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REVIEW

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Electromagnetic radiation and Alzheimer's disease

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ABSTRACT

This study aims to explore whether there is a relationship between different electromagnetic radiations, such as extremely low-frequency magnetic field (ELF-MF), radiofrequency (RF) radiation and ionizing radiation, and Alzheimer's disease. Resources related to the subject were scanned and 46 articles that were important to clarify the subject were evaluated. The results of the study investigating the relationship between Alzheimer's disease (AD) and electromagnetic fields were still contradictory. Whereas many researchers suggest that some electromagnetic radiation has prepared the ground for AD, others claim that RF radiation has a positive effect on the disease in question. The current state of knowledge calls for further detailed studies to clarify the issue.

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Electromagnetic radiation; radiofrequency radiation; ELF magnetic field; Alzheimer's disease; ionizing radiation

Introduction

Uncontrolled use of tools that emit ionizing and non-ionizing electromagnetic waves causes electromagnetic pollution to increase day by day in the world we live in. It is a known fact that the increase in both types of radiation in the environments we live in invites some diseases. Many scientific articles indicating the relationship between radiofrequency radiation (RF) and some diseases, which have rapidly increased in the recent decade, concern the public. However, studies suggest that there is a relationship between diseases and especially brain-related diseases and ionizing radiation. In this review, we attempt to evaluate whether there is a relationship between both ionizing and non-ionizing radiation and Alzheimer's disease (AD), which is one of the most common diseases of today.

The increase in mobile phone usage has increased concerns about the potential health risks of radiofrequency (RF) radiation exposure. Extensive research has been conducted over the years on the impact of RF fields generated by mobile phones on the human brain. Numerous studies found that RF–electromagnetic fields (EMFs) cause hazards to the brain. Studies reported that RF-EMFs from mobile phones could cause the initiation and progression of malignant brain tumors [1, 2], neuroma and glioma [3], indicating the damaging effect of RF-EMF on neurobehavioral function. Further RF-EMF was classified as a possible human carcinogen [4] (Group 2B).

The EC Scientific Committee on Emerging and Newly Identified Health Risks report indicates that a long-term mobile phone use could cause an acoustic neuroma, a benign tumor of the auditory nerve. The report refers to an increased number of cases of acoustic neuroma that could be linked to long-term exposure to mobile phone use. However, the report indicates more studies to clarify this link [5]. The report refers to RF fields generated by mobile telephony and wireless networks that are between 100 kHz and 300 GHz.

Pettersson et al. [6] researched the potential link between the effects of RF fields generated by mobile phones and cancer risk. The study did not support that long-term mobile phone use increases the risk of acoustic neuroma, yet it suggested that phone use might increase the likelihood that an acoustic neuroma case is detected [6]. Although numerous studies have been carried out on the exposure to ionizing and non-ionizing radiation on adverse health effects some studies reported that, to date, a clear judgment cannot be made about Alzheimer's disease (AD) [7]. This study intends to report the findings of the

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previous and recent studies on the effect of electromagnetic radiation on Alzheimer's irreversible deterioration of the brain cells.

AD is a progressive, irreversible mental deterioration [8]. People with AD have damaged brain cells that cause loss of memory, thinking and language skills, which are "irreversible, a progressive brain disorder that slowly destroys memory and thinking skills, and eventually the ability to carry out the simplest tasks" [8]. It has been estimated that 44 million people worldwide suffer from AD [9]. The cost of caring for Alzheimer's patients in the United States was about $236 billion in 2016; and estimated to be $259 billion in 2017 [9, 10]. The cost of AD worldwide is estimated to be $605 billion [9]. U.S. Alzheimer's Organization estimates the disease could cost as high as $1.1 trillion by 2050 only in the U.S [10]. To date, it is still not clear what triggers the disease in most people, yet it is reported that a combination of numerous genetic, environmental and lifestyle factors could play a role in triggering the disease [8, 11, 12]. Although the exact cause of the disease is not fully revealed, most research has in common that people suffering from AD have abnormal amounts of protein (amyloid plaques); intracellular neurofibrillary tangles (tau) in their brain [13–17]. Beta-pathies, conformation of protein molecules to the formation of beta chain polymers, are associated with neorogenerative diseases [18]. Abnormal protein beta chain irreversible conformation, caused by the conversion of the alpha spirals of brain proteins into rigid, insoluble beta chain polymers that clump together, increases neurotoxic deposition [18]. Beta chain polymers, susceptible to aggregation, contain clumps of beta sheets that form into microscopic amyloid plaques [18]. The accumulation of amyloid plaques and fibers blocks neurotransmitters that carry messages to and from the brain, change the metabolism of iron and cause the destruction of nerve cells and eventually destroy them [15–19]. A high level of Amyloid-beta is reported as a risk factor for AD [19]. Also, the accumulation of amyloid plaques in AD patients decreases plasmalogens which protect cells against the damaging effects of reactive oxygen species [20–22].

