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Swedish Research Council for Health, Working Life and Welfare

AGEING AND MEMORY

Naturally or pathologically forgetful?

An increasing number of people are surviving to old age → Cognitive abilities deteriorate naturally during the ageing process but for some they develop into dementia → Some 160,000 people are currently living with dementia in Sweden → The number of people with dementia is expected to double by the year 2050 → There are major gaps in knowledge about the changes in the brain that lead to cognitive ageing

SUMMARY

Cognitive abilities such as memory and language deteriorate with age. These skills are important for productivity, health and the opportunity to live an independent life in old age. It is likely that many different changes in the brain contribute towards cognitive ageing, but it is not known which are the most significant. There is also considerable variation in cognitive ageing between individuals. Dementia is the most common background to cognitive changes that seriously affect quality of life for older people. An increasing number of people are surviving into old age. This trend means that we can expect the number of people with dementia in Sweden, which is today an estimated 160,000, to double by the year 2050. In addition to genetic factors, such things as childhood conditions, education, work environment, psychosocial factors, blood pressure, excess weight, high alcohol consumption, smoking and vascular diseases also exhibit a connection with cognitive ageing and dementia. The ageing brain also becomes more sensitive to many types of medications, with the result that certain medications can have significant effects on cognitive function in older individuals. But there are still huge gaps in knowledge when it comes to the changes in the brain that lead to cognitive ageing and dementia, the effects of various drugs on the cognitive abilities of older people, and the mechanisms behind the factors that protect against cognitive ageing and dementia.

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1. Normal cognitive ability

1.1 Cognitive abilities during normal ageing

Cognitive abilities such as memory, intelligence and language skills deteriorate with age. These changes are obvious, even in groups of people that are not affected by any form of serious age-related illness. According to studies that have followed the same individuals for an extended period of time, for many people the deterioration of the ability to recall new events and new information begins around the age of 60–65 (Rönnlund et al., 2005). General knowledge, for example that New Delhi is the capital of India, and certain language skills, such as vocabulary, improve in the middle-aged brain and are less affected by ageing (Rönnlund et al., 2005; Schaie, 2005). Deterioration of abilities such as logical inference, mental agility and spatial problem-solving begin as young as under the age of 50 (see figure 1). Studies of a cross-section of the population, in which the performance of various individuals of different ages is compared on one occasion, report that there are already age-related differences in cognitive performance between today's 20- and 30-year-olds. But these results are influenced by the fact that, for a long time, each new generation has outperformed the previous one (Flynn, 1984).

1.2 Differences between people in cognitive abilities

There are major differences between individuals in terms of cognitive ability, and these differences change relatively little during young adult life (de Frias et al., 2007; Deary et al., 2000). However, older people are affected by varying degrees of cognitive ageing (de Frias et al., 2007; Lindenberger & Ghisletta, 2009). Genetics and environmental factors interact to generate these individual differences and affect the older individual's functional capacity in two primary ways: by determining the functional level the individual has when entering old age, and by the degree of changes that an ageing individual experiences. If the individual enters old age with strong cognitive abilities, there is a longer period of changes in ability before these changes start to create functional obstacles in everyday life. If an older person experiences deterioration less quickly, it also takes longer before the person requires help in managing daily tasks. If you want to understand and identify the factors behind independent living as an older person, you therefore need to take account of genetics, childhood environment and behaviour during adult life, and the ageing process (Hertzog et al., 2009; Lövdén et al., 2010).

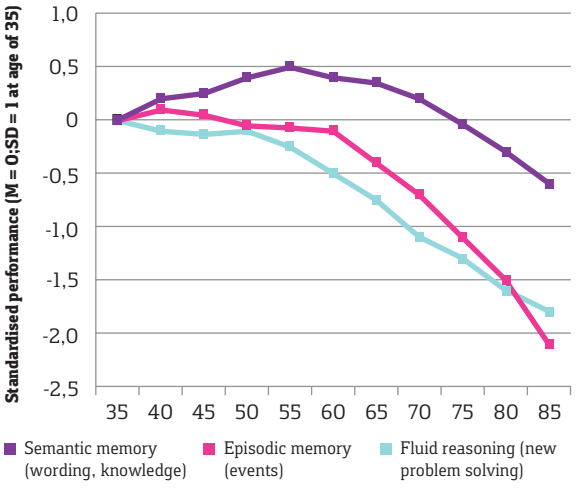

Figure 1. Changes in cognitive ability over adult life for groups of people that are not affected by serious age-related illnesses (such as dementia). Longitudinal study (repeated measurement of the same individuals) from Rönnlund, Nyberg, Bäckman & Nilsson, 2005 and Rönnlund & Nilsson, 2006.

1.3 Changes in the brain and cognitive ageing

The brain experiences a number of changes during the normal ageing process. For example, access to many neurotransmitters such as dopamine declines (Bäckman et al., 2006) and the volume of the brain's grey matter, which contains nerve cell nuclei, decreases (Raz et al., 2005). Damage to the brain's white matter, which contains long connectors between different regions of grey matter, and damage to the vascular system, such as minor haemorrhages (Farkas & Luiten, 2001), increase with age. The extent to which these and other age-related changes in the brain affect cognitive abilities, which of these changes constitute the most significant explanation for cognitive ageing and which happen first are all things that remain relatively unknown.

