

# Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project

Laura Fratiglioni\*, Bengt Winblad, Eva von Strauss

*Karolinska Institutet, Aging Research Center (ARC; www.ki-su-arc.se), Divisions of Geriatric Epidemiology and Medicine, NVS, and Stockholm Gerontology Research Center, Gävlegatan 16, S-113 30 Stockholm, Sweden*

## Abstract

The aging of the population is a worldwide phenomenon, and studying age-related diseases has become a relevant issue from both a scientific and a public health perspective. This review summarises the major findings concerning prevention of Alzheimer's disease (AD) and other dementias from a population-based study, the Kungsholmen Project. The study addresses risk- and protective factors for AD and dementia from a lifetime perspective: at birth, during childhood, in adult life, and in old age. Although many aspects of the dementias are still unclear, some risk factors have been identified and interesting hypotheses have been suggested for other putative risk or protective factors. At the moment it is also possible to delineate some preventative strategies for dementia.

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## 1. Introduction

Due to the aging of the populations, dementia has become a major public health issue. Dementia is a clinical syndrome characterized by the development of multiple cognitive deficits that are severe enough to interfere with daily functioning, including social and professional functioning [1]. 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. Alzheimer's disease (AD) is the most common cause of dementia in the elderly, accounting for 60–70% of all demented cases [2,3].

A combination of various factors makes dementia a relevant issue from both a scientific and a public health perspective. First, aging of the population has become a worldwide phenomenon that is no longer confined to western societies. In 1990, 26 nations had more than 2 million elderly citizens (65+ years); and projections to the year 2030 indicate that an additional 34 countries will join the list by 2030 [4]. Moreover, the developed countries, which have already seen a dramatic increase in the population aged 65+ years, will experience a progressive aging

of the elderly population itself. In most of these countries, the oldest old (those 80 years and older) are the fastest growing segment of the elderly population [4]. Second, due to high incidence and prevalence, dementia is one of the most common diseases in the elderly. The occurrence of the disease increases exponentially with age [2,5], affecting 5% of the population aged over 65, and 50% at the age of 90+ [6,7]. Third, dementia is a major cause of disability [8], institutionalization [9] and death [10] in the elderly.

For most developed nations and some less developed countries, dementia is imposing a tremendous economic impact on both affected individuals and the entire society [11]. It has been estimated that 24 million persons are currently affected by dementia in the whole world [12], and almost half of them lives in Asia. Over 4.5 million elderly are currently suffering from AD in the United States, leading to an annual cost of nearly USD 100 billion for the disease [13]. In Sweden, the gross cost of dementia was estimated to be USD 4.8 billion in the early 1990s [14].

In the last decades, an increasing amount of attention from the scientific world has been focused on dementia and specific dementing disorders. Epidemiology is one of the leading research areas, with the ultimate objective to develop preventative strategies. Prevention is traditionally divided into three

\* Corresponding author. Tel.: +46 8 690 58 18; fax: +46 8 690 59 54.  
E-mail address: [Laura.Fratiglioni@ki.se](mailto:Laura.Fratiglioni@ki.se) (L. Fratiglioni).

### Potential preventive strategies for dementia

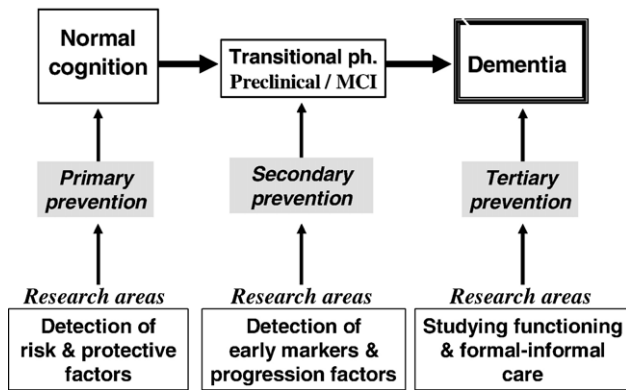


Fig. 1. Potential preventive strategies for dementing disorders at different times of disease development.

levels: primary, secondary, and tertiary prevention (Fig. 1). *Primary prevention* aims to reduce the incidence of the disease by eliminating or treating specific risk factors which may decrease or delay the development of dementia. *Secondary prevention* aims to reduce the prevalence of disease by shortening its duration, for example the identification of clinical or biological markers for AD might lead to an early detection of subjects who are not yet demented but will develop dementia in a few years. *Tertiary prevention* aims to reduce the impact of complications of long-term disease and disability, and consists of measures aimed at: 1) evaluating care provided to demented subjects at different stage of the disease and to compare different care strategies in terms of specific individual and family outcomes; 2) minimizing suffering; and 3) maximizing potential years of useful life.

