Education and dementing disorders. The role of schooling in dementia and cognitive impairment

av

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Abstract

This doctoral thesis aimed to investigate the complex relationship between education, dementias, and cognitive impairment. Two different databases were used: the Faenza and the AIDS Projects. The *Faenza Project* is a longitudinal study on ageing and dementia, targeting 7,930 inhabitants of Faenza (including the village of Granarolo), Italy, aged 61 years and older in 1991. The study population derives from an area which has been one of the wealthiest in Italy since the beginning of the 1950s, but with a high percentage of noneducated subjects. Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised diagnostic criteria were used for the clinical diagnosis of dementia, while a person was classified as affected by cognitive impairment, no dementia if he/she scored two or more standard deviations lower than the mean score of the corrected Mini-Mental State Examination calculated among the nondemented people. The *AIDS Project* is a longitudinal study on HIV-1-related cognitive impairment. The study sample included 282 consecutive subjects examined at the Division of Infectious Diseases, University of Bologna, Italy. HIV cognitive impairment was defined as poor performance on at least two of the seven neuropsychological tests included in the neuropsychological battery. Poor performance in a test was considered as a score of two or more standard deviations lower than the mean of the seronegative group in the corresponding risk behavior strata (injecting drug users, hemophiliacs, and other risk behaviors). Data were analyzed with logistic regression models. The major findings from the five research papers included in this thesis are summarized below.

**Study I.** In the subpopulation of Granarolo, the relationship between Alzheimer's disease (AD) and other dementias with education was examined. Having no education was associated with dementia independent of all other putative risk factors (OR 4.7; 95% CI=2.3-9.6). This association was stronger among younger old persons, and decreased with increasing age. Similar findings were found for AD and Vascular dementia, separately.

**Study II.** We examined the relationship between HIV-1-related cognitive impairment and education, controlling also for risk behaviors and clinical status. Low education was a strong risk factor for cognitive impairment in HIV-1-seropositive persons: adjusted OR in subjects with less than six years of education was 18.9 (95% CI=3.7-97.6), and 1.3 (95% CI=0.5-3.2) in subjects with five to eight years of education, when compared to subjects with nine+ years of schooling.

**Study III.** The effect of education on both cognitive impairment and dementia was investigated in the Faenza cohort. Very low education was a major determinant of both dementia and cognitive impairment. No education was associated with an increased risk of both CIND (OR 16.7; 95% CI=11.2-25.0) and dementia (OR 10.9; 95% CI=7.0-16.7) with a dose-response relationship.

**Study IV.** We found that stroke does not completely explain the association between low education and dementia or cognitive impairment. The effect of stroke on dementia was stronger among the higher educated subjects (four+ years of schooling, RR 6.5; 95% CI=4.9-8.2) as well as among the younger old. These findings support the hypothesis that having a stroke nullifies the beneficial effect of high education and younger age against dementia and cognitive impairment.

**Study V.** Low education and low occupation-based socioeconomic status (SES) were both independent risk factors for dementia and cognitive impairment. Subjects with low education and low SES had the highest risk of dementia (OR 5.1, 95% CI=3.5-7.3) and cognitive impairment (OR 5.2; 95% CI=3.6-7.6). These findings suggest that low occupation-based SES is not a mediator for the association between low education and dementia or cognitive impairment.

**In summary,** mental activity stimulated by education during childhood, could be a possible mechanism explaining how high education protects against cognitive decline and dementia. The cognitive reserve hypothesis could provide the biological plausibility for this theory. The additive dementia risk observed in subjects with both low education and low SES implies that exposure acting at adult life might increase the risk due to education related exposure in childhood. However, the protective effect of high SES during adult life might balance the risk given by a low education.

**Keywords:** education, cognitive impairment, MCI, dementia, Alzheimer's disease, socioeconomic status, risk factors, cognitive reserve, prevalence, stroke, occupation

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EDUCATION AND DEMENTING DISORDERS. THE ROLE OF SCHOOLING IN DEMENTIA AND COGNITIVE IMPAIRMENT

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EDUCATION AND DEMENTING DISORDERS.
THE ROLE OF SCHOOLING IN DEMENTIA
AND COGNITIVE IMPAIRMENT

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ABSTRACT

This doctoral thesis aimed to investigate the complex relationship between education, dementias, and cognitive impairment. Two different databases were used: the Faenza and the AIDS Projects. The Faenza Project is a longitudinal study on ageing and dementia, targeting 7,930 inhabitants of Faenza (including the village of Granarolo), Italy, aged 61 years and older in 1991. The study population derives from an area which has been one of the wealthiest in Italy since the beginning of the 1950s, but with a high percentage of noneducated subjects. Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised diagnostic criteria were used for the clinical diagnosis of dementia, while a person was classified as affected by cognitive impairment, no dementia if he/she scored two or more standard deviations lower than the mean score of the corrected Mini-Mental State Examination calculated among the nondemented people. The AIDS Project is a longitudinal study on HIV-1-related cognitive impairment. The study sample included 282 consecutive subjects examined at the Division of Infectious Diseases, University of Bologna, Italy. HIV cognitive impairment was defined as poor performance on at least two of the seven neuropsychological tests included in the neuropsychological battery. Poor performance in a test was considered as a score of two or more standard deviations lower than the mean of the seronegative group in the corresponding risk behavior strata (injecting drug users, hemophiliacs, and other risk behaviors). Data were analyzed with logistic regression models. The major findings from the five research papers included in this thesis are summarized below.

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Study III. The effect of education on both cognitive impairment and dementia was investigated in the Faenza cohort. Very low education was a major determinant of both dementia and cognitive impairment. No education was associated with an increased risk of both CIND (OR 16.7; 95% CI=11.2-25.0) and dementia (OR 10.9; 95% CI=7.0-16.7) with a dose-response relationship.

Study IV. We found that stroke does not completely explain the association between low education and dementia or cognitive impairment. The effect of stroke on dementia was stronger among the higher educated subjects (four+ years of schooling) RR 6.5; 95% CI=4.9-8.2) as well as among the younger old. These findings support the hypothesis that having a stroke nullifies the beneficial effect of high education and younger age against dementia and cognitive impairment.

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In summary, mental activity stimulated by education during childhood, could be a possible mechanism explaining how high education protects against cognitive decline and dementia. The cognitive reserve hypothesis could provide the biological plausibility for this theory. The additive dementia risk observed in subjects with both low education and low SES implies that exposure acting at adult life might increase the risk due to education related exposure in childhood. However, the protective effect of high SES during adult life might balance the risk given by a low education.

Keywords: education, cognitive impairment, MCI, dementia, Alzheimer’s disease, socioeconomic status, risk factors, cognitive reserve, prevalence, stroke, occupation
Abstract

Swedish


Studie I. I subpopulationen i Granarolo studerades förhållandet mellan utbildning och Alzheimers sjukdom (AS) och andra demenssjukdomar. Att inte ha någon utbildning alls hade ett samband med demens oberoende av alla andra förmodade riskfaktorer (OR 4.7; 95% CI 2.3-9.6). Detta samband var starkare hos yngre äldre personer och minskade med ökad ålder. Resultaten var liknande för både AS och vaskulär demens.

Studie II. Vi undersökte sambandet mellan HIV-1-relaterad kognitiv nedsättning och utbildning genom att också kontrollera för riskbeteende och klinisk status. Låg utbildning är en stark riskfaktor för kognitiv nedsättning för HIV-1-serumpositiva personer: justerat OR för personer med mindre än sex års utbildning var 18.9 (95% CI=3.7-97.6) och 1.3 (95% CI=0.5-3.2) för personer med fem till åtta års utbildning, jämfört med personer med över 8 års utbildning.

Studie III. I kohorten från Faenza studerades effekten av utbildning på kognitiv nedsättning och demens. Mycket låg utbildning är en av de främsta avgörande faktorerna för både demens och kognitiv nedsättning. Vi fann ett samband mellan analphabetism och en ökad risk för både CIND (OR=16.7; 95% CI=11.2-25.0) och demens (OR=10.9; 95% CI=7.0-16.7) och detta samband var dosrelaterat.

Studie IV. Vi fann att stroke inte helt kan förklara sambandet mellan låg utbildning och demens eller kognitiv nedsättning. Effekten av stroke på demens är starkare bland personer med högre utbildning (4+ års utbildning, RR=6.5; 95% CI=4.9-8.2) såväl som bland de yngre äldre. Dessa fand stödjer hypotesen att en stroke störst av stabilitet i kognitiva effekten av hög utbildning och yngre ålder avseende demens och kognitiv nedsättning.

Studie V. Både låg utbildning och låg yrkesbaserad SES är oberoende riskfaktorer för demens och kognitiv nedsättning. Personer med låg utbildning och låg SES hade den högsta risken att få demens (OR=5.1, 95% CI=3.5-7.3) och kognitiv nedsättning (OR=5.2, 95% CI=3.6-7.6). Dessa fand tyder på att låg yrkesbaserad SES inte är en förmedlare av sambandet mellan låg utbildning och demens eller kognitiv nedsättning.

Sammanfattningssvis, den mentala aktivitet som stimulerats av utbildning i barndomen kan vara den mekanism som förklarar hur hög utbildning kan skydda mot kognitiv nedsättning och demens. Hypotesen om ”den kognitiva reserven” kan ge den biologiska sannolikheten för denna teori. Den additiva risk som observerats hos personer med både låg utbildning och låg SES antyder att exponering av vuxen ålder kan öka risken beroende på utbildningsnivån i barndomen. Emellertid kanske den skyddande effekten man får av hög SES i vuxen ålder kan balansera risken av att ha en låg utbildning.

Nyckelord: utbildning, kognitiv nedsättning, MCI, demens, Alzheimers sjukdom, SES, riskfaktorer, kognitiv reserv, prevalens, stroke, yrke
RIASSUNTO

Questa tesi di dottorato, svolta presso il Karolinska Institutet di Stoccolma, ha esaminato le possibili correlazioni fra livello di scolarizzazione, demenze e deterioramento cognitivo. Gli studi sono stati condotti nell’ambito di due progetti di ricerca: lo Studio Epidemiologico sulla Demenza di Faenza ed il Progetto AIDS. Il Progetto Faenza è uno studio longitudinale sull’invecchiamento e le demenze iniziato nel 1991, nell’ambito del quale sono stati già esaminati 7.930 abitanti di Faenza e Granarolo d’età oltre i 60 anni. La popolazione indagata vive in un’area economicamente ricca, almeno fin dai primi anni ’50, ma caratterizzata da un basso livello di scolarizzazione. La diagnosi di demenza ha seguito i criteri del Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised, mentre la diagnosi di Compromissione cognitiva si è basata su un punteggio al Mini-Mental State Examination inferiore di due o più deviazioni standard rispetto alla media corretta per età e scolarità, calcolata sui non dementi. Il Progetto AIDS è uno studio longitudinale sui deficit cognitivi associati all’infezione da HIV-1. 282 soggetti sono stati esaminati presso il Dipartimento di Malattie Infettive dell’Università di Bologna. Il deficit cognitivo da HIV è stato definito come una performance inferiore alla media di due deviazioni standard in almeno due di sette test cognitivi. La media di riferimento ai test cognitivi era quella fornita da un gruppo di sieronegativi. Il confronto è stato effettuato fra sieropositivi e sieronegativi appartenenti allo stesso comportamento a rischio (eroinomani, emofilaci, e altri comportamenti a rischio). I dati sono stati analizzati usando la regressione logistica. I principali risultati dei cinque studi presentati in questa tesi sono di seguito riassunti:

**Studio I.** Le correlazioni fra scolarizzazione, Morbo di Alzheimer (AD) e altre demenze sono state studiate negli abitanti anziani di Granarolo. L’assenza di scolarizzazione comporta un rischio maggiore di demenza, anche dopo la verifica di tutti gli altri possibili fattori di rischio (OR=4.7, 95% CI=2.3-9.6). Il rischio legato all’assenza di scolarizzazione è più elevato nei più giovani fra gli anziani, e diminuisce con l’aumentare dell’età. Risultati simili sono stati trovati per l’AD e la demenza vascolare.

**Studio II.** Abbiamo studiato le correlazioni fra scolarizzazione e deficit cognitivi associati all’infezione da HIV-1, verificando anche altri possibili fattori di confondimento, quali comportamenti a rischio e quadro immunologico. La bassa scolarizzazione è un importante fattore di rischio per deficit cognitivi in pazienti HIV-1 sieropositivi. L’odds ratio nelle persone con meno di sei anni di scolarità è 18.9 (95% CI=3.7-97.6), mentre è 1.3 (95% CI=0.5-3.2) in soggetti con scolarizzazione dai cinque agli otto anni.

**Studio III.** L’effetto della scolarizzazione sui deficit cognitivi e la demenza è stato studiato nell’intera popolazione anziana di Faenza. Un livello di scolarizzazione molto basso si è confermato essere uno dei maggiori fattori di rischio sia di deficit cognitivi (OR=16.7, 95%CI=11.2-25.0) che di demenza (OR=10.9, 95% CI=7.0-16.7).

**Studio IV.** L’ictus da solo non è sufficiente a spiegare l’associazione tra bassa scolarizzazione e deficit cognitivi o demenza. L’effetto dell’ictus sulla demenza è più evidente nelle persone con più elevata scolarizzazione (oltre i 4 anni, RR=6.5, 95% CI=4.9-8.2), così come è più rilevante nei più giovani degli anziani. Questi risultati indicano che l’ictus annulla i benefici derivanti da un’elevata scolarizzazione e da una relativamente giovane età nei confronti dell’insorgenza di demenza e deficit cognitivi.

**Studio V.** La bassa scolarizzazione e un modesto livello socio-economico basato sul lavoro sono entrambi fattori indipendenti di rischio per demenza e deficit cognitivi. Le persone con scarsa scolarizzazione e modesto livello socio-economico sono a maggior rischio di demenza (OR=5.1, 95% CI=3.5-7.3) e di deficit cognitivi (OR=5.2, 95% CI=3.6-7.6). Questi dati suggeriscono che il basso livello socio-economico non sia il mediatore per spiegare l’associazione esistente tra bassa scolarizzazione e demenza o deficit cognitivi.

**Riassumendo:** durante l’infanzia, l’attività mentale stimolata dalla scolarizzazione può essere la spiegazione di come l’elevata scolarità protegga dai deficit cognitivi e dalla demenza nell’età anziana. L’ipotesi della riserva cognitiva può fornire la plausibilità biologica a questa teoria. Il rischio addizionale di demenza osservato in soggetti aventi sia bassa scolarità che basso livello socio-economico implica che l’esposizione durante la vita adulta al disagio socio-economico può aumentare il rischio legato ad una scarsa scolarizzazione durante l’infanzia. Da verificare, poi, se l’effetto protettivo di un alto livello socio-economico durante la vita adulta possa bilanciare il rischio associato alla bassa scolarizzazione.

**Keywords:** scolarità, deficit cognitivi, MCI, demenza, Morbo di Alzheimer, livello socio-economico, fattori di rischio, riserva cognitiva, prevalenza, ictus, occupazione
LIST OF ORIGINAL PAPERS

This doctoral thesis is based on the following original papers, which are referred to in the text by their Roman numerals.