In addition to abnormal protein accumulation, free radicals, reactive metabolites of oxygen, that are connected with oxidative stress may reduce the oxygen supply to cells and cause oxidative damage in the brain which leads to pathogenesis and neurodegenerative diseases [17]. While studies have been conducted on abnormal protein accumulation and free radicals in getting insights into AD, studies on the role of affective computing in the management and diagnosis of depression of AD have also been proved beneficial [23]. Researchers discovered that affective computing, which can sense, recognize and interpret the emotional state of a patient, could simulate empathy and therefore provide an appropriate response to these emotions [23]. It is suggested to apply affective computing for behavioral treatments of AD patients with depression, as the treatment can monitor the emotion of patients and help them increase their concentration and alertness [23]. The impact of free-radical interactions, immunological patho-phenomenology [17] and oxidative RNA damage at the early stages of AD has been a common finding in some previous studies [24, 25].

Material and methods

In this study, a detailed literature review was performed to find whether there is a relationship between Alzheimer's disease and exposure to some electromagnetic radiation. In the scan, 46 sources related to the subject with different results were evaluated with a neutral perspective.

Results and discussion

Although many studies have reported the negative effects of RF on the human brain and the adverse health effects, such as cancer, of the exposure to ionizing and non-ionizing radiation, numerous studies on the effect of RF fields and electromagnetic radiation on Alzheimer's disease (AD) have reported contradictory results.

Effect of radiofrequency radiation on Alzheimer's disease: No clear judgment

Nieden et al. [7] did a literature survey on the studies for the period between 1993 and 2005 to investigate the findings on the effect of mobile radio technology on some health conditions including AD and dementia . Nieden et al. [7] concluded that a clear judgment cannot be made for AD and, dementia, due to the methodological limitations in the available databases that were used in the study. The World Health Organization also reported evidence of possible relation between electromagnetic field and exposure to radiation and AD, yet stated that the available data were limited to be able to reach a clear conclusion.

Dasdag et al. [26] investigated the effect of mobile phone exposure on apoptotic glial cells and the status

of oxidative stress in rat brain. Rats were exposed to radiation 2 h per day (7 days a week) for 10 months. After the exposure period, the brains of the rats were removed and analyzed to measure the total antioxidative capacity (TAC), catalase, total oxidant status (TOS) and oxidative stress index. Compared to the sham group, the rats exposed to the radiation had a higher level of total antioxidant capacity and catalase in their brains. There was no statistically significant difference in the total oxidative stress and oxidative stress index levels between the two groups of rats. The researchers concluded that 900 MHz radiation exposure similar to the exposure of global systems for mobile communication (GSM) cellular phone could play a role in altering the final score for apoptosis, total antioxidant capacity and catalase activity in rat brain but more research is needed to conclude statistically significant results [26].

Effect of radiofrequency radiation on Alzheimer's disease: Beneficial

Another study that researched the link between the exposure to RF fields from mobile phones and AD in 313 subjects used serum transthyretin (TTR) as a marker of cerebrospinal fluid TTR [27]. A major pathological hallmark of AD is an abnormal accumulation of Amyloid-beta in the brain. TTR seizes Amyloid-beta, and therefore prevents the formation of Amyloid-beta plaques in the brain. The researchers explained that studies indicate that patients with AD have lowered TTR concentrations in the cerebrospinal fluid, and attributed the onset of AD to insufficient sequestering of Amyloid-beta by TTR. The researchers explained that in earlier studies on AD mice, RF exposure reduced brain Amyloid-beta deposition through the decreased aggregation of Amyloid-beta and increase in soluble Amyloid-beta levels. The researchers argue that that TTR could play a role in the findings of RF exposure benefit in AD mice. A study that investigates the link between TTR and AD found that TTR is involved in the AD pathological process and also should be considered a possible peripheral biomarker for AD diagnosis in serum level [28]. The researchers sampled 111 AD patients and 90 non-demented controls in their study and observed significantly lower serum TTR levels in AD patients. The study indicated a clear negative correlation between serum TTR levels and AD [28].

