# Simultaneous exposure to noise and carbon monoxide increases the risk of Alzheimer's disease: a literature review

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## Abstract

Dementia is a syndrome of cognitive and functional decline, commonly occurring in later life as a result of neurodegenerative and cerebrovascular processes beginning earlier in the life course. An excess of free radicals has an essential role in neurodegenerative diseases and aging. This paper aims to review the effects of noise and carbon monoxide as a risk factor in Alzheimer's disease as well as the role of free radicals in the progress of Alzheimer's disease. Articles included in this review were identified through a search of the databases PubMed, Scopus, and Google Scholar using the search terms Alzheimer's disease, dementia, noise, reactive oxygen species, and Carbon Monoxide. The literature search was restricted to the years 1982 to 2020 and articles published in the English language. The metabolism rate of the body is very high when exposed to noise and carbon monoxide; this leads to overproduction of reactive oxygen species and oxidative stress conditions. Oxidative stress has an essential role in the mechanisms concerned in Alzheimer's disease. In addition to the consequences of noise and a chemical substance on the auditory system, they also have non-auditory effects that affect the brain and induced neurodegenerative disease.

**Key words:** Alzheimer's disease; auditory system; carbon monoxide; dementia; free radicals; noise; older adults; oxidative stress; reactive oxygen species

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## Introduction

Epidemiologic studies show that 11% of the world's population is over 60 years of age; this is projected to increase, by 2050, to 22% of the population.[1] The most prevalence of aging is in the developing countries and the population of people living with Alzheimer's disease (AD) is predicted to reach 115 million by 2050.[2] AD is a prevalent age-related neurodegenerative disease; it is the main cause of a decrease in cognitive performance.[3] Environmental and lifestyle factors are the risk factors that contributing to this disease.[4] Stress can affect cognitive functions, and loud noise exposure is an important external source of stress.[5]

Noise is an auditory stimulus that adversely affects the health condition and has adverse effects on the activities and behaviors. Several studies have been shown that chronic exposure to noise involved several skills of auditory processing ability such as sustain attention, a short span of memory, and speech perception.[6-8]

Moreover, exposure to a high level of noise causes an enhancement of stress hormones that affect brain.[9] The adverse effects of noise on the auditory system depend on the level and duration of the exposure. Noise induce temporary threshold shift, which was suddenly created by exposure to excessive levels of sound and noise-induced permanent threshold shift that can be created by chronic exposure to high levels of sound.[10]

Carbon monoxide (CO) is generated as a part of exhaled air in the normal metabolite of healthy body and exposure to low levels of CO has no neurotoxic effect, but chronic exposure to CO is considered as a factor related to the development of central nervous system impairments.[11]

In this review, the researchers aim to examine the evidence of whether exposure to noise and CO can increase the risk of AD.

## Search Methods

Of 298 primary articles, 99 potentially eligible articles were reviewed. Articles included in this review were identified through searching the databases of PubMed, Medline, Scopus, Google Scholar and Scientific Information Database using the search terms of Alzheimer's disease, Noise, Carbon monoxide, Free radical, and hearing stress oxidative. We considered the factors related to AD, such as noise and CO. The literature search was restricted to the years 1982 to 2020 and the English language. **Figure 1** shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of study selection.

## Results

### Noise as a stressor and induced reactive oxygen species

The need for the industry in diverse societies has led to the creation of various factories and industries, and industrialization has also led the workforce to be in constant contact with machinery and equipment. The effects of widespread use of machinery and equipment make people more vulnerable to workplace hazards, including noise, which is the most commonly damaging physical hazard in the workplace.[12]