Our current knowledge on risk factors of the dementias derives mostly from community follow-up surveys (cohort studies), which were initiated in the 1990s. Several studies with similar design are ongoing throughout the world; one of these is the Kungsholmen Project [15]. In this article, we will report the major findings concerning primary prevention deriving from this project.

### 2. The design of the Kungsholmen Project

The Kungsholmen Project began in 1987 and included all inhabitants who were 75+ years old at that time and living in the Kungsholmen area in central Stockholm, Sweden. There were 1810 participants, with a response rate of 76%. After the baseline contact, the survivors were contacted every three years until the last follow-up, which ended in the year 2000 (Fig. 2).

At each contact the subjects were interviewed by nurses, clinically examined by physicians, and psychologically assessed with a cognitive test battery. The nurses collected social and demographic data, measured functional disability, administered brief cognitive tests, took blood pressure, height and weight measurements, and blood samples. In addition, a family interview with a next-of-kin or other close person was

carried out. The clinical examination was similar to the comprehensive physical, neurological, and psychiatric examination usually performed in clinical practice, but more structured and defined with scoring criteria. Clinical diagnoses are made according to established criteria [1,16]. All diagnoses of dementia and dementia types were verified by specialists, and discordant diagnoses were reviewed by a senior physician. Information on hospitalisation and causes of hospitalisation, as well as death certificates were also collected for all participants.

The Kungsholmen Project was approved by the Ethics Committee of the Karolinska Institute. Research within the project followed the guidelines of the Swedish Council for Research in the Humanities and Social Sciences [17].

### 3. Lifetime perspective

Research within the Kungsholmen Project has followed a lifetime perspective to identify risk and protective factors for AD and dementia. Dementia is a common disorder after 75 years of age, but rare before age 60 [2]. The occurrence of dementia in the late ages can be due to a cumulated risk during the whole life span. 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 old age. In addition, this model introduces the relevant concept of “time at exposure”, which might be extremely relevant for a chronic disorder such as dementia, which develops in a long time period. A certain factor might increase the risk of the disease if a subject is exposed in a specific time, but the same factor may have a decreased effect in another life period, due to different interaction with other risk factors or due to selective survival.

In our research we have divided life into five major periods; birth, childhood (1st and 2nd decade), adult life (middle age), transitional age (between 60 and 75 years), and old age (after 75). Most studies have focused on AD whereas data concerning vascular dementia and other dementia types are limited. More recently, we have used dementia as the major outcome without

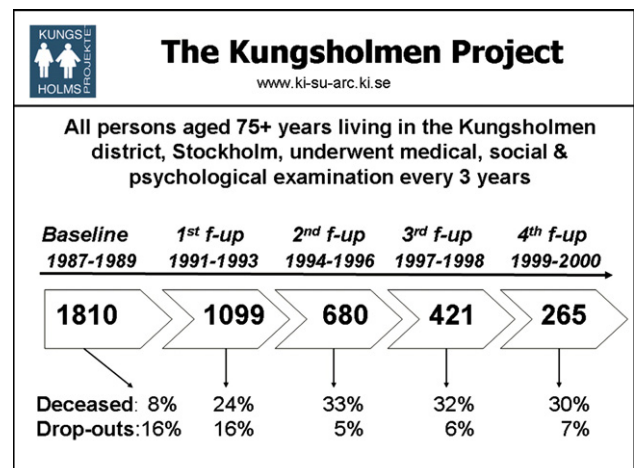


Fig. 2. Schematic overview of the Kungsholmen Project study design.

taking into account the specific dementing disorders. This approach reflects an orientation towards prevention, as the detection of any risk factor that can be eliminated or treated can help to decrease or delay the incidence of the dementia syndrome. In addition, this approach allows studying multiple-cause dementia, under the assumption that in the very old ages, vascular, degenerative and other mechanisms may all play a simultaneous role in causing the dementia syndrome.

#### 4. Risk and protective factors for AD and dementia

The 13-years old database of the Kungsholmen Project has already led to 34 PhD theses, and numerous studies on the occurrence, risk factors, and natural history of AD and other dementias. This paper summarises the major research findings from the Kungsholmen Project concerning detection of risk and protective factors for AD and dementia, following the lifetime model as described above (see Tables 1 and 2).