Numerous studies on transgenic AD mice revealed a progressive regression of AD after controlled exposure to mobile phone radiations. Studies observed positive effects of RF-EMF exposure in AD and reported that "high frequency" electromagnetic fields, such as those emitted by cell phones, do not induce AD. For instance, numerous studies on AD mice reveal that RF radiation could provide a beneficial effect on AD by improving the cognition in mice and reducing Amyloid-beta deposition, without increasing the indices of oxidative stress in the brain [29, 30].

Arendash et al. [29] reported that RF exposure prevented Aβ aggregation and improved cognitive impairment in AD mice. In the study, normal and transgenic mice with Alzheimer's-like cognitive impairment were exposed to cell phone radiation (918 MHz, 0.25 W/kg) (the same high-frequency EMF level that the human head is exposed to) for 8 $^1/_2$ months. In the experiment, the long-term EMF exposure reduced brain Amyloid-beta deposition through Amyloid-beta anti-aggregation actions and increased brain temperature during exposure periods in Alzheimer's mice. The study showed that in AD, the exposure of mice to EMFs significantly reduced brain Amyloid-beta deposition in the entorhinal cortex and hippocampus through Amyloid-beta anti-aggregation actions. In the study, the researchers observed cognitive impairment effects of EMF exposure on both normal and transgenic mice destined to develop AD. The researchers reported that EMF action triggered increased Amyloid-beta clearance from the brains of AD mice, increased neuronal activity, and increased cerebral blood flow. The researchers concluded that long-term EMF exposure directly associated with cell phone use (918 MHz; 0.25 w/kg) provides cognitive benefits, and EMF exposure could be beneficial in AD as protecting against cognitive impairment in AD [29].

Banaceur et al. [30] studied the bioeffects of the long term exposure of 2.4 GHz Wi-Fi signals on cognitive impairment in transgenic mice with AD. In the study, mice were exposed to (RF) signals (2.4 GHz), for 2 h per day during one month at a Specific Absorption Rate (SAR) of 1.60 W/kg. The researchers used cognitive tasks, including the Flex field activity system test, the two-compartment box test and the Barnes maze test, to measure the mice's memory. Researchers found that RF exposure improved the cognitive behavior of 3xTg-AD mice and worked as an effective memory-enhancing approach in AD [30]. Mesiti et al. [31] studied the modeling and analysis of exposure to RF radiation on biological systems and reported that controlled RF exposure could be used as a potential strategy for the treatment of neurodegenerative diseases.

Effect of electromagnetic radiation on Alzheimer's disease: Harmful

Lowe et al. [32] reported that the early brain response to low-dose radiation (10 cGy) exposure induced low-dose genes that were associated with special pathways that are related to brain tissue and cognitive functions including advanced aging and AD. The researchers found that the molecular response of the mouse brain within a few hours after low-dose irradiation could trigger neural pathways in the brain that lead to cognitive dysfunctions seen in normal aging and AD [32].

Based on a literature review of recent developments in the research on the biological and cognitive effects of ionizing radiation on brain functions, Begum et al. [33] reported that low and high doses of ionizing radiation could trigger cognitive molecular mechanisms and could increase the risk of developing AD.

Davanipour and Sobel [34] reported that long-term significant occupational exposure to an electromagnetic field may trigger the risk of AD causing an increased production of Amyloid-beta and decreased production of melatonin. Their previous studies included 7.4–12.0% of the cases and 3.4–5.3% of the controls that had primary occupations associated with medium or high extremely low-frequency magnetic field (ELF-MF) exposure. The researchers found that electromagnetic field exposure induced a significant increase in Amyloid-beta, which is known as a common risk factor for AD [35–37]. Garcia et al.'s [38] meta-analysis reported a significant risk for exposure to extremely low frequency electric and magnetic fields on AD. Huss et al. [39] studied mortality from neurodegenerative diseases of the residents living near power lines in a longitudinal study of the Swiss population. The results of the study showed that magnetic field exposure plays a role in AD. They found that people living within 50 meters of high voltage power lines (220-380 kV) were more likely to die with AD [39].