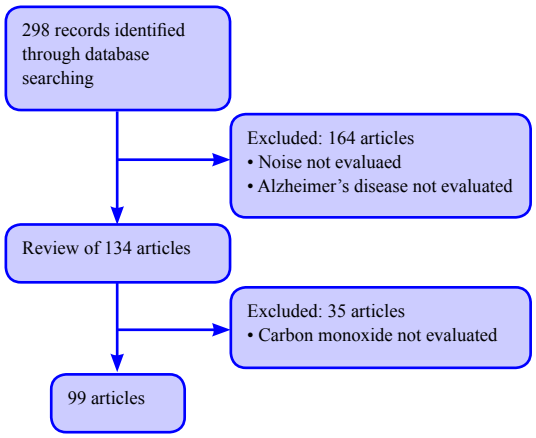


**Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for the study selection.**

Noise-induced hearing loss (NIHL) is one of the most common occupational injuries. In developed and developing countries, it is estimated that over 600 million people are exposed to excessive noise, with a significant proportion of them suffering from hearing loss or hearing loss shortly.[13] NIHL after age-related hearing loss (or presbycusis) is the most common cause of hearing loss in older adults, and also NIHL is the most commonly reported occupational disease in the United States.[14]

NIHL not only causes mechanical damage but also leads to metabolic changes.[15] Several mechanical damages have been observed in the NIHL, such as the reduction of the number of synapse between hair cells and auditory nerve fibers in the cochlea, decrease of synaptic vesicles, and reduction of the size of the synapse body. Moreover, inflammation of the dendrites (accumulation of additional glomerular neurotransmitters due to glutamate in the inner hair cells synapse) and neuronal changes in the nucleus of the cochlea and to the superior olivary complex have been observed.[16]

Metabolic disturbance after exposure to noise can increase the free radicals in the mitochondria.[17] Free radicals are reactive substances that can be grown in our body by exposure to several risk factors such as smoking, air pollution, chronic exposure to noise, and chemical substances (e.g., CO).

Reducing the blood flow of the cochlea after the formation of free radicals due to exposure to noise causes a lack of oxygen in the cochlea, and all of these factors ultimately lead to apoptosis and cell death.[18,19] In addition to the mentioned effects, exposure to environmental noise can induce psychosocial responses such as stress, anxiety, sleep disturbances, behavioral, and performance variation. There is some evidence based on the effects of background noise on the event-related potential concerning attentive and cognitive alterations.[20]

Oxidative stress and also cytokine production increased after exposure to noise in the brain.[21] The prenatal noise stress and even chronic exposure to noise caused an excess of amyloid β-peptide (Aβ) plaques and also increased the size of plaque across a lifetime.[22-24] Aβ plaques have been implicated in AD.[25-31]

Noise as a stressor factor has adverse effects on memory. Stress disturbed neuroanatomical in the brain, particularly in the hippocampus and induced changes in the size and number of neurons.[32,33] The hippocampus has the leading role in memory.[34] The loss of synapse and neurons in the hippocampus are the clinical features of AD.[35] Also, neuroinflammation in the hippocampus and accumulation of reactive oxygen species (ROS) are the significant features of AD.[36] So the stress caused by exposure to noise could increase the risk of AD.

## Carbon monoxide exacerbates the effects of noise

CO is classified as an asphyxiant gas. The CO is a colorless, odorless, and tasteless, flammable gas produced by incomplete combustion of organic materials such as coal, wood, paper, and oil. Motor vehicles and industries are among the most critical sources of CO production in the environment. CO excessively produced where fuel engines are used in closed spaces with improper ventilation. Many workers simultaneously exposed to CO and noise in workplaces.[37]

CO is considered as one of the most crucial air pollutants both in the environment and in industrial environments.[38] It has been estimated that in some areas such as enclosed environments, road tunnels, car parks, and underground subways, CO levels can exceed 100 per parts of million.[39] Vehicles in cities are the source of 60% of CO gas. CO level fluctuates depending on the season so that its amount is lower in the summer. Toxic gases in the air have adverse effects on the central nervous system. Animal studies have shown that chronic exposure to air pollution leads to a decrease in cognitive function and neuroinflammation, inflammation could contribute to AD-pathogenesis.[40]