IV. De Ronchi D, Palmer K, Pioggiosi PP, Berardi D, Ferrari B, Dalmonte E, Fratiglioni L. The combined effect of age, education and stroke on dementia and cognitive impairment in the elderly. *(Submitted manuscript).*

V. De Ronchi D, Atti AR, Karp A, Berardi D, Dalmonte E, Fratiglioni L. Low education and low occupation-based socioeconomic status as risk factors for dementia and cognitive impairment. The Faenza Project. *(Manuscript).*

All three published articles have been reprinted with kind permission of the publishers of the respective journals: Lippincott Williams & Wilkins (Paper I), American Medical Association (Paper II), and S. Karger AG (Paper III).
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LIST OF ABBREVIATIONS

AD            Alzheimer's disease
ADC           AIDS dementia complex
AIDS          Acquired immune deficiency syndrome
APOE          Apolipoprotein E
BRC           Brain reserve capacity
CDC           Centers for Disease Control and Prevention
CI            Confidence interval
CIND          Cognitive impairment, no dementia
CNS           Central nervous system
CVD           Cerebrovascular disorder
DSM-III-R     Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV        Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GDS           Global Deterioration Scale
HAART         Highly Active Antiretroviral Therapy
HIS           Hachinski Ischemic Score
HIV           Human immunodeficiency virus
ICD-8         International Classification of Disease, Eight Revision
IDUs          Injecting drug users
IQ            Intelligence Quotient
MCI           Mild cognitive impairment
MCMD          Minor cognitive motor disorder
MMSE          Mini-Mental State Examination
NINCDS-ADRDA  National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer's Disease and Related Disorders Association
NINDS-AIREN   The National Institute for Neurological Diseases and Syndromes – Association Internationale pour la Recherche et l’Enseignement en Neurosciences
NSAID         Non-steroid anti-inflammatory drugs
OR            Odds ratio
RR            Relative risk
SD            Standard deviation
SES           Socioeconomic status
VaD           Vascular dementia
\( \epsilon 4 \)  Epsilon 4 allele
INTRODUCTION

DEMENTIA IN AN AGEING WORLD

During the past few decades, the ageing of the population has become a world-wide phenomenon, no longer confined to the western societies [1]. According to the medium variant, the world’s population aged >65 years is expected to grow from 550 million today to 973 million in 2030. The proportion of 65+ old persons will increase from 15.5% to 24.3% in Europe, from 12.6% to 20.3% in North America, from 6.0% to 12.0% in Asia, and from 5.5% to 11.6% in Latin America and the Caribbean [2]. By 2050, due to unprecedented declines in mortality and fertility, the number of the elderly in the world will exceed the number of young for the first time in history [3]. The largest increases in absolute numbers of older persons will occur in developing countries. During 2000-2030, the number of the elderly in developing countries is projected to almost triple, from approximately 249 million in 2000 to an estimated 690 million in 2030 [4]. Global life expectancy in 2000–2005 is estimated at 65 years, and in 2045–50, at 74 years. Over the same interval, life expectancy in affluent countries is expected to rise from 76 to 82 years and in poorer countries from 63 to 73 years [5]. The developed countries, which have already experienced a dramatic increase in the population aged 65+, will face a progressive ageing of the elderly population itself. In most of these countries, the oldest (those 80 years and older) are the fastest growing part of the elderly population [1]. The Italian population follows the same pattern of demographic changes characteristic of the industrialized countries, and in the coming half century Italy will experience a further increase of the very elderly population (Table 1, Figure 1).

| Table 1. Profile of ageing in Italy, percentage in older ages |
|-----------------|-------|-------|-------|-------|-------|
| Age             | 1950  | 1975  | 2000  | 2025  | 2050  |
| Total           | 60+   | 12.2  | 17.4  | 24.1  | 34    | 42.3  |
|                 | 65+   | 8.3   | 12    | 18.1  | 25.7  | 35.9  |
|                 | 80+   | 1.1   | 1.9   | 3.9   | 7.5   | 14.1  |
| Women           | 60+   | 13.1  | 19.3  | 26.8  | 37.1  | 45.7  |
|                 | 65+   | 8.8   | 13.7  | 20.7  | 28.8  | 39.5  |
|                 | 80+   | 1.2   | 2.4   | 5.1   | 9.6   | 17.2  |
| Men             | 60+   | 11.3  | 15.4  | 21.2  | 30.8  | 38.6  |
|                 | 65+   | 7.7   | 10.3  | 15.3  | 22.4  | 32    |
|                 | 80+   | 1     | 1.4   | 2.6   | 5.3   | 10.7  |

Population ageing is profound, enduring, and pervasive, with major consequences and implications for human life [3]. Both developed and developing countries will face the challenge of coping with a high frequency of chronic diseases such as dementia and cognitive impairment [1]. Dementia incidence increases with increasing age, even in the most advanced ages. Every year one person among 1000 people aged 60-65 becomes demented; and 90 new cases of dementia will occur among 1000 people aged 95+. A similar age-related pattern is seen for prevalence figures. Prevalence is very low in subjects under the age of 60 (0.3-0.7 per 100 persons), and increases even in the most advanced ages (33.3-68.3 per 100 persons) [1]. Therefore dementia is an emerging public health problem as it is one of the most common diseases in the elderly, the major cause of disability and a major cause of mortality [1].

Wimo et al [6] estimated the absolute number of dementia cases in the world in 2000, 2030, and in 2050. In 2000 the number of persons with dementia was estimated at about 25.5 million. Approximately 46% of the demented elderly lived in Asia, 30% in Europe, and 12% in North America. Fifty-two percent lived in less developed regions. About 6% of 65+ old populations suffer from dementia and 59% are women. The forecast indicated a considerable increase in the number of demented elderly from 25 million in the year 2000 to 63 million in 2030 (41 million in less developed regions) and to 114 million in 2050 (84 million in less developed regions). Wimo et al concluded that the majority of demented elders live in less developed regions, and this proportion will increase consistently in the next half century [6] (figure 2).
DEMENTIA AND COGNITIVE IMPAIRMENT

Dementia: definition and diagnostic criteria

Dementia is a clinical syndrome characterized by the development of multiple cognitive deficits, including impairment in memory, that are severe enough to interfere with daily functioning, including social and professional functioning [7]. The cognitive deficits include memory impairment and at least one of the other cognitive domains, such as aphasia, apraxia, agnosia, or disturbances in executive functioning. These cognitive changes are frequently accompanied by disturbances of mood, behavior, and personality. Because dementia can be produced by many different underlying diseases, the order of onset and relative prominence of the cognitive disturbances and associated symptoms vary with different dementing disorders [8,9]. However, uniform diagnostic criteria have been developed and are commonly implemented for the identification of the dementia syndrome [8].
**Diagnostic criteria for dementia**

The most frequently used criteria are provided by the American Psychiatric Association in the third revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, 1987) [7] or by the latest published edition (DSM-IV-TR, 2000). DSM-III-R criteria are reliable and should be used routinely, according to the guidelines of the American Academy of Neurology [9]. Other criteria are those defined by the diagnostic guidelines described in the International Classification of Disease (ICD-10, 1992) [10]. The diagnostic criteria for dementia according to these three classification systems is reported in Table 2.

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<tr>
<td>Impairment in memory and at least one of following: abstract thinking, judgement, aphasia, agnosia, or personality change</td>
<td>Decline in both memory and thinking, of a degree sufficient to impair functioning in daily living</td>
<td>Impairment in memory and at least one of the following: agnosia, apraxia, aphasia, or executive functioning.</td>
</tr>
<tr>
<td>Cognitive deficits interfere with work or social activities or relationships with others</td>
<td>Cognitive deficits are severe enough to interfere with occupational/social activities and represent a decline from previous level</td>
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From Fratiglioni, 1998 [8]

The validity of dementia diagnosis is influenced by several factors. First, it is difficult to distinguish between mild cognitive impairment (MCI) and cognitive changes in normal ageing. Second, old people are frequently affected by multimorbidity, which can interfere with cognitive functioning and cognitive tests. Third, the elderly frequently experience a decrease in social and work activities depending on other circumstances than their degree of cognitive level [11]. Finally, the role of the physician is crucial, due to the need of an accurate clinical history for differential diagnosis [12].
Classification of dementing disorders

Different classifications have been proposed either based on clinical [13], etiopathological [14], or clinicopathological [15] aspects. Several diagnostic criteria have been developed, especially for the most common dementing disorders: Alzheimer’s disease (AD) and Vascular dementia (VaD).

Diagnostic criteria for Alzheimer’s disease

AD is the main subtype of dementia, accounting for 50-70% of the total dementia prevalence in most western countries [1]. Due to a lack of biological markers, the diagnosis of AD is essentially a clinical one. According to the guidelines of the American Academy of Neurology [9], the National Institute of Neurologic, Communicative Disorders and Stroke–Alzheimer’s disease and Related Disorders Association (NINCDS-ADRDA) or DSM-III-R diagnostic criteria for AD have sufficient reliability and validity to be used both in research and clinical settings. The three different diagnostic criteria, DSM, ICD and NINCDS-ADRDA, share many common features. To make a diagnosis of AD, all three classifications require: 1) an insidious onset 2) a gradually progressive deteriorating course, and 3) the exclusion of all other specific causes of dementia. The NINCDS-ADRDA criteria take a somewhat different approach by grading the level of diagnostic certainty into definite, probable, and possible AD diagnosis, thus reflecting the available information and how closely the patient's syndrome resembles "classic" AD [8]. In ICD-10, the presence of apoplectic onset or focal neurological signs early in the illness are exclusion criteria. The validity of AD diagnosis has been studied in terms of reproducibility and confirmation at autopsy. The accuracy rates of clinically based diagnosis when compared to pathological findings vary from 0.62 to 0.92 [16].

Diagnostic criteria for Vascular dementia

VaD, the second most common type of dementia after AD, accounting for one-third of all dementia cases in western societies, is usually defined as an acquired intellectual deficit resulting from brain injury due to a cerebrovascular disorder (CVD) [17]. CVD includes both hemorrhagic and ischemic events, with the last one considered as the predominant cause of VaD. However, recognition is increasing that other vascular pathologies (i.e. small vessel disease) can lead to dementia [18]. Although different sets of criteria have been proposed [9], diagnosis of VaD is still controversial [8]. In addition there is increasing evidence for overlapping between degenerative and vascular dementias. In fact, research performed during recent years has shown the relevant contribution of vascular
risk factors even to the development of AD [19]. Some authors have suggested that AD may be primarily a vascular disorder [20].

**Definition of cognitive impairment**

The concept of MCI has received a considerable amount of interest during the last years, especially as a possible prodromal phase of AD [21]. Initially, MCI was a term suggested to indicate a transitional stage between normal ageing and dementia [22,23]. However, in the general population, MCI showed a heterogeneous clinical presentation and a multiple etiologies, such as ischaemia, trauma, metabolic disturbance, and psychiatric diseases [21,24]. For that reason, different cognitive impairment subtypes have been suggested [25].

Clinically, MCI refers to impairment in one or more cognitive domains, usually memory, in subjects with adequate general functioning, not fulfilling the diagnostic criteria for dementia [26]. According to Petersen et al, the diagnosis of MCI takes into account the following criteria: 1) persons should be judged as not normal besides not fulfilling diagnostic criteria for dementia; 2) functional activities of the persons are mainly preserved, or at least that impairment is minimal; 3) persons should have evidence of cognitive decline, measured either by self and/or informant report in conjunction with deficits on objective cognitive tasks, and/or evidence of decline over time on objective neuropsychological tests.

Table 3 suggests a list of possible etiologies of MCI.

<table>
<thead>
<tr>
<th>Degenerative</th>
<th>AD, Frontal lobe dementia, Dementia with Lewy bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Vascular, Ischemic stroke, Hemorrhagic stroke, White matter lesion</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hypoglycemia, Diabetes, Hypothyroidism</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Head trauma</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Depression, Anxiety</td>
</tr>
<tr>
<td>Drugs</td>
<td>Psychotropic drugs, Anticholinergic drugs</td>
</tr>
<tr>
<td>Others</td>
<td>?</td>
</tr>
</tbody>
</table>

Adapted, from Winblad et al, 2004 [21]

MCI is the most widely used concept, whereas other terms, such as Cognitive Impairment, No Dementia (CIND) have been applied in literature especially to describe cognitive impairment in the general population. Both the
Canadian Study of Health and Aging [27] and the Kungsholmen Project [28] use a CIND definition. In the Swedish study, global cognitive impairment with no dementia was defined as scoring one standard deviation (SD) below the age- and education-specific mean on the Mini-Mental State Examination (MMSE), an easy to administer test of global cognitive functioning. The effects of age and education on MMSE score were taken into account by stratifying performance into age- and education-specific groups. The Canadian Study of Health and Aging uses a consensus conference to decide which persons are cognitively impaired.

The prevalence figures of cognitive impairment vary largely [29], from 5.3 [30] to 22.9 [31] per 100 subjects among persons over 65 years due to the large variation in definition criteria (Figure 3).

Figure 3. Prevalence per 100 population for cognitive impairment across different population studies, distribution by age [27,30-35]

In all population-based studies, the prevalence of cognitive impairment increases with age, and seems to reach a plateau in people aged 85 years and older [32,36]. The definition from the Kungsholmen Project reported in this figure did not adjust for age and education.
HIV cognitive impairment and AIDS dementia complex

In the third decade of the human immunodeficiency virus (HIV) pandemic the number of infected persons continues to increase. Approximately 38 million people worldwide are now infected with HIV [37]. Until recently, before the widespread use of Highly Active Antiretroviral Therapy (HAART) in the developed world, the most common neurologic complication in the later stages of HIV infection was a subacute or chronic HIV encephalitis presenting as a form of dementia (AIDS dementia complex, ADC) [38], which affected ~20–30% of HIV seropositive individuals. ADC is the leading cause of dementia in the young people, with 10,000 new cases occurring annually in the USA. A scheme to stage ADC has been developed (Table 4).

| Stage 0 (normal) | Normal mental and motor function |
| Stage 0.5 (subclinical) | Minimal or equivocal symptoms of cognitive or motor dysfunction characteristic of ADC, or signs (snout response, slowed extremity movements), but without impairment of work or capacity to perform activities of daily living (ADL). Gait and strength are normal. |
| Stage 1 (mild) | Unequivocal evidence (symptoms, signs, neuropsychological test performance) of functional, intellectual or motor impairment characteristic of ADC, but able to perform all but the more demanding aspects of work or ADL. Can walk without assistance. |
| Stage 2 (moderate) | Cannot work or maintain the more demanding aspects of daily life, but able to perform basic activities of self-care. Ambulatory but may require a single prop |
| Stage 3 (severe) | Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or Motor disability (cannot walk unassisted, requires walker or personal support, usually also with slowing and clumsiness of arms) |
| Stage 4 (end stage) | Nearly vegetative, intellectual and social comprehension and responses are at a rudimentary level, nearly or absolutely mute. Paraparetic or paraplegic with double incontinence |

From Price et al, 1988 [39]

ADC evolves relatively rapidly, over a period of months; survival after the onset of dementia is generally three to six months but it may be considerably longer.

In the past few years, morbidity and mortality rates of HIV have plummeted due to HAART. With the use of HAART, a more subtle form of central nervous system dysfunction — minor cognitive motor disorder (MCMD) — has become more common [40]. It has recently been reported that 10% of HIV-infected subjects have ADC but that MCMD affects as many as 30-40% of HIV-
infected persons [40]. Furthermore, MCMD is associated with a worse prognosis for HIV infected individuals [41]. MCMD development may be due to slow progressive neurodegeneration caused by low-level viral replication, as occurs with the successful HAART regimens. This is consistent with the much longer lifespan of treated patients [42] and possibly with the insufficient penetration of antiretroviral drugs into the brain [43].

**RISK FACTORS FOR DEMENTIA: CURRENT KNOWLEDGE**

The search for risk factors for dementia is one of the major research lines both for the development of preventive strategies and for the understanding of the underlying etiopathogenetic mechanisms of the different dementing disorders. Most of the etiological studies focus on AD, whereas data concerning VaD and other dementia types are more limited. In the last few years, it has been proposed that better progress in understanding the causes of dementia may come from studying risk factors for dementia overall, rather than for specific dementing disorders. In summary, dementia and AD are multifactorial diseases, in which both genetic and environmental factors are believed to be involved [44] (figure 4).

![Risk Factors](image)

**Figure 4.** The timeline of risk and protective factors for dementia. Time for each factor is identified from the available studies. SES=socioeconomic status. Adapted from Fratiglioni et al, 2004 [45].
Figure 4 represents a model of the life course exposure to different risk and protective factors for dementia. The factors and the reported times are derived from the available studies detected in the literature according to Fratiglioni et al [44,46]. Persons are born with different genetic predisposition and during life they are exposed to both risk and protective factors. The balance of these aspects will lead to dementia risk in late life. A certain factor might increase the risk of the disease if a subject is exposed at a specific time, but the same factor may have a decreased effect in another life period, due to different interactions with other risk factors or due to selective survival [47,48]

**Risk factors for Alzheimer’s disease**

Of the major subtypes of dementia, AD is the most widely examined. There is strong evidence that age [49], familial aggregation [50], and the epsilon 4 (ɛ4) allele of the Apolipoprotein E (APOE) gene [46] are risk factors for the disease [44]. Less evidence is present for other associated factors. Several prevalence and incidence studies suggest a higher risk for AD among women [51]. Hypertension, which is the most powerful risk factor for cerebrovascular disease and stroke, is believed to be an important risk factor for dementia overall, and vascular dementia in particular [52]. However, some reports have implicated hypertension and vascular pathology, notably atherosclerosis, white matter lesions, and mid life arterial hypertension as risk factors specifically for AD, too [53,54]. Several other possible risk factors such as exposure to diabetes, high total homocysteine, being overweight, and dietary factors are involved in the pathogenesis and progression of dementia and AD [44]. Socioeconomic status (SES) [55], occupational exposure (e.g. electromagnetic fields) [56], head trauma, smoking, and alcohol may play a role in dementia and AD [44].

Several protective factors for dementia and AD have also been suggested. Apart from high level of education [57], which will be discussed in details later, a rich social network [58], frequent participation in social and leisure activities [59], physical activities [60], light to moderate alcohol consumption [61], non-steroid anti-inflammatory drugs (NSAID) [62], antihypertensive medications [63], lipid-lowering drugs [64], and APOE ɛ2 allele [46] are putative protective factors against dementia and AD. The protective effect of postmenopausal estrogen therapy has being recently re-examined. Treatments with oestrogens with or without medroxyprogesterone acetate, given to women age 65 years and older, did not protect against dementia or cognitive decline, but substantially increased the risk of dementia of any cause and cognitive decline [65].
Risk factors for vascular dementia

Studies of risk factors for VaD are hampered by the difficulties in definition and diagnostic criteria of this disorder. Main risk factors identified for VaD are age, male sex, hypertension, myocardial infarction, coronary heart disease, diabetes, generalized atherosclerosis, smoking, high lipid concentrations, and a history of stroke [44,66].

Risk factors for HIV-1 cognitive impairment

It is well-established that both ADC and MCMD mainly develop in patients with advanced HIV-1 infection and severe immunosuppression [40]. Other factors that might increase the risk of early neuropsychological abnormalities are controversial. Some authors have claimed that injecting drug users (IDUs) are at a higher risk for ADC than subjects with other risk behaviors [67-69], but this finding has been dismissed by others [70-72]. Other factors have been sporadically associated with a higher occurrence of dementia and cognitive impairment in HIV-1 infected patients: increased age [69,73-75], female gender [74], low education [76-79], decreased hemoglobin levels [70,73,77,80], lower body mass index [73], vitamin B12 deficiency [81-83], previous traumatic brain injury [84], and concurrent depressive symptoms [69,85,86]. Conversely, antiretroviral treatment has been found to protect against dementia and cognitive impairment [87,88].