A longitudinal study on the effect of low-frequency electromagnetic field exposure on AD investigated 20,141 individuals employed by the Swiss railway during the period 1972 – 2002. The study found that the train drivers (the occupation with the highest level of exposure to radiation) had a 3.15 times higher hazard ratio of developing Alzheimer's (95% CI = 0.90–11.04) compared to station masters. Roosli et al. [40] suggested an association between exposure to ELF-MF and AD.

Dasdag et al. [41] investigated the effect of chronic exposure of Wi-Fi radiation on some miRNA in the brain. MicroRNAs (small and non-protein-coding RNA molecules) have a crucial function in the growth and maintenance of neuronal cells and the pathogenesis of neoplasias [42]. MicroRNAs were found as major regulators of the neuronal phenotype and the dysfunction of microRNA pathways is suggested to be a possible trigger of the pathogenesis of major neurodegenerative disorders such as Alzheimer' s disease and Parkinson' s disease [43]. Dasdag et al. [41] rationalized that, although most prior studies investigating the interaction between radiation and microRNAs focused on the effects of ultraviolet and ionizing radiation [41, 44, 45], studies on the direct impact of Wi-Fi radiation on the brain were not available yet. The researchers studied the effects of 2.4 GHz RF radiation emitted from Wi-Fi equipment on microRNA expression in brain tissue of adult male rats for one year. After the exposure period, researchers analyzed the brain tissue of the rats and observed that long-term exposure of 2.4 GHz Wi-Fi radiation altered miR-106b-5p and miR-107 and did not affect miR-9-5p, miR-29a-3p and miR-125a-3p levels in the brain of the rats. The study concluded that long-term exposure to 2.4 GHz RF may play a role in causing adverse effects such as neurodegenerative diseases originating from the alteration of some miRNA expression. The researchers stated that more studies on the effects of RF radiation on miRNA expression levels should be carried out to underpin the impact of RF radiation on brain cells [41].

Dasdag et al. [46] further investigated whether the long-term and excessive use of 900 MHz RF radiation alter microRNA expression in the brain. Rats in the study were exposed to 900 MHz RF radiation for 3 h per day for a one-year period. After the one-year exposure period, their brains were removed and rno-miR-9-5p, rno-miR-29a-3p, rno-miR-106b-5p, rno-miR-107 and rno-miR-125a-3p in the brain were investigated. The results showed that 900 MHz RF radiation decreased the rno-miR107 levels and did not alter other microRNAs. The researchers concluded that 900 MHz RF radiation can play a role in altering some miRNAs and may lead to adverse effects on brain function [46]. Dasdag et al. also studied the effect of 900 MHz RF radiation on Amyloid-beta, protein carbonyl and malondialdehyde in the rat brain, rationalizing that there are limited studies on the interaction between long-term exposure of RF radiation and biomolecules in the brain. Rats in the study were exposed to 900 MHz RF radiation 2 h per day (7 days a week) for 10 months. After the exposure period, rat brains were removed and analyzed. Compared to the sham group, the rats exposed to radiation had a higher level

Table 1. Beneficial and harmful effects of electromagnetic field in terms of AD.

