cohort studies, RRs for PD in current smokers versus never smokers ranged between 0.27 and 0.56; and in past smokers versus never smokers it was between 0.50 and 0.78 [121–123]. The inverse association persisted when possible confounders such as coffee and alcohol consumption were adjusted for. A significant inverse dose–response relationship was detected in all prospective studies except one [124]. The largest cohort study also showed that longer duration of smoking is needed for a risk reduction [123]. In men, an inverse association was observed for cigar or pipe smoking (OR 0.46) [125]. There is some evidence that smoking may also delay onset of PD. Two retrospective case series studies reported that PD patients who smoked had later onset of disease compared to never smokers [126,127]. Despite the amount of evidences, it is still debated whether the protective effect of smoking on PD could be in part explained by various biases (information bias, selection bias, reverse causation, confounding factors). Nevertheless different forms of information and selection bias as well as reverse causation are all unlikely in a prospective design and confounding by genetic factors has been adequately addressed in family-based designs [128,129]. Furthermore, experimental studies have indicated a link between primarily nicotine and α-synuclein [130]. The relationship seems to be less strong for ALS. A meta-analysis does not support an overall strong association of smoking with ALS risk but suggests that smoking might be associated with a higher risk of ALS in women [131]. Also in a large population-based study in the UK, smoking was associated with ALS risk and worse survival in women but not in men [132]. A pooled analysis of five prospective cohorts supports the hypothesis that cigarette-smoking increases the risk of ALS and that the risk increases as age at smoking initiation decreases [133]. Another population-based study in Netherlands found that current smoking is associated with an increased risk of ALS, as well as a worse prognosis [134].

## Alcohol

Middle-aged heavy drinkers, especially *apoE4* allele carriers, were found to have a more than threefold higher risk of dementia and AD later in their lives [135]. On the other hand, a recent review of the literature confirmed the protective effect of light to moderate alcohol consumption on incident overall dementia and AD, in particular in the absence of the AD-associated *apoE4* allele and where wine is the beverage [136]. In the Nurses Health Study [137], a cohort study of 120 000 nurses in the USA, moderate drinkers (those who consumed <15.0 g of alcohol per day, i.e. about one drink) had better mean cognitive scores than non-drinkers. Among moderate drinkers, as compared with non-drinkers, the relative risk of cognitive impairment was almost 25% less on test of general cognition and 20% less on global cognitive score based on combination of the results of all tests investigating each cognitive domain. It is possible therefore that one drink per day (wine or beer) does not impair cognitive function and may actually decrease the risk of cognitive decline. In the ILSA (Italian Longitudinal Study on Aging), a population-based study surveying about 5000 subjects, among those with mild cognitive impairment those who consumed less than one drink per day had a lower rate of progression to dementia than abstainers (85% less) [138].

It is possible that a weak inverse association between alcohol and PD exists given that several studies reported relative risk estimates below unity, but few estimates were statistically significant [128,139,140]. Only a few studies examined the effects of different types of beverages, but some results indicate that the effect may be stronger for beer than for wine or liquor [141–143]. The results of a recent, large, prospective study do not support an association between alcohol intake and risk of PD) [144].

The association between alcohol consumption and ALS is not clear.

## Coffee and tea

Several case–control and prospective studies reported an inverse association of PD with coffee or total amount of caffeine intake [129,139,142,145–147]; a few also reported a dose–response

