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# Effects of intermittent fasting on cognitive health and Alzheimer's disease

Alby Elias , Noushad Padinjakara , and Nicola T. Lautenschlager 

**Objective:** Caloric restriction by intermittent fasting produces several metabolic changes, such as increased insulin sensitivity and use of ketone bodies as energy sources. In humans, intermittent fasting has been studied in hypertension, diabetes, and related conditions, but, to date, not as a strategy to reduce the risk of emergent dementia. In this scoping review, the relevance of intermittent fasting as a potential preventive intervention for Alzheimer's dementia is explored. **Background:** The beneficial effects of calorie restriction have been documented in animals and humans. Decreased oxidative stress damage and attenuated inflammatory responses are associated with intermittent fasting. These changes have a favorable impact on the vascular endothelium and stress-induced cellular adaptation. **Results:** Physiological alterations associated with fasting have profound implications for pathological mechanisms associated with dementias, particularly Alzheimer's disease. Compared with ad libitum feeding, caloric restriction in animals was associated with a reduction in  $\beta$ -amyloid accumulation, which is the cardinal pathological marker of Alzheimer's disease. Animal studies have demonstrated synaptic adaptations in the hippocampus and enhanced cognitive function after fasting, consistent with these theoretical frameworks. Furthermore, vascular dysfunction plays a crucial role in Alzheimer's disease pathology, and intermittent fasting promotes vascular health. **Conclusions:** These observations lead to a hypothesis that intermittent fasting over the years will potentially reverse or delay the pathological process in Alzheimer's disease.

## INTRODUCTION

A dramatic increase in the human lifespan in the past century has not translated to an increase in healthy years of life (health span), especially in older age.<sup>1</sup> It is estimated that the proportion of people older than 65 years will double from 8.5% to 17% by 2050.<sup>2</sup> Such a demographic transition poses extraordinary challenges for the

medical community and policy makers, given that older age is one of the strongest risk factors for cardiovascular diseases, cancers, metabolic syndrome, and neurodegenerative syndromes, including dementia.<sup>3-5</sup> The 2017 Global Burden of Diseases study identified 92 age-related diseases, and these accounted for 51.3% of all disease.<sup>5</sup>

The process of aging is complex and not well understood. For instance, chronological age indicates

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calendar-years and does not always predict biological health, changes at the cellular level, morbidity, or death.<sup>6</sup> Oxidative damage is one of the most discussed mechanisms of aging.<sup>7–9</sup> Accordingly, reactive oxygen and nitrogen free species that are constantly produced as the byproducts of cellular metabolism bombard the cell nucleus. The body's antioxidant defense system normally neutralizes these species. An imbalance favoring reactive species causes cumulative cellular damage and subsequent aging over time. Also, DNA telomeric shortening is associated with aging. Caloric restriction without malnutrition has been proven to reduce the rate of cellular metabolism, the production of reactive species responsible for oxidative damage, and telomeric shortening, and hence has been proposed to have the potential to combat age-related diseases.<sup>10–12</sup>

### Intermittent fasting

Beneficial effects of intermittent fasting on aging have increasingly attracted interest in recent years.<sup>13,14</sup> People have practiced intermittent fasting for millennia.<sup>15</sup> In the preliterate society, intermittent fasting was often the norm when food was scarce. The past few decades have witnessed a renewed interest in intermittent fasting and a concerted research effort focusing on the various health benefits of fasting. Studies have addressed both clinical and biochemical changes associated with fasting. These studies were conducted in animals to a large extent, but human trials have also been conducted recently.<sup>13,15</sup>

There is no uniform definition of intermittent fasting. Fasting is characterized by longer intervals between meals without enduring nutritional deficiency.<sup>16</sup> It is a dietary pattern consisting of cycles of fasting for a duration varying from 12 hours to 24 hours alternating with periods of normal food intake. Thus, it is not related to a particular type of diet; it is a pattern of eating. Different regimens of intermittent fasting are practiced. The common patterns include 12–16 hours of daily fasting, 20–24 hours of fasting 2 days a week, or more intense patterns, such as alternate-day fasting.<sup>13,17,18</sup> Prolonged food deprivation beyond 24 hours is starvation and considered different from fasting, given its unique and harmful biochemical changes. Ad libitum feeding is the consumption of food without restrictions.