Frequency	Topic	Results	References
Mobile radio technology	Effect of RF radiation on some health conditions including Alzheimer's disease and dementia	Clear judgment cannot be made for Alzheimer's disease and dementia	Nieden et al. [7]
Mobile phone	Effect of mobile phone exposure on apoptotic glial cells and the status of oxidative stress	Alteration of final score for apoptosis, total antioxidant capacity and catalase activity in brain	Dasdag et al. [26]
Mobile phone	Link between the exposure to RF fields and Alzheimer's disease	Increase in serum transthyretin (TTR)	Söderqvist et al. [27, 49]
Mobile phone	Relation between RF radiation and Alzheimer's disease	Beneficial effect on Alzheimer's disease	Arendash et al. [29]
Mobile phone	Relation between RF radiation and Alzheimer's disease	Beneficial effect on Alzheimer's disease	Banaceur et al. [30]
Radiofrequency	Relation between RF radiation and neurodegenerative diseases	Controlled RF exposure could be used as a potential strategy for the treatment of neurodegenerative diseases	Mesiti et al. [31]
Low-dose radiation (10 cGy)	Relation between low-dose radiation and Alzheimer's disease	Cognitive dysfunctions seen in normal aging and Alzheimer's disease	Lowe et al. [32]
Low and high doses of ionizing radiation	Relation between ionizing radiation and Alzheimer's disease	Triggers cognitive molecular mechanisms and increases the risk of developing Alzheimer's disease	Begum et al. [33]
ELF magnetic field	Relation between long-term significant occupational exposure and Alzheimer's disease	Triggers the risk of Alzheimer's disease, causing increased production of amyloid-beta and decreased production of melatonin	Davanipour and Sobel [34]
ELF electric and magnetic fields	Relation between ELF electric and magnetic fields and Alzheimer's disease	Significant risk of Alzheimer's disease	Garcia et al. [38]
ELF magnetic field	Mortality from neurodegenerative diseases of the residents living near power lines	Magnetic field exposure plays a role in Alzheimer's disease	Huss et al. [39]
Low-frequency electromagnetic field exposure	Relation between exposure of train drivers and AD	Train drivers had a 3.15 times hazard ratio of developing Alzheimer's disease compared to station masters	Roosli et al. [40]
2.4 GHz Wi-Fi exposure	Relation between RF exposure and microRNAs in brain	Long-term exposure of 2.4 GHz RF may play a role in causing adverse effects such as neurodegenerative diseases originating from the altered expression of some microRNAs	Dasdag et al. [41]
900 MHz RF exposure	Relation between RF and beta-amyloid protein, protein carbonyl and malondialdehyde in brain	Higher level of Beta-amyloid protein, protein carbonyl (PC) and malondialdehyde; only PC found statistically significant	Dasdag et al. [47]

of Amyloid-beta, protein carbonyl and malondialdehyde levels in their brains. The increase in protein carbonyl was statistically significant. The researchers concluded that 900 MHz radiation emitted from mobile/cellular phones can affect some biomolecules such as proteins [47].

In another study, Dasdag et al. [48] additionally investigated the effects of long-term 900 MHz mobile phone exposure on some miRNAs in brain tissues. In the study, rats were exposed to 900 MHz RF radiation for 3 h per day (7 days a week) for one year. The expression levels of miRNAs, such as rno-miR-22-3p, rno-miR-24-1-3p, rno-miR-132-3p, rno-miR-145-5p, rno-miR-181a-5p, rno-miR-186-5p, rno-miR-195-5p, rno-miR-219a-5p, rno-miR-221-3p and rno-miR-222-3p, were investigated. The results of Dasdag et al. [48] indicated that long-term exposure to 900 MHz RF radiation increased only the expression level of rno-miR-145-5p, where 1 g average SAR value in the brain was 0.198 W/kg.

Electromagnetic radiation and Alzheimer's disease: is prevention possible?

A summary of some reports on the relation between electromagnetic field and AD is presented in Table 1 to provide a wide perspective to readers. Söderqvist et al. [27] found a statistically significant positive β coefficient for serum TTR as a marker of cerebrospinal fluid TTR that seizes Amyloid-beta for time since the first use of mobile phones and desktop cordless phones combined. They stated that TTR sequesters Amyloid-beta, and therefore prevents the formation of Amyloid-beta plaques in the brain. In their provocation study on 41 persons exposed for 30 min to an 890-MHz GSM signal with a specific absorption rate of