**Table 1.2** Principal modifiable risk and protective factors for neurodegenerative diseases

| | AD | ALS | PD |
|---|---|---|---|
| Cigarette smoking | RF | RF | PF |
| Light to moderate alcohol consumption | PF | CR | CR |
| Coffee | NA | PF | PF |
| Tea | NS | NS | PF |
| Vascular factors | | | |
| Homocysteine | CR | RF | RF |
| Metabolic syndrome | RF | NS | NS |
| Midlife central obesity | RF | PF | CR |
| Late-life weight loss | RF | RF | NS |
| Diabetes and impaired glucose regulation | RF | NS | NA |
| Insulin abnormalities | RF | NS | NS |
| Midlife increased blood pressure | RF | NS | CR |
| Late-life low blood pressure | RF | NS | NS |
| Mediterranean diet | PF | NS | PF |
| Heavy metals | | | |
| Aluminium | CR | NS | NS |
| Zinc | CR | NS | CR |
| Copper | RF | NS | CR |
| Iron | RF | NS | RF |
| Lead | CR | CR | CR |
| Mercury | CR | CR | RF |
| Manganese | NS | CR | CR |
| Pesticides | RF | CR | RF |
| Electromagnetic fields | RF | RF | RF |
| Physical activity | PF | CR | NA |
| Head injury | CR | CR | NA |
| Viral infections | RF | RF | CR |
| Neuroleptics | NS | NS | RF |
| Cyanobacteria | NS | RF | NS |

AD, Alzheimer's disease; ALS. amyotrophic lateral sclerosis; CR, conflicting results; NA, no association; NS, not studied; PD, Parkinson's disease; PF, protective factor; RF, risk factor.



relationship [139,141], although others found no such association [140,148]. This inverse association seems to be gender-specific with the protective effect of coffee more evident in males than in females [149,150]. Recent results from a large, prospective study of men and women are consistent with a protective effect of caffeine intake on PD incidence [151]. A possible preventive role has also been hypothesized for coffee in ALS [152]. A large population-based study demonstrated that there were no significant associations between coffee or caffeine intake and risk of cognitive impairment, overall dementia, AD, and VaD [153]. Results regarding tea intake are still conflicting, with some studies reporting an inverse association [146,149,154], some reporting no association [148,155], and others an increase in risk [156]. One study explored the effects of different varieties of tea (black vs green) and displayed a decreased risk of PD with black tea consumption [157].

## Metabolism and diet

Plasma homocysteine (Hcy) has been shown to be directly related to Aβ-40 levels, while the association with Aβ-42 was not significant, suggesting that Hcy is related to ageing but not specifically to AD, but it could interact to affect AD risk and cognition in PD [158]. Elevated Hcy is a risk factor for cardiovascular disease but its relation with AD risk is unknown. To date a causal relationship between a high Hcy level and risk of developing dementia is not supported [159].

Plasma Hcy levels were found elevated in patients with ALS, in particular with fast disease progression [160,161], and in patients with PD, in particular in levodopa-treated patients [162].

Over the last two decades, the role of *metabolic syndrome* (MetS) and MetS components (impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridaemia, and reduced high-density lipoprotein cholesterol) in the development of cognitive decline and dementia, either from vascular or degenerative origin, has emerged, so the definition of a 'metabolic cognitive syndrome' (MCS) has been proposed [163]. Several population and clinical studies suggested that the presence of MetS increases the risk of developing age-related cognitive decline, mild cognitive impairment (MCI), AD, and VaD [164–166], and the risk of progression from MCI to dementia [166]. Furthermore, individual components of MetS have been linked to the risk of developing cognitive decline and dementia. *Midlife overweight or obesity* (measured by body mass index (BMI)) and *midlife central obesity* (measured by waist circumference) have been related to an increased risk of cognitive decline [167,168], as well as *late-life underweight and weight loss* [169,170]. Epidemiological studies and clinical observations have disclosed an association between *diabetes mellitus* and increased risk of cognitive impairment and dementia [171]. Also *borderline diabetes* and *impaired glucose regulation* have been found to increase the risk of developing cognitive decline [172,173]. In the Nurses Health Study women with type 2 diabetes showed increased odds of poor cognitive function and substantial cognitive decline. Interestingly the use of oral hypoglycaemic therapy, however, may ameliorate risk [174]. From some longitudinal studies, an association between *insulin abnormalities* and dementia has also been reported [175,176]. A study conducted in a multiethnic elderly cohort showed that MetS was not associated with an increased dementia risk, but two of its components (diabetes and hyperinsulinaemia) were) [177]. *Increased blood pressure in middle age*, especially if uncontrolled, was associated with a higher risk of the later development of AD [178,179]. On the other hand, analytical studies suggested that *low blood pressure in late age* may contribute to the development of dementia including AD [180,181].