### Biology of intermittent fasting

Glucose is the primary energy source for humans. Glucose metabolism is time dependent in that it is a function of time since the last meal. In humans, the blood glucose level falls shortly after consumption of a carbohydrate meal. Depending on the amount of

glycogen stored in the liver and the energy expenditure after that, the glycogen level will be diminished and fat metabolism becomes the energy source, through the production of ketone bodies during the 12–36 hours after carbohydrate intake.<sup>18,19</sup> Several organs, including the brain, can use ketone bodies for energy requirements.<sup>13,16</sup> This kind of metabolic switch, from glucose to ketone bodies, is the most characteristic metabolic feature of fasting.<sup>18</sup> Ketone bodies that are naturally produced during fasting are only minimally increased in the first 24 hours after the last meal.<sup>19,20</sup>

The key mechanism of benefits of fasting is through heightened insulin sensitivity.<sup>12,21,22</sup> It is well known that insulin sensitivity is decreased in type 2 diabetes mellitus.<sup>23–26</sup> Insulin resistance promotes atherosclerosis and subsequent vascular diseases.<sup>27,28</sup> In addition to the effect on insulin level and sensitivity, fasting has been associated with reduced lipids and blood pressure levels in controlled clinical trials in humans.<sup>29–34</sup> These changes exert highly beneficial effects on blood vessels. In a nutshell, intermittent fasting promotes vascular health.

At a molecular level, fasting is associated with optimization of cellular metabolism.<sup>15,16,35</sup> This is evident in alterations in thyroid hormones and the amount of free oxygen radicals.<sup>10–12</sup> Oxygen free radicals are produced as the byproducts of normal oxidative metabolism. Free radicals have the potential to cause genome mutations and diseases. During fasting, metabolism and protein synthesis are temporarily reduced and, hence, the formation of free radicals is attenuated.<sup>36</sup> Also, cells undergo stress response and adaptation during fasting. These changes include enhanced antioxidant mechanisms, DNA repair, removal of cellular waste products, or autophagy.<sup>13,37</sup> Upon restoration of feeding and the glucose supply, cells regain homeostasis and thus become more stress resistant. Brain cells in animals maintained on intermittent fasting exhibited improved function and adaptive response to metabolic, traumatic, and oxidative stress.<sup>36</sup>

### Pathology of Alzheimer's disease

Before discussing fasting in Alzheimer's disease (AD), it is worthwhile to recapitulate the disease pathology (Table 1). Extracellular  $\beta$ -amyloid plaques and intracellular tangles are the characteristic neurological lesions in AD.<sup>38,39</sup> The neurofibrillary tangles are composed of abnormally phosphorylated tau proteins, which are regarded as the downstream effect of excess  $\beta$ -amyloid.<sup>40,41</sup> Although early-onset AD arises from the excess production of  $\beta$ -amyloid, late onset AD, the most common type, results from decreased clearance of  $\beta$ -amyloid from the brain.<sup>42,43</sup> Apolipoprotein E  $\epsilon$ 4 is

**Table 1 Putative mechanisms of benefits of intermittent fasting in Alzheimer's disease**

Pathological factors in Alzheimer's disease	Findings
$\beta$ -Amyloid and tau deposition	Increase in ketone bodies as a result of fasting may reduce $\beta$ -amyloid level. Caloric restriction reduced both $\beta$ -amyloid level and tau. Fasting may not reduce the amyloid level in cases of Alzheimer's disease with a strong genetic load.
Cerebrovascular diseases	Enhanced vascular integrity after fasting Diminished impact of stroke Potentially synergetic effects of cardiovascular and cerebrovascular health
Inflammation	Inflammation may play a key role in Alzheimer's disease. Intermittent fasting is associated with reduced levels of inflammation.

associated with impaired clearance of  $\beta$ -amyloid and hence contributes to an increased risk of dementia.<sup>44–46</sup>