1.4 Cognitive ability, health and productivity

Individual differences in cognitive performance, as measured in laboratory tests, have a powerful connection with differences in health and productivity (Salthouse, 2012). Cognitive performance among older individuals is related to being able to carry out daily activities independently, such as cooking, managing finances, taking medicine and travelling (Allaire & Marsiske, 2002). Lower cognitive performance in early adulthood is related to more illnesses, poorer health (Der et al., 2009) and shorter lifespan (Batty et al., 2007), even when differences in socioeconomic status are taken into account statistically. Cognitive abilities are also related to performance at work (Hunter & Hunter, 1984). But with the exception of professions that place exceptional demands on cognitive abilities, such as air traffic controllers, performance at work is not generally lower for groups of older individuals under the age of about 65 anyway, which is the age up to which it has most commonly been studied (Salthouse, 2012). These findings are somewhat paradoxical, since changes in work performance are to be expected given the relationship between cognitive ability and work performance, and that some age-related deterioration in cognitive ability begins before the typical age of retirement. This paradox can possibly be explained by the fact that older individuals' intact or increased knowledge base can compensate for

negative changes in other cognitive abilities (Salthouse, 2012). Older individuals also tend to show less fluctuation in their cognitive performance over hours and days (Schmiedek et al., 2013), which may be an important factor in professions where it is more important to consistently avoid mistakes than to sometimes perform at maximum capacity.

2. Pathological changes in cognitive ability

2.1 Conditions that affect cognitive ability

There are many conditions and illnesses that affect cognitive ability in older people. For example, vitamin B12 and folic acid deficiencies are a common cause of impaired cognitive ability in older people (Hooshmand et al., 2012). Long-term abuse of alcohol or other drugs can lead to cognitive problems (Oscar-Berman, 2012). Diabetes (Wahlin et al., 2002) and Parkinson's disease (Cooper et al., 1991) can affect cognitive ability. Depression is sometimes followed by impaired memory (Zahodne et al., 2014). The most common form of serious reduction in cognitive ability is dementia, particularly dementia diagnoses such as Alzheimer's disease or vascular dementia (Marengoni et al., 2008).

2.2 Dementia

Dementia is a collective term for a number of different behavioural symptoms caused by brain damage. Dementia is mainly something that affects older people. This means that cognitive ageing and dementia are closely related (Drachman, 2007) and can be difficult to separate in very old age, and both are a result of, in part, the same biological changes and brain damage (Whalley, 2006). However, dementia displays more serious symptoms than normal age-related changes in cognitive abilities. To receive a dementia diagnosis, the individual must have an impaired ability to remember new events and new information, along with an impaired ability in at least one additional cognitive area. The cognitive functional impairment should create significant deterioration in social or professional functions and involve a considerable drop from a previous functional level (American Psychiatric Association, 2000).

The most common specific dementia diagnoses are dementia of the Alzheimer's type, which accounts for 60–70 percent of diagnoses, and vascular dementia, which accounts for 20–30 percent of diagnoses (Fratiglioni & Rocca, 2001). To receive a diagnosis of vascular dementia, serious damage to the vascular system, such as via a stroke or several minor haemorrhages, must be confirmed and identified as the most likely causes behind changes in cognitive ability. For an Alzheimer's diagnosis, such causes and other similar causes can be ruled out. There are currently no specific biological markers for Alzheimer's.

The traditional diagnostic criteria are currently undergoing a major review around the world. This work has partly come about as a result of lack of clarity around the causes of dementia and the growing opinion that dementia is caused by a number of different kinds of factors (Bartzokis, 2009; Solomon et al., 2014). For example, the changes in the brain that were previously taken as being characteristic of Alzheimer's (known as plaques and tangles, mainly in the parietal and temporal lobes) are also found in some older people displaying typical cognitive ability for their age (Savva, 2009; Schneider et al., 2009). Neither is there a complete separation between vascular dementia and Alzheimer's. Over half of the people who have received a clinical diagnosis of dementia of the Alzheimer's type also have other types of brain damage, including vascular damage (Savva, 2009; Schneider et al., 2009). The majority of people diagnosed with dementia after the age of 75 have arguably both vascular damage and changes in the brain that are characteristic of Alzheimer's (Schneider et al., 2007; Viswanathan et al., 2009).

3. Demetia prevalence

3.1 Current prevalence of dementia

There is at present no comprehensive data available on the number of people who have dementia in Sweden, but a recently published report, based on a relatively representative section of the population, estimates that about 160,000 people in Sweden are currently living with some form of dementia (Wimo et al., 2014). Since the age-specific prevalence of dementia does not differ greatly between different countries in the western world, it is possible to combine several studies from different countries to increase the reliability of the assessment. Figure 2A shows esti-

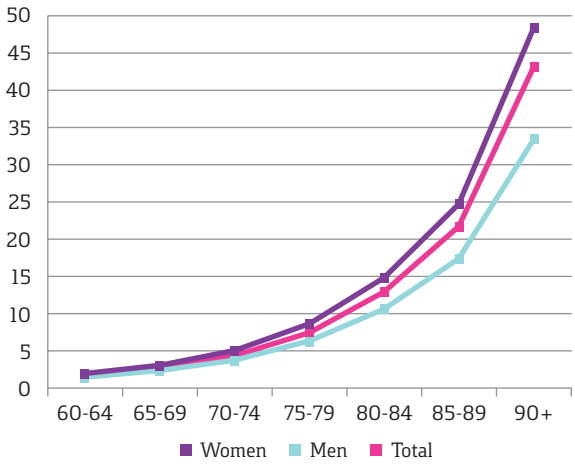

Figure 2A. Prevalence of dementia illnesses in men and women in different age groups in Western Europe (based on Prince et al., 2013). Percent.

mates of the prevalence of dementia made on the basis of one such systematic compilation of a number of studies (Prince et al., 2013). The graph illustrates that there are clear gender differences in the likelihood of receiving a dementia diagnosis, the likelihood being higher for women than for men. Furthermore, the likelihood of a dementia diagnosis increases dramatically with age. In the 60–64 age group, just 1.4 percent of the men and 1.9 percent of the women have dementia. Among those aged 90 and over however, a third of the men and almost half of the women have a dementia diagnosis.