ALS is associated with several defects in energy metabolism, including weight loss, hypermetabolism, and hyperlipidaemia [182]. A beneficial *vascular risk profile* (low BMI, low use of cholesterol-lowering agents, low LDL/HDL ratio, low homocysteine levels) was reported to be associated with ALS, supporting the hypothesis that a higher metabolic rate plays a role in ALS [183]. A recent European population-based study showed that increased prediagnostic *body fat* is associated with a decreased risk of ALS mortality [184]. Epidemiological evidence does not support a strong relationship between *adiposity* and PD risk, even though studies are few and the results conflicting. A large prospective study reported that higher waist circumference and waist to hip ratio were associated to increased risk of PD [185]. A large Finnish cohort study reported increased risk of PD with increasing BMI, controlling for a large number of possible confounders [186]. Another prospected study showed no association [187].

*Nutrition* may play a protective role in AD onset. Consumption of one meal per week of *fish rich in omega-3 fatty acids* reduced the risk of developing AD by 60% in the Chicago Health and Aging Project [188]. *Mediterranean diet*, a diet characterized by a high intake of plant foods and fish (with olive oil as the primary source of monounsaturated fat), a moderate intake of wine, and a low intake of red meat and poultry, has been found to reduce the risk of AD, the progression from MCI to AD, all-cause mortality in AD patients, and PD [189–192]. A *diet poor in antioxidants* (green-yellow vegetables, fruit, and carotenoids) is associated with an increased risk of ALS [193,194]. Nutritional epidemiological studies in PD have focused on groups of food items or macronutrients (such as protein, fat, and carbohydrates). Available evidences support a role for *dairy products* in PD, especially in men: a meta-analysis of all prospective studies on dairy products yielded a RR of 1.8 in men and 1.3 in women [195]. An increased risk of PD was also recently described with *milk intake* [196]. Lower risk of PD has been associated with intake of *meat products* [197–199], fish [200], and *fruits and vegetables, especially peas* [193,201]. Lower risk of PD was observed for higher intake of cholesterol [202], total fat and unsaturated fat [203], monounsaturated fat [157], and polyunsaturated fat [196], especially in men. High intake of calories and saturated fat was associated with an increased risk of PD [204]. Dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry and a low intake of saturated fat and a moderate intake of alcohol may protect against PD [205]. Although data from cohort studies suggest that diabetes is a risk factor for PD, there is no conclusive evidence on this association [206].

## Workplace exposures (occupations)

Certain occupations and workplace exposures may be associated with increased risk of ALS. A case–control study in New England showed a higher risk of ALS for construction workers excluding supervisors (OR = 2.9) and precision metal workers (OR = 3.5). A 60–90% increased risk related to self-reported exposures to paint strippers; cutting, cooling, or lubricating oils; antifreeze or coolants; mineral or white spirits; dry cleaning agents; other chemical agents (aliphatic chlorinated hydrocarbons, glycols, glycol ethers, and hexane). Relative risks associated with these workplace exposures and chemicals were greater among non-smokers [207]. Several studies investigated possible associations between a broad range of occupations and PD. An excess risk has been reported among carpenters and cleaners [198], forestry, logging, mining or oil field workers, teachers, medical, social science or legal workers [208], railway and transport workers [209], painters and decorators, woodworkers, or assistant nurses [210], while a decreased risk has been described for construction workers [211]. However, the results overall are not consistent, especially for methodological limitations including use of hospital-based samples and lack of adjustment for possible confounders, such as smoking and education.