##### 4.1. At birth

###### 4.1.1. Familial aggregation

At the beginning of the 1990s, epidemiological studies showed that subjects with a first-degree relative affected by dementia had a three times increased risk of AD after 65 [3]. Familial aggregation in AD (at least one first degree relative with dementia) was first found in early-onset cases. In the Kungsholmen Project, a high familiarity was reported even in late-onset AD [18]. Finally, we verified whether the familial aggregation of dementia and AD could be explained by Apolipoprotein E (APOE) genotypes [19]. Family history of dementia was still associated with an increased risk of dementia

and AD in the very old (75+ years), but only among APOE  $\epsilon$ 4 carriers. This implies that other familial (genetic or environmental) risk factors might be active among APOE  $\epsilon$ 4 carriers [19].

###### 4.1.2. Apolipoprotein E (APOE)

In the Kungsholmen Project, the genetic influences on cognitive performance in old age have explored only the role of APOE gene. APOE is a plasma protein involved in cholesterol transportation. It has three major alleles,  $\epsilon$ 2,  $\epsilon$ 4, and  $\epsilon$ 3, the last of which is most common. APOE  $\epsilon$ 4 allele is associated with an increased risk of developing AD [20] as well as with an earlier disease onset [21]. In addition, data from our project have demonstrated that APOE  $\epsilon$ 4 is associated with an increased risk of AD, but not with vascular dementia or stroke [22,23]. APOE  $\epsilon$ 4 was also reported to be associated with shortened survival time among cognitively normal people [24]. More recently, we reported that the APOE genotype specific effects on AD after age 75 vary by age and gender, in which the  $\epsilon$ 4 allele has a stronger risk effect in men, and the  $\epsilon$ 2 allele confers a protective effect only among the 75–84 old subjects [25].

##### 4.2. Childhood

###### 4.2.1. Education

It has consistently been reported that subjects with low education are at a higher risk to develop dementia and AD [3]. Our group found that subjects with 2–7 years of education had an increased risk for AD and dementia, but not for AD or dementia mortality. Different hypotheses have been suggested to explain such an association: education may increase brain reserve as well as mental activity throughout life; or education

Table 1  
Genetic and biological factors associated with an increased or decreased risk for dementia and AD

	Life time of exposure	Dementia RR (95% CI)	AD RR (95% CI)	Comments (reference)
<i>Genetic factors</i>				
Familial aggregation	At birth	–	3.2 (1.8–5.7)	Prevalent cases [18]
APOE allele $\epsilon$ 4	At birth	1.9 (1.1–3.4)	2.2 (1.2–4.1)	Incident cases of APOE $\epsilon$ 4 carriers [19]
		–	1.4 (1.0–2.0)	Incident cases, one $\epsilon$ 4 [20,22–25]
		–	3.1 (1.6–5.9)	Incident cases, two $\epsilon$ 4 [20,22–25]
<i>Biological factors</i>				
Age (5-year increment)	After 75	1.4 (1.2–1.7)	1.6 (1.3–1.9)	Incident cases [43]
		1.9 (1.7–2.2)	2.1 (1.9–2.5)	Prevalent cases [6]
Female gender	After 75	1.9 (1.2–3.0)	3.1 (1.6–6.0)	Incident cases [43]
		1.9 (1.3–2.6)	2.3 (1.6–3.4)	Prevalent cases [6]
Anaemia	After 75	1.6 (1.1–2.4)	–	Incident cases [35]
<i>Vascular factors</i>				
High blood pressure (SBP > 180)	After 75	1.5 (1.0–2.1)	1.4 (0.9–2.1)	Incident cases [20,30,31]
Low diastolic pressure (DBP < 65)	After 75	1.5 (1.0–2.1)	1.7 (1.1–2.4)	Incident cases [20,30,31,44]
SBP reduction (>15 mHg; 4–6 years before diagnosis)	After 75	3.1 (1.5–6.3)	3.1 (1.3–7.0)	Incident cases; subpopulation of subjects with initial SBP < 160 [31,32]
Heart failure	After 75	1.8 (1.3–2.5)	1.8 (1.2–2.6)	Incident cases [33]
Recent Stroke (3 years)	After 70	2.4 (1.4–4.2)	–	Incident cases: additive effect with APOE [23]
Diabetes	After 75	1.5 (1.0–2.1)	1.3 (0.9–2.1)	Incident cases [34]

Major findings from the Kungsholmen Project.