3.2 Future prevalence of dementia

There are currently no results that emphatically show that the age-specific prevalence of dementia has changed markedly over time (Fratiglioni & Qiu, 2013). On the other hand, the population increase combined with longer life expectancy has meant that an increasing number of people have reached old age, which in turn has led to a rise in the number of people living with dementia.

It is difficult to make projections about the future, but it is also important to try. Figure 2B shows the increase in the number of people aged 75 years and over in Sweden between 1970 and 2013, with a forecast up to the year 2050 (SCB, 2014). The graph shows that the number of people in this age group has doubled between 1970 and 2013, from just over 400,000 to just over 800,000. The forecast also suggests that the increase is set to continue at a rate that will mean a further doubling of the number of people in this age group by the year 2050, when the number of people aged 75 and over is expected to amount to just over 1.6 million. This means, assuming there is no change in the age-specific likelihood of receiving a dementia diagnosis, that there will be a substantial rise in the number of people with dementia in the near future.

However, some research results indicate that the likelihood of developing dementia at a particular age may be changing. It has long been known that later-born cohorts tend to have better cognitive function than do earlier-born cohorts of the same age, which has meant that the population's average cognitive function has improved considerably over time (Flynn, 1984; Rönnlund & Nilsson, 2008). Studies with a specific focus on older people have also shown that average cognitive ability has improved over time among older people as well (Christenssen et al., 2013; Skirbekk et al., 2013). A number of factors could explain these increases in cognitive ability, but improved vascular health and perhaps in particular longer education are assumed to be key factors (Rönnlund & Nilsson, 2008). As general education levels in society increase, they also increase among older people. A number of school reforms in the 1900s have led to the extension of compulsory schooling and moreover it has become increasingly common to progress to further education following compulsory education. Since education is related to improved cognitive function and reduced risk of developing dementia, it is possible that the increase in average levels of education may also lead to fewer people developing dementia. This hypothesis is supported by results from a study carried out in Kungsholmen in central Stockholm. The study revealed that survival rates among people with a dementia diagnosis rose between 1987 and 1994, and between 2001 and 2008. That is to say that, on average, people with a dementia diagnosis were living longer with their diagnosis at the end of the period compared to the beginning. Despite this, the prevalence of dementia was unchanged during the period, which could suggest that the risk of developing it at a particular age actually fell during the period (Qiu et al., 2013).

So all in all, despite a positive trend in several senses, the number of older people living with a dementia diagnosis is highly likely to continue to rise as the number of older people increases. A rough forecast based on the age-specific prevalence of dementia in Western Europe today (Prince et al., 2013) and Statistics Sweden's population projections (SCB, 2014) reveals that just over 320,000 people in Sweden can be expected to have a dementia illness by the year 2050, unless the trend changes. That is twice the current figure. However, this type of forecast should be interpreted with caution; there are considerable uncertainty margins, but these forecasts can at least provide a rough idea of future trends.

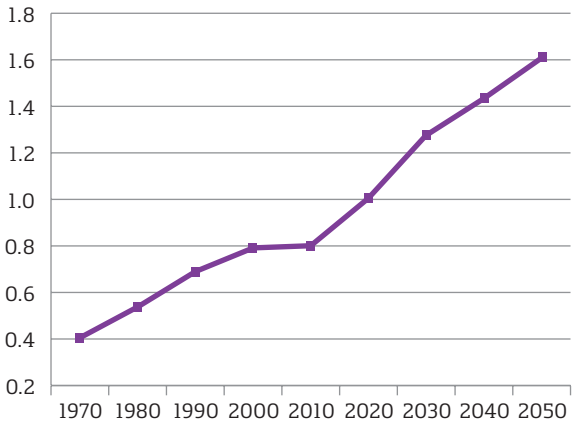

Figure 2B. Number of people aged 75 and above in Sweden, 1970 – 2013, with forecast for the trend during the 2014 – 2050 period (based on SCB, 2014). Millions.

4. Modifying factors

4.1 Protective factors and risk factors

A number of factors have been identified that are related to the degree of cognitive ageing and the risk of receiving a dementia diagnosis in older age. Some of these factors, such as education, mainly have an effect during childhood; for example, by having a positive impact on cognitive performance, which in turn leads to it taking a longer time for the ageing process to result in a serious deterioration

of quality of life. Such factors can also offer the individual greater opportunities to deal with negative biological changes as he/she ages; for example, through the individual having a larger store of behaviour strategies for coping with different situations (Stern, 2009). Other factors have effects on cognitive ability during adult life, or affect ability more immediately in old age. Individually, most of the factors explain a relatively small portion of cognitive ageing and the risk of dementia in old age.

4.2 Genetic factors

Research indicates that between 40 and 70 percent of the individual variation in cognitive ability can be explained by heredity (Deary et al., 2009). Individual differences in the change in cognitive ability during normal development from early childhood to old age also have a hereditary component, but it is weaker (Deary et al., 2012). Some 58–78 percent of the individual differences in the risk of developing dementia in old age are attributable to heredity, and the rest are down to non-genetic environmental factors (Gatz et al., 2006). But few individual genetic markers have displayed a connection with cognitive ability and a dementia diagnosis in old age, and those that have been identified only explain a very small portion of the individual differences in cognitive ability among older individuals. The APOE gene is the only single genetic factor that is demonstrably related to the risk of dementia in old age, but the connection is not absolute: i.e. not all individuals with the negative variant of this gene develop dementia, while many people without the negative variant do in fact develop dementia.