EDUCATION AND DEMENTIA: A SYSTEMATIC REVIEW

It is well established that education exerts a positive influence on well being in older age and on survival. A paper investigating mortality among 306 Roman Catholic nuns during the period 1936-1988 reported that the median age at death was 89.4 years for sisters with educational attainment of a Bachelor's degree or higher, in comparison to 82.2 years for sisters with high school or college education, and 82.0 years for sisters with only a grade school education. Odds ratio (OR) calculated for "survival and independence" was 2.7 (95% CI=1.2-6.2) for sisters with a Bachelor's degree or higher (reference group was high school or college). Sisters with a Bachelor's degree or higher were also found to survive to older age maintaining their ability to perform self-care activities [89]. Education also influences survival among diseased patients, for example in patients affected by cancer [90,91]. Low levels of education have been associated in elderly people with poorer psychological function (less mastery, efficacy, happiness), less optimal health behaviors (alcohol
consumption, high-density lipoprotein cholesterol, increased tobacco consumption, and decreased levels of physical activity), poorer biological conditions (decreased pulmonary function, increased body mass index and waist-to-hip ratio), and poorer social networks (less number of contacts, negative support) [92].

Already in 1988, Mortimer suggested that a higher educational level might provide protection against AD, especially the late-onset subtype [93]. In 1993, Katzman concluded that lower education represents an actual risk factor for AD [94]. Since then, a large amount of papers have been published on this topic. The first findings were derived from cross-sectional studies, and only in the late 1990 have longitudinal studies addressed this issue.

To enlighten the role of education in the pathogenesis and development of dementia, the following review analyses all published longitudinal and case-control studies about the effect of education on cognitive impairment and/or dementia risk, as well as dementia-related mortality. Finally, the different hypotheses about the possible “biological mechanism of action” of education as a protective factor against cognitive impairment and dementia are discussed.

**Search strategy and selection criteria**

A Medline research in PubMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi) was carried out, using the following keywords: “Alzheimer Disease”, “education”, “age”, “dementia” and “cognitive impairment”. When the same study was replicated in the same population at different times, only the most recent figures were taken into account. Only population-based studies have been taken into account.

**Effect of education on cognition**

Cognition was assessed in the various studies with different methods.

**Cross-sectional and case-control studies**

Seven studies were found, as shown in table 5 [32,33,95-99]. All the studies found an inverse association between educational level and cognitive deficits. Two of them analyzed also the association between educational level and dementia [96,100], and two analyzed the presence of CIND [32,33].

**Longitudinal studies**

Eight studies regarding the possible association between educational level and cognitive decline were found [101-108]. All incidence studies, similarly to the
cross-sectional and case-control studies, detected an inverse relationship between cognition and education. The major characteristics of the longitudinal studies on this topic are shown in table 6. Three studies were done in North America (two in USA and one in Canada), and five in Europe (in France, Sweden, Finland and Netherlands). Most of these studies were population-based studies from cohort surveys focused on ageing. In two studies [102,105], both people living in community and in institutions were included. Three studies [103,105,106] considered education as a dichotomous variable (low education vs. high education). Most studies used the MMSE to assess cognitive status; Leibovici and colleagues [103] used other neuropsychological tests, such as ECO (Examen Cognitif par Ordinateur). The length of the follow-up ranged from one to ten years. Most studies controlled for age and sex, but many others factors may influence the relationship between level of education and cognitive decline. In fact, some studies controlled for other confounding factors, such as premorbid intelligence, SES, lifestyle (smoking status, alcohol consumption, physical activity) and health indicators (diabetes mellitus, cardiac disease, and depression). Farmer et al [102] and White et al [101] considered also residential status.

**Effect of education on dementia risk**

**Cross-sectional and case-control studies**

In table 7 the findings about cross-sectional and case-control studies investigating the association between educational level and presence of AD and other dementias are reported. Twenty-six cross-sectional and case-control studies were found [33,96,100,109-133]. Fourteen studies examined the relationship between education and dementia, seventeen education and AD, and five education and VaD. Ten studies out of fourteen confirmed the inverse association between educational level and dementia [33,96,100,111,116, 117,120,124,126,130,133], twelve out of seventeen between education and AD [100,110,112,115,117, 121,125,127-129,131,132], and four out of five between educational level and VaD [100,115,117,131]. Conversely, four studies examining dementia [114,122,123,129], five studies on AD [109,113,118,119,123], and one on VaD [121] did not find any association with educational levels.

**Longitudinal studies**

Fifteen studies concerning the possible association between low education and dementia were detected in the search [32,57,104,134-146]. Table 8 summarizes the methodological features and major results of all longitudinal studies on this
topic. All studies were done in Europe or North America, all were population-based incidence studies of dementia and AD, and all included the nondemented people identified in the initial cohort. The length of follow-up ranged from one [104] to seventeen years [136]. Several of these incidence studies [57,104,134,137-139,143-146], as pooled incidence data from the EURODEM study [147] confirmed the inverse association between education and AD or dementia. Some of these studies found this association to exist for women only [147] or to be stronger for women [57]. In 2000, Ganguli et al showed that subjects with less than high school education had significantly higher incidence rates of questionable dementia than those with more education. Rates did not vary significantly by sex or education for probable/possible AD or for dementia with a Clinical Dementia Rating Scale (CDR) score of one or less [140]. Finally, other incidence studies [135,136,141,142] have failed to find any relationship between education and AD or dementia. As Qiu et al pointed out [57], the effects of potential confounders, such as cognitive functioning prior to dementia, vascular diseases, and SES, have been largely neglected by most studies addressing this topic.

Effect of education on dementia-related mortality

Eight studies regarding the possible association between education level and mortality in patients affected by dementia were found. Table 9 shows the major characteristics of studies on this topic [57,148-154]. The subjects of these studies were gathered from community-based studies, such as the Kungsholmen Project, the Canadian Study of Health and Aging or the PAQUID Study, except for a study by Stern et al [152] in which the authors developed a registry of patients with AD based on referrals and screening of elders from regional hospitals. All studies controlled for age and sex, but some studies also controlled for other confounding factors, such as SES, dementia severity according to the CDR [57,152], and cognitive and functional status. Low education, AD, and dementia emerged as risk factors for death even in oldest old people [57,148,155,156]. In addition, in most studies, subjects with AD or dementia with a low educational level had a decreased risk of death compared to patients with a high educational level. The reported association by the remaining studies between low educational levels and increased mortality in patients with AD or dementia may be biased by confounders, most prominently dementia severity, as shown by Qiu et al [57]. These findings suggest that education may influence the clinical expression or the detection of AD or dementia, rather than affecting the underlying pathologic process of the disease.
Summary of the evidence

In the past 10 years extensive research has increased our knowledge of the relationship between education and dementing disorders. A quantitative summary of the findings concerning the relation between education and dementia/cognitive impairment is shown in figure 5.

All the population-based studies, either cross-sectional, case-control or longitudinal studies consistently found an inverse association between educational level and cognition. Conversely, the relationship between education and AD or dementia yielded mixed evidence, although an inverse association between educational level and the risk of AD or dementia has been reported in most cross-sectional, case-control and longitudinal studies. Lower educational attainment was found to be associated with an increased risk of dementia and AD in nine out of eleven longitudinal studies, and in six out of nine, respectively. The remaining two [135,136] and three [136,141,142] longitudinal studies that investigated dementia did not find an association between lower educational attainment and increased risk of dementia and AD.
Table 5. Cross sectional and case control studies concerning the association between education and cognition

<table>
<thead>
<tr>
<th>Study, Year, Country</th>
<th>n</th>
<th>Age (years)</th>
<th>Education</th>
<th>Methods/Criteria</th>
<th>Reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osterweil et al, 1994,</td>
<td>201</td>
<td>Mean age</td>
<td>Years of schooling: 0-4, 5-8, 9-12, 13-20</td>
<td>MMSE, Inglis P-A Learning Test, Digit Span, Cube Copying, Boston Diagnostic Aphas</td>
<td>Low education associated with poorer cognitive performance</td>
</tr>
<tr>
<td>USA [95]</td>
<td></td>
<td>84.7 ± 5.6</td>
<td></td>
<td>Exam</td>
<td></td>
</tr>
<tr>
<td>Callahan et al, 1996, USA</td>
<td>2,212</td>
<td>65+</td>
<td>Years of schooling: &lt;6, 6-9, &gt;10</td>
<td>CSI-D, DSM-III-R, NINCDS-ADRDA</td>
<td>Low education independently associated with cognitive impairment and dementia</td>
</tr>
<tr>
<td>[96]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kilander et al, 1997,</td>
<td>504</td>
<td>69-74</td>
<td>Low (elementary), medium (secondary school), high</td>
<td>13 standard psychometric tests</td>
<td>Low education associated with poorer cognitive performance</td>
</tr>
<tr>
<td>Sweden [97]</td>
<td>men</td>
<td></td>
<td>(university studies)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gallacher et al, 1999, UK</td>
<td>1,870</td>
<td>55-69</td>
<td>7-point scale according to the degree or</td>
<td>AH4, CAMCOG, MMSE, NART, various memory tests</td>
<td>Performances on tests improved with increasing level of education. After adjustment</td>
</tr>
<tr>
<td>[98]</td>
<td>men</td>
<td></td>
<td>certificate obtained</td>
<td></td>
<td>for age, mood, and social class, a change was evident in the performance on some</td>
</tr>
<tr>
<td>Di Carlo et al, 2000, Italy</td>
<td>3,145</td>
<td>65-84</td>
<td>Years of schooling: ≤5, 6-10, ≥11</td>
<td>DSM-III-R</td>
<td>of the tests but education was still significantly associated to cognitive</td>
</tr>
<tr>
<td>[32]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>performance</td>
</tr>
<tr>
<td>Salemi et al, 2002, Italy</td>
<td>3,999</td>
<td>50+</td>
<td>Years of schooling: none, ≤5, 6-8, ≥9</td>
<td>SPMSQ</td>
<td>Low education associated with CIND (OR=0.6, 95% CI=0.6-07)</td>
</tr>
<tr>
<td>[99]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Ronchi et al, 2005,</td>
<td>7,930</td>
<td>61+</td>
<td>Years of schooling: none, 1-3, 4-5, ≥6</td>
<td>MMSE, GDS, DSM-III-R</td>
<td>Low education associated with CIND (OR=16.7, 95% CI=11.2-25.0) and dementia (OR=10.9,</td>
</tr>
<tr>
<td>Italy [33]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% CI=7.0-16.7)</td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; GDS = Global Deterioration Scale; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/the Alzheimer’s Disease and Related Disorders Association; CIND = Cognitive impairment, no dementia; CAMCOG = the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly; CSI-D = Community screening interview for dementia; AH4-1 = Heim Intelligence test score; NART = National Adult Reading Test; SPMSQ = Short Portable Mental Status Questionnaire
<table>
<thead>
<tr>
<th>Study, Year, Country</th>
<th>n</th>
<th>Age at baseline (years)</th>
<th>Follow-up (yrs)</th>
<th>Education</th>
<th>Methods/Criteria</th>
<th>Reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>White et al, 1994, USA [101]</td>
<td>10,294</td>
<td>65+</td>
<td>6</td>
<td>Years of schooling: ≤8, 9-11, ≥12</td>
<td>SPMSQ, interview questions</td>
<td>≤8 years of education significant predictor of cognitive decline after controlling for age, sex, stroke, and baseline SPMSQ score</td>
</tr>
<tr>
<td>Farmer et al, 1995, USA [102]</td>
<td>14,883</td>
<td>&gt;18, two age strata (&lt;65 and ≥65 years)</td>
<td>1</td>
<td>Years of schooling: 0-9, 10-12, some college education</td>
<td>Cognitive impairment defined by MMSE ≤23; Cognitive decline defined by 3 point decline at 1 yr follow-up</td>
<td>In cognitively intact subjects fewer years of education predicted cognitive decline in both age strata</td>
</tr>
<tr>
<td>Leibovici et al, 1996, France [103]</td>
<td>283</td>
<td>&gt;60</td>
<td>1</td>
<td>Low education (no formal education or primary school) versus high education (secondary and tertiary school)</td>
<td>Examen cognitif par Ordinateur (ECO), NART</td>
<td>Low education and young-adult IQ were related to cognitive decline, especially in the older age group. Education had a greater impact than age</td>
</tr>
<tr>
<td>Schmand et al, 1997, Netherlands [104]</td>
<td>1,774</td>
<td>55-84</td>
<td>1</td>
<td>9-point ordinal scale ranging from incomplete elementary education (&lt;6 years) to university education (18 years)</td>
<td>Screening interview and computerized testing</td>
<td>Inverse association between educational level and dementia incidence. Low education was further related to faster memory decline and an earlier onset of dementia</td>
</tr>
<tr>
<td>Aervarsson &amp; Skoog, 2000, Sweden [105]</td>
<td>494</td>
<td>85-88</td>
<td>3</td>
<td>Years of schooling: ≤6 vs. &gt; 6</td>
<td>MMSE</td>
<td>High education related to higher scores on MMSE at 85 years of age and to a smaller decline on MMSE scores during the 3-year follow up</td>
</tr>
<tr>
<td>Winnock et al, 2002, France [106]</td>
<td>600</td>
<td>65+</td>
<td>10</td>
<td>Primary with diploma versus no school or primary school without diploma</td>
<td>MMSE</td>
<td>Low education associated with lower cognitive performance at baseline but not with the evolution of the cognitive performance</td>
</tr>
<tr>
<td>Tuckko et al, 2003; Canada [107]</td>
<td>844</td>
<td>65+</td>
<td>5</td>
<td>Years of schooling: 0-6 (low), 7-10 (average), ≥11 (high)</td>
<td>CIND at several neuropsychological tests</td>
<td>High functioning subjects (defined by educational and occupational attainment and estimated pre-morbid IQ) had a smaller cognitive decline in performance on neuropsychological tests and a lower incidence of dementia. Ascertainment biases were suggested by the authors</td>
</tr>
<tr>
<td>Tervo et al, 2004, Finland [108]</td>
<td>1,150</td>
<td>60-76</td>
<td>3</td>
<td>Years of schooling: 7-4 (SD) 2.4 in converted subjects vs. 9.6 (3.4) in non-converted subjects</td>
<td>MMSE and several neuropsychological tests</td>
<td>High education protective towards conversion to mild cognitive impairment (MCI). Yearly reduction in risk: OR=0.8, 95% CI=0.7-0.9</td>
</tr>
</tbody>
</table>