The combination of CO with hemoglobin causes arterial carboxyl hemoglobin that reduces the amount of oxygen in the tissues and organs of the body especially has a direct toxic effect on mitochondria with the prevention of Cytochrome oxidase (**Figure 2**) and leads to hypoxic brain damage. Chronic exposure to CO can lead to anoxia, migraine, fatigue, decreased physical function, dizziness, nausea, vomiting, visual impairment, auditory abnormalities, Parkinson's disease, heart ischemia, heart disease, and atherosclerosis.[41] Loss of consciousness may appear when exposure to CO raises levels of carboxyl hemoglobin in the blood.[42] Studies have been shown that exposure to high-dose CO has adverse effects on the central nervous system and leads to abnormal white matter levels or neuronal degeneration.[43-45] All smokes contain CO that causes increased free radicals and damage to the cerebral cortex.[46]

The evidence demonstrated the relation between air pollution, noise, and cognitive decline and dementia risk.[47,48]

So the change of brain structure can cause earlier memory loss and onset of AD. The possible mechanisms of exposure to noise and CO in AD are shown in **Figure 3**.

Both human and animal studies have been shown the increasing impact of exposure to CO on NIHL.[49,50] Their results showed that the level of ROS in the animals simultaneously exposed to CO and noise was significantly higher than that exposed to noise only.[51] ROS is one of the most important free radicals. CO toxicity is also believed to result in tissue hypoxia and increased oxidative stress (due to the formation of free

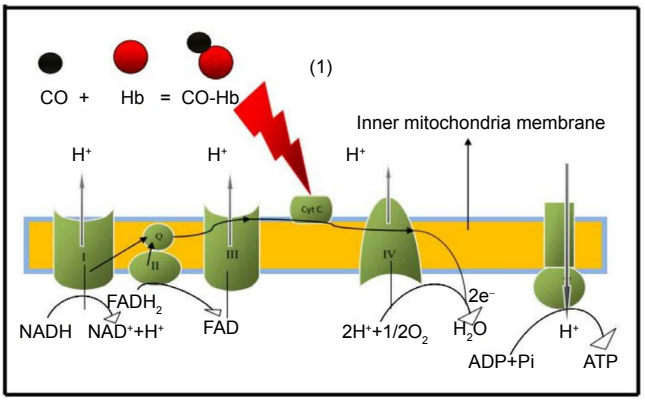


**Figure 2: Schematic representation of toxic direct effect of COHb on mitochondria**

Note: ADP: Adenosine diphosphate; ATP: adenosine triphosphate; CO: carbon monoxide; COHb: carboxyl hemoglobin; cyt C: cytochrome c; e: electron; FADH2: reduced form of flavin adenine dinucleotide; Hb: hemoglobin; I-V: complex I-V; NAD: nicotinamide adenine dinucleotide; NADH: reduced form of nicotinamide adenine dinucleotide; Pi: phosphoric acid; Q: coenzyme Q.

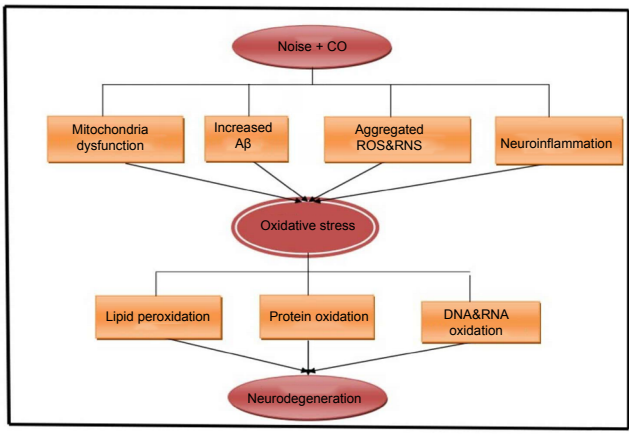


**Figure 3: The possible mechanisms of exposed to noise and CO in Alzheimer's disease.**

Note: Aβ: Amyloid β-peptide; CO: carbon monoxide; RNS: reactive nitrogen species; ROS: reactive oxygen species.

radicals in the brain and the inner ear), as well as increased glutamate secretion.[52]