4.3 Childhood conditions

The conditions in which we live during childhood have an impact on cognitive function throughout the rest of our lives. Experience of disadvantageous socioeconomic conditions such as poverty during childhood has a negative association with cognitive ability (Richard & Hatch, 2011). Furthermore, links have been found between prolonged exposure to poverty and cognitive impairment in older age (Lynch et al., 1997). These links are probably partly the result of chronic stress, physical ill-health at birth and during childhood, and inadequate cognitive and emotional stimuli, along with deficient material conditions during childhood and adolescence (Richard & Hatch, 2011; Guo & Harris, 2000). Results from certain studies also suggest that individuals who have grown up in disadvantaged socioeconomic conditions run an increased risk of being affected by dementia later in life (Scazufca et al., 2008; Zeki Al Hazzouri et al., 2011).

4.4 Education

Individuals who have a higher level of education tend to have better cognitive ability (Deary et al., 2006; Strenze, 2007). Results from many, but not all, studies also indicate that people with a lower level of education run a higher risk of developing dementia illnesses in older age (Sharp & Gatz, 2011). However, here it is likely that the causal links run parallel to each other in different directions. On the one hand, differences in level of education can be partly explained by individual differences in fundamental cognitive conditions, where individuals with better conditions also tend to cope better in school and remain in education for longer (Deary et al., 2006). On the other hand, there are many indications today that education per se has a positive effect on cognitive function (Lager et al., 2012; Clouston et al., 2012). Most findings, however, suggest that education only affects the level of cognitive performance that an individual has when he or she begins the ageing process, and not the actual pace of age-related changes (Lövdén et al., 2004; Piccinin et al., 2013: Zahodne et al., 2011).

4.5 Profession

There is currently a certain amount of scientific support for the idea that work environment can affect cognitive function and the risk of developing dementia illnesses in later life. A small number of studies have indicated that individuals who have physically demanding or low-qualified professions, along with professions that involve exposure to solvents and electromagnetic fields, run an increased risk of dementia in later life. These results should be interpreted with caution, as other studies have failed to give support to such links (SBU 2008). Another research question is the extent to which the intellectual complexity of work tasks affects cognitive function and the risk of developing dementia in later life. Several studies have shown the link between complex tasks and cognitive ability, where people who are in professions that are characterised by complex tasks tend to have better cognitive function than those who work with a lower degree of complexity. This is in part due to the fact that people with high cognitive function tend to have more complex tasks. But the results also suggest that complex tasks in turn have a beneficial effect on cognitive function (Schooler, Mulatu & Oates, 1999). Several studies have also shown that individuals who have had professions involving intellectually complex tasks run a lower risk of developing dementia illnesses in old age (Andel et al., 2005; Karp et al., 2009).

4.6 Blood pressure, weight and vascular function

In middle age, high blood pressure, the key risk factor for vascular diseases, is strongly linked with changes in the brain in old age (Raz et al., 2005) and with cognitive ability and the risk of both vascular dementia and Alzheimer's (Qiu et al., 2005). But this link is weaker in old age, as only extremely high blood pressure and abnormally low blood pressure are related to an increased risk of dementia (Fratiglioni & Qiu, 2013). Being overweight, obesity and abdominal obesity during middle age increase the risk of developing dementia later, while substantial weight reductions in old age often precede a dementia diagnosis (Gustafsson, 2006). These links are consistent with

the central role of the blood vessels in cognitive ageing and dementia. Many other conditions related to vascular function, such as diabetes, stroke and heart diseases, also increase the risk of dementia in old age (Fratiglioni & Qiu, 2013).

4.7 Smoking and alcohol consumption

Early studies into the link between smoking and dementia suggested that smoking appeared to reduce the risk of dementia. Later studies have revealed that these results have probably arisen because smokers who survive to old age tend, at group level, to be unusual, and that smoking, particularly during middle age but also in old age, actually increases the risk of being affected by dementia (Fratiglioni & Qiu, 2013). Prolonged alcohol abuse can lead to alcohol-related dementia and high alcohol consumption during middle age increases the risk of other types of dementia, while according to some studies moderate alcohol consumption is linked to a reduced risk of dementia (Fratiglioni & Qiu, 2013).

4.8 Psychosocial factors

Individual differences in exercise, participation in mentally stimulating leisure activities and social stimuli have a connection with the level of and change in cognitive ability in older people (Hertzog et al., 2009). Lower levels of participation in leisure activities precede a deterioration in cognitive ability in old age (Lövdén et al., 2005), which indicates that the connection is partly due to the fact that these lifestyle factors have a genuine impact on cognitive development in old age. The same factors are also related to the risk of dementia in old age (Fratiglioni & Qiu, 2013). The importance of physical, mental and social stimulation to retaining cognitive function in old age is also supported by the negative effect of retirement on cognitive ability (Rohwedder & Willis, 2010), particularly for groups of individuals that have had jobs involving plenty of social interaction (Finkel et al., 2009).

4.9 Dietary factors

The effect of nutrition and diet on cognitive ageing and the risk of dementia is difficult to study and the results are diverse, but it is currently fairly well established that a diet that contributes, for example, to improved vascular health also reduces the risk of developing dementia in old age (Fratiglioni & Qiu, 2013). This involves avoiding saturated fats and increasing intake of polyunsaturated fats. The positive effects of dietary patterns that include higher consumption of nuts, vegetables, fruit and fish, and lower consumption of fat-rich dairy products, red meat and butter are consistent with these conclusions. However, results on the effects of nutritional supplements are very mixed and sometimes even reveal negative effects, which means that nutritional supplements are not currently recommended unless a deficiency has been identified (Morris, 2012).

