Proper beverages may reduce the risk of Alzheimer’s disease

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Alzheimer’s disease (AD) is one of the most common neurodegenerative disorders, characterized by a progressive decline in cognitive ability. Around 50 million people worldwide are reportedly affected, with annual losses estimated at about $1 trillion [1]. Nevertheless, there remains unknown about the exact pathological mechanisms of AD and currently available treatments have a lack of efficacy. Thus, experts have reached a consensus that interventions in the preclinical stage of AD should be prioritized [2], especially when the amount of patients is set to reach 78 million by the end of this decade [3]. Recently, the proposition “integrating food and nutrition into healthcare” has been promoted [4]. Prevention from dietary eating and drinking may be an effective and age-friendly method. Nowadays, many beverages have been proven to offer great preventative benefits to AD like coffee, soy milk, tea, and wine.

Coffee, consumed by tens of thousands of people every day, has been proven in several epidemiological studies to have a protective effect against AD [5–7]. A study including 411 individuals shows that significant negative correlation between stratified lifetime coffee intake and \( \beta \)-amyloid positivity [8]. In other words, higher coffee intake (≥ 2 cups/day) is associated with lower risk of AD. However, a Mendelian randomization (MR) analysis came to the opposite conclusion, with an additional 1 cup of coffee per day being associated with a 1.16-fold increased risk of developing AD [9]. In meta-analyses of cohort studies, it was proposed that there was a non-linear “U-shaped” link between coffee consumption and AD, with 3–4 cups per day being optimal [10]. In addition to the possibility that different conclusions are due to inconsistent estimations of coffee intake and populations in these studies, research recently proposed a hypothesis that the cytochrome P450 1A2 played an essential role in the metabolism of coffee in the human body [11]. Rs762551 is its most representative and commonly studied single nucleotide polymorphism. In detail, carriers of the rs762551 gene metabolize caffeine more rapidly and are at greater risk of developing AD when they consume large amounts of coffee. Conversely, people with slow caffeine metabolism who consume more coffee would have a preventive effect on AD, which might be a result of being exposed to coffee for a longer duration of time to the point of absorbing more potential beneficial effects of caffeine.

Although green coffee has so far been considered to have the most health benefits [12], there is experimental evidence that espresso coffee extracts have properties that prevent aggregation, condensation, and seeding activity in the tau repeat region in vitro and cell experiments [13] and roasted coffee beans will generate pyrocatechol which reduces \( \beta \)-amyloid production [14, 15]. Besides pyrocatechol, other bioactive compounds in coffee, such as caffeine, coffee polyphenols [16], and so on, can also play a role in preventing AD. In addition, the literature indicates the neuroprotective effect of caffeine may vary across the sexes, but it is not clear which gender is better suited to caffeine [17].

A study including 248 patients with AD concluded that the dietary pattern of coffee/tea was a protective factor in improving cognitive performance in patients with AD [18]. People have considered tea as a healthy beverage since 3000 B.C.E. in China. In recent years, tea has been recognized as having a preventive effect against AD, whether in animal experiments [19], epidemiological investigations, or genetic analysis. There is an agreement that moderate consumption (1–6 cups/day) of tea can exert significant protective effects [20, 21]. However, from the results of two-sample MR, daily consumption of more than 13 cups of tea may increase the risk effects [21]. The subgroup analyses conducted by Hu et al. [20] showed that middle-aged participants or males benefited more from tea consumption. The conclusions were in line with a cross-sectional study in China that green tea consumption was effective in males against amnestic mild cognitive impairment, particularly in males aged < 70 years [22].

Depending on the processing technique, there are several subclasses of tea, such as green, black, dark, yellow, white and oolong teas. These teas vary in catechin and caffeine content, but they all can inhibit amyloid protein formation associated with aging [23]. In general, Asians prefer green tea, while black tea is preferred by Europeans and Americans [24]. However, both coffee and tea contain caffeine, albeit in different amounts. Given that chronic stress may predispose genetically vulnerable individuals to AD, excessive daily caffeine intake may exacerbate stress and is not suggested. Hence, some scholars recommend that naturally caffeine-free plant-based beverages could be used as an alternative, such as Rooibos herbal tea, a drink unique to South Africa, so that it could be consumed in high daily quantities [25]. Nevertheless, it should be emphasized that more research on the effects of Rooibos herbal tea in the field of supporting emotional well-being should be conducted.

