Expert Views

Alzheimer's Disease and Dementia
Footprint Scenario

A research report series
Volume 1 - Introduction

SCOR
The Art & Science of Risk

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Introduction

Alzheimer's disease and dementia are major public health challenges around the world, especially in areas with an aging population such as Western Europe and North America, but also in countries like Latin America and China, where aging nor dementia was not an issue a few decades ago. Fifty million people are currently estimated to have dementia worldwide. About two-thirds of them have Alzheimer's, according to Alzheimer's Disease International (2018).

Research on Alzheimer's and dementia has recently gained increasing support, with large private and public funding supporting work on new screening, diagnostic and therapeutic applications. Many experts are optimistic about breakthroughs in Alzheimer's and dementia in the short to mid-term future.

SCOR Knowledge team has developed an in-depth footprint scenario analysis, using sophisticated modeling and implementation of a shock on Alzheimer's and dementia mortality, assessing its impact on life expectancy in multiple scenarios, ranging from reductions to the elimination of Alzheimer's and dementia mortality.

This article is the first part of the footprint analysis series, focusing on the medical discussion on Alzheimer's and dementia. It covers basic information about the diseases, progress in risk detention, risk reduction and prevention, and advances in treatment. It also discusses how the progress and emission of Alzheimer's and dementia may affect the life insurance, critical illness and long-term care business.

Understanding Alzheimer's and dementia

Dementia is not a single disease, but a general term describing a syndrome that includes memory loss and other mental abilities severe enough to interfere with daily life. It covers a wide range of specific medical conditions caused by physical changes in the brain. Alzheimer's is the most common type of dementia, but there are many others such as vascular dementia, Lewy body dementia and Huntington's disease, etc.

Dementia is responsible for about 1.5 million annually worldwide, according to Alzheimer's Association (2021a), making it the second leading cause of death in high-income countries in 2019, overtaking stroke, see World Health Organization (2020). In the U.S., more than 6 million Americans are living with Alzheimer's disease. By 2050, this number is projected to rise to nearly 13 million, Alzheimer's Association (2021b). In 2021, Alzheimer's and other dementias will cost the U.S. $355 Billion. These costs are projected to balloon, hitting an estimated $1.1 Trillion by 2050.

Types of dementia

Different types of dementia are associated with particular types of brain cell damage in specific regions of the brain. Figure 1 displays the most common types of dementia and their popularity.

Alzheimer's disease accounts for 60-80% of cases. In this disease, high levels of certain proteins inside and outside brain cells make it hard for brain cells to stay healthy and communicate with each other. Two abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells.

Vascular dementia, which occurs because of microscopic bleeding and blood vessel occlusion depriving various brain regions of oxygen and nutrients, is the second most common cause of dementia. About 5% to 10% of persons with dementia have vascular dementia alone although it is more common as a part of mixed dementia.

Lewy bodies dementia is the third most common cause of dementia, accounting for 5 to 10 percent of cases. It is a progressive dementia that deteriorates thinking, reasoning and independent functions because of abnormal microscopic deposits that damage brain cells over time.

Frontotemporal dementia refers to a group of disorders caused by progressive nerve cell loss in the brain's frontal lobes (the areas behind the forehead) or its temporal lobes (the regions behind the ears). Most people with Frontotemporal dementia are diagnosed in their 40s, 50s or early 60s while Alzheimer's grows more common with increasing age.