5. Use of medication

5.1 Ageing leads to increased sensitivity to drugs

Ageing brings changes in the body that influence the turnover of drugs and their effect. In general terms, it means that drugs remain in the body for longer and that their effects are amplified, which increases the risk of prolonged effect and side effects (Fastbom, 2006).

As we age, the amount of water in the body drops due to reduced muscle mass. The proportion of fat then increases, which means fat-soluble drugs, mainly those that affect the brain, such as psychotropic medications, remain in the body for longer. This may for example make sleeping tablets cause tiredness during the day. The liver's ability to break down certain medications also deteriorates with age. This is the case with the sedative diazepam (for example, Stesolid®), which can therefore have both a stronger and more prolonged effect. Kidney function begins to slow down around the age of 30-40 and is reduced by roughly half by the time we reach the age of 80. Many drugs are dependent on the kidneys for the excretion from the body, which means they can accumulate and cause side effects. This applies, for example, to several cardiac drugs, certain antibiotics and a number of pain-relieving drugs.

In the ageing body, the effect of many drugs is also amplified owing to changes in the sensitivity of cells, organs or different regulatory mechanisms. The brain has a heightened sensitivity to many types of medications, including psychotropic medications and morphine-related painkillers (opioids). This increases the risk of side effects such as drowsiness, dizziness and cognitive effects, as well as the risk of falls. Sensitivity is particularly high for drugs with so called anticholinergic effects. These block the effect of the neurotransmitter acetylcholine, which is important for the brain's cognitive functions and are therefore particularly prone to producing cognitive disorders. The most common medications with anticholinergic effects are drugs for treating incontinence, certain sedatives (for example Atarax® and Theralen®) and the older type of antidepressants.

Older people also often have difficulties to regulate their blood pressure, which can produce symptoms such as a drop in blood pressure when rising up. It often manifests itself as dizziness or unsteadiness, but it can also cause cognitive disruption and, in more serious cases, fainting. This age-related change also brings an increased sensitivity to medication to reduce blood pressure, such as cardiovascular drugs, medication for Parkinson's disease, antipsychotic drugs and antidepressants.

5.2 Medication can affect cognitive ability

The cognitive side effects of drugs can manifest themselves in a number of different ways. The most dramatic form is confusion. Confusion typically has a rapid onset, varies over time and is associated with reduced conciousness and a

feeling of disorientation. Sometimes a person can experience hallucinations and delusions. Drugs can also produce dementia-like symptoms, but this is relatively rare. In many cases, the cognitive impact of drugs is instead more subtle and, for example, manifests itself in the form of minor memory lapses. The problem is then that it may go undetected, or be misinterpreted as an age-related symptom.

One important factor to be considered here, is that older people use a high number of medications; on average 5-6 drugs per person in the elderly population and 10 drugs per person in nursing homes (Fastbom, 2006), a phenomenon is called polypharmacy. Polypharmacy increases the risk of side effects and drug-drug interactions (one drug either strengthening or weakening the effect of another), and decreases the patient's adherence to doctor's prescriptions. All these effects can have a negative impact on cognitive ability.

5.3 Use of medication in older people with dementia

Older people with dementia often take more drugs compared to those without dementia, which is largely owing to a more extensive use of psychotropic medications. Studies from the beginning of the 2000s revealed that the use of such medications was around twice as high in older people with dementia (Haasum et al., 2011), and at nursing homes up to 80 percent higher in this patient group (Olsson et al., 2010; Haasum et al., 2011). But over the past ten years, use of these medications in older people, particularly antipsychotic drugs, has fallen noticeably (National Swedish Board of Health and Welfare, 2013). This suggests that people with dementia today are less likely to be taking psychotropic medications and are hopefully receiving better nursing instead.

5.4 Use of dementia drugs

There are two types of drugs that are approved for the treatment of cognitive symptoms in Alzheimer's: cholinesterase inhibitors for treatment of mild to moderate dementia and memantine for moderate to severe dementia (National Swedish Board of Health and Welfare, 2010). It is not currently possible to cure or slow down the course of the disease, but these drugs can help people with the illness to preserve their cognitive ability and functional capacity for a period. However, not all patients benefit from these drugs. Roughly two in three patients who are treated with cholinesterase inhibitors see a measurable improvement as a result of the drug. It is therefore important to follow up the effect of the treatment, both some time after it is initiated and at regular intervals for as long as the treatment continues. The treatment can also be affected by the fact that some patients suffer from side effects. Cholinesterase inhibitors generate side effects in 10-15 percent of those being treated, primarily in the form of nausea, vomiting and diarrhoea.

In 2012, dementia medication was prescribed to 1.6 percent of people aged 65 and above in Sweden (men: 1.3 percent; women: 1.8 percent). Roughly two thirds of these drugs were cholinesterase inhibitors and one third was memantine. The percentage of older people (≥ 65 years) who have Alzheimer's in Sweden is estimated to be just over 5 percent, which therefore means that almost one in three patients with this illness is being treated with dementia medication (National Swedish Board of Health and Welfare, 2014).

6. Gaps in knowledge

Despite many years of research, the changes in the brain that are behind cognitive ageing and dementia have yet to be fully explored and understood. It is important to fill this knowledge gap, because we need this knowledge to identify goals for prevention and intervention. The identification of biomarkers for dementia diagnoses and the development of new and more effective treatment for dementia also depend on this knowledge. Research into normal ageing is just as important here as research into dementia, as dementia is closely related to cognitive ageing and both are partly a result of the same biological changes. Greater understanding of similarities and differences between the causes of cognitive ageing and dementia is also essential for improving dementia diagnostics. Longitudinal studies with repeated measurements, both of cognitive function and the brain, are important for gathering knowledge in this area.