Another free-of-caffeine beverage, milk, rich in nutrients and bioactive molecules, is recognized as one of the healthiest foods in the world. Whereas, it is uncertain whether milk is beneficial in preventing AD due to contradictory findings in previous studies on the relationship between milk consumption and cognitive decline [26]. Undeniably, previous studies have suffered from the influence of potential confounders and a lack of exploration of milk types. To address the first issue, MR analysis is a good choice to reduce the bias from confounding. The systematic review of MR studies revealed additional inverse associations of genetically predicted milk consumption with AD [27], which confirmed milk has a preventive effect on AD. For the second concern, a large-scale cohort study explored the association between different types of milk and the risk of dementia [28]. Compared to full-cream milk, skimmed milk, and other milk, soy milk showed a lower risk of AD (hazard ratio = 0.7; 95% confidence interval = 0.51–0.94; \( P = 0.02 \)), which may improve cognitive function through soy isoflavones, the bioactive component in soy milk. In the future, the dosage or frequency of soy milk consumption deserves further study. Moreover, camel milk and high-altitude Tibetan fermented milk can enhance cognition and sensorimotor activity in AD rats [29, 30].

New study suggests the pathogenesis of AD may involve alterations in oral and gut microbiota [31]. Therefore, natural live yoghurt [32, 33] or red wine [31] could be an important preventive agent for AD by optimizing the oral flora. While the hypothesis is put forward that yogurt can prevent AD, there is a lack of evidence of the association between them. For red wine, it can regulate the composition and integrity of the oral microbiota, due to its high content of polyphenolic compounds [34]. Furthermore, vitro and in vivo evidence reports on the effects of gut microbiota-wine polyphenol interactions on brain function and AD protection [35]. Studies have

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also shown that drinking more red wine is associated with increased fluid intelligence and slower cognitive decline [36]. A prospective cohort study in Germany found that a higher intake of red wine only reduced the incidence of AD in males but increased the risk in females in the same circumstances [37]. However, the confounding factors between men and women weakened the credibility of the results, such as physical activity, educational level, psychological condition and so on. In addition to red wine, infrequent, light and moderate alcoholic beverages consumption is confirmed to be good for AD. In a cohort study in the US population, the degree was categorized as infrequent (1–11 drinks in the past year), light (≥12 drinks in the past year but ≤3 drinks per week), and moderate (≥3 to ≤7 drinks per week for women and ≥3 to ≤14 drinks per week for men) and one alcoholic beverage equivalent is a beverage containing 14 g of pure alcohol [38]. However, moderate wine intake and a lower risk of AD was limited to the people without the Apolipoprotein E4 allele, from a genetic point of view [39].

In conclusion, faced with the massive aging of the population as a result of the increasing longevity of the human race, it is never too early to prevent AD with a dietary approach. Beverages, as one of the most important sources of nutrition, have a good preventive effect. A number of studies have explored the relationship between different beverages and AD as Figure 1. However, there is still controversy about the optimal amount of different beverages to drink. Different populations or genders may react differently to various beverages for the different genes they carried and a rising number of studies have shown that genes play an important role in preventing disease. In the future, more in-depth studies should be conducted to give people different drinking recommendations according to different regions, ethnic groups, levels of economic development, etc. For beverages that are currently only tested on animals, it is desirable to develop the research in human subjects to demonstrate reliability, such as espresso coffee, Rooibos and Taxus chinensis fruit wine [40].

![Figure 1 Different beverages and Alzheimer's disease. Aβ, β-amyloid](image)

Recently, the widespread application of MR has provided us with new ideas and insights, which is an effective epidemiological method that can strengthen causal inference between exposure and outcome by using genetic instrumental variables [41]. Different from cohort studies which are difficult to eliminate the effects of confounders, MR studies have the advantage of reducing the effects of confounding factors. Significantly, caution is needed in interpreting the results of these studies.

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Competing interests
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Abbreviations
AD, Alzheimer’s disease; MR, Mendelian randomization.

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