Note: MMSE = Mini-Mental State Examination; SPMSQ = Short Portable Mental Status Questionnaire; NART = National Adult Reading Test; IQ = Intelligence Quotient
<table>
<thead>
<tr>
<th>Study, Year, Country</th>
<th>n</th>
<th>Age (years)</th>
<th>Education</th>
<th>Methods/Criteria</th>
<th>Reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beard et al, 1992, USA [109]</td>
<td>241 AD, 241 CTRL</td>
<td>60+</td>
<td>Years of schooling: &lt;9, 9-11, 12, 13; and &lt;9, ≥19</td>
<td>Clinical evaluation, AD diagnosis</td>
<td>No association between education and AD: OR=1.1, 95% CI=0.7-1.8</td>
</tr>
<tr>
<td>Moritz &amp; Petitti, 1993, USA [110]</td>
<td>1,658 AD</td>
<td>40+</td>
<td>Years of schooling: 0-8, 9-11, 12, 13</td>
<td>Neuropsychological tests, medical records, BRDRS</td>
<td>Increasing education related to decreased age at dementia onset and higher severity of symptoms at presentation (p&lt;0.008)</td>
</tr>
<tr>
<td>Hill et al, 1993, China [111]</td>
<td>554</td>
<td>55+</td>
<td>Illiterate, elementary, middle or higher education</td>
<td>DSM-III, NINCDS-ADRDA</td>
<td>Low education associated with increased age-specific risk of dementia</td>
</tr>
<tr>
<td>The Canadian Study of Health and Ageing, 1994, Canada [112]</td>
<td>258 AD, 535 CTRL</td>
<td>65+</td>
<td>Years of schooling: 0-6, 7-9, ≥10</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>Those with less education (≤6 years) were at higher risk of AD (OR=4.0, 95% CI=2.5-6.4), compared to those with high education (≥10 years)</td>
</tr>
<tr>
<td>Prince et al, 1994 [113]</td>
<td>1,545</td>
<td>65+</td>
<td>Limited education (&lt;10 years), no tertiary education, and no secondary school qualifications</td>
<td>NINCDS-ADRDA</td>
<td>No significant association between education and AD</td>
</tr>
<tr>
<td>Bonaiuto et al, 1995, Italy [114]</td>
<td>48 AD, 96 CTRL</td>
<td>59+</td>
<td>Illiterate, no formal education or up to 4th grade, over 4th grade</td>
<td>MMSE, BRDRS, DSM-III</td>
<td>No significant association with prevalence of dementia after adjustment for sex, age, education (OR=1.4, 95% CI=0.6-3.1)</td>
</tr>
<tr>
<td>Mortel et al, 1995, USA [115]</td>
<td>440</td>
<td>60-98</td>
<td>Years of schooling: &lt;7, 7-11, high school graduation, some college, college graduation, post graduate, technical or vocational studies</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>Low education associated with AD (OR=2.4, 95% CI=1.3-4.3) and VaD (OR=1.8, 95% CI=1.4-4.5) also in the occupation-adjusted model</td>
</tr>
<tr>
<td>Prencipe et al, 1996, Italy [117]</td>
<td>1,147</td>
<td>64+</td>
<td>Years of schooling: 0, 1-2, 3-4, 5, 5, &gt;5</td>
<td>MMSE, MSQ, HDRS, CDR, DSM-III, NINCDS-ADRDA</td>
<td>Higher prevalence rate of both AD and VaD in subjects with low educational level, association between low education and dementia (OR 2.0, 95% CI=1.2-3.3)</td>
</tr>
<tr>
<td>Callahan et al, 1996, USA [96]</td>
<td>2,212</td>
<td>65+</td>
<td>Years of schooling: &lt;6, 6-9, &gt;10</td>
<td>CSI-D, DSM-III-R, NINCDS-ADRDA</td>
<td>Low education independently associated with cognitive impairment and dementia</td>
</tr>
<tr>
<td>Duara et al, 1996, USA [118]</td>
<td>197</td>
<td>60+</td>
<td>Years of schooling: 7±4, 12±3, in different ethnic groups</td>
<td>NINCDS-ADRDA</td>
<td>No association with AD</td>
</tr>
<tr>
<td>Tsolaki et al, 1997, Greece [119]</td>
<td>65 AD, 69 CTRL</td>
<td>70+</td>
<td>Years of schooling: &lt;3, 3-5, ≥6</td>
<td>DSM-IV, CT, MRI</td>
<td>No statistical differences in cases compared to controls concerning education</td>
</tr>
<tr>
<td>Schmand et al, 1997, Netherlands [120]</td>
<td>1,774</td>
<td>55-84</td>
<td>9-point ordinal scale: from incomplete elementary education (&lt;6 years) to university education (18 years)</td>
<td>Screening interview and computer testing</td>
<td>Inverse association between educational level and dementia prevalence</td>
</tr>
<tr>
<td>De Ronchi et al, 1998, Italy [100]</td>
<td>495</td>
<td>60+</td>
<td>Years of schooling: 0, 1-3, ≥4; yes vs. no</td>
<td>MMSE, GDS, DSM-III-R</td>
<td>Full-adjusted OR for subjects with no education compared with subjects having any grade of education: OR=4.7, 95% CI=2.3-9.6, especially in the youngest group</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Mean Age</td>
<td>Low Education Characteristics</td>
<td>Cognitive Tests</td>
<td>Findings</td>
</tr>
<tr>
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</tr>
<tr>
<td>Lin et al., 1998, Taiwan [121]</td>
<td>2,915</td>
<td>65+</td>
<td>Illiterate, graduate school, high school; Illiterate vs. Literate</td>
<td>MMSE, CERAD, ICD-10, NINCDS-ADRDA, NINCDS- AIREN</td>
<td>Illiteracy associated with AD but not with VAD or Mixed Dementia</td>
</tr>
<tr>
<td>Farrag et al., 1998, Egypt [122]</td>
<td>2,000</td>
<td>60+</td>
<td>Illiterate, elementary, high school, college</td>
<td>MMSE, DSM-III-R, NINCDS- ADRDA, HIS</td>
<td>Level of education did not affect prevalence or severity of dementia</td>
</tr>
<tr>
<td>Chandra et al., 1998, India [123]</td>
<td>5,126</td>
<td>55+</td>
<td>Illiterate and literate</td>
<td>MMSE, CDR, NINCDS- ADRDA</td>
<td>Illiteracy not associated with AD and dementia</td>
</tr>
<tr>
<td>Yamada et al., 1999, Japan [124]</td>
<td>1,784</td>
<td>60+</td>
<td>Number of years of schooling and level of attainment</td>
<td>CASI, DSM-III-R, IQCODE, CDR</td>
<td>Decreased dementia risk for a 3-year increase in education (OR=0.4, 95% CI=0.2-0.7)</td>
</tr>
<tr>
<td>Harwood et al., 1999, USA [125]</td>
<td>866</td>
<td>65+</td>
<td>Years of schooling: ≤10, &gt;10</td>
<td>NINCDS- ADRDA</td>
<td>Low education increased the risk of AD in non-hispanic Caucasians (OR=3.1, 95% CI=1.8-5.9), but not in Caucasian Hispanics</td>
</tr>
<tr>
<td>Moceri et al., 2000, USA [126]</td>
<td>393 AD, 377 CTRL</td>
<td>60+</td>
<td>&lt;high school, high school graduate, &gt;high school</td>
<td>NINCDS- ADRDA</td>
<td>Protective effect of having a high education: OR=0.4, 95% CI=0.3-0.6, after adjustment for: area of residence, number of siblings and ApoE allele</td>
</tr>
<tr>
<td>Hall et al., 2000, USA [127]</td>
<td>2,212</td>
<td>65+</td>
<td>Years of schooling: ≤6, ≥7</td>
<td>NINCDS- ADRDA, CDR</td>
<td>Lower mean number of education years in AD than in non AD. Significant association between low education and AD only for subjects living in a rural area during childhood</td>
</tr>
<tr>
<td>Bowirrat et al., 2001, Saudi Arabia [128]</td>
<td>821</td>
<td>60+</td>
<td>Schooling yes vs. no</td>
<td>DSM-IV</td>
<td>Extremely high prevalence of illiteracy and dementia. Strong association between illiteracy and AD: OR=7.9, 95% CI=3.8-16.9</td>
</tr>
<tr>
<td>Gatz et al., 2001, Sweden [129]</td>
<td>221 AD, 442 CTRL</td>
<td>50+</td>
<td>Years of schooling: ≤6, &gt;6; elementary, secondary, vocational, gymnasiurn, university</td>
<td>CERAD, DSM-III-R, NINCDS- ADRDA, NINCDS- AIREN</td>
<td>Low education associated with AD, but not with dementia on the whole. No statistical difference in education between twins in the matched-pair analysis</td>
</tr>
<tr>
<td>Herrera et al., 2002, Brazil [130]</td>
<td>1,656</td>
<td>65+</td>
<td>Years of schooling: none, 1-3, 4-7, ≥8</td>
<td>MMSE, PFAQ, CT</td>
<td>Low education associated with higher prevalence of dementia</td>
</tr>
<tr>
<td>Ravaglia et al., 2002, Italy [131]</td>
<td>1,016</td>
<td>65-97</td>
<td>Years of schooling: 0-1, 2-3, &gt;3</td>
<td>NINCDS- ADRDA, DSM IV</td>
<td>Low education associated with both AD and VaD: OR=17.2, 95% CI=7.3-30.8 and OR=10.3, 95% CI=3.0-22.4, respectively</td>
</tr>
<tr>
<td>Harmanci et al., 2003, Turkey [132]</td>
<td>57 AD, 127 CTRL</td>
<td>≥70</td>
<td>Level of education was recorded as the school last graduated. Those who did not graduate from primary school (5 years), whether literate or illiterate, were grouped under &quot;no schooling&quot;</td>
<td>DSM-III-R, NINCDS- ADRDA</td>
<td>A strong protective effect of having an university college degree on AD risk: OR=0.1, 95% CI=0.0-0.5</td>
</tr>
<tr>
<td>Kahana et al., 2003, Israel [133]</td>
<td>1,501</td>
<td>75+</td>
<td>Years of schooling: 0, 1-7, 8-11, ≥12</td>
<td>DSM-III-R</td>
<td>Illiterates had an increased risk of dementia: OR=4.0, 95% CI=1.8-8.7</td>
</tr>
</tbody>
</table>

Note: BDRDS = Blessed-Roth Dementia Rating Scale; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; NINCDS- ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; MMSE = Mini-Mental State Examination; GMS = Geriatric Mental State; CAMDEX = Cambridge Examination for Mental Disorders of the Elderly; MSQ = Mental Status Questionnaire; CDR = Clinical Dementia Rating; HDRS = Hamilton Depression Rating Scale; CT = computed tomography; MRI = magnetic resonance imaging; CERAD = The Consortium to Establish a Registry for Alzheimer's Disease; NINCDS- AIREN = the National Institute for Neurological Diseases and Stroke ; Association Internationale pour la Recherche et l'Enseignement en Neurosciences; HIS = The Hachinski Ischemic Score; IQCODE = The Informant Questionnaire on cognitive decline in the elderly; CASI = Cognitive Ability Screening Instrument; PFAQ = the Pfeffer Functional Activities Questionnaire; CTRL = controls
Table 8. Longitudinal studies concerning the association between education and dementia

<table>
<thead>
<tr>
<th>Study, Year, Country</th>
<th>n</th>
<th>Age at baseline (years)</th>
<th>Follow-up (yrs)</th>
<th>Education</th>
<th>Methods/Criteria</th>
<th>Reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al, 1994, USA [134]</td>
<td>593</td>
<td>60-99</td>
<td>1-4</td>
<td>Low education (&lt;8) vs. high education (≥8)</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>Low education doubled the risk of dementia. The association was even stronger in subjects with low occupational attainment: OR=2.9, 95% CI=1.3-3.8</td>
</tr>
<tr>
<td>Paykel et al, 1994, UK [135]</td>
<td>1,195</td>
<td>&gt;75</td>
<td>2.4</td>
<td>Age of leaving school: &gt;14 and ≤14</td>
<td>CAMDEX</td>
<td>Incidence rates for dementia did not differ significantly by education</td>
</tr>
<tr>
<td>Cobb et al, 1995, USA [136]</td>
<td>3,330</td>
<td>55-88</td>
<td>17</td>
<td>&lt;grade school, &lt;high school graduate, high school graduate or beyond</td>
<td>DSM-III, NINCDS-ADRDA</td>
<td>Low education associated with increased risk of non-AD dementia: OR=1.8, 95% CI=1.0-3.0. No significant association with dementia in general or AD</td>
</tr>
<tr>
<td>Evans et al, 1997, USA [137]</td>
<td>642</td>
<td>65+</td>
<td>4.3</td>
<td>Years of schooling: 0-7, 8, 9-11, ≥12</td>
<td>NINCDS-ADRDA</td>
<td>Risk of dementia was decreased by 17% for each year-increase in education. Incidence rate of dementia decreased with increasing education</td>
</tr>
<tr>
<td>Schmand et al, 1997, Netherlands [104]</td>
<td>1,774</td>
<td>55-84</td>
<td>1</td>
<td>9-point ordinal scale ranging from incomplete elementary education (&lt;6 years) to university education (18 years)</td>
<td>Screening interview and computerized testing</td>
<td>Inverse association between educational level and dementia incidence. Low education was further related to faster memory decline and an earlier onset of dementia</td>
</tr>
<tr>
<td>Letenneur et al, 1999, France [138]</td>
<td>2,881</td>
<td>65+</td>
<td>5</td>
<td>No education, primary school (1-5), secondary school (6-12 years), and university level (&gt;12 years)</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>After adjustment for sex and age, lower educational attainment increased the risk of dementia (HR=1.8, 95% CI=1.4-2.4, and AD (HR=1.8, 95% CI=1.3-2.4)</td>
</tr>
<tr>
<td>Ott et al, 1999, Netherlands [139]</td>
<td>6,827</td>
<td>55+</td>
<td>2.1</td>
<td>High level education (11 years), medium level secondary education (7-10 years), lowest level (&lt;7 years)</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>Association between low education and dementia in women but not in men</td>
</tr>
<tr>
<td>Authors</td>
<td>N</td>
<td>Age</td>
<td>Years of Schooling</td>
<td>Education/AD</td>
<td>Notes</td>
<td></td>
</tr>
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<td>----------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ganguli et al, 2000, USA</td>
<td>1,298</td>
<td>65+</td>
<td>2</td>
<td>Less than high school graduation vs. high school graduation</td>
<td>DSM-III-R, NINCDS-ADRDA, CDR. Among subjects with CDR =0.5, less than high-school education was associated with higher incidence of all dementias and AD. Results no longer significant if CDR was ≥1.</td>
<td></td>
</tr>
<tr>
<td>Kawas et al, 2000, USA</td>
<td>1,236</td>
<td>55-97</td>
<td>13</td>
<td>High school or less (4-12 years), college education (13-16 years), graduate school education (17-25 years)</td>
<td>DSM-III-R, NINCDS-ADRDA. No significant association between lower education and higher risk of AD but a trend was observed towards increasing incidence rate of AD with decreasing education.</td>
<td></td>
</tr>
<tr>
<td>Borenstein Graves et al,</td>
<td>1,869</td>
<td>≥65</td>
<td>3.8</td>
<td>Years of schooling: ≤11, &gt;11</td>
<td>NART-R. No association between education and AD after adjustment for ApoE, IQ, BMI and head circumference.</td>
<td></td>
</tr>
<tr>
<td>Qu et al, 2001, Sweden</td>
<td>1,296</td>
<td>≥75</td>
<td>8</td>
<td>Elementary school (&lt;8 and/or vocational training) vs. high school (8-10 years) or university (≥11 years)</td>
<td>DSM-III-R, CDR. Low education increased the risk of developing clinical AD: OR=2.6, 95% CI=1.5-4.4 or dementia OR=1.7, 95% CI=1.1-2.6. Stronger effect in woman.</td>
<td></td>
</tr>
<tr>
<td>Tyas et al, 2001, Canada</td>
<td>694</td>
<td>65+</td>
<td>5</td>
<td>Years of schooling: mean (SD) 10.6 (3.2)</td>
<td>NINCDS-ADRDA. For a 1-year increment in education, reduction in risk of AD: RR=0.9, 95% CI=0.8-1.0.</td>
<td></td>
</tr>
<tr>
<td>Di Carlo et al, 2002,</td>
<td>2,498</td>
<td>65+</td>
<td>mean=3.8</td>
<td>Years of schooling: ≤5, 6-10, ≥11</td>
<td>MMSE, DSM-III-R, NINCDS-ADRDA, ICD-10. Education protective for all dementias and AD but not for VaD.</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitzpatrick et al, 2004,</td>
<td>3,602</td>
<td>≥65</td>
<td>5.5</td>
<td>Less than high school, high school graduate, some college/college graduate</td>
<td>MMSE, IADL-ADL, Digit Symbol Substitution Test, CES-D. Incident rates of dementia varied according to educational level but results were statistically significant only among whites.</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindsay &amp; Anderson,</td>
<td>10,263</td>
<td>65+</td>
<td>5</td>
<td>Years of schooling: 0-6, 7-9, ≥10</td>
<td>DSM-III-R, NINCDS-ADRDA, ICD-10. Low education with an increased risk of AD.</td>
<td></td>
</tr>
<tr>
<td>2004, Canada</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Note: DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; CAMDEX = Cambridge Examination for Mental Disorders of the Elderly; CDR = Clinical Dementia Rating; NART = National Adult Reading Test; ICD-10 International Classification of Disease, Tenth Revision; MMSE = Mini-Mental State Examination; ADL and IADL = Activities of daily living and instrumental activities of daily living; CES-D = Center for Epidemiologic Study of Depression scale.
<table>
<thead>
<tr>
<th>Study, Year, Country</th>
<th>n</th>
<th>Age at baseline (years)</th>
<th>Follow-up (years)</th>
<th>Education</th>
<th>Methods/Criteria</th>
<th>Reported associations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stern et al, 1995, USA [132]</td>
<td>246</td>
<td>Mean age=83.9</td>
<td>1-4</td>
<td>Years of schooling: ≤8, &gt;8</td>
<td>DSM-III-R, NINCDS-ADRDA</td>
<td>Increased mortality in patients with higher education: RR=1.8 95% CI=1.1 - 2.8</td>
</tr>
<tr>
<td>Geerlings et al, 1997, Netherlands [150]</td>
<td>4,051</td>
<td>65-84</td>
<td>4</td>
<td>8-point ordinal scale; lower education (uncompleted and completed primary high school, approximately ≤6 years) vs. higher education (some secondary education through university, approximately &gt;6 years)</td>
<td>CAMDEX, NINCDS-ADRDA</td>
<td>Decreased mortality in patients with higher education: RR=0.9 95% CI=0.9-1.0 in the whole pop., RR=0.9, 95% CI=0.6-1.2 in AD cases</td>
</tr>
<tr>
<td>Helmer et al, 2001, France [151]</td>
<td>3,675</td>
<td>65+</td>
<td>8</td>
<td>With or without CEP (Certificat d'Etudes primaires, primary school certificate)</td>
<td>DSM-III-R NINCDS-ADRDA, Hachinski score</td>
<td>No significant effect of education on survival: RR=1.0 95% CI=0.7-1.5 for dementia cases and RR=0.9 95% CI=0.5-1.4 for AD cases</td>
</tr>
<tr>
<td>Qiu et al, 2001, Sweden [57]</td>
<td>1,296</td>
<td>≥75</td>
<td>8</td>
<td>Elementary school and/or vocational training (&lt;8 years) vs. high school (8-10 years) or university (≥11 years)</td>
<td>DSM-III-R, CDR</td>
<td>Decreased mortality in subjects with low education. Results no longer significant after adjustment for dementia severity (CDR score)</td>
</tr>
<tr>
<td>Wolfson et al, 2001, USA [148]</td>
<td>14,026</td>
<td>65+</td>
<td>5</td>
<td>Years of schooling: ≤8, &gt;8</td>
<td>DSM-III-R, NINCDS-ADRDA, ICD-10</td>
<td>There was no significant difference in survival between subjects with more than eight years of education and those with eight or fewer years of education</td>
</tr>
<tr>
<td>Brehaut et al, 2004, Canada [149]</td>
<td>10,263</td>
<td>65+</td>
<td>5</td>
<td>Low education (&lt;8 years), medium education (8-12 years), high education (&gt;12 years)</td>
<td>DSM-III-R, NINCDS-ADRDA, ICD-10</td>
<td>In demented or cognitively impaired subjects, no relationship between education and mortality. In cognitively intact subjects an inverse relation between education and mortality was found</td>
</tr>
<tr>
<td>Tschanz et al, 2004, USA [153]</td>
<td>355 individuals with dementia and 4,328 without</td>
<td>Mean age 83.3 (SD 7.0) years with dementia and 73.7 (SD 6.8) years without</td>
<td>5</td>
<td>Years of schooling: mean (SD) 12.4 (2.8)</td>
<td>DSM-III-R, CDR</td>
<td>After inclusion of all covariates, there was only a slight trend toward inverse association of education with mortality risk (adjusted HR for 1-year increase of schooling=0.98, 95% CI=0.96-1.01).</td>
</tr>
<tr>
<td>Nitrini et al, 2005, Brazil [154]</td>
<td>1,393</td>
<td>65+</td>
<td>3</td>
<td>Educational level: greater than or equal to vs. less than the median of years of schooling; illiterate vs. literate</td>
<td>DSM-IV, NINCDS-ADRDA, NINDS-AIREN</td>
<td>Illiteracy was associated with higher mortality in the population as a whole, however, this was not included in the multivariate analysis</td>
</tr>
</tbody>
</table>

Note: DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association; CAMDEX = Cambridge Examination for Mental Disorders of the Elderly; CDR = Clinical Dementia Rating; ICD-10 = International Classification of Disease, Tenth Revision; NINDS-AIREN = the National Institute for Neurological Diseases and Stroke—Association Internationale pour la Recherche et l'Enseignement en Neurosciences
Interpretation of the findings

In which way could education and cognitive impairment, or full dementia, interact with each other? In the interpretation of the findings some issues have to be taken into account. Firstly, the effects of potential confounders, such as cognitive functioning prior to dementia, vascular diseases, and SES, have been largely neglected by most studies addressing the association of education and dementia. Secondly, there are some differences in the studies that do not allow a complete comparability of the results. In particular, the studies differ in population structure and educational levels. Some studies included only highly educated subjects and actively excluded illiterates; other studies examined only few illiterates. In addition the years of education are not completely comparable among different countries.