## Heavy metals

Different metals have been linked to an increased risk of developing AD. Research data have not always supported the association between *aluminium* and AD [212]. A systemic review of epidemiological reports found that 68% established a link, 23.5% were inconclusive, and 8.5% did not establish a relationship [213]. There have also been several studies linking *zinc* to AD, but the role is controversial. Some reports have found an increase in levels of zinc in human brain of AD patients [214]. Zinc overload also exacerbates Aβ deposition in transgenic mouse models [215]. Also

elevated levels of *copper* and *iron* in the brain have been linked to the development or progression of AD [216,217]. Developmental *lead* exposure has also been implicated. Lead exposure is a significant risk factor for accelerated declines in cognition [218,219]. Lead-exposed primates had increased amyloidogenesis, senile plaque deposition, and upregulation of key proteins in the amyloid processing pathway, such as APP and beta-site APP-cleaving enzyme 1 (BACE1) [220]. Exposure to *lead, selenium,* and *mercury* seems to be associated with a slight increased risk of ALS [221–224]. However, inconsistent results have been reported between the concentration in tissue and cerebrospinal fluid (CSF) and their correlation with the risk of developing ALS. Some authors reported a neuroprotective effect of lead in ALS [225]. There is no convincing epidemiological evidence that exposure to specific metals causes PD, even though an increase in risk of PD has been related to *manganese* [226,227], *lead* [226,228,229], *mercury* [230], *iron* [231–233], and *copper* [226,234] exposures. However, most studies were small and prospective data are lacking for most metals. A recent meta-analysis showed that welding and manganese exposure are not associated with increased PD risk [235].

## Chemical agents and pesticides

A French cohort study on older people linked occupational exposure to pesticides to an increased risk of developing AD in men [236]. Other studies found increased and statistically significant associations between pesticide exposure and AD, especially with defoliants and fumigants [237] and organophosphates [238]. Pesticide exposure and especially organophosphates gained prominence in their association with ALS following the observation that Gulf War veterans presented an increased incidence of ALS [239,240]. Organophosphates have been investigated as a potential risk factor in development of ALS, with conflicting results, and an increased risk related to defects in detoxifying enzymes [241,242]. A large prospective study of chemical exposures and ALS did not uncover any evidence for an association with exposure to pesticides/herbicides; however, there was an increased risk of ALS with formaldehyde exposure [243]. A recent meta-analysis supports the relationship of exposure to pesticides and development of ALS among male cases compared to controls [244]. A meta-analysis of 19 case–control studies published between 1989 and 1999 reported a pooled risk of PD related to exposure to pesticides overall at 1.94 (95% CI 1.49–2.53), with no dose–response relationship [245]. In the largest prospective study investigating the role of pesticides in PD, exposure to pesticides in general or herbicides was associated with increased risk of PD with a RR of 1.7 but with no dose–response relationship [246]. A review of 39 case–control studies, 4 cohort studies, and 3 cross-sectional studies affirms the evidence that exposure to herbicides and insecticides increases the risk of PD [247]. Among a growing number of studies on the effects of exposure to specific pesticides ($n = 20$), an increased PD risk has been associated with insecticides, especially chlorpyrifos and organochlorines, in six studies (OR 1.8–4.4), and with the herbicide paraquat, the fungicide maneb, or the combination of both [248].

## Electromagnetic fields

A meta-analysis of 14 different case–control and cohort studies suggested an association between occupational exposure to electromagnetic fields and AD [249], but with indication of publication bias and a large statistical heterogeneity between the study results. A recent meta-analysis suggested a slight but significant ALS risk increase related to high levels of job exposure to extremely low-frequency electromagnetic fields [250]. Increased risk of PD mortality was observed for having an electrical occupation versus not having an electrical occupation (OR 1.55, 95% CI 0.98–2.45) and for definite or probable magnetic field exposure versus no magnetic field exposure according to the combination of occupation and industry codes (OR 1.76, 95% CI 1.17–2.65) [251].