In order to increase the knowledge of the effects of drugs on cognitive ability we need studies with longitudinal designs encompassing many different types of drugs, on large databases such as population databases or registers. Unfortunately, the studies we have today are often focused on a specific group of drugs or based on limited patient materials.

Epidemiological research has identified many protective factors and risk factors that are related to cognitive ageing and the risk of developing dementia, but in many cases the mechanisms and causal links are unknown. Identifying these mechanisms is an important task, as this knowledge is vital to the formation of effective prevention and intervention measures. There are also likely to be considerable individual differences in how factors such as leisure activities and retirement affect cognitive ability. These differences need to be analysed. Possible interactions between different protective factors and risk factors also remain largely unexplored. We need mechanism-oriented experimental studies and randomised and controlled intervention studies, together with a holistic approach to the individual, in order to take the next step in this field of research.

References

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Allaire, J.C., Marsiske, M., 2002. Well- and ill-defined measures of everyday cognition: relationships to older adults' intellectual ability and functional status. Psychology and Aging 17, 101-115.

America Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders, 4th ed, Washington, Dc.

Andel, R., Crowe, M., Pedersen, N. L., Mortimer, J., Crimmins, E., Johansson, B. & Gatz, M. (2005). Complexity of work and risk of Alzheimer's disease: A population-based study of Swedish twins. *Journal of Gerontology: Psychological Sciences*, 60B, 251-258.

Bartzokis, G., 2009. Alzheimer's disease as homeostatic responses to age-related myelin breakdown. Neurobiology of Aging.

Batty, G.D., Deary, I.J., Gottfredson, L.S., 2007. Premorbid (early life) IQ and later mortality risk: systematic review. Ann Epidemiol 17, 278-288.

Behrer, L., Erickson, K. I., Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive function in older adults. Journal of aging research.

Bäckman, L., Nyberg, L., Lindenberger, U., Li, S.C., Farde, L., 2006. The correlative triad among aging, dopamine, and cognition: Current status and future prospects. Neuroscience and Biobehavioral Reviews 30, 791-807.

Christensen, K., Thinggaard, M., Oksuzyan, A., Steenstrup, T., Andersen-Ranberg, K., Jeune, B., McGue, M. & Vaupel, J. W. (2013). Physical and cognitive functioning of people older than 90 years: a comparison of two Danish cohorts born 10 years apart. *The Lancet*, 382, 1507-1513.

Clouston, S. A. P., Kuh, D., Herd, P., Elliot, J., Richards, M. & Hofer, S. M. (2012). Benefits of educational attainment on adult fluid cognition: international evidence from three birth cohorts. *International Journal of Epidemiology*, 41, 1729-1736.

Cooper, J.A., Sagar, H.J., Jordan, N., 1991. Cognitive impairment in early, untreated, Parkinson's disease and its relationship to motor disability. Brain 114, 2095-2122.

de Frias, C.M., Lovden, M., Lindenberger, U., Nilsson, L.G., 2007. Revisiting the dedifferentiation hypothesis with longitudinal multi-cohort data. Intelligence 35, 381-392.

Deary, I. J., Johnson, W. & Houlihan, L. M. Genetic foundations of human intelligence. Hum. Genet. 126, 215–232 (2009).

Deary, I. J., Strand, S., Smith, P. & Fernandes, C. (2007). Intelligence and educational achievement. *Intelligence*, 35, 13-21.

Deary, I.J., Whalley, L.J., Lemmon, H., Crawford, J.R., Starr, J.M., 2000. The Stability of Individual Differences in Mental Ability from Childhood to Old Age: Follow-up of the 1932 Scottish Mental Survey. Intelligence 28, 49-55.

Deary, I.J., Yang, J., Davies, G., Harris, S.E., Tenesa, A., Liewald, D., Luciano, M., Lopez, L.M., Gow, A.J., Corley, J., Redmond, P., Fox, H.C., Rowe, S.J., Haggarty, P., McNeill, G., Goddard, M.E., Porteous, D.J., Whalley, L.J., Starr, J.M., Visscher, P.M., 2012. Genetic contributions to stability and change in intelligence from childhood to old age. Nature 482, 212-215.

Der, G., Batty, G.D., Deary, I.J., 2009. The association between IQ in adolescence and a range of health outcomes at 40 in the 1979 US National Longitudinal Study of Youth. Intelligence 37, 573-580.

Drachman, D., 2007. Rethinking Alzheimer's disease: The role of age-related changes. Current Neurology and Neuroscience Reports 7, 265-268.

Farkas, E., Luiten, P.G.M., 2001. Cerebral microvascular pathology in aging and Alzheimer's disease. Progress in Neurobiology 64, 575-611.

Fastbom, J. (2006). Äldre och Läkemedel. Liber AB.

Fastbom J. Drug-induced Cognitive Impairment. In Dementia – Diagnostic and Therapeutic Interventions. A Systematic Review. Volume 2. SBU-rapport 172E/2. 2008. Statens beredning för medicinsk utvärdering, Stockholm. pp 413-481.

Finkel, D., Andel, R., Gatz, M., Pedersen, N.L., 2009. The role of occupational complexity in trajectories of cognitive aging before and after retirement. Psychology and Aging 24, 563-573.

Flynn, J.R., 1984. The mean IQ of Americans: Massive gains from 1932 to 1978. Psychological Bulletin 95, 29-51.

Fratiglioni, L. & Qiu, C. (2013). Epidemiology of dementia. In Dening, T. & Thomas, A. (Eds.), *Oxford textbook of old age psychiatry* (2nd ed., pp. 389-414). Oxford: Oxford University Press.