Several explanations have been proposed to justify the relationship between education and dementing disorders:

1. Education increases brain reserve (Katzman, 1993 [94])
2. Education is an indicator of mental activity throughout life, which increases cognitive reserve (Stern, 1994 [134]; Orrell & Sahakian, 1995 [157]; Fratiglioni, 2000 [58]; Wang, 2002 [59])
3. Education is an indicator of SES (Fratiglioni, 1991 [158]) or an indicator of multiple exposures to which low educated subjects are more exposed (brain battering hypothesis) (Del Ser, 1999 [159])
4. Education is a surrogate of intelligence (Plassman, 1995 [160]; Gatz, 2001 [129])
5. Education determines a detection bias (Qiu, 2001 [57])
6. Education determines a test bias (Ganguli, 1991 [161])

Education increases brain reserve

According to Katzman [94], people with higher education are thought to have greater “brain reserve” in the form of increased synaptic density in the neocortex. In these subjects, the onset of dementia symptoms would be delayed and, at the same level of clinical severity, brain damage is worse than in subjects with less education. Many studies have, in fact, found the presence of a large cognitive variation between individuals with similar brain structural changes, with regard to location and extent [162]. The source of such differences seem to originate from various contributing factors, including environmental condition in childhood, such as nutrition [163-166], or genetics [167,168].

This hypothesis has been classified by Stern et al [169] as a passive model of the cognitive reserve theory. It presupposes that there are individual differences in brain reserve capacity (BRC) that might include different brain size
or synapse count. There is a critical threshold of BRC, and clinical manifestations of cognitive deficits emerge only when this threshold is exceeded. According to this hypothesis, individuals with bigger brain size have a higher number of healthy synapses or neurons and an increased number of remaining available ones during the pathological process, so that they can tolerate more pathology than those with less reserve. This can be seen as a passive role of cognitive reserve, which focuses on the “hardware” of the brain [170-175].

**Education is an indicator of mental activity throughout life (cognitive reserve)**

Stern et al introduced the concept of “cognitive reserve” [134] in the form of a not well-identified coping reserve against dementia in persons with higher educational attainment. This hypothesis arises from the repeated observation that clinical manifestations of dementia are not directly related to the degree of brain pathology or brain damage. Something must account for this disjunction, and the concept of reserve has been proposed to serve this purpose. Brain cognitive reserve is a complex concept that can be determined and defined by different components, which are not mutually exclusive: 1) the initial number of neurons and/or the density of their interconnections in youth after full development (the so-called passive model of the cognitive reserve hypothesis); 2) the collection of strategies for solving problems, that is to say the ability to cope with advancing brain pathological abnormalities, remaining free from cognitive impairment symptoms; and 3) the amount of brain functional tissue remaining at any age.

This hypothesis is supported by the findings of a lower risk of dementia in subjects with a high level of intellectual components in occupational attainment [176]. Furthermore, even mental stimulation during old age has been suggested to protect against cognitive decline and dementia [45]. In conclusion, according to this hypothesis, education could be considered a component of lifestyle in general. For all the three-lifestyle components (social, mental and physical), a beneficial effect on cognition and a protective effect against dementia is suggested. Thus, both social interaction and intellectual stimuli may be relevant for preserving mental functioning in the elderly [58,59].

This hypothesis is referred to by Stern [177] as an “active model of the reserve hypothesis” as it focuses on the potential active aspects of cognitive reserve; the “software” of the brain. Cognitive reserve could be increased both by a more efficient use of the same brain network normally involved in everyday brain activity, or by a recruitment of alternative brain networks. Aspects of life experience, like education, occupation, and leisure activities, could increase the
synaptic activity, and make circuits of synaptic connectivity more efficient, even if the number of neurons or synapses might be the same. In response to brain damage, patients in whom pathology compromises the ability to mediate tasks through the same brain network used by the controls, compensate by using alternative brain structures or areas during task performance (compensation theory).

**Education is an indicator of socioeconomic status or multiple exposure**

According to this hypothesis, educational attainment is an indicator of SES. Individuals with a lower educational level generally gather a lower SES than those with higher education, linked to a more risky lifestyle which favors the exposure to environmental and behavioral risk factors of dementia [158]. As reviewed by Mortimer [93], higher education levels might stand for good lifestyle in general, better nutrition, low-risk behaviors and health practices, lower exposures to environmental risk factors, and higher self-care in general.

One possible explanation is that higher education contributes to preserve individuals from vascular brain lesions, in which an association with low SES is well documented [58,94,116,178-182]. In fact, several experimental, neuropathological, and epidemiological studies suggest the role of vascular disorders and vascular risk factors on the pathogenesis and progression of dementia and cognitive impairment [52,183]. Qiu et al [184], found that both low diastolic and high diastolic pressure are associated with an increased risk of AD and dementia in the elderly. In addition, SES related conditions such as obesity [185], smoking [186] and high alcohol consumption [187] are related to an increased risk of dementia.

Del Ser et al [159], expanded this hypothesis by suggesting that people with greater educational attainment reach higher SES and thus may be exposed to fewer toxins and enjoy a generally healthier lifestyle. This protects the brain from lesions leading to dementing disorders (the so called "brain battering" hypothesis) [159,188].

**Education is a surrogate of intelligence**

According to this hypothesis, educational level is unlikely to directly influence the pathogenic events that could lead to the development of dementia, but genetic or environmental factors which affect Intelligence Quotient (IQ) and cognitive ability could be mediators of the association [89,189]. Intelligence in childhood was demonstrated to substantially determine the level of cognitive ability in old age [190]. Educational and occupational levels are, according to this hypothesis, likely surrogates for intelligence [129,160]. In order to shed more light on this...
topic, Plassman et al [160], examined the relation of education and intelligence in early adult life to cognitive functioning in a group of 930 elderly male twins. The findings suggested that basic cognitive abilities in late life are related to cognitive performance measures from early adult life (i.e., education and IQ).

**Education determines a detection bias**

Low education could induce an anticipation of a dementia diagnosis due to lower capability to find compensatory strategies of those subjects in comparison with more educated people. The fact that lower education is not associated with increased dementia-related mortality (see previous paragraph) supports this hypothesis. Lower educated subjects would be diagnosed in earlier stages of AD than higher educated people [57] when symptoms and neuropathological lesions are in earlier stages. This means that education will affect time of diagnosis but not the course of the disease [57]. This hypothesis is supported by a longitudinal study [191], where more rapid decline was detected in AD patients with higher educational attainment. The association of education to cognitive decline might shift after dementia is clinically evident, with high educated patients experiencing more rapid cognitive decline because they are supposed to have a relatively greater burden of AD pathology, and the protective role of education are assumed to decrease as the level of pathology increases [191]. However, Le Carret et al [192] proposed an alternative explanation of these findings still in line with cognitive reserve hypothesis. In fact, this study showed that the cognitive deterioration of AD patients involves different cognitive domains depending on education, although the global performance was similar in all patients. The low educated patients had greater impairment of memory and attentional function, whereas the high educated patients exhibited greater impairment of abstract thinking. This finding suggests that some cognitive processes, such as abstract thinking, decline more quickly in high educated patients while others seem to progress more slowly if compared to low educated subjects. Le Carret and colleagues concluded that, in this latter case, high educated patients may still benefit from cognitive reserve after the diagnosis of the dementia.

**Education determines a test bias**

Low educated subjects perform worse in neuropsychological tests independently of pathological processes. Several studies have shown how persons with higher education perform better in cognitive tests than less educated ones [161]. In particular, education was found to slow the rate of decline on crystallized
intelligence, but not other cognitive abilities. Lower education seems to be predictive of decline on tests of language and knowledge, but not on tests of cognitive speed, memory, or reaction time, and to be independent from health, disability, or activity level [193,194]. However, dementia diagnosis is based on a clinical judgment integrating results from neuropsychological tests and clinical examination. This procedure should be less affected by educational levels.

CONCLUSIONS

The analysis of the literature shows the relevance of education as a risk factor for dementia and cognitive disorders. While there is strong evidence that low education increases the risk of dementia and cognitive impairment, there are still several questions concerning the possible mechanisms underlying this association. The investigation of the biological mechanisms that lead to the formation and preservation of cognitive reserve could be the starting point for the development of a set of preventative strategies, to avoid or delay the onset of cognitive impairment and dementia in the elderly.

Further research is needed to clarify the role of possible confounders, such as personality or intelligence in childhood and adulthood. The other open question concerns the relationship between educational level and occupational attainment and their reciprocal interaction with dementia and cognitive impairment. It is especially relevant to verify this issue in populations with different sociocultural environments.
AIMS

The general aim of this doctoral thesis is to explore the complex relationship between education, dementias, and cognitive impairment. The specific aims addressed in five studies are summarized as follows:

**Study I**: To assess the association between AD and other dementias with education under the hypothesis that high educational levels may protect against these disorders;

**Study II**: To examine the relationship between HIV-1-related cognitive impairment and education, controlling also for risk behaviors and clinical status;

**Study III**: To detect the effect of education on both cognitive impairment and dementia in a large population of 61+ old persons;

**Study IV**: To explore whether the association between low education and dementia or cognitive impairment may be explained by the presence of other diseases such as vascular diseases or other severe conditions;

**Study V**: To determine whether the reported association between low education and increased risk of cognitive impairment and dementia could be explained by occupation-based SES.
METHODS

The data of this thesis are gathered from two different sources: the Faenza and the AIDS Projects.

THE FAENZA PROJECT: STUDIES I, III, IV, AND V

General description and study population

The Faenza Project is a longitudinal study on ageing and dementia, targeting all the inhabitants of Faenza (including the village of Granarolo), Italy, aged 61 years and older on December 31, 1991. Of the eligible subjects, 7,930 participated in the survey. Faenza and Granarolo are towns in a wealthy rural area of central Italy. Lists of residents were obtained from the administrative office in the town. All persons registered at the administrative office were included in the study.

Study design

A two-phase study design was implemented in order to identify demented subjects. To minimize the number of false negatives, two screening instruments were used, one more cognitively oriented (MMSE [195]), and the other more functionally oriented (Global Deterioration Scale; GDS [196]). The MMSE and GDS were administered to each person at their home by two trained nurses and by two physicians, respectively. On the same occasion, each individual received a semi-structured interview assessing information on medical history and sociodemographic variables, including education, occupational exposure, alcohol consumption, and smoking habits. Data were obtained directly from the cognitively intact participant and/or from an informant, who was usually a close relative, when the subject was cognitively impaired.

Persons who had MMSE ≤28 and/or GDS ≥2 were clinically examined in the second phase by specialists using a semistructured general and neurological examination. Table 10 summarizes the time schedule, the study population and types of examination in the Faenza Project.
In Study I, the study population consisted of the subpopulation of Granarolo. Granarolo is a village in a rural area of northern Italy with middle to high SES since the beginning of the 1950s. In this subpopulation, the clinical examination and the neuropsychological assessment was more comprehensive than in the whole project. The screened-positive subjects underwent a general and neurological examination, and testing with a neuropsychological battery, which included 1) the 12-item Information Orientation (I/O) subscale from the Clifton Assessment Procedures for the Elderly [197]; 2) the Wechsler Memory Scales logical memory test [198]; 3) the Buschke and Fuld Test [199]; and 4) the Blessed-Roth [200] Information-memory-concentration test. Depression was assessed by the Geriatric Depression Scale [201].

### Data collection

#### Education

Education was assessed by asking the numbers of years of schooling. For the persons who did not participate, information for education was gathered from the Municipality Demographic Office. In Italy, at the time subjects went to school the first and second educational degrees were achieved after three and five years of schooling. For that reason we used the following categories of education: a) no education; b) one to three years of education; c) four to five years of education; d) over five years of education.

#### Occupation

As occupation can be used to define SES [55], the occupation held for the longest period during working life was recorded and used to create simple occupation-based SES categories: high SES (white-collar, craftsmen, shopkeepers) and low SES (farmers, factory workers, homemakers). This grouping took into account...
the type of economy present in that area when participants were of working age; mainly agriculture, commerce, and crafts. For some participants, data concerning working activity were not available leading to missing values for SES in 396 subjects out of 7930 (5.0%).

**Life habits**
The maximum alcohol consumption, held for at least one year during the whole life, was registered. Categories of alcohol consumption were: 1) no consumption; 2) up to half a liter of wine, or equivalent, per day; 3) from half to one liter of wine, or equivalent, per day; 4) over one liter of wine, or equivalent, per day. In the analyses, alcohol consumption was dichotomized into consumption of more than half liter of wine per day vs. less than half liter or no consumption. Smoking habit, held for the longest period in life, was recorded using the following categories: 1) no smoking; 2) up to ten cigarettes per day; 3) from ten to twenty cigarettes per day; 4) over twenty cigarettes per day. In the analyses, smoking habit was dichotomized into smoking at least ten cigarettes per day vs. none to nine cigarettes per day.

**Diagnosis of dementia**
The DSM-III-R [7] diagnostic criteria were used for the clinical diagnosis of dementia. We used a double diagnostic procedure to improve the validity of the final diagnosis [158]. A first preliminary diagnosis was made by the two physicians who had examined the patients and a second diagnosis was made by a psychiatrist, who was blind to the previous clinical conclusions. If the two diagnoses were in agreement, no further examination was made. If they differed, the data were re-examined independently, and if disagreement persisted, a final diagnosis was made by a senior clinician.

In **Study I**, the differential diagnosis between AD and VaD was based on clinical data because neuroimaging was not carried out in all cases. The Hachinski Ischemic Score [202] was added to the neurological evaluation to help in differentiating AD from VaD: a score over six indicated VaD, a score under five indicated AD, and five or six indicated mixed dementia (MD). In addition, the temporal sequence of events (the onset of dementia symptoms and occurrence of stroke) was considered by the physician.

**Diagnosis of Cognitive Impairment No Dementia**
CIND was defined by using the MMSE scores, corrected for age and education according to Magni et al [203]. These authors provided normative scores derived from an 1169-large population in North Italy. Sixteen adjustment coefficients for
the MMSE raw scores of four age intervals (every five years from 65 to 89), and four educational levels (0-4, 5-7, 8-12, and 13-17 years of schooling), were estimated by Magni et al. For subjects aged 61-64 and over 89 years, the same coefficients as that of the closest categories were used in our study.

A subject was classified as affected by CIND, if he/she scored two or more standard deviations lower than the mean score of the corrected MMSE calculated among the nondemented people.

**Diagnosis of stroke**

Stroke was defined according to the World Health Organization criteria (ICD-8, codes 430-438). The diagnosis was based on direct questioning of the participant and the next of kin or caregiver supplemented by a neurological examination, and/or review of existing medical records. The Faenza medical center has been the major health care provider in Faenza, and approximately 95% of all stroke patients in that region are hospitalized there.

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**THE AIDS PROJECT: STUDY II**

The AIDS Project is a longitudinal study on HIV-1-related cognitive impairment.