An epidemiological and mechanistic association exists between cerebrovascular risk factors and Alzheimer's dementia.<sup>47–49</sup> Originally proposed in 2001, the neurovascular unit in the brain received abundant interest in the following years, and recently emerged evidence suggests an important role of this vascular unit in the genesis of AD pathology.<sup>49,50</sup> A neurovascular unit comprises brain endothelial cells lining the cerebral vasculature, pericytes covering capillaries, vascular smooth cells, glia, and surrounding neurons. The blood-brain barrier (BBB) lies within the neurovascular unit and regulates the transport of molecules between the brain interstitial fluid and cerebrovascular compartment. The BBB plays a critical role in the clearance of  $\beta$ -amyloid from the brain.<sup>51–53</sup> Cerebrovascular diseases, particularly chronic small-vessel disease, lead to BBB disruption and dysfunction and act as a risk factor for AD.<sup>54–56</sup> In support of this hypothesis, neuroimaging studies have documented 20% lower cerebral blood flow and reduced pulse pressure in patients with Alzheimer's dementia compared with individuals without dementia.<sup>57</sup> Postmortem data indicate BBB damage in AD.<sup>58</sup> Adding to accruing evidence, authors of a recent study identified gene expressions that implicate dysregulated blood flow in AD.<sup>59</sup> These findings suggest profound alterations of cerebral vasculature in AD.

Although anti-inflammatory drug trials in the setting of AD have generated inconsistent findings, and there is no definite evidence supporting their use in preventing Alzheimer's dementia, other findings suggest a role of inflammation in the pathogenesis of AD.<sup>60–62</sup>  $\beta$ -Amyloid and tau tangles are necessary but not sufficient in themselves in the causation of Alzheimer's dementia. Robust evidence supports the hypothesis of sustained

inflammation as a driving factor for progression of AD to clinical dementia.<sup>63,64</sup> This is evidenced in neuroimaging and human postmortem studies.<sup>62,65–67</sup> Intriguing findings from a recent positron emission tomographic study suggest a biphasic inflammatory reaction in AD: the initial phase is caused by  $\beta$ -amyloid plaques and the second phase is triggered by tau tangles.<sup>68</sup>  $\beta$ -Amyloid-induced neuroinflammation occurring in the early stage of prodromal Alzheimer's dementia may be protective, but later in the prodromal stage, activated microglia fail to clear  $\beta$ -amyloid deposition, and the inflammatory response diminishes. As  $\beta$ -amyloid continues to increase, it triggers tau propagation through a yet unknown mechanism with which the second wave of inflammation ensues.<sup>68</sup> The implication is that reducing inflammation in the appropriate stage may attenuate the disease process and either delay or prevent the onset of clinical manifestations of AD, including mild cognitive impairment.

In view of the aforementioned biological mechanisms associated with intermittent fasting and their implications for pathological processes in AD, the aim for this scoping review was to explore the potential benefits, safety, and feasibility of intermittent fasting in reducing the risk of AD.

## METHOD

The search of literature included the following keywords: “intermittent fasting,” “Alzheimer's disease,” and “dementia.” The search sources included the Medline (through PubMed), Scopus, and Embase databases; no language or time restrictions were imposed. Titles and abstracts were screened, and relevant full-article texts were extracted, reviewed, and downloaded to Endnote (Clarivate). Uncertainty was resolved through consultation among all authors.

## RESULTS

### Intermittent fasting and Alzheimer's disease pathology

$\beta$ -Amyloid and tau Fasting leads to an increase in ketone bodies.<sup>69</sup> The earliest evidence for the protective effect of ketone bodies against the toxic effect of  $\beta$ -amyloid came in 2000.<sup>70</sup> Later, Versele et al<sup>71</sup> demonstrated that ketone bodies augmented  $\beta$ -amyloid efflux across the BBB to blood in a human in vitro model. A subsequent experiment proved that compared with ad libitum feeding, caloric restriction was associated with a lower level of phospho tau in the hippocampus and  $\beta$ -amyloid in mice expressing dominantly inherited genes for amyloid precursor protein and presenilin I, and

intermittent fasting was associated with better cognitive performance in comparison with ad libitum feeding.<sup>72</sup> In animal studies, intermittent fasting was associated with reduced levels of brain  $\beta$ -amyloid through various mechanisms.<sup>73</sup> Researchers later demonstrated that a diet containing physiological precursors of ketone bodies was associated with improved performance on learning and memory tasks in the mouse model of AD, along with a reduction in  $\beta$ -amyloid and hyperphosphorylated tau levels.<sup>74</sup> As shown earlier, increase in ketone body levels is the metabolic signature of intermittent fasting. In line with these observations, increased risk for death resulting from focal ischemic stroke diminished in middle-aged mice undergoing intermittent fasting compared with a control group. Markers of inflammation such as cytokine levels also decreased with intermittent fasting.<sup>75</sup>