## Physical activity

Physical activity in the form of various leisure activities rather than sports or specific physical exercise, even low-intensity physical activity such as walking, led to a decrease in the risk of dementia and AD [252,253]. This reduction in risk is more evident in case of regular physical activity in middle age and in persons with the *apoE4* allele [254]. General physical activity during work or free time does not seem to be associated with an increased risk of ALS [255,256]. Football (soccer) is frequently associated with ALS. Wicks et al. reported three cases of soccer players who developed the disease simultaneously [257]. Chiò et al reported a high risk of ALS among Italian football players [258], and subsequently showed that the risk might be soccer specific and significantly increased for midfielders but not for other positions [259]. A revision of literature on physical activity in ALS concluded that evidence from epidemiological research remains conflicting and inconclusive [260]. However, a recent well-designed epidemiological study on a large cohort of Swedish males found that the risk of developing ALS was related to a higher weight-adjusted physical fitness during young adult life, stressing the concept that a common body phenotype could underlie both fitness and ALS [261]. Finally, a large population-based study found an increased risk of ALS with higher levels of leisure-time physical activity, but not with occupational physical activity and the absence of a dose–response relationship, strengthening the hypothesis that not increased physical activity per se but rather a genetic profile or lifestyle promoting physical fitness increases ALS susceptibility [262]. Relatively few case–control studies examined the relationship between physical activity and PD. Several suggest that vigorous physical activity may lower the risk [263,264]. However, the association is probably weak or absent [265,266].

## Head injury

The relation between head injury and the risk of AD remains inconclusive. A meta-analysis of 15 case–control studies indicated an excess history of head injury in patients with AD (OR 1.58, 95% CI 1.21 to 2.06), but when the authors stratified by sex, they found an increased OR only in men (OR 2.26; 95% CI 1.13 to 4.53) [267]. A recent case–control study done in a large European population concluded that antecedent trauma, repeated trauma, and severe trauma may be risk factors for ALS [268]. However, a literature review of 14 studies concluded that there is no certainty that a single instance of head trauma is a risk factor for ALS [269]. A latest Swedish population-based study has shown there was an association of ALS risk with severe head injury 1 year before diagnosis (OR: 3.9) but not for severe head injury more than 3 years before ALS diagnosis, nor was ALS associated with subtypes of head

injury or repeated injuries occurring more than 3 years before diagnosis [270]. An increased frequency of hospital contacts for a head injury during the months preceding a first diagnosis of PD, but not during the 10 years before, has been described [271], suggesting that it could be a consequence of the disease rather than its cause. A recent nested case–control study on a Swedish population confirmed the non-causal relationship between head injuries and PD [272].

### Viral infections and drugs

Persistent viral infections were indicated as a predisposing factor for the development of ALS [273]. Persistent enterovirus infection has been reported as causing sporadic ALS, given the tropism of the poliovirus by motor neurons [274]. Some retroviruses were also described in association with ALS-like syndromes, since motor neuron syndromes may be associated with HIV and HTLV-1 retrovirus subtypes [275]. Conclusive evidence regarding the possible relation between viral infections and PD is lacking. Because influenza A virus may affect brain regions implicated in PD (including the substantia nigra) [276], it has been hypothesized to play a role in PD [277]. A recent study has provided preliminary evidence for an association between central nervous system (CNS) infections and a higher future risk of PD [278]. Another study showed that PD was significantly related to mumps, scarlet fever, influenza, whooping cough, and herpes simplex infections [279]. In a recent European elderly cohort study, the risk of probable PD was increased by 3.2-fold after exposure to neuroleptics [280].

### Cyanobacteria

Recent evidence has strengthened the theory that chronic environmental exposure to the neurotoxic amino acid β-*N*-methylamino-L-alanine (BMAA) produced by cyanobacteria may be an environmental risk factor for ALS, given the high rate of ALS on Guam [281].