Table 2  
Environmental factors and life habits associated with an increased or decreased risk for dementia and AD

	Life time of exposure	Dementia RR (95% CI)	AD RR (95% CI)	Comments (reference)
<i>Environmental factors</i>				
Occupation (manual work)	Adult life	– 1.4 (0.9–2.1)	5.3 (1.1–25.5) 1.6 (1.0–2.5)	Prevalent cases; only men [18] Incident cases; manual work with goods production [28]
ELF-MF <sup>a</sup>	Middle age	2.0 (1.1–3.7)	2.3 (1.0–5.1)	Incident cases; only men [29]
<i>Life habits</i>				
Alcohol	After 75	–	4.4 (1.4–13.8)	Prevalent cases [18]
High intake		–	0.5 (0.3–0.7)	Incident cases [41]
Light to moderate intake		0.5 (0.3–0.7)	0.5 (0.3–0.7)	Incident cases [40]
Smoking	After 75	1.4 (0.8–2.7)	1.1 (0.5–2.4)	Incident cases [42]
Diet: low B12 and folate	After 75	1.8 (1.1–2.8)	2.1 (1.2–3.5)	Incident cases [42]
<i>Social factors</i>				
Low education (2–7 years)	Childhood/adolescence	1.7 (1.1–2.6)	2.6 (1.5–4.4)	Incident cases [26]
SES	Adult life	–	–	–
High SES/high education		1	1	Incident cases [27]
Low SES/high education		1.3 (0.4–4.4)	0.7 (0.1–5.5)	–
High SES/low education		2.3 (1.3–4.1)	3.2 (1.6–6.1)	–
Low SES/low education		2.4 (1.5–4.0)	3.1 (1.6–5.7)	–
Social network	After 75	–	–	–
Poor vs rich/moderate		1.6 (1.2–2.1)	–	Incident cases [36]
Leisure activities	After 75	–	–	–
Mental		0.6 (0.4–1.0)	–	Incident cases [37]
Social		0.6 (0.4–0.9)	–	–
Productive		0.6 (0.4–0.9)	–	–
High score of mental, physical and social components	After 75	0.6 (0.4–0.9)	–	Incident cases [39]
<i>Medication</i>				
Antihypertensive treatment	After 75	–	0.7 (0.6–0.9)	Incident cases [45]
		–	0.6 (0.5–0.9)	Incident cases [30]
NSAID use	After 75	0.8 (0.5–1.3)	0.6 (0.3–1.2)	Incident cases [46]

Major findings from the Kungsholmen Project.

<sup>a</sup> Extremely-low-frequency magnetic field.

may be an indicator of intelligence, socio-economic status or other factors related to the first decade of life. A possible alternative interpretation is that subjects with lower educational level may be clinically diagnosed at an earlier point in time than higher educated persons [26].

#### 4.2.2. Socio-economic status (SES)

To verify whether the association between low educational level and increased risk of AD and dementia may be explained by occupation-based SES, data was gathered about the lifetime occupational history and SES mobility. An occupation-based SES at ages 20, 40, and 60 years was computed in order to estimate individual SES mobility patterns. A low level of education and a low occupation-based SES are individually associated with increased risk of AD and dementia, but only low education remains as a risk factor when both variables are examined simultaneously. An increased risk of dementia was found in subjects with only elementary schooling independently of their occupation-based SES or SES-mobility during life, whereas high-educated subjects with low SES were not at higher risk of dementia [27]. These findings suggest that factors operating during the first two decades of life are involved in the development of dementia in late life [27].

#### 4.3. Adult life

##### 4.3.1. Occupation

Our group was the first to suggest that goods production manual work may play an independent role in the development of AD and dementia [28]. Having manual work as the lifetime principal work, and work involving goods production in particular, was found to be related to a significantly increased risk of AD and all types of dementia. These results support previous findings from a case-control study in our group, which indicated that blue-collar work was related to late-onset AD [18], suggesting that some pollutants or work-related exposure may be involved in the development of AD and dementia. For that reason we explored the lifetime occupational exposure to extremely-low-frequency magnetic field (ELF-MF) in relation to increased risk of AD and dementia. ELF-MF exposure was assessed using a job-exposure matrix, measurement on historical equipment, and expert estimation. ELF-MF is mainly present in the vicinity of electrical motors and other electric appliances containing coils. We found that long-term occupational exposure to a higher ELF-MF level may increase the risk of AD and dementia in men. Similar patterns were not seen in women, which may in part be the result of a greater misclassification in

women than in men, as the matrix had been especially developed for male jobs and women could be categorized in fewer job titles [29].