Patients can have more than one cause of dementia **(mixed dementia)**. In the study carried on by James et al. (2016) involving long-term cognitive assessments followed by brain autopsy, 94% of participants who were diagnosed with dementia were diagnosed with Alzheimer's. The autopsies of those diagnosed with Alzheimer's showed that 54% had coexisting pathology in addition to Alzheimer's brain changes. The most common coexisting abnormality was vascular disease. Lewy bodies were the second most common coexisting brain change.
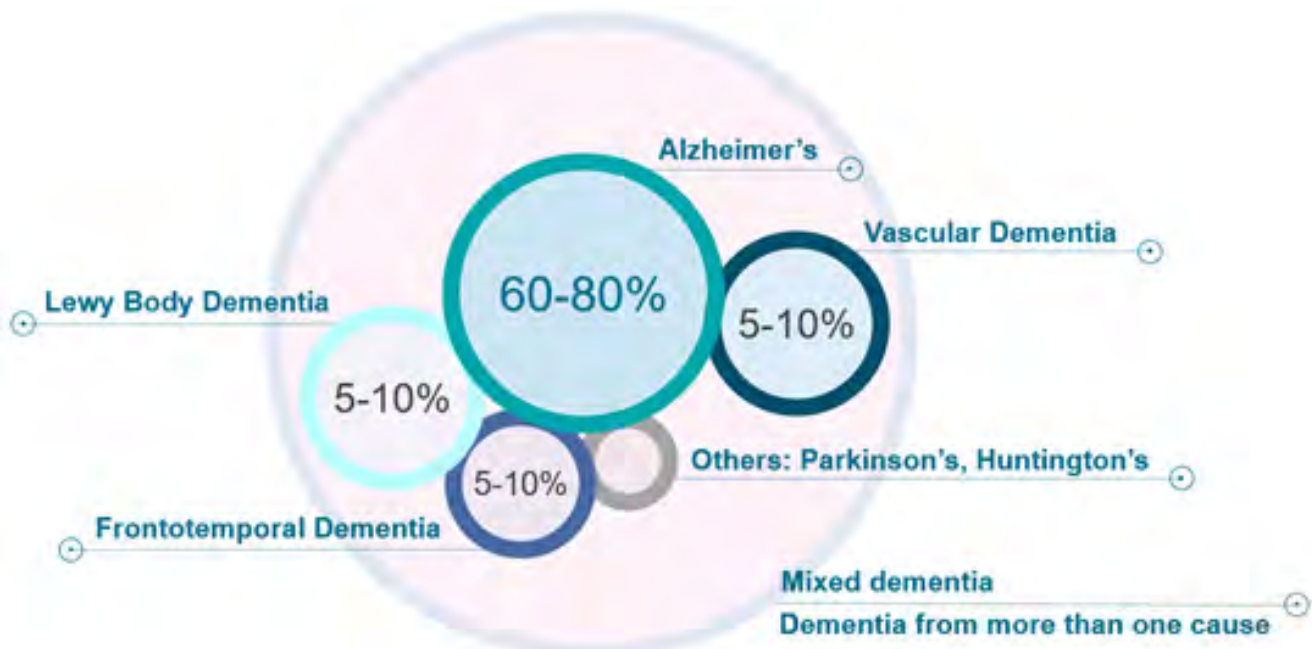

Figure 1: *Types of dementia. Source: Alzheimer's Association (2021)*

Symptoms

Changes in the brain begin years before any signs of the diseases. This time period, which can last for years, is referred to as a preclinical disease.

Most of the conditions are progressive, which means that the signs of dementia start out slowly and gradually get worse. Table 1 provides an overall idea of how abilities change once symptoms appear for the four most common types of dementia.

Table 1: *Symptoms related to the four most common types of dementia. Source: Alzheimer's Association (2021)*

Type of Dementia	Symptoms
Alzheimer's disease	The symptoms worsen over time. The stages are separated into three categories: 1. Early-stage (mild): Symptoms may not be widely apparent, but the person may experience memory lapses. 2. Middle-stage (moderate): It is the longest stage. Symptoms are more pronounced. Damage to nerve cells in the brain makes it difficult for the person to express thoughts and perform routine tasks without assistance. 3. Late-stage (severe): Individuals lose the ability to respond to their environment. Significant personality changes may occur and individuals need extensive care. They also become vulnerable to infections, especially pneumonia.
Vascular dementia	The impact of vascular conditions on thinking skills varies widely, depending on the extent and severity of the blood vessel damage and the part of the brain it affects. Symptoms is usually obvious when they happen soon after a major stroke. Sudden post-stroke changes in thinking and perception may include: confusion, disorientation, trouble speaking or understanding speech, physical stroke symptoms, such as a sudden headache, difficulty walking; poor balance and paralysis on one side of the face or the body.
Lewy body dementia	Changes in thinking and reasoning, confusion and alertness that varies significantly from one time of day to another or from one day to the next, imbalance and other parkinsonian movement features, Visual hallucinations, delusions., malfunctions of the autonomic nervous system. Memory loss may be significant but less prominent than in Alzheimer's.
Frontotemporal dementia	Behavior variant of frontotemporal dementia is characterized by prominent changes in personality and behavior. Primary progressive aphasia is the second major form of frontotemporal degeneration that affects language skills, speaking, writing and comprehension. Disturbances of motor (movement or muscle) function include three disorders that produce changes in muscle or motor functions with or without behavior or language problems