## Prevention

Clinical cohort studies suggest that there may be very subtle cognitive alterations that are detectable years before meeting criteria for MCI or AD dementia [282] and data from normal ageing individuals identified presence of AD pathology related to the Aβ cascade, also in asymptomatic older people [283,284], suggesting that AD may be characterized by a long preclinical phase. The new factors in the risk assessment of AD are biomarkers: amyloid deposition evaluated by amyloid positron emission tomography (PET) imaging and/or a reduction in levels of Aβ42 in the CSF, and neurodegeneration demonstrated by CSF and functional and structural imaging (e.g. tau of CSF, FDG-PET, and structural MRI) [285]. Autosomal dominant AD is associated with a series of pathophysiological changes over decades in CSF biochemical markers of AD, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment. Change in Aβ happens more than 20 years before disease onset [286]. The relative weight of these risk factors is still unknown, but at least 33% of cognitively normal persons over age 65 are 'biomarker positive' and at increased risk of developing AD, so that a new diagnostic category of 'preclinical AD' has been proposed by a National Institute on Aging (NIA) task force for such individuals [287]. Considering not modifiable (age, gender, education, family history, *ApoE4*+, autosomal dominant mutation carrier) and modifiable risk factors (systolic blood pressure, BMI, total cholesterol level in blood, level of physical activity), and biomarker positivity, a gradation of risk for AD in asymptomatic persons has been proposed [288]. This could be a good starting point to develop and actuate prevention strategies. The current lifetime risk of AD dementia for a 65-year-old is estimated to be 10.5%. Recent statistical models suggest that a screening instrument for markers of the pathophysiological process of AD (with 90% sensitivity and specificity) and a treatment that slows down progression by 50% would reduce that risk to 5.7% [287]. There is sufficient epidemiological evidence to implement large intervention studies to prevent/delay dementia onset [289]. A score to identify high-risk individuals have been proposed based on 12 factors [290]. The CAIDE Dementia Risk Score has been used in a Finnish cohort for a trial for prevention of dementia involving 1200 participants aged 60–77 years [291] testing the effects of a 2-year multidomain intervention targeting several risk factors simultaneously. The prevention of AD require large investment of time and money, but the return on investment may be huge, considering the projections of costs for patients with dementia in the near future.

As exemplified by rapid eye movement sleep behavior disorder (RBD) and olfactory symptoms, there is growing evidence for a long preclinical period also in PD, before the motor manifestations. Better characterization of the premotor phase with respect to its duration and associated features is extremely important. Although both genetic and environmental risk factors in PD have been documented, there is very limited information on gene–environment interactions and the real role of environmental factors has not been well characterized. In a 2012 meta-analysis [292] the risk factors associated with later PD diagnosis were family history of PD or tremor, a history of constipation, and lack of smoking history. The family history (presence of PD in first or second-degree relatives) was the strongest risk factor for PD (relative risk of around 4), indicating the key role of genetic determinants or of environmental risk factors early in life. Hence, based on present knowledge, our hopes of preventing PD through primary intervention in the foreseeable future are not high.

Prevention in ALS is even more difficult due to the lack of a premorbid phenotype and the difficulty in identifying people who are at higher risk for developing disease. Furthermore, whether ALS is characterized by a presymptomatic period, like AD, PD, and Huntington's disease, and if so how long this period lasts, is unclear. Definitively answering this question is likely to have profound implications for understanding disease biology, uncovering environmental risk factors, developing effective therapies, and even primary prevention strategies. These answers might probably derive from longitudinal cohort studies on presymptomatic gene mutation carriers. A robust framework for this process has recently been established [293].

To sum up, due to the lack of disease-modifying therapies for neurodegenerative disease, the identification of possible prevention strategies aiming to interfere with modifiable risk factors is key. Prevention should reduce the risk of evolving from normal ageing to preclinical phase of a neurodegenerative disorder (primary prevention) and from the preclinical phase to the clinical manifestation of the disease (secondary prevention). (Figure 1.3). The prevention strategy is probably happening mainly in the area of dementias.