1.0 W/kg to the temporal area of the brain, they found statistically significantly increased serum TTR 60 min after exposure [27]. However, the same group reported association of long-term mobile phone use with brain tumors [1, 3]. The International Agency for Research on Cancer (IARC), which is a branch of WHO, classified RF radiation as 2B (Possible carcinogenic) after several studies determined the relation between brain tumors and RF exposure. Meanwhile, Söderqvist et al. [27] reported a beneficial effect of nicotine, which is a well-known carcinogen, on AD. If evaluations are made considering these two studies, the people/patients may have to make a choice between cancer and AD. Similarly, long-term exposure to electromagnetic field (EMF) decreased the Amyloid-beta deposition in the brain of AD transgenic mice [29]. RF exposure improved the cognitive behavior of 3xTg-AD mice and worked as an effective memory-enhancing approach in AD [30]. Mesiti et al. [31] suggested that controlled RF exposure could be used as a potential strategy for the treatment of neurodegenerative diseases. On the other hand, 900 MHz radiation exposure similar to GSM cellular phone could play a role in altering the final score for apoptosis, total antioxidant capacity and catalase in rat brain [26]. Exposure of rats' head to 900 MHz RF radiation 2 h per day (7 days a week) for 10 months resulted in higher level of Amyloid-beta protein, protein carbonyl and malondialdehyde in the brain but only the increase in protein carbonyl was statistically significant compared to the sham group rats [47].In this study, which is similar to the animal studies mentioned above on the beneficial effects of RF, no evidence was found that Amyloid-beta decreased [47]. The difference in the results obtained by Arendash et al. [29] and Dasdag et al. [47] may be due to the use of AD transgenic rats in the one and the use of normal rats in the other.

On the other hand, researchers concluded that long-term exposure of 2.4 GHz RF may play a role in causing adverse effects such as neurodegenerative diseases originated from the alteration of some miRNA expression levels such as miR-106b-5p and miR-107 [41]. Similarly, long-term and excessive use of 900 MHz RF radiation decreased the expression levels of microRNAs such as rno-miR107 and increased the expression of rno-miR-145-5p in rat brain, where 1 g average SAR value in the brain was 0.198 W/kg [46, 48].

There are also studies investigating whether there is a relationship between ELF-MF and AD. For example, long-term significant occupational exposure to electromagnetic fields such as ELF and RF may trigger the risk of AD, causing the increased production of Amyloid-beta and decreased production of melatonin [34–37]. Exposure to extremely low frequency electric and magnetic fields was associated with significant risk of Alzheimer's disease [38]. Magnetic field exposure likely plays a role in AD, since people living within 50 meters of high voltage power lines were more likely to die with AD [39]. Exposure to ELF-MF showed association with AD [40].

One of the remarkable points here is that some researchers who claim that long-term RF exposure has healing effects on AD, suggest that RF radiation can cause brain tumors. It is very important to evaluate very carefully whether the suggested possibly favorable effects on AD could outweigh the potential risks of RF-induced brain tumors. As stated above, some investigations on the relationship between ionizing radiation and AD have found that the molecular response of the mouse brain within a few hours after exposure to low-dose ionizing irradiation could trigger neural pathways in the brain that lead to cognitive dysfunctions seen in normal aging and AD [32]. Low- and high-dose ionizing radiation could trigger cognitive molecular mechanisms and increase the risk of developing AD [33].

Conclusions

The overview of relevant literature demonstrates that there is still a high level of controversy about the association between RF radiations and brain-related diseases, AD in particular. Although some evidence suggests that RF radiation may have a beneficial effect on AD, a considerable amount of literature claims that RF radiation will affect AD negatively. The wide spectrum of reported effects may be attributed, at least in part, to a complex interplay between an array of factors, including the type of electromagnetic radiation, its dosage, the duration of exposure, the type of study model and so on. From the perspective of public health and prevention, it is especially important to identify whether long-term occupational, residential or life style exposure to RF radiation could contribute to health risks. The inclusion of RF radiation in the category of possible carcinogens (2 D) in 2011 further emphasizes that the relationship between the potential effects of RF radiation on cancer and AD is also important. Considering the studies on RF radiation in general, the potential of forming a brain tumor cannot be excluded even if these rays have a benefit on AD as suggested by some reports. As a result, the relationship between RF radiation and AD seems to be a

double-edged sword for now. Future research needs to focus on providing better evidence as to whether RF radiation reduces Amyloid-beta deposition, or otherwise. Another poorly explored point that calls for further attention is whether RF radiation could induce an increase or decrease in the expression of some microRNAs. From the perspective of preventive medicine, it is essential to address the question of whether RF exposure at a young age may or may not have a potential beneficial effect on the risk of developing AD in the future, while still keeping in mind the potential carcinogenic effect of RFs, which is a serious health problem. Finally, uncontrolled electromagnetic radiation may not be as harmless as expected. Therefore, many serious, objective and detailed further studies are needed to clarify the issue.

Disclosure statement

No potential conflict of interest was reported by the authors.

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