Causes and risk factors

The greatest known risk factor for Alzheimer's and other dementias is increasing age, but it is not a direct cause of Alzheimer's disease. Other risk factors for Alzheimer's include genetics and lifestyle. Other types of dementia such as Lewy body dementia and Frontotemporal dementia do not have any known specific causes.

Table 2: *Causes and risk factors related to the four most common types of dementia. Source: Alzheimer's Association (2021)*

Type of Dementia	Causes and Risk Factors
Alzheimer's disease	Researchers believe there is no single cause of Alzheimer's disease. It likely develops from multiple factors, such as genetics, lifestyle and environment. **Age:** After age 65, the risk of Alzheimer's doubles every five years. After age 85, the risk reaches nearly one-third. **Genetics:** Alzheimer's genes have been found in both risk genes and deterministic genes categories. APOE-e4 is the first gene identified with a strong association that increases the risk for Alzheimer. Between 40-65% of people diagnosed with Alzheimer's have the APOE-e4 gene. However, it is estimated that less than 1% of Alzheimer's cases are caused by yet unidentified genes. **Lifestyle and heart-head connection:** Heart disease, diabetes, stroke, high blood pressure and high cholesterol. Common causes of symptoms are depression, untreated sleep apnea, delirium, side effects of medications, thyroid problems, certain vitamin deficiencies and excessive alcohol consumption.
Vascular dementia	Any condition that damages blood vessels anywhere in the body can cause brain changes linked to vascular dementia. As with Alzheimer's disease, **advancing age** is a major risk factor. Additional risk factors for **vascular dementia** coincide with those that increase the cardiovascular risk for heart disease, stroke and other conditions affecting blood vessels.
Lewy body dementia	**Researchers have not yet identified any specific causes.**
Frontotemporal dementia	**There are no known risk factors** for any frontotemporal degenerations except for family history or a similar disorder.

Diagnosis and treatment

There is no single diagnostic test that can determine if a person has Alzheimer's disease and dementia. Physicians and specialists such as neurologists, neuropsychologists, geriatricians and geriatric psychiatrists use a variety of approaches and tools to make a diagnosis.

As of now, there is no cure for Alzheimer's and dementia, but there are treatments that may change disease progression, and drug and non-drug options that may help to treat the symptoms. The table below shows major treatments and outcomes for each type of dementia.

Table 3: Diagnosis, treatment and outcomes related to the four most common types of dementia. Sources: Alzheimer's Association (2021), Eisai (2021)