**General description and study population**

The study sample included consecutive outpatients examined at the Division of Infectious Diseases, University of Bologna, Italy. Participants were recruited between December 1994 and December 1997. Every person attending the outpatient service was asked to participate. All patients underwent a neurological examination before enrollment. We excluded from the sample subjects affected by previous/current cerebral opportunistic infections or other neurological diseases and/or psychiatric pathologies (such as schizophrenia, delusional disorders, mood disorders, anxiety disorders).

**HIV-1 Infection**

All subjects were evaluated with HIV-1 serological tests using standardized methods. On the basis of this analysis the subjects were divided into HIV-1-seronegatives and HIV-1-seropositives. The staging in asymptomatic and symptomatic subjects was performed according to the Centers for Disease Control and Prevention.
Control and Prevention of Atlanta (CDC) criteria [204], without taking into account the CD4+ cell count. Information concerning CD4+ cell counts was available in 73.1% of seropositive persons. These subjects were grouped in three levels of CD4+ cell count [205]: less than 200/μL, 200 to 499/μL, and 500/μL or greater. Finally, according to the self-reported at-risk behavior, people were classified into four groups: 1) homosexual/bisexual, 2) heterosexual, 3) injecting drug users (IDUs), and 4) hemophiliacs. Concerning IDUs a "significant" history of drug abuse was required, which is an abuse of psychoactive drugs for more than five years, with a frequency of use of at least three times per week [88]. No individuals from our sample, according to the self-reported at-risk behavior, reported both homosexual/bisexuality and injecting drug use behaviors.

**Data collection**
Each individual was first examined by a physician performing a comprehensive clinical examination and was then evaluated by a neuropsychologist. The clinical examination included a semi-structured interview concerning sociodemographic variables, education expressed as years of schooling, medical history, personal psychiatric history (including previous/current psychoactive substance use disorders), and previous/current antiretroviral treatment. Data were obtained from an informant (usually a close relative) when the subject was cognitively impaired.

During the second contact, a neuropsychological evaluation and a psychiatric assessment were carried out by specialists. The HIV-1 serostatus and any on-going antiretroviral treatment were unknown to the examiners. Depression was assessed by the Hamilton Depression Scale [206], in which a score of at least sixteen indicated the presence of prominent depressive symptoms. The neuropsychological battery included tests that were used in previous studies concerning HIV-1 and cognition [207]. These tests were: the Verbal Fluency test [208], the Rey 15 Words Short Term (ST) and Long Term (LT) [209], and subtests from Wechsler Scale [210] (Digit span; Digit Symbol; Vocabulary; Block Design). The neuropsychological battery was administered in a fixed order.

**Definition of cognitive impairment**
HIV-1-related cognitive impairment was defined on the basis of a cognitive battery where the cut-off scores for each test were derived from normative values [77] or from HIV-1-seronegative controls [78,79]. However, a wide range of neuropsychological deficits are reported to be associated with substance abuse [211,212-215] and hemophiliacs [216,217] are more likely to have cognitive
deficits due to brain damage as compared to homo-bisexuals/heterosexuals. Thus, risk behaviors were taken into account in the definition of cognitive impairment.

![Figure 6. Performance of the 90 HIV-1-seronegatives in Verbal fluency, Vocabulary, Digit span, Digit symbol, Block design, Rey 15W-ST and Rey 15W-LT expressed as mean values](image)

Cognitive impairment was defined as poor performance on at least two of the seven neuropsychological tests included in the battery. Poor performance in a test was considered as a score of two or more standard deviations lower than the mean of the seronegative group in the corresponding risk behavior strata (IDUs, hemophiliacs, and other risk behaviors). The following figure report the means
for each test, according to different risk behaviors, in the seronegative group (figure 6, and table 1, Study II).

**Statistical analyses**

Table 11 summarizes the outcome variables, the determinants under study, and the potential confounders (covariates) that were considered in the five studies. Specific analyses for each study are also reported.

**Ethical issues**

Both the Faenza and the AIDS Projects have received ethical approvals from the Italian and the Swedish Ethical Commissions. All steps have been taken to ensure complete information, informed consent, respect of privacy, and confidentiality. Unuseful burden was always avoided.

All subjects were examined at their homes or received in a warm and comfortable atmosphere, and the examiners provided extra time to establish a friendly environment during the examination.
<table>
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<tr>
<th>Study</th>
<th>Statistical model</th>
<th>Dependent variables</th>
<th>Educational categories</th>
<th>Independent variables</th>
<th>Logistic regression models</th>
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<td><strong>Study I</strong></td>
<td>Logistic regression</td>
<td>Dementia, Alzheimer’s disease, Vascular dementia</td>
<td>As an indicator variable (No education, 1-3 years, and 4+ years), and as a dichotomous variable (0 years vs. 11 years of schooling)</td>
<td>Age (ten years intervals); gender (male vs. female); occupation (homemakers; farmers; factory workers, and white collar workers); alcohol consumption (more than half a liter of wine per day vs less than half liter or no consumption); smoking habit (at least 10 cigarettes per day vs 0-9 cigarettes per day)</td>
<td>A first model included age, gender, and education, and a second included age, gender, education, and occupation. Data on other potential confounders such as smoking, alcohol habits, and blood pressure were available and were introduced in a third model</td>
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<tr>
<td><strong>Study II</strong></td>
<td>Logistic regression</td>
<td>HIV-related cognitive impairment</td>
<td>As an indicator variable (&lt;6 years, 6-8 years, and &gt;8 years), and as a dichotomous variable (&lt;6 years vs. 6+ years of schooling)</td>
<td>Age (1 year increment); gender (female vs male); risk behavior (homosexual/bisexual, heterosexual, and IDU; hemophiliac, and IDU/haemophiliac vs. homosexual/bisexual and heterosexual); CD4+ cell count (&lt;200/µL, 200-499/µL, and ≥500/µL); stage of HIV-1 infection (symptomatic vs asymptomatic); presence of prominent depressive symptoms (no vs yes); and antiretroviral treatment (any vs none)</td>
<td>A first model included age, gender and education; a second included age, gender, education, and stage of HIV-1 infection; a third included age, gender, education, stage of HIV-1 infection, and antiretroviral treatment; a fourth included age, gender, education, stage of HIV-1 infection, antiretroviral treatment, and risk behaviors. Analyses were repeated separately for symptomatics and asymptomatics. Sensitivity analysis of missing CD4+ cell counts was conducted by producing 2 extreme imputations. This analysis assumed that all participants with missing CD4+ cell counts had counts of 499/µL or less (imputation 1) or counts of 500/µL or greater (imputation 2). All the analyses were repeated in these 2 imputations</td>
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<td>Study III</td>
<td>Logistic regression</td>
<td>Dementia, Cognitive Impairment No Dementia (CIND)</td>
<td>As an indicator variable (No education, 1-3 years, 4-5 years, and 6+ years), and as a dichotomous variable (0-3 years vs. 4+ years of schooling)</td>
<td>Age (five years intervals; 75+ years vs. 61-74 years); gender (male vs. female)</td>
<td>A first model included age, gender and education. In a second model we repeated the logistic regression analysis in the two subpopulations of lower (0-3 years of schooling) and higher (4+ years of schooling) educated subjects. In a third model we investigated whether there was a synergistic effect between gender and years of schooling on the risk of dementia and CIND by including an interaction term in the logistic regression model</td>
</tr>
<tr>
<td>Study IV</td>
<td>Logistic regression</td>
<td>Dementia, cognitive impairment</td>
<td>As a dichotomous variable (0-3 years vs. 4+ years)</td>
<td>Age (75+ years vs. 61-74 years); gender (male vs. female); stroke (absent vs. present)</td>
<td>A first model included stroke, age, gender and education. The combined effect of age (younger vs. older), schooling (lower vs. higher education) and stroke on level of cognitive functioning was assessed by combining them in an indicator variable, with the reference group as being young (61-74 years) with higher education (4+ years of schooling) and no history of stroke. Additional models were used to verify the possible confounding effect of occupation, and life habits (smoking and alcohol intake)</td>
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<tr>
<td>Study V</td>
<td>Logistic regression</td>
<td>Dementia, cognitive impairment</td>
<td>As an indicator variable (No education, 1-3 years, 4-5 years, and 6+ years), and as a dichotomous variable (0-3 years vs. 4+ years of schooling)</td>
<td>Age (1 year increment, and 60-75 vs. &gt;75 years); gender (male vs. female); occupation-based SES (low vs high)</td>
<td>A first model included age, gender, and education; a second model included age, gender, and occupation; a third model included age, gender, education and occupation. To investigate the combined effect of both education and SES the following pairs of possible combinations were tested: low education and low SES; low education and high SES, high education and low SES and high education and high SES (reference)</td>
</tr>
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</table>
RESULTS

THE FAENZA PROJECT

Characteristics of the educational level of the study population

Of the 12,743 subjects aged 61 years and older at prevalence day in Faenza, 811 (6.4%) died before they were examined and 4002 (31.4%) refused participation, leaving 7,930 people included in the study population (table 1, Study III).

Dead subjects. Results of a logistic regression model, where being dead was the dependent variable, showed that the deceased subjects were older and more frequently men. The odds ratios (OR) for death were 1.09 (95% CI=1.08-1.10) for an increment of one year of age, 0.5 (95% CI=0.4-0.6) for being a woman. No significant differences between deceased subjects and participants were found for years of education.

Refusals. Results of a logistic regression model, where being a refusal was the dependent variable, indicated that the subjects who refused to participate in the study were younger, more frequently men, and less educated than the people who underwent the clinical examination. The ORs were 0.97 (95% CI=0.96-0.97) for an increment of one year of age, 0.7 (95% CI=0.7-0.8) for being a woman, and 0.95 (95% CI=0.94-0.97) for an increment of one year of education.

In the Granarolo subpopulation, 76 persons (13.6%) did not complete the two phases of the study. They were younger than the examined subjects (60.3% were aged 61-69 years, $\chi^2=40.6$, $p<0.001$) and more frequently men (55.3%, $\chi^2=5.6$, $p=0.018$). The dropouts were due to death (n=6), refusal (n=61), or to changes in residence (n=9).

Participants. The participants were 7,930 subjects, 3,145 men and 4,785 women (table 1, Study III). The mean age ($\pm$SD) was 72.6 ($\pm$8.2) years, ranging between 61 and 107. The mean years of education ($\pm$SD) were 5.1 ($\pm$3.8) with a range of 0-18. Men were younger (72.0$\pm$7.7 vs. 73.0$\pm$8.4, ANOVA, F=29.0, $p>0.001$) and more educated than women (4.7$\pm$3.7 vs. 5.6$\pm$4.0 years of education, ANOVA, F=112.3, $p<0.001$), with double percentage of noneducated persons in the 90+ age group (34.3% among women and 17.1% among men). Among all participants, noneducated subjects accounted for 8.3% among men and 12.4% among women. The distribution of educational levels by age and gender of the Faenza and Granarolo study population is shown in figures 7 and 8.
Results

The Granarolo subpopulation consisted of 557 subjects with similar age, gender and education distribution to the Faenza cohort.
Occurrence of dementia and cognitive impairment in relation to education

Cases. After the diagnostic procedure, 513 subjects were diagnosed as affected by clinically definite dementia and 402 by CIND. No dementia cases were detected among men before the age of 65. Among women, eleven cases were identified in this age group. Eight of the eleven demented women had less than four years of schooling. In contrast, 40 CIND cases were detected among both sexes in this younger old population, and 34 of the 40 cases were educated for less than four years. The majority of the demented cases, both men and women, had a low level of education, as 80.5% had less than four years of schooling. The corresponding figure for CIND cases was 75.6%.

Prevalence of dementia and CIND. The prevalence of dementia was 4.9 per 100 (95% CI=4.2-5.7) among men and 7.5 per 100 (95% CI= 6.7-8.2) among women. The prevalence of CIND was 4.1 per 100 (95% CI=3.4-4.8) and 5.7 per 100 (95% CI= 5.1-6.4) among men and women, respectively. The age- and gender-specific prevalence of dementia and CIND are reported in table 12.

| Table 12. Number of dementia and CIND cases (No), gender-specific prevalence (p) and 95% CI per 100 population in Faenza and Grinarolo |
|---------------------------------------------------------------|-------|-------------|-------|-------------|
| Age groups | Dementia | | | CIND | | |
| | No. | p | 95% CI | No. | p | 95% CI |
| 61-64 | | | | | | |
| 65-69 | 6 | 0.8 | 0.2-1.4 | 13 | 1.2 | 0.5-1.8 |
| 70-74 | 10 | 1.8 | 0.7-2.9 | 25 | 3.2 | 2.0-4.5 |
| 75-79 | 34 | 5.6 | 3.8-7.4 | 51 | 6.0 | 4.4-7.6 |
| 80-84 | 55 | 15.0 | 11.4-18.7 | 89 | 13.1 | 10.6-15.7 |
| 85-89 | 39 | 23.1 | 16.7-29.4 | 86 | 26.9 | 22.0-31.7 |
| 90+ | 11 | 26.8 | 13.3-40.4 | 83 | 49.1 | 41.6-56.6 |
| Total | 155 | 4.9 | 4.2-5.7 | 358 | 7.5 | 6.7-8.2 |
| Age groups | Dementia | | | CIND | | |
| | No. | p | 95% CI | No. | p | 95% CI |
| 61-64 | 15 | 2.4 | 1.2-3.7 | 40 | 4.6 | 3.2-6.0 |
| 65-69 | 20 | 2.5 | 1.4-3.6 | 29 | 2.6 | 1.6-3.5 |
| 70-74 | 18 | 3.2 | 1.8-4.7 | 37 | 4.8 | 3.3-6.3 |
| 75-79 | 29 | 4.8 | 3.1-6.5 | 71 | 8.4 | 6.5-10.3 |
| 80-84 | 29 | 7.9 | 5.2-10.7 | 55 | 8.1 | 6.1-10.2 |
| 85-89 | 14 | 8.3 | 4.1-12.4 | 27 | 8.4 | 5.4-11.5 |
| 90+ | 3 | 7.3 | 0.0-15.3 | 15 | 8.9 | 4.6-13.2 |
| Total | 128 | 4.1 | 3.4-4.8 | 274 | 5.7 | 5.1-6.4 |
The prevalence of CIND was higher than dementia prevalence in the youngest old groups (61-74 years) both in men and women, whereas the opposite pattern was present among the older old (75+). In the older age groups, dementia prevalence increased exponentially with age, while CIND prevalence was stable. There was not a substantial gender difference in CIND prevalence in all ages. Very old women had higher prevalence of dementia than men, but this difference was not statistically significant.

Age- and education-specific prevalence figures, separately for dementia and CIND, are reported in figures 9 and 10. A twofold prevalence was found in 75+ years old women than in coetaneous men in the subpopulation of more highly educated subjects.
In Study I, the differential diagnosis between AD, VaD and other dementia types was also made. Of the 56 demented subjects, 29 subjects (51.8%) were affected by AD, 14 by VaD (25%), nine (16.1%) by mixed dementia and four cases (7.1%) by secondary dementias. The secondary cases of dementia consisted of two patients with dementia in Parkinson's disease, one case of alcoholic dementia, and one patient with an intracranial tumor. AD accounted for approximately half of the prevalence of all dementias in all age groups. The prevalence of all dementias, as well as AD, increased steeply every five years of age for both men and women up to 90 years of age. Women had a higher prevalence of all dementias and AD than men, and was more evident in the advanced ages.

Figure 11 displays the prevalence of AD according to age and three educational levels (no education, one to three years, and more than three years of education).

![Figure 11. Age-specific prevalence per 100 persons for Alzheimer's disease by education in the Granarolo's study population.](image)

The prevalence of AD was much higher among noneducated subjects than among the other subjects in all age groups. However, no reliable difference was found between subjects who received education up to the three years and subjects who were educated for over three years. The distribution by education exhibited similar patterns after stratification by gender.
Results

Effect of education on dementia and CIND risk

In *Study III*, when age, gender, and education were introduced in the same logistic regression model (table 3, *Study III*), the results confirmed an exponential increase of prevalence with increasing age only for dementia, but not for CIND, and showed no gender differences either for dementia or CIND. In addition, a dramatic increased risk for both dementia and CIND was associated with no education (table 13).

Due to the strong effect of education, we repeated the logistic regression analysis in the two subpopulations of lower (no to three years of schooling) and higher (four or more years of schooling) educated subjects (table 4, *Study III*). The effect of age on dementia and CIND occurrence was similar in the two subpopulations, but a higher risk among women than in men was detected in the higher educated people. Further, we investigated whether there was a synergistic effect between gender and years of schooling on the risk of dementia and CIND by including an interaction term in the logistic regression models. No significant interaction was detected.

Effect of education on dementia types risk

In *Study I*, several logistic regression models were constructed to examine the association between gender, age and educational levels, for AD and VaD (table 14). Occupation was taken into account as a possible confounder, but the introduction of this variable in the models did not change the results at all.
When alcohol consumption, smoking habit, and current or previous history of hypertension were introduced in the models, the results on education remained unchanged.

Following the hypothesis that noneducated subjects may develop dementia at an earlier age, we studied the effect of no education on dementia in different age strata. The ORs separately for different age groups are reported in Table 6, Study I. We found an extraordinarily strong association between no education and dementia among people aged 61-69 years, and a decreasing trend with increasing age (table 15).