#### 4.4. Old age (after 75)

##### 4.4.1. Blood pressure (high/low)

Several research groups have reported that high blood pressure is a risk factor for dementia. In the Kungsholmen Project we found that subjects with a very high systolic pressure, >180 millimeters of mercury (mm Hg), had a 50% increased risk of developing AD and dementia. In addition, we demonstrated that the use of antihypertensive drugs may decrease the risk of dementia and AD [20]. We have now suggested a possible mechanism accounting for this finding: antihypertensive drugs may counteract the combined effect on dementia due to the genetic risk factor apoE-e4 and high systolic blood pressure [30]. In our project, we have found that not only high systolic blood pressure but also low diastolic blood pressure is predictive of AD and dementia [31]. Low diastolic pressure (<65 mm Hg) led to a 40% increased risk of developing AD or dementia. The direction of causality remains unclear, as dementia pathology may lower blood pressure even some years before diagnosis. If the association reveals a causal relationship, two possible mechanisms can be active: first, the atherosclerotic process may explain the observed associations, and second, low diastolic pressure may increase dementia risk by affecting cerebral perfusion. A study published in *Stroke* [32] showed that a drop in systolic blood pressure of 15 mm Hg or more, was linked to a three-fold increased risk of developing AD and dementias 4–6 years later, but only in people with a systolic pressure of less than 160 mm Hg. These findings imply that hypoperfusion in the brain, resulting from an extensive decline in blood pressure, may promote the dementia process.

##### 4.4.2. Heart failure

In a recent study [33] examining the relationship between heart failure and risk of dementia and AD, we found that heart failure was significantly associated with an over 80% increased risk of dementia and AD. Moreover, heart failure and low diastolic pressure (<70 mm Hg) had an additive effect on dementia risk.

##### 4.4.3. Diabetes

Diabetes mellitus increases the risk of dementia in very old people [34], even when a number of potential confounders including some vascular disorders are taken into account. Also, diabetic patients who used oral antidiabetic medications were at substantial risk for all dementias, especially vascular dementia.

##### 4.4.4. Anaemia

Earlier cross-sectional studies have reported an association between anaemia and dementia, whereas longitudinal studies have provided contradictory results. In a recent study [35], we have shown that anaemia and low haemoglobin concentration is a possible risk factor for dementia, even after adjusting for chronic diseases, inflammatory markers, and indicators of nutritional status.

##### 4.4.5. Social network and leisure activities

After the first report of a 60% increased risk of dementia among subjects with poor or limited social network [36], we have confirmed that intellectual and social stimulation protects against dementia [37]. This result was based on the engagement in different leisure activities assessed 6 year before the dementia diagnosis. The topic has been systematically reviewed by Fratiglioni et al. [38]. In a recent study, we found that even small contributions of the mental, physical or social components mattered when accumulated [39]. These results also indicate that engaging in activities that cover more than one of the mental, physical or social components seems to be more beneficial than to be engaged in only one type of activity [39].

##### 4.4.6. Life habits (smoking/alcohol)

Our data indicates that smoking does not have a protective effect against AD or dementia. After some initial reports in which smoking was claimed to protect against AD, analysis of prospective data did not confirm this hypothesis. In the Kungsholmen Project, we found that smoking affected survival in persons with AD much more than in non-demented subjects, and the protective effect of smoking on the occurrence of AD was no longer present when incident AD cases were studied [40]. The previously reported association from cross-sectional studies was probably due to differential mortality.

The role of alcohol consumption in the development of dementia and AD remains controversial. In the Kungsholmen population we found that light to moderate alcohol drinking might protect against dementia and AD, although the possibility that such an association may be due to information bias cannot be totally ruled out [41].

Finally, we have suggested that malnutrition and/or absorption problems may be the cause of low levels of vitamin B12 and folate which were found related to a two-fold increased risk of AD in a study from the Kungsholmen Project [42].

## 5. Concluding remarks

Population-based studies, such as the Kungsholmen Project, have made a great contribution to our knowledge of dementia and AD. Although many aspects of the dementias are still unclear, we are now able to make more accurate diagnoses than before, and the pattern of dementia distribution has been sufficiently described to guide the planning of medical and social services. Some risk factors have also been identified and interesting hypothesis has been suggested for other putative risk or protective factors. At the moment it is also possible to delineate two preventative strategies for dementia:

### 5.1. A good control of blood pressure, both in adult and late life

It is important to monitor the antihypertensive treatment to avoid too low levels of diastolic blood pressure or drastic reduction of systolic blood pressure, especially in subjects with other vascular diseases. Monitoring and appropriately treating diseases such as heart failure and anaemia which may lead to chronic hypoxia in the brain is also relevant.

## 5.2. An active and socially integrated life in old age

It is important for old people to participate to mentally as well as socially and physically stimulating activities. Such active life may postpone the onset of dementia.

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