Type of Dementia	Diagnosis, Treatment and Outcomes
Alzheimer's disease	**Diagnosis:** Information from a physical exam and laboratory tests can help identify health issues that can cause symptoms such as thyroid problems and certain vitamin deficiencies. Use of neurological exam to look for conditions that may impair memory or thinking. **Treatment and outcomes:** Aducanumab (Aduhelm™), a drug granted accelerated approval by the FDA in 2021, designed with an intention to reduce cognitive and functional decline in people living with early Alzheimer's. In addition, Lecanemab (Eisai and Biogen Companies) was granted Fast Track designation by the FDA in late 2021. Several other amyloid-targeting therapies are also in development.
Vascular dementia	**Diagnosis:** Neurocognitive testing that provide a detailed evaluation of specific thinking skills such as judgment, planning, problem-solving, reasoning and memory. Brain imaging evidence, usually with magnetic resonance imaging (MRI) can confirm a recent stroke, or other vascular brain changes. **Treatment:** Good control of cardiovascular risk factors is important. FDA has not approved any drugs specifically to treat symptoms of vascular dementia, but there is evidence from clinical trials that drugs approved to treat Alzheimer's symptoms may also offer a modest benefit in people with vascular dementia.
Lewy body dementia	**Diagnosis:** By "clinical" diagnosis, which means a doctor's best professional judgment about the reason for a person's symptoms. **Treatment:** There are no treatments that can slow or stop the brain cell damage caused by Lewy body dementia. Current strategies focus on helping symptoms.
Frontotemporal dementia	**Diagnosis:** Type of problems experienced by the patient and the results of neurological exams. Brain scans such as MRI and glucose positron emission scans are very helpful additional tests. **Treatment:** There are no specific treatments for any of the frontotemporal subtypes. There are medications that can reduce agitation, irritability and/or depression which improve quality of life.

Potential cure breakthrough and implications to life insurance

Clinical and preclinical research on Alzheimer's and dementia diseases has gained increasing support in recent years, with large private and public funding supporting work on new screening, diagnostic and therapeutic applications. In 2021, the National Institutes of Health spent an estimated $3.2 billion on research into Alzheimer's and dementia, Alzheimer's Association (2021c). As a result of this unprecedented funding, scientists can work at a more rapid pace to advance basic disease knowledge, explore ways to reduce risk, reveal new biomarkers for early diagnosis and drug targeting, and develop potential treatments.

Many experts are optimistic about breakthroughs in Alzheimer's and dementia in the short to mid-term future. Shekelle et al. (2020) judge ten breakthroughs as being at least 70% likely to occur by 2037. This optimism is also reflected in the clinical pipeline for new therapies addressing disease-modifying biologics, cognitive impairment and neuropsychiatric symptoms with symptom-reducing agents now in Phase II and III clinical trials as reviewed by Cummings et al (2021).

The widespread media attention surrounding the approval of Aduhelm™ (Aducanumab) by the U.S. Food and Drug Administration (2021) for the treatment of Alzheimer's is also expected to serve to educate the public, promote more patient visits to their healthcare providers, and lead to greater participation in clinical research reports, according to Weiner et al. (2021).

Progress in risk detection

As most dementia diagnoses happen when the patient begins to experience memory loss late in life, research in the accurate and widespread early risk identification will be among the most active areas in Alzheimer's and dementia science. Below are various progress on detection, cures and treatments as well as their implication to life insurance.

Neuroimaging is among the most promising areas of research focused on the early detection of Alzheimer's and dementia disease. Application of deep learning and other AI methods are expected to speed up risk identification. Odusami et al. (2021) developed a deep learning-based method that can predict the possible onset of Alzheimer's disease from brain images with an accuracy of over 99%. Gaubert et al. (2021) introduced a deep learning tool that can predict Alzheimer's disease five years before the symptoms. They used a combination of demographic, neuropsychological data, genetic testing for APOE-e4 and hippocampal volumetry.

Genetic profiling may become a valuable risk assessment tool. To date, around 70 genetic variants have been reported to be associated with Alzheimer's disease risk, according to Raybould and Sims (2021). These discoveries have indicated the involvement of pathways, additional to amyloid precursor protein (APP) metabolism, such as immunity, ubiquitination, endocytosis, lipid metabolism and tau binding. The identification of new pathways has also made it possible to identify new biomarkers.