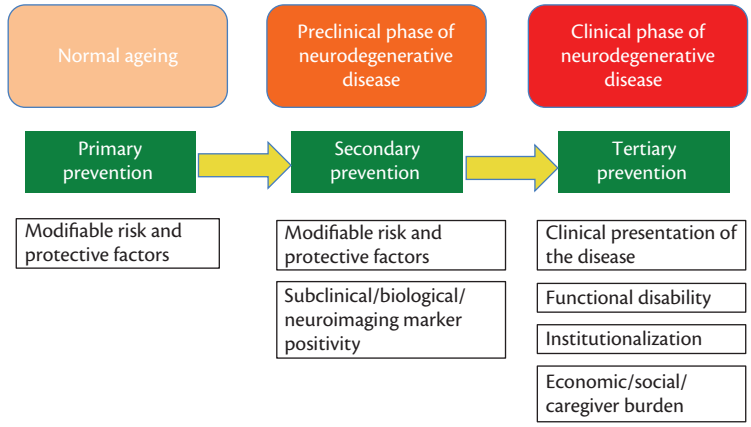


**Fig. 1.3** Prevention of neurodegenerative diseases.

## New challenges in the epidemiology of neurodegenerative diseases

### Epidemiology of the oldest old

The oldest old (85+) are the fastest growing segment of the population in western Europe and the USA. This segment of the population will increase by 30–40% in the next decade and became five time larger in the next five decades. The major consequence is the change of distribution of all conditions characterized by cognitive impairment with an increasing proportion being in the segment of the oldest old. The largest number of cases of dementia will be in this segment of the population in the 2050s. This group is characterized by high comorbidity and frailty. The functional status impact on cognitive status in this age group may be different. Finally, the norm and the definition of cognitive impairment and dementia in these groups should be probably redefined [294]. Risk factors and protective factors for dementia are different in this group. In a population-based study with 5-year follow-up, depression at the baseline was associated with a higher risk of dementia (OR = 2.91) while more social contact and a higher mini-mental state examination score at baseline were associated with lower risk of incident dementia [295].

These demographic changes are probably making an impact also on the epidemiology of rare conditions like ALS. In the survey conducted in Europe by the EURALS group there were only three patients over 90 years of age [70]. Applying time trends from mortality studies in the USA and Europe [296,297] we can expect a lot of cases also in this segment also.

### Underdiagnosis

In surveys of neurological diseases the reported figures are based on diagnosed cases. The only alternative is active search, which is possible in active surveys in population-based setting only for common diseases such as AD and PD. This approach indicates that even in countries with high-quality heath services like the Netherlands, PD is often not diagnosed (40%) [105]. The success of descriptive studies for rare diseases such as ALS is based on the ability to collect for referral all cases diagnosed in the medical facilities in the geographical region of interest. This omits undiagnosed subjects. Women, disadvantaged ethnic groups, and people over 70 are less likely to have access to diagnosis and care in ALS [298], and probably in all neurodegenerative diseases.

### Time trends

Studying change of patterns in neurodegenerative diseases may give important clues to disease aetiology. The identification of time trends and the presence of different trends in different groups of subjects may help to identify areas for intervention for subjects in categories with higher risk of disease or prevention, especially if modifiable risk factors are identified.

Recent data have shown a change in trends in the last few decades in neurodegenerative diseases, and how changes in risk factors may be responsible for these findings. A recent community survey in three US states conducted at the Mayo Clinic showed a decline of AD incidence in the last 20 years. Similarly, in the Rotterdam Study the incidence of dementia in 2005 was lower than the incidence in 1990. Better control of vascular risk factors and vascular diseases like hypertension has been hypothesized as responsible for the decline in AD incidence.

Time trends are more difficult to study in rare diseases like ALS than in a common disease like AD, for lack of data collected in the same source population for a sufficient time period (at least one decade). ALS prevalence and incidence is generally higher in more recent studies compared to studies conducted before the 1990s. In a recent meta-analysis a clear trend between rate of prevalence and incidence and year of study publication has been shown [299]. In particular the incidence and prevalence rate were higher for studies conducted after the publication of the El Escorial Criteria in 1994 [300]. These two examples indicate that change in time trends may be determined by different factors.

## Conclusions

Recent epidemiological research has contributed substantially to implement strategies to reduce the risk of AD and to better management of the AD clinical course. The reduction of vascular risk factors, more physical exercise, and healthy diet may reduce the risk of AD. Individuals with high risk for AD may be identified. No such conclusions may be drawn for PD or ALS. Based on results of observational studies some clinical trials in AD have been conducted with disappointing results, (oestrogen replacements, non-steroidal anti-inflammatory medications).

The contrast between observational studies and clinical trials has been confirmed in neurodegenerative diseases. However, the role of observational studies in addressing biological questions on the whole life course remains unique.

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