Fratiglioni, L., Rocca, W., 2001. Epidemiology of dementia. In: Boller, F., Cappa, S.F. (Eds.), Handbook of neuropsychology: aging and dementia. Elsevier, Amsterdam, pp. 193-215.

Gatz, M., et al. (2006). Role of genes and environments for explaining Alzheimer disease. Archives of General Psychiatry, 63, 168–74.

Guo, G. & Harris, K. M. (2000). The mechanisms mediating the effects of poverty on children's intellectual development. *Demography*, 37, 431-447.

Haasum Y, Fastbom J, Fratiglioni L, Kåreholt I, Johnell K. Pain treatment in elderly persons with and without dementia: a population-based study of institutionalized and home-dwelling elderly. Drugs Aging. 2011 Apr 1;28(4):283-93.

Hertzog, C., Kramer, A.F., Wilson, R.S., Lindenberger, U., 2009. Enrichment effects on adults cognitive development. Psychological Science in the Public Interest 9, 1-65.

Hooshmand, B., Solomon, A., Kåreholt, I., Rusanen, M., Hänninen, T., Leiviskä, J., Winblad, B., Laatikainen, T., Soininen, H., Kivipelto, M., 2012. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. Jounral of internal Medicine 271, 204-212.

Hunter, J.E., Hunter, R.F., 1984. Validity and utility of alternative predictors of job performance. Psychological Bulletin 96, 72-98.

Judge, T.A., Klinger, R.L., Simon, L.S., 2010. Time is on my side: time, general mental ability, human capital, and extrinsic career success. J Appl Psychol 95, 92-107.

Karp, A., Andel, R., Parker, M. G., Wang, H. X., Winblad, B. & Fratiglioni, L. (2009). Mentally stimulating activities at work at midlife and dementia risk after age 75: a follow-up study from the Kungsholmen project. *The American Journal of Geriatric Psychiatry*, 17, 227-236.

Lager, A. C. J., Modin, B. E., De Stavola, B. L. & Vågerö, D. (2012). Social origin, schooling and individual change in intelligence during childhood influence long-term mortality: a 68-year follow-up study. International Journal of Epidemiology, 41, 398-404.

Lindenberger, U., Ghisletta, P., 2009. Cognitive and Sensory Declines in Old Age: Gauging the Evidence for a Common Cause. Psychology and Aging 24, 1-16.

Lynch, J. W., Kaplan, G. A. & Shema, S. J. (1997). Cumulative impact of sustained economic hardship on physical, cognitive, psychological, and social functioning. *The New England Journal of Medicine*, 337, 1889-1895.

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., Schmiedek, F., 2010. A Theoretical Framework for the Study of Adult Cognitive Plasticity. Psychological Bulletin 136, 659-676.

Lövdén, M., Ghisletta, P., Lindenberger, U., 2005. Social participation attenuates decline in perceptual speed in old and very old age. Psychology and Aging 20, 423-434.

Lövdén, M., Rönnlund, M., Wahlin, A., Bäckman, L., Nyberg, L., Nilsson, L.G., 2004. The extent of stability and change in episodic and semantic memory in old age: Demographic predictors of level and change. Journals of Gerontology Series B: Psychological Sciences and Social Sciences 59, P130-P134.

Marengoni, A., Winbald, B., Karp, A., Fratiglioni, L., 2008. Prevalence of chronic diseases and multimorbidity among the elderly population in Sweden. American Journal of Public Health 98, 1198-1200.

Morris MC. Nutritional determinants of cognitive aging and dementia. Proc Nutr Soc 2012; 71:1 – 13.

Olsson J, Bergman A, Carlsten A, Oké T, Bernsten C, Schmidt IK, Fastbom J. Quality of drug prescribing in elderly people in nursing homes and special care units for dementia: a cross-sectional computerized pharmacy register analysis. Clin Drug Investig. 2010;30(5):289-300.

Oscar-Berman, M., 2012. Function and Dysfunction of Prefrontal Brain Circuitry in Alcoholic Korsakoff's Syndrome. Neuropsychology Review 22, 154-169.

Piccinin, A. M., Muniz, G., Clouston, S., Reynolds, C. A., Thorvaldsson, V., Deary, I. J., Deeg, D., Johansson, B., Mackinnon, A., Spiro, A., Starr, J. M., Skoog, I., Hofer, S. M. (2013). Coordinated analysis of age, sex, and education effects on change in MMSE scores. *Journal of Gerontology: Psychological Sciences*, 68, 374–390.

Prince, M., Bryce, R., Albanese, E., Wimo, A., Riberio, W. & Ferri, C. P. (2013). The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's & Dementia*, 9, 63-75.

Qiu, C., von Strauss, E., Bäckman, L., Winblad, B. & Fratiglioni, L. (2013). Twenty-year changes in dementia occurrence suggest decreasing incidence in central Stockholm, Sweden. *Neurology*, 80, 1888-1894.

Qiu, C., Winblad B, and Fratiglioni L (2005). The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurology, 4, 487–99.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex 15, 1676-1689.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex 15, 1676-1689.

Richards, M. & Deary, I. J. (2014). A life course approach to cognitive capability. In Kuh, D., Cooper, R., Hardy, R., Richards, M. & Ben-Shlomo, Y. (Eds.). *A life course approach to healthy ageing* (pp. 32-45). Oxford: Oxford University Press.

Richards, M. & Hatch, S. L. (2011). A life course approach to the development of mental skills. *Journal of Gerontology: Psychological Sciences*, 66B (S1), i26-i35.

Rohwedder, S., Willis, R.J., 2010. Mental Retirement. J Econ Perspect 24, 119-138.