### Table 14. Adjusted Odds ratios (ORs) and 95% confidence intervals (95% CI) for AD and VaD due to different educational levels. Data from logistic regression models

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s Disease</th>
<th>Vascular dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age- and gender-</td>
<td>Age- and gender-</td>
</tr>
<tr>
<td></td>
<td>and occupation-</td>
<td>and occupation-</td>
</tr>
<tr>
<td></td>
<td>adjusted OR</td>
<td>adjusted OR</td>
</tr>
<tr>
<td></td>
<td>(95%CI)</td>
<td>(95%CI)</td>
</tr>
<tr>
<td>No education</td>
<td>11.7 (2.4-57.1)</td>
<td>4.3 (0.9-19.4)</td>
</tr>
<tr>
<td>1-3 years of education</td>
<td>2.9 (0.6-13.6)</td>
<td>0.8 (0.2-3.8)</td>
</tr>
<tr>
<td>4+ years of education</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.0)</td>
</tr>
</tbody>
</table>

### Table 15. Number of demented cases in illiterates and subjects with at least one year of education

<table>
<thead>
<tr>
<th>Age groups (y)</th>
<th>No education</th>
<th>1+ years of education</th>
</tr>
</thead>
<tbody>
<tr>
<td>61-69</td>
<td>3/11</td>
<td>0/186</td>
</tr>
<tr>
<td>70-79</td>
<td>6/21</td>
<td>8/154</td>
</tr>
<tr>
<td>80+</td>
<td>15/33</td>
<td>24/90</td>
</tr>
</tbody>
</table>
Stoke, education, dementia, and cognitive impairment

The age- and gender-specific prevalence of dementia and cognitive impairment in patients with and without a history of stroke are reported in figure 12. The prevalence of dementia and cognitive impairment was higher among stroke patients than among individuals with no history of stroke. Dementia prevalence reached the high value of about twenty per cent in the age group of 75-79 years in the subpopulation with a history of stroke, while the same prevalence was present in the age group of 85-89 years in the subpopulation without a history of stroke. In persons without a history of stroke, dementia prevalence became more frequent than cognitive impairment prevalence at age 85 years, while in patients with a history of stroke dementia became more frequent than cognitive impairment prevalence at age 75 years. These results were similar when men and women were analyzed separately.

Effect of stroke on dementia and cognitive impairment by age and education

History of stroke was more strongly associated with dementia (OR=3.7, 95% CI 3.1-4.4) than with cognitive impairment (OR=1.7, 95% CI 1.4-2.2). Analyses were repeated separately for men and women, for younger old (61-74 years) and older old (75 years and over), and for subjects with low or high education (Table 3, Study IV).
Gender did not modify the effect of stroke on dementia and cognitive impairment. In contrast, the association between stroke and dementia was heavily modified by both age and education. The risk was two-fold stronger in younger old people than in the oldest old, and in higher educated than lower educated persons (Table 16). No clear modification due to age was present for cognitive impairment.

Table 16. Association between history of stroke and dementia and cognitive impairment: age- and gender-adjusted Risk Ratios (RRs) and 95% Confidence Intervals (95% CI) of cognitive impairment and dementia for stroke

<table>
<thead>
<tr>
<th>Education</th>
<th>Adjusted* RR (95% CI) of dementia due to stroke</th>
<th>Adjusted* RR (95% CI) of cognitive impairment due to stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among lower educated (0-3 years of schooling)</td>
<td>2.9 (2.4-3.7)</td>
<td>1.5 (1.1-2.0)</td>
</tr>
<tr>
<td>Among higher educated (4+ years of schooling)</td>
<td>6.5 (4.9-8.2)</td>
<td>2.9 (1.8-4.4)</td>
</tr>
</tbody>
</table>

As age, education, and occurrence of stroke are strongly correlated, we analyzed the combined effect of these three factors on the occurrence of dementia and cognitive impairment (Table 4, Study IV). A combined effect was detected for increasing age, stroke, and decreasing years of schooling both in dementia and cognitive impairment. Among younger old persons, history of stroke and low education increased the risk of dementia twelve-fold, whereas among older subjects, stroke and low education only doubled the risk of dementia. A different pattern was found in cognitively impaired subjects; stroke and low education had a similar effect on cognitive impairment risk in both younger and older people (Figure 13).

**Occupation-based socioeconomic status, education, dementia, and cognitive impairment**

Education and occupation-based SES were tested in the same logistic regression model which also included age and gender. Both having low education and a low occupation-based SES remained significantly associated with dementia and cognitive impairment (table 17).
Figure 13. Combined effect of stroke, age and education on dementia and cognitive impairment: adjusted risk ratios (RRs)

Table 17. Age- and gender adjusted odds ratios (ORs) of dementia and cognitive impairment associated with education and occupation-based socioeconomic status (SES), derived from the same logistic regression model

<table>
<thead>
<tr>
<th></th>
<th>All subjects (no.)</th>
<th>Dementia cases</th>
<th>OR 95% CI</th>
<th>Cognitive impairment cases</th>
<th>OR† 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low vs. High education</td>
<td>3,529</td>
<td>398</td>
<td>2.8 2.16-3.59</td>
<td>303</td>
<td>3.2 2.45-4.09</td>
</tr>
<tr>
<td>Low vs. High SES</td>
<td>5,161</td>
<td>422</td>
<td>1.9 1.43-2.54</td>
<td>333</td>
<td>1.7 1.30-2.33</td>
</tr>
</tbody>
</table>

Stratified analysis by gender demonstrated the same results but the association between education and dementia was stronger in men than in women; male subjects with low education had an OR (95% CI) for dementia of 4.3 (2.7-6.8), female gender of 2.2 (1.6-3.0) after adjustment for age and occupation-based SES; conversely the risk due to low SES, when age and occupation were simultaneously included into the same model, was the same in both gender strata.

The following table illustrates four combinations of education and occupation-based SES in relation to the risk of dementia and cognitive impairment (table 18). Subjects with low education and low SES had the highest risk of dementia (OR=5.1, 95% CI=3.5-7.3) and cognitive impairment (OR=5.2, 95% CI=3.6-7.6). The data suggest an additive effect of low education and low SES in relation to the risk of dementia with similar results when cognitive impairment was considered as the dependent variable.
Table 18. Combined effect of education, occupation-based SES on dementia and cognitive impairment: age- and gender adjusted Odds Ratios (ORs)

<table>
<thead>
<tr>
<th>Educational level</th>
<th>Occupation based SES</th>
<th>Dementia</th>
<th>Cognitive impairment</th>
<th>Dementia</th>
<th>Cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>1.0</td>
<td>1.0</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>2.5</td>
<td>2.8</td>
<td>5.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

When stratified analysis according to gender was performed (table 4, Study V), after taking into account age, men in the low education and low SES group were three times more likely to develop dementia than women (OR, 95% CI, respectively 9.4, 4.9-18.0, vs. 3.4, 2.2-5.3). On the whole, the combined effect of education and SES was more relevant in men than in women, in fact both men with high education and low occupation based SES and men with low education and high occupation based SES had an increased risk of dementia (OR=2.5; 95% CI=1.2-5.5, and OR=6.1; 95% CI=2.7-13.7, respectively), while the association was no longer significant in female gender (OR=1.3; 95% CI=0.8-2.3, and 1.4; 95% CI=0.7-2.6, respectively). Moreover, after taking into account age, in the low education and low SES group the risk of dementia was three times higher among men than among women (OR=9.4; 95% CI=4.9-18.0 vs. OR=3.4; 95% CI=2.2-5.3, table 4, Study V).
THE AIDS PROJECT

Effect of education on HIV-1 cognitive impairment occurrence

During the period December 1994 to December 1997, 272 consecutive subjects were examined and did not meet any of the exclusion criteria (such as schizophrenia, delusional disorders, mood disorders, anxiety disorders). Among them, 90 (33.1%) were HIV-1-seronegatives, and 182 (66.9%) were HIV-1-seropositives, which included 88 asymptomatic and 94 symptomatic persons.

In figures 14 and 15 some clinical and demographic characteristics of the HIV seropositives are reported.

*Figure 14. HIV-1 study population: distribution of age and educational levels*
Among the HIV-1-seropositive persons, on the basis of performance on the neuropsychological battery, 37 seropositives were classified as cognitively impaired, and 145 as non-cognitively impaired. The prevalence of cognitive impairment according to educational level, risk behavior, and antiretroviral therapy use of the HIV-1-seropositive persons is reported in table 19. Prevalence was higher in subjects with less than six years of schooling than more highly educated people, among persons with no antiretroviral treatment than among treated people, and among heterosexuals than IDUs and hemophiliacs.
The adjusted OR for HIV-1-related cognitive impairment in subjects with less than six years of education was 18.9 (95% CI=3.7-97.6), and 1.3 (95% CI=0.5-3.2) in subjects with five to eight years of education, when compared to subjects with nine+ years of education. Based on these results, education was used as a dichotomous variable and assessed in two multiajusted logistic regression models (models 1 and 2, table 20). Antiretroviral therapy was consistently inversely associated with cognitive impairment. A high OR for HIV-1-related cognitive impairment in both homo-bisexual, and heterosexual, when compared to IDU risk behavior was detected. All previous results were confirmed when the data were adjusted for prominent depressive symptoms.

Table 19. Number of subjects, number of cases and prevalence of cognitive impairment according to educational level, risk behavior, and antiretroviral therapy use

<table>
<thead>
<tr>
<th>Factor</th>
<th>HIV-1–Seropositive Subjects, No.</th>
<th>Cognitive impairment Cases, No.</th>
<th>Prevalence per 100</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>12</td>
<td>7</td>
<td>58.3</td>
<td>30.4-86.2</td>
</tr>
<tr>
<td>6-8</td>
<td>87</td>
<td>16</td>
<td>18.4</td>
<td>10.3-26.5</td>
</tr>
<tr>
<td>≥9</td>
<td>83</td>
<td>14</td>
<td>16.9</td>
<td>8.8-24.9</td>
</tr>
<tr>
<td><strong>Risk behavior</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDUs</td>
<td>104</td>
<td>12</td>
<td>11.5</td>
<td>5.4-17.7</td>
</tr>
<tr>
<td>Homosexual/bisexuals</td>
<td>18</td>
<td>6</td>
<td>33.3</td>
<td>11.6-55.1</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td>45</td>
<td>18</td>
<td>40</td>
<td>25.7-54.3</td>
</tr>
<tr>
<td>Hemophiliacs</td>
<td>15</td>
<td>1</td>
<td>6.7</td>
<td>0.0-19.3</td>
</tr>
<tr>
<td><strong>Antiretroviral therapy use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>156</td>
<td>24</td>
<td>15.4</td>
<td>9.7-21.0</td>
</tr>
<tr>
<td>No</td>
<td>26</td>
<td>13</td>
<td>50</td>
<td>30.8-69.2</td>
</tr>
</tbody>
</table>

Table 20. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (95% CI) for HIV-1 related cognitive impairment. Data from logistic regression models

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Age (for increment of 1 year)</strong></td>
<td>1.0 (1.0-1.1)</td>
<td>1.0 (0.9-1.1)</td>
</tr>
<tr>
<td><strong>Female gender</strong></td>
<td>2.3 (1.0-5.6)</td>
<td>1.6 (0.6-4.8)</td>
</tr>
<tr>
<td><strong>Less than 6 years of education</strong></td>
<td>8.4 (2.2-32.2)</td>
<td>17.2 (3.6-83.3)</td>
</tr>
<tr>
<td><strong>HIV-1 Symptomatics</strong></td>
<td>0.8 (0.4-1.9)</td>
<td>1.4 (0.6-3.5)</td>
</tr>
<tr>
<td><strong>Antiretroviral therapy</strong></td>
<td>0.1 (0.1-0.4)</td>
<td>0.1 (0.0-0.3)</td>
</tr>
<tr>
<td><strong>Risk behaviors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexuals/bisexuals</td>
<td>-</td>
<td>9.6 (2.2-42.7)</td>
</tr>
<tr>
<td>Heterosexuals</td>
<td>-</td>
<td>6.3 (2.2-18.3)</td>
</tr>
<tr>
<td>Hemophiliacs</td>
<td>-</td>
<td>0.3 (0.0-2.5)</td>
</tr>
<tr>
<td>Injecting drug users</td>
<td>-</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>
DISCUSSION

This thesis specifically addresses the role of education in the development of dementing disorders, including dementia, AD, VaD, cognitive impairment, stroke-related cognitive impairment, and HIV1-related cognitive impairment.

The main findings from the thesis are summarized in the following points:

- Low and especially very low education were major determinants of both dementia and cognitive impairment.
- Low education was associated with an increased risk of both cognitive impairment and dementia with a dose-response relationship. The increase was especially evident in subjects with no schooling.
- The strongest association was found between no education and dementia prevalence. This association, although present in all age groups, was stronger among the youngest subjects (61-69 years). The association decreased with increasing age.
- Similar findings were found for AD and VaD, separately.
- Education and age modified the effect of stroke on dementia. The effect was stronger among the younger old (61-74 years of age) and the higher educated subjects (four+ years of schooling).
- The combined effect of stroke with age and education was more evident among the younger old subjects (61-74 years of age) than among the oldest old subjects (75+ years of age).
- Low education and low occupation-based SES were both independent risk factors for dementia and cognitive impairment, and the risk increased in an additive way for subjects with low education and low SES.
- Low education emerged as an independent risk factor also for HIV-1-related cognitive impairment.

We will first discuss issues of internal validity, second we will compare our findings with previous research, and third we will analyze possible interpretations of the results.

INTERNAL VALIDITY

Some general aspects of the design of our studies need to be discussed. The studies in this thesis have the advantage of having well-defined study populations, but are limited by the use of prevalent cases. Our findings are based on prevalence figures, which implies that differential survival among demented subjects with different educational levels or different SES needs to be taken into account. However, low education has been reported associated with lower survival, both in demented [218] and non-demented
subjects [219]. In addition, the cases were ascertained by a two-phase study design probably introducing selection bias due to the use of a screening test (see below). Another disadvantage concerns the exposure assessment, which was retrospective and taken from an informant when the subjects was demented or severely cognitive impaired. In addition the reliability of the assessment of some confounders may be questioned.

Results emerging from this thesis may be affected by selection bias, misclassification of disease, and misclassification of exposures.

**Selection bias**
In the Faenza Project, selection bias may be introduced by the use of a screening phase, as some highly educated cases may have resulted as false negatives. All studied risk factors that are correlated with education, such as occupation, smoking habits, and alcohol intake, can be affected by this underrepresentation of higher educated people among the cases. However, screening bias was minimized by the inclusion of two screening tests, both of which adopted very high cut-off points to ensure high sensitivity, as recommended by Schmand et al [220].

A second source of potential selection bias is the dropouts. The dropouts were more frequently men, had lower education, and were younger. Thus, it is possible that younger men with low education were missed. Risk factors such as stroke, alcohol consumption, smoking habits, and occupation may be affected by this selection. We think that this bias, if any, may have introduced a dilution of the effect. Moreover, this bias may have affected Studies III, IV, and V but not Study I due to low dropout rates.

**Misclassification of disease**
All studies may be affected by bias due to misclassification of disease, but it is likely that the misclassification was nondifferential. In fact, due to the double diagnostic procedure a differential misclassification is less likely to be present. The clinicians involved in the double diagnoses had different specializations (in the first preliminary diagnosis the clinicians were neurologists, and in the second preliminary diagnosis the clinician was a psychiatrist) and came from different schools and different cultural backgrounds.

In Study I, a special type of misclassification bias may be present due to the fact that dementia may be diagnosed at an earlier point in time among noneducated subjects than higher educated persons [94]. However, we attempted to overcome these difficulties by strictly applying the DSM-III-R diagnostic criteria, where evidence of cognitive impairment must be supported by formal functional impairment in social and work activities. The subjects and/or informants, who were usually close relatives, were asked about any changes in daily activities. Indeed, it is possible to speculate that strict
application of the DSM-III-R criteria may result in a bias in the opposite direction, leading to an earlier detection of cognitive impairment in higher educated subjects who are usually asked to perform more demanding activities. An additional potential limitation is the validity of clinical diagnoses for dementia types, as the diagnoses were not supported by neuroimaging investigations. Thus, results concerning differences between AD and VaD need to be considered cautiously.

Studies III, IV, and V share with the other reports on this topic the difficulties in defining cognitive impairment. In spite of the increasing amount of research on cognitive impairment in the elderly, the definition of this condition is still debated [23,221,222]. We tried to overcome some difficulties by adopting age- and education- adjusted scores on a global cognitive test derived from independent research performed in a similar population in northern Italy [203]. We also included other cognitive domains than memory and we did not take into account clinical judgment. In our study, the adjustment for age and education determined a 31% decrease in the number of cognitively impaired subjects from 584 to 402. As expected, the adjustment affected mostly the 80+ old subjects and those with less than four years of education. Despite the age and education adjustment, we still found a higher prevalence of cognitive impairment in the younger old ages than among the oldest, and a higher prevalence of cognitive impairment in low educated persons. Due to our definition of cognitive impairment, the effect of age and education might be underestimated. However, we preferred this conservative approach, as we did not have the possibility to verify cognitive decline over time for each individual. If we had used non-adjusted scores, different performances among groups could have been due only to the different educational background. Second, the use of a global measure of cognitive performance may be questionable. However, MMSE has been suggested as a useful tool for assessing the degree of cognitive impairment in the guidelines for the Report of the Quality Standards Subcommittee of the American Academy of Neurology [22]. In addition, the overall performance of MMSE has good concurrent validity with other comprehensive neuropsychological assessment instruments [223], and the MMSE scores were found to be reliable predictors of AD [224].