Biomarkers are believed to offer one of the most promising paths. Researchers are currently investigating whether Alzheimer's and dementia cause consistent and measurable **changes in blood** levels of tau, beta-amyloid or other biomarkers before symptoms appear. In addition, they are exploring whether early detectable changes can appear elsewhere in the body such as ocular changes by **neuroretinal exams.**

Progress in risk reduction and prevention

Interventions targeting and modifying modifiable risk factors are expected to prevent, delay the onset and/or slow the progression of the disease. According to Montero-Odasso et al. (2021) more than a third of dementia cases can be prevented in the next 25 years by addressing the risk factors. More and more evidence confirm nine previously identified risk factors for dementia - low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and poor social contact. Three new factors, excessive alcohol use, traumatic brain injury, and air pollution, were also recently added to the list. According to Livingston et al. (2020), these 12 risk factors together account for around 40% of dementias worldwide. Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors for dementia are presented in Figure 2.

Advances in treatment

All the progress in treatment as described above would decrease the rate of progression of the disease and could modify its long-term trajectory. In addition, future treatment would target the disease in its earliest stages, before irreversible brain damage or mental decline occurred.

As of December 2021, more than 160 agents with diverse mechanisms of action have been registered in the clinical trials for Alzheimer's disease, U.S. National Library of Medicine (2021). There are currently 113 clinical studies in phase 2/3 and 48 in phase 3 clinical trials. These studies are evaluating the safety and efficacy of new molecules and repurposed drugs. The large majority of the various therapeutic approaches used to develop agents are illustrated in Figure 3.

Figure 2: Possible brain mechanisms for enhancing or maintaining cognitive reserve and population attributable fraction of potentially modifiable risk factors for dementia. Source: Livingston et al. (2020)
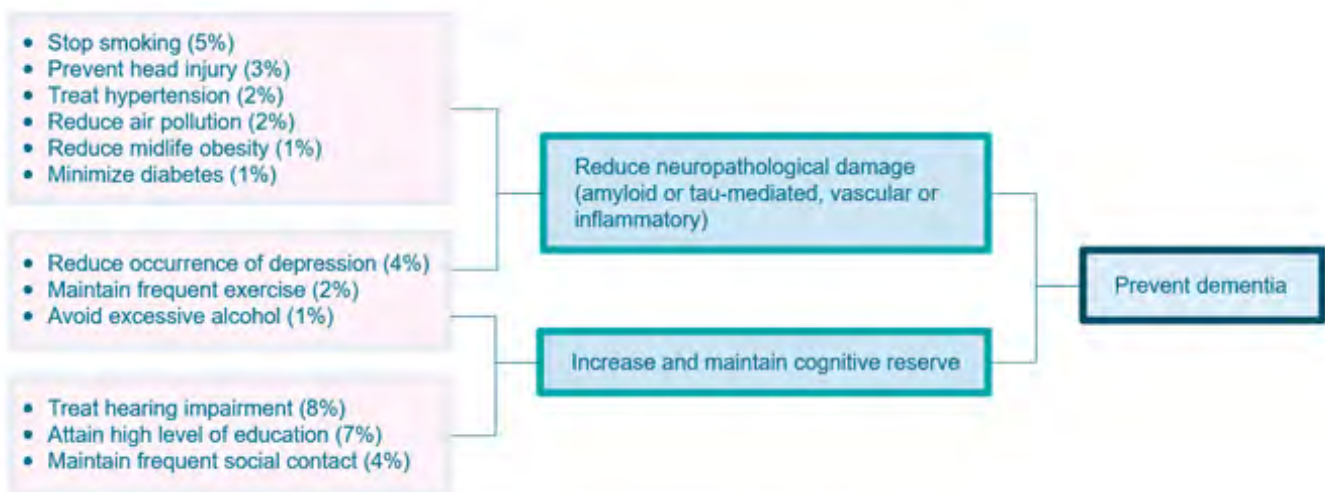
Tau directed therapy: Tau is a protein that forms neurofibrillary tangles (NFTs), a key indicator characterizing Alzheimer's disease. Accumulation of tau was found to correlate closely with the severity of dementia. Current trials are on tau immunotherapies are discussed in Bomasang-Layno and Bronsther (2021) and Gupta and Samant (2021).