## The relation between reactive oxygen species and Alzheimer's disease

AD is a progressive age-related disorder that degenerates neurons of the central nervous system and is the most cause of memory loss.[53,54] The decline of synapses, especially in the hippocampus causes the atrophy of the brain in an individual with AD.[55]

Production of free radicals such as ROS and reactive nitrogen species and the reduction of defense mechanism antioxidants result in oxidative stress condition.[56] Antioxidants are molecules that eliminate the ROS when high levels of ROS are accumulated.[53]

Various studies have shown that there are several risk factors for the development of AD, such as smoking, alcohol, obesity, stress, cardiovascular disease, but all of these risk factors have the same root in that they increase oxidative stress.[57] Oxidative stress has an essential role in the mechanisms concerned in AD.[58-66] Oxidative stress occurs in the initial stages of the progression of AD, and accumulation of oxidative stress along with a decrease of antioxidant defense levels accelerates the advance process of AD.[67-71] The brain sensitive to ROS more than other tissues because of the high consumption of oxygen in the brain, so oxidative stress contributes to brain injury.[72-76] Besides, iron ($Fe^{2+}$) ions that necessary for proper functions of the human brain are with a high level in the brain, and when this ions reacting with hydrogen peroxide ($H_2O_2$) take part in the fenton reaction and produced highly reactive hydroxyl radical (•OH).[77]

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + \bullet OH + OH^- \quad (2)$$

AD is one of the pathological conditions of the brain in which oxidative stress causes neuronal cell injury.[31,78-80] Free radicals can impose damage to the mitochondrial electron transfer complex, thus limiting the production of adenosine triphosphate and increasing the production of free radicals.[81,82] Mitochondrial dysfunction has been shown in neurodegenerative disorders such as AD.[83-86] It is well demonstrated that mitochondrial are the main source of adenosine adenosine triphosphate production; in normal condition, 98% of oxygen is used to produce adenosine triphosphate, and 1–2% of remaining oxygen produce ROS such as superoxide anion ($O_2^-$). Under this normal condition, the antioxidative defense systems which contain intracellular enzymes (e.g., glutathione peroxidase, superoxide dismutase, and catalase) cope with ROS. But when the body is exposed to high levels of metabolism, this causes increased body oxygen consumption and then leads to OH and $H_2O_2$ production with very high reactivity. Therefore ROS overcome to the antioxidative defense systems and cause damage to the body.[87-89] Noise and CO exposure is a condition capable of increasing the rate of metabolism of the body.

Insoluble Aβ plaques, neurofibrillary tangles, and synapse loss in the brain are an essential feature of AD.[90] ROS leads to an excess of Aβ peptides and Aβ increase during AD progression.[91-93] An increase in the markers of oxidative damage to proteins, DNA, RNA, and lipids peroxidation has been shown in the brain of Alzheimer's suffers.[94-98] Also, inflammation and oxidative stress are strongly related that chronic inflammation can be triggered by rising levels of oxidative stress in AD.[59,99] The antioxidative defense systems to cope with oxidative stress are very important. The brain is very vulnerable to free radical damage because of the low capacity of antioxidants, and the high content of polyunsaturated fatty acids.[69] So this is the possibility that chronic stress (exposure to noise and CO) changed the structure and function of the brain at one hand, and involved memory on the other side. Perhaps if people know the effects on health outcomes of such an exposure to noise and CO, they would pay more attention to determining noise and CO acceptable levels both in working and in a living environment.

## Conclusion

In addition to the consequences of noise and a chemical substance on the auditory system, they also have non-auditory effects that affect the brain and induced neurodegenerative

disease. In this review article, we conclude that noise plus CO exposure lead to oxidative stress condition, which has a vital role in causing the AD. Given that a large number of workers are simultaneously exposed to high levels of CO and noise. Current engineering and management controls are not effective in preventing the complications caused by these factors. So the new solutions such as biochemical methods should be used to prevent these effects.

**Author contributions**
Both authors contributed to the study design and writing.
**Conflicts of interest**
The authors declare no potential conflict of interest on publishing this paper.
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