In Study II, diagnostic bias was minimized by the use of a reliable neuropsychological battery and by the fact that risk behaviors were taken into account in the definition of cognitive impairment, which adjusted indirectly for education, too. Last but not least, contrary to many previous investigations carried out in the research field, persons were consecutively recruited from outpatient units to which they had been referred for medical advice.
Misclassification of exposure
As with the disease diagnosis, the exposure assessment might be biased by misclassification. Imprecision is implicit in the assessment of risk factors by surrogate informants. Moreover, imprecision in the assessment of some risk factors is inherent in their operational definition or due to the formulation of the questions [225] as in the assessment of the occupational exposure in Studies I and V. Only wide categories were taken into account, giving more information about general social class than specific work activity.

In Studies I, III, IV, and V, unbalanced collection of medical history and sociodemographic data has also to be taken into account, as this information was self-reported by nondemented subjects, and collected from proxy respondents when a subject was demented.

In Study IV, we could study only clinically overt stroke since neuroimaging data were not available. Moreover, impairments after stroke are classically in attentional and executive cognitive domains [226] which are very poorly captured by the MMSE [227]. Therefore, the definition of cognitive impairment on this basis may explain why stroke has seemingly little impact on cognitive impairment compared to dementia.

In Study V, no specific measures to assess SES were used. Thus, the description of socioeconomic status in our study is only based on the occupation held for the longest period during working life. Second, estimation of SES from occupation was difficult for the homemakers in the population (20.9%). Third, we did not investigate social mobility patterns to explore whether later advancement or setbacks in occupation-based SES may affect the relation between education and dementia and cognitive impairment prevalence.

Potential confounding
The major confounders, which are potentially associated with both outcome and determinant variables [228], were carefully chosen and assessed, and the confounding effects were controlled for by using proper approaches (i.e. developing multiple models or performing stratified analyses) in all the five studies. Information on potential confounding variables has been discussed in each study.

EXTERNAL VALIDITY AND INTERPRETATION
Low education as a major determinant of dementia and cognitive impairment
In line with several previous population-based studies [32,33,96,100,110,112,115, 117,120,121,124-133] we found that lower educated subjects had a higher prevalence of both dementia and cognitive impairment, even when several potential confounding
factors are controlled for. When compared to higher educated persons, subjects without any schooling had ORs of 10.9 (95% CI=7.0-16.7) and 16.7 (95% CI=11.2-25.0) for dementia and cognitive impairment, respectively. These findings support the cerebral reserve hypothesis suggested by Katzman [94], Stern [134], and others [96,116,117,157,178, 229,230].

An alternative hypothesis that the deleterious effects of no education or low education may be due to other related factors acting during childhood [157] is also likely. This population derives from an area which has been one of the wealthiest in Italy, since the beginning of the 1950s, and the higher prevalence among noneducated subjects remained unchanged when the main occupation in life was taken into account, as well as alcohol use, smoking, and current or previous history of hypertension. Thus, the effect of education cannot be mediated by factors related to SES present during adult age. Unfortunately information about SES factors during childhood was not taken.

Finally, we have to consider that the subjects enrolled in our study were born between 1889 and 1930 and might not have the possibility of receiving any education, independently of their intelligence. However, since over 60% of subjects in all age groups received some education, and since we do not have any estimate of premorbid IQ, we cannot exclude the hypothesis that education simply measures intelligence, which is the real determinant of both low education and dementia as suggested by Plassman et al [160].

**Dose-response relationship: subjects with no schooling were at the highest risk of dementia and cognitive impairment**

Low education was associated with an increased risk of both cognitive impairment and dementia with a dose-response relationship. This result is consistent with other reports [99,115,117,130,131,133,137,143]. In our study, the increasing risk with decreasing educational level became dramatically steeper in subjects with no schooling, especially in cognitive impairment. It is noteworthy that the effect of education on cognitive impairment was present in spite of the adjustment of the MMSE score for age and education. Noneducated persons had an almost seventeen fold higher risk than those with six+ years of schooling of developing cognitive impairment. Our results support previous studies suggesting that lack of education has a major role on dementia occurrence [229]. There is growing evidence that etiological heterogeneity among persons with cognitive impairment could be greater than previously reported [28,231]. This heterogeneity could be partially explained by education-related factors such as vascular risk factors [18,108,232]. However, our findings are also consistent with the cognitive reserve hypothesis [94,134], which might also be valid for cognitive impairment.
**The strongest association between no education and dementia was present among the youngest subjects (61-69 years)**

Following the hypothesis that noneducated subjects may develop dementia at an earlier age, in *Study I* we examined the effect of no education on dementia in different age strata. We found an extraordinarily strong association between no education and dementia among people aged 61-69 years, and, unexpectedly, a decreasing trend with increasing age. The association remained unchanged when occupation, life habits, and current or previous history of hypertension were taken into account. This finding is in agreement with the Kungsholmen Project [57], where the association between a low level of education and an increased risk of AD or dementia was more evident in the younger old age group (i.e., 75-84 years) than in the oldest old age group (85+ years). These results may partly account for the finding of no association between educational level and the risk of AD or dementia in some previous studies [136].

**Strong association between education and different dementia subtypes**

We also found a strong association between no education and AD and VaD. Some authors [136] have suggested that the association between education and dementia might be due to other dementias than AD. Our data do not confirm this hypothesis. In fact, the association between noneducation and AD was more than double the association between noneducation and VaD. Moreover, factors related to VaD and other types of dementia, such as alcohol consumption, smoking habit and hypertension had comparable frequencies among noneducated subjects and educated subjects and when they were introduced in the logistic regression analyses, the results did not change.

**Education modified the effect of stroke on dementia**

The findings that stroke was more strongly associated with dementia in younger old than in older old subjects, and in higher than in lower educated persons are in agreement with the reports from the Rochester and Framingham studies [233,234]. In the Framingham study [234], stroke increased the risk of dementia 2.6 times in subjects aged up to 80 years, and 2.4 times in subjects who had completed high school. These findings together strongly support the hypothesis that having a stroke nullifies the beneficial effect of high education and low age against dementia and cognitive impairment. Fewer years of schooling is a well-documented risk factor, as it is consistently associated with a higher risk of both post-stroke dementia [233] and vascular cognitive impairment [235,236]. Even these findings support the cognitive reserve hypothesis [94], which could also be valid for vascular cognitive impairment [237,238].

*Study IV* also confirms the relevant contribution of stroke in cognitive disturbances of the elderly, especially as a strong risk factor for dementia among
younger old and higher educated subjects. Stroke accounted for twenty-one and six percent of the dementia and cognitive impairment cases.

**Combined effect of stroke with age and education was more evident in the younger old subjects**

The combined effect of stroke with age and low education greatly increased the risk of both dementia and cognitive impairment in the younger old subjects, but in the oldest old subjects, the increased risk due to separate effect of stroke and low education was very close to the combined effects of the two factors. The interpretation of these findings needs to take into account the fact that our study is based on prevalence figures, which implies possible differential survival in subjects with different ages and educational levels. It is possible that younger and highly educated stroke subjects survive longer, thus increasing their risk of developing dementia. Pooled incidence data from Europe demonstrated that both men and women with a low educational level had significantly higher stroke mortality rates than those with middle or high educational level [239]. It is also possible that younger and highly educated demented subjects with a history of stroke survive longer than older and low educated demented subjects without stroke. It is unlikely that the survival bias could completely explain the modifying effect of stroke on dementia due to age and education. Moreover, our findings are in agreement with the Framingham study [234], where incidence rates were used.

**Low education and low occupation-based socioeconomic status were independent risk factors for dementia and cognitive impairment**

In line with some previous studies [114,240-242] both low education and low occupation-based SES were significantly associated with dementia. In addition, in subjects with low education and low occupation-based SES, the risk increased in an additive way. Therefore, we can hypothesize that SES is not a mediator of the association between education and cognitive status, but rather a concurrent factor acting during adult life. The additive risk observed in subjects with both low education and low SES implies that exposure acting during adult life might increase the risk due to exposure acting in childhood, and conversely we can speculate that achieving a good socioeconomic position might reduce the risk given by a lower education.

Disagreement between our and previous findings could be due to differences in the study populations [55,137,243,244]. Karp et al [55], for example, found that low education but not low SES was still significantly associated with the development of dementia when both were included in the same model. These results were derived from a Swedish urban population with different age and sex distribution. The discrepancy in the educational attainment of the two populations is evident from the mean number of years
of education: 6.7 in Sweden and 3.7 in Italy. However, even other studies with a socioeconomic background comparable to the Faenza area, demonstrated results different than ours, such as the PAQUID study [244].

**Low education was a risk factor for HIV-1-related cognitive impairment**

When compared to subjects with higher levels of education, subjects with less than six years of schooling had an OR of 17.2 (95% CI=3.6-83.3) for HIV-1 cognitive impairment, independent of age, gender, disease stage, antiretroviral therapy, and risk behavior. In agreement with Stern [77], Maj [78], and Satz [79], our findings suggest that low education (less than six years of schooling) increases the risk of HIV-1-related cognitive impairment in HIV-1-seropositive persons, both in asymptomatic and symptomatic cases.

Analogous to AD, these findings regarding education may be interpreted according to the cerebral reserve hypothesis [94]. Higher education might delay the onset of cognitive impairment by providing extra brain reserve that allows an individual to cope longer before cognitive impairment is expressed clinically. However, the alternative hypothesis, that the deleterious effects of low education may be due to other related factors [78,100,157,245], is also likely. In effect, low educated subjects are more likely to belong to a low SES level, where factors not considered in our study, such as other infectious diseases and malnutrition, may per se affect cognition.
CONCLUSIONS

The data from the five studies suggest the following conclusions on the effect of education on dementia and cognitive impairment occurrence:

Study I
Having no education is associated with dementia independent of gender, occupation, life habits, and hypertension. This association was stronger among young old persons, and decreased with increasing age. Similar findings were found for AD and VaD, separately. The findings suggest that the first decade of life is a critical period for developing dementia later in life. The decrease in dementia risk may be due to schooling, according to the cerebral reserve hypothesis, or to other factors associated with higher educational level during childhood.

Study II
Low education, low CD4+ cell count, and homo-bisexual/heterosexual risk behaviors are risk factors for cognitive impairment in HIV-1-seropositive persons. Antiretroviral therapy exerts a beneficial effect against cognitive impairment in symptomatic subjects. Our findings suggest that homo-bisexual/heterosexual persons who survive longer are expected to be the group at highest risk for cognitive impairment. However, the protective effect of antiretroviral therapy may balance this increased risk.

Study III
This large community-based study including 61+ old subjects support the previous findings that very low education is a major determinant of both dementia and cognitive impairment. Low education is associated with an increased risk of both CIND and dementia with a dose-response relationship. The increasing risk with decreasing educational level gets dramatically steeper in subjects with no schooling, especially in cognitively impaired persons.

Study IV
Stroke per se did not explain the association between low education and dementia or cognitive impairment. However, the effect of stroke on dementia was modified by age and education: the association was stronger among the younger old (61-74 years of age) and the higher educated subjects (four+ years of schooling). These findings together strongly support the hypothesis that having a stroke nullifies the beneficial effect of high education and low age against dementia and cognitive impairment. Our findings again
support the cognitive reserve hypothesis, which could also be valid for vascular cognitive impairment [238].

**Study V**
Low education and low occupation-based SES are both independent risk factors for dementia and cognitive impairment, suggesting that low occupation-based SES is not a mediator for the association between low education and dementia or cognitive impairment. The risk for dementia and cognitive impairment is increased in an additive way for subjects with low education and low SES. The additive risk observed in subjects with both low education and low SES implies that exposure acting at adult life might increase the risk due to exposure acting in childhood and conversely we can speculate that achieving a good SES position might reduce the risk given by a lower education.

**Interpretation of the findings: summary**
The integration of our results with data from other epidemiological studies suggests that mental activity during childhood (first decade, through education) could be the possible mechanism explaining how high education may protect against cognitive decline and dementia [45]. The cognitive-reserve hypothesis could provide the biological plausibility for this hypothesis [45].

**Biological plausibility**
Several experimental studies support the cognitive reserve hypothesis [45]. Studies on rats have highlighted that environmentally enriched conditions may prevent or reduce cognitive deficits in young and even in adult rats [246,247], and that the deleterious effects of an impoverished environment on memory and learning are, at least partly, reversible [248]. Moreover, studies on brain plasticity support the functional reserve hypothesis, because independent of the methods or the level (molecular, cellular, structural), the stimuli required to elicit plasticity are thought to be activity-dependent [249]. Recently, many studies on brain plasticity in adult life have shown the existence of angiogenesis, synaptogenesis, and neurogenesis [250,251]. It has been stressed that at least some regions of the adult brain can respond, even until periods in later life, to environmental stimuli by adding new neurons [246]. Neurogenesis has been demonstrated in the adult rodent hippocampus, the olfactory bulb, and the cerebral cortex of primates and human beings [250]. Furthermore, even human brain-imaging studies support the hypothesis that subjects with higher reserve, as evaluated by using educational level and occupation, may tolerate more pathology [252]. Finally, Cabeza et
al showed that high-performing older adults counteracted age-related neural decline through a plastic reorganization of neurocognitive networks [253].
GENERALIZABILITY

The generalizability of a study first requires internal validity [228]. Internal validity comes from the appropriateness of comparisons and the valid assessments on outcomes and exposures as well as a proper control of biases and confounding effects within the study population itself. These issues have been already discussed.

The external validity of a study depends, in part, on the degree to which the study population is representative of the target population or the extent to which its results can be generalized to other populations. The Faenza population consisted of persons in the entire period of old age (61+ years of age) who were living in a geographically defined area: the municipalities of Faenza and Granarolo, Ravenna province, Italy. This population had comparable age and sex compositions as well as a similar health care system as in other cities of northern Italy. However, the Faenza and Granarolo populations did differ from the rest of the northern Italian cities in that there was a high percentage of noneducated subjects with middle to high SES. In effect, this population derives from an area which is one of the wealthiest in Italy, and has been since the beginning of the 1950s, but with low levels of education.

We think that our results are generalizable to all western societies where the phenomenon of the economical improvement after the Second World War occurred at every level of the population including illiterate people.

Study II requires more complex discussion. The generalizability of these findings may be questioned, as the subjects may not be representative of all different risk behaviors. For instance, the exclusion of persons affected by previous/current psychiatric pathologies may limit the generalizability of our results. Nevertheless, our sample may be considered representative of at least the Italian HIV-1-seropositive persons, since a similar distribution in age, gender, and risk behaviors has been reported by Chiesi et al [254] for the inception cohort of the Italian National AIDS Registry.
RELEVANCE AND IMPLICATIONS

Scientific relevance
From a scientific point of view our findings contribute to the understanding of the etiopathogenetic mechanisms of the different dementing disorders. Our findings support the hypothesis that both dementia and cognitive impairment are multifactorial disorders, and that their risk in late life is result of a cumulative exposure during the life course. From our research, it emerges that not only the first decade of life is a critical period for developing dementia and cognitive impairment later in life, but also that educational attainment together with SES related factors contribute to brain plasticity all life long. Other studies [55] have expanded this issue suggesting that early life SES-related factors are involved in the development of AD in late life. Finally, our findings also support recent developments in neuroscience which have shown a possibility for regeneration in the brain even in adult life.

Clinical relevance
Due to the elevated number of subjects in these youngest ages, the impact of CIND in absolute numbers is dramatic. We can estimate that in Italy the number of CIND subjects is 627,274 in comparison to the 775,249 number of subjects affected by dementia. As CIND subjects are totally independent, their care needs are not comparable to those of demented persons, but they have similar or even larger needs for accurate diagnostic assessment. Longitudinal studies show that at least one third of those with CIND develop dementia within three years [24], and that cognitive impairment is a significant predictor of mortality [255], whereas other causes of cognitive impairment are not yet well identified. Our findings that low education is strongly related to this condition, as well as to dementia, support the hypothesis that in both disorders education-related factors, such as vascular risk factors, may play a major role. The clinicians have to be aware of the frequency of these disorders as well as the impact of vascular risk factors in cognitive ageing.

Public health relevance
From a public health perspective, the knowledge that a good socioeconomical level may compensate an increased dementia risk accumulated during earlier life due to low education, independently of the underlying biological mechanisms, provides important tools to implement preventative strategies.
The life course model for dementia development introduces the relevant concept of “time at exposure”, which might be extremely pertinent for a chronic disorder such as dementia, which develops over a long time period. A certain factor might increase the risk of the disease if a subject is exposed at a specific time, but the same factor may have a decreased effect in another life period, due to a different interaction with other risk factors or due to selective survival [47].

The emerging importance of events in childhood and adult life in affecting cognitive outcomes at older ages has important potential implications, also from a worldwide perspective. The developing countries with a high fertility rate together with low educational attainment and poor income but an increased mean life expectancy will experience a tremendous increase in dementia occurrence [34] without an effective program of prevention.

Illiteracy remains high in the less developed regions among older people, especially women and the oldest groups (Figures 16 and 17).

Available evidence suggests that, as of the year 2000, only about half of all persons 60 and older in those regions were literate [3]. Given that illiteracy dramatically increases the risk of dementia as suggested by the present thesis, the impact of dementia and cognitive impairment in absolute numbers in the next half century will be dramatic.
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