Anti-neuroinflammatory drugs: Neuroinflammation is a key factor of neurodegenerative disorder. Several independent observational studies have demonstrated that anti-inflammatory drugs use is associated with a lower risk of developing Alzheimer's disease. Several ongoing clinical trials on *drugs targeting neuroinflammation* are reviewed by Athar et al. (2021) and Gupta and Samant (2021).

Antioxidants: Antioxidants improve cognitive performance in patients with Alzheimer's disease. Several studies have reported effective *results on cellular oxidative stress* and amyloid pathology of these antioxidants, Gupta and Samant (2021). Other large-scale epidemiological studies have shown promising results that consumption of foods high in antioxidant supplements, ⍺-carotene, vitamin C and vitamin E is linked to a lower risk of dementia. Additionally, benfotiamine, a derivative of thiamine, acts as a synthetic variant of vitamin B1. Various studies reporting that increasing thiamine levels in the brain may show beneficial results in patients with Alzheimer's disease are mentioned in Gupta and Samant (2021).

Stem cell therapy: The therapeutic potential of *stem cells* in Alzheimer's disease is reviewed by Chan et al. (2021). Studies have successfully differentiated stem cells into neurons in vitro, indicating the potential viability of stem cell therapy in neurodegenerative diseases. Preclinical studies have also shown successful improvements in cognitive performance in animal models. Although few clinical trials have been completed and many trials are still in phases I and II, the first reactions confirm the results of the preclinical studies. The use of stem cells appears to be promising in the treatment of Alzheimer's disease in terms of efficacy and safety.

Drugs: *Drug repositioning and repurposing* are strategies to accelerate the drug discovery and development process. Drug repurposing involves the use of an approved existing drug for some new therapeutic indication while drug repositioning occurs during the development process in biopharmaceutical industries and refers to the development of a drug for an indication different than its original intended indication. Applications of drug repurposing and repositioning to identify novel molecules for the treatment of Alzheimer's disease are reported in Ballard et al. (2020).

Figure 3: *Various therapeutic strategies used to develop agents for Alzheimer's disease.*
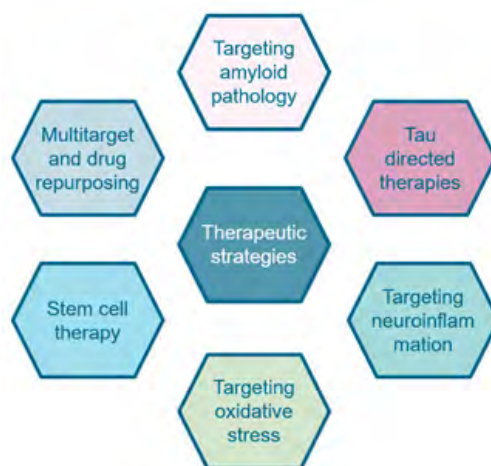
Implications to the Insurance Industry

Many existing insurance policies cover Alzheimer's and dementia, including life insurance, critical illness and long-term care. The impact of the population change, either growth or decline of those who suffer from these diseases will be significant. In addition to mortality impact, the cost associated with the care and treatment for patients of which insurers need to share the burden can be significant.

18.6 billion hours of care to people with Alzheimer's or other dementias have been provided by 16 million family members or other unpaid caregivers in 2019. This care is estimated at $244 billion. Average per-person Medicare payments for services to beneficiaries age 65 and older with dementias are more than three times as great as payments for beneficiaries without these conditions, and Medicaid payments are more than 23 times as great. Total payments in 2020 for health care, long-term care and hospice services for people age 65 and older with dementia are estimated to be as much as $305 billion, according to Alzheimer's Association (2021b). Moreover, non-monetary negative impact on caregivers and family members such as mental and physical health will be considerably high.

If we can turn this negative trend around with the advancement in cure and treatment combined with increased prevention efforts as mentioned in the report, it would be a tremendously positive effect not only to the insurance industry but also to society. Insurance and reinsurance companies have a massive stake in this global effort to fight against Alzheimer's and Dementia. SCOR is committed to take a proactive part with several initiatives including internal R&D initiatives such as this footprint scenario analysis.

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