Rönnlund, M., Nilsson, L.-G., 2008. The magnitude, generality, and determinants of Flynn effects on forms of declarative memory and visuospatial ability: Time-sequential analyses of data from a Swedish cohort study. Intelligence 36, 192-209.

Rönnlund, M., Nilsson, L.G., 2006. Adult life-span patterns in WAIS-R Block Design performance: Cross-sectional versus longitudinal age gradients and relations to demographic factors. Intelligence 34, 63-78.

Rönnlund, M., Nyberg, L., Bäckman, L., Nilsson, L.G., 2005. Stability, growth, and decline in adult life span development of declarative memory: Cross-sectional and longitudinal data from a population-based study. Psychology and Aging 20, 3-18.

Salthouse, T., 2012. Consequences of age-related cognitive declines. Annual Review of Psychology 63, 201-226.

Salthouse, T.A., 2011. Neuroanatomical substrates of age-related cognitive decline. Psychological Bulletin 137, 753-784.

Savva, G.M., 2009. Age, neuropathology, and dementia. New England Journal of Medicine 360, 2302-2309.

SBU. (2008). *Dementia – Etiology and Epidemiology: a systematic review*. Volume 1. Stockholm: SBU.

Scazufca, M., Menezes, P. R., Araya, R., Di Rienzo, V. D., Almeida, O. P., Gunnell, D. & Lawlor, D. A. (2008). Risk factors across the life course and dementia in a Brazilian population: results from the Sao Paulo Ageing & Health Study (SPAH). *International Journal of Epidemiology*, 37, 879-890.

SCB. (2014). Data hämtad från Statistiska Centralbyråns statistikdatabas 2014-04-29.

Schaie, K.W., 2005. Developmental influences on adult intelligence: The Seattle longitudinal study. Oxford University Press, New York.

Schmiedek, F., Lovden, M., Lindenberger, U., 2013. Keeping it steady: older adults perform more consistently on cognitive tasks than younger adults. Psychological Science 24, 1747-1754.

Schneider, J.A., Arvanitakis, Z., Bang, W., Bennett, D.A., 2007. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology 69, 2197-2204.

Schneider, J.A., Arvanitakis, Z., Leurgans, S.E., Bennett, D.A., 2009. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Annals of Neurology 66, 200-208.

Schooler, C., Mulatu, M. S. & Oates, G. (1999). The continuing effects of substantively complex work on the intellectual functioning of older workers. *Psychology and Aging*, 14, 483-506.

Sharp, E. S. & Gatz, M. (2011). Relationship between education and dementia: an updated systematic review. *Alzheimer Disease & Associated Disorders*, 25, 289-304.

Skirbekk, V., Stonawski, M., Bonsang, E. & Staudinger, U. M. (2013). The Flynn effect and population aging. *Intelligence*, 41, 169-177.

Socialstyrelsen. (2010). Nationella riktlinjer för vård och omsorg vid demenssjukdom 2010 – stöd för styrning och ledning, Socialstyrelsen 2010-5-1.

Socialstyrelsen. (2013). Stimulansbidrag till insatser för vård och omsorg om äldre – Slutredovisning perioden 2007–2012. Socialstyrelsen 2013-10-27.

Socialstyrelsen. (2014). Nationell utvärdering – Vård och omsorg vid demenssjukdom 2014 – Indikatorer och underlag för bedömningar. Socialstyrelsen 2014-2-1.

Solomon, A., Mangialasche, F., Richard, E., Andrieu, S., Bennett, D.A., Breteler, M., Fratiglioni, L., Hooshmand, B., Khachaturian, A.S., Schneider, L.S., Skoog, I., Kivipelto, M., 2014. Advances in the prevention of Alzheimer's disease and dementia. Journal of Internal Medicine 275, 229-250.

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, 47, 2015-2028.

Strenze, T. (2007). Intelligence and socioeconomic success: A meta-analytic review of longitudinal research. *Intelligence*, 35, 401-426.

Viswanathan, A., Rocca, W.A., Tzourio, C., 2009. Vacular risk factors and dementia. Neurology 72, 368-374.

Wahlin, A., Nilsson, E., Fastbom, J., 2002. Cognitive performance in very old diabetic persons: The impact of semantic structure, preclinical dementia, and impending death. Neuropsychology 16, 208-216.

Whalley, L., 2006. A life-course approach to the aetiology of dementias. . Lancet Neurology 5.

Wimo, A., Jönsson, L., Fratiglioni, L., Sandman, P. O., Gustavsson, A., & Sköldunger, A. (2014). Demensjukdomarnas samhällskostnader i Sverige 2102. www.socialstyrelsen.se

Zagorsky, J.L., 2007. Do you have to be smart to be rich? The impact of IQ on wealth, income and financial distress. Intelligence 35, 489-501.

Zahodne, L.B., Glymour, M.M., Sparks, C., Bontempo, D., Dixon, R.A., MacDonald, S.W., Manly, J.J., 2011. Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. Journal of the International Neuropsychological Society : JINS 17, 1039-1046.

Zahodne, L.B., Stern, Y., Manly, J.J., 2014. Depressive Symptoms Precede Memory Decline, but Not Vice Versa, in Non-Demented Older Adults. Journal of the American Geriatrics Society 62, 130-134.

Zeki Al Hazzouri, A., Haan, M. N., Kalbfleisch, J. D., Galea, S., Lisabeth, L. D. & Aiello, A. E. (2011). Life-course socioeconomic position and incidence of dementia and cognitive impairment without dementia in older Mexican Americans: results from the Sacramento Area Latino Study on Aging. *American Journal of Epidemiology*, 173, 1148-1158.