Studies assessing the impact of intermittent fasting on  $\beta$ -amyloid level have yielded conflicting results, however.<sup>72,73,76,77</sup> The outcomes of alternate-day fasting varied based on study protocols and disease models. For instance, Zhang et al<sup>73</sup> studied double-transgenic mice at the age of 5 months and found benefits of intermittent fasting in reducing cognitive impairment and  $\beta$ -amyloid level. Halagappa et al<sup>72</sup> found improved cognitive performance with intermittent fasting at 17 months in a triple-transgenic mouse model but no reduction in  $\beta$ -amyloid compared with the control diet. Lazic et al<sup>76</sup> studied a mouse model with 5 mutations and found that every-other-day feeding was associated with increased inflammatory and neurodegenerative changes without alterations in the  $\beta$ -amyloid level.<sup>76</sup> In rats subjected to ovariectomy and  $\beta$ -amyloid infusion, 3-hour feeding per day intermittent fasting prevented memory loss but exacerbated bone density loss.<sup>77</sup> Extrapolating these findings to humans, it could be possible that intermittent fasting may not reduce the amyloid load in cases of AD with a strong genetic load, such as familial AD. In contrast, the  $\beta$ -amyloid deposition in late-onset sporadic AD may be amenable to fasting.

#### *Intermittent fasting and cerebrovascular diseases*

Endothelial cells play a major role in the movements of ions, molecules, and cells into and out of the brain and, thus, the thromboresistance property of vessels and vascular homeostasis.<sup>78</sup> Endothelial dysfunction is a broad term encompassing oxidative stress, low-grade inflammation, increased vascular tone, loss of BBB integrity, atherosclerosis, and thrombosis.<sup>78</sup> Therefore, endothelial dysfunction acts as a risk factor for stroke.<sup>79</sup> Human trials have shown improved endothelial function as assessed by markers of endothelial integrity, such as asymmetric dimethylarginine and cutaneous microcirculation with laser Doppler scan, in individuals after

fasting.<sup>80–82</sup> Prolonged fasting in mice was associated with an increase in endothelial progenitor cells and improved stroke outcome.<sup>83</sup> In animal models of ischemia, intermittent fasting reduced infarct size, brain edema, the amount of neuronal loss through autophagy, and minimized apoptosis.<sup>84,85</sup> Given the similar size of the vasculature in the heart and brain with the same endothelial structure and function and shared risk factors, there is a pathophysiological relationship between cardiovascular and cerebrovascular diseases.<sup>86</sup> Animals maintained on intermittent fasting had improved heart rate variability, a sign of adaptive cardiovascular health.<sup>87</sup> Low heart rate variability is an independent risk factor for coronary artery disease, and its presence predicts the presence of myocardial ischemia 2-fold.<sup>88</sup>

*Intermittent fasting and inflammation* Intermittent fasting reduces inflammation. In a randomized controlled trial (RCT) of patients with rheumatoid arthritis, fasting was associated with improvement in symptoms of inflammation such as swelling and pain and inflammatory markers, namely, erythrocyte sedimentation rate, C-reactive protein level, and white blood cell count.<sup>89</sup> These findings were replicated in subsequent trials, and authors of a meta-analysis concluded that long-term benefits followed fasting in rheumatoid arthritis.<sup>90</sup> In the same vein, in a trial of participants with asthma, those who maintained intermittent fasting had reduced inflammatory markers compared with those who followed an ad libitum diet.<sup>17</sup> Obesity is associated with many serious diseases, including cerebrovascular disease and AD.<sup>91–93</sup> Obesity is considered a state of chronic inflammation.<sup>94</sup> There is high-quality evidence for the efficacy of intermittent fasting in reducing obesity and improving cardiometabolic parameters.<sup>95</sup> Inflammatory markers, such as circulating peripheral monocytes, are reduced during intermittent fasting.<sup>96,97</sup> Ramadan fasting in healthy adults was followed by significant reduction in proinflammatory cytokines, tumor necrosis factor  $\alpha$ , and the number of immune cells.<sup>96</sup> In a recent RCT, levels of galectin-3, an inflammation modulating substance, increased after 26 weeks of 24-hour water-only fasting twice weekly for 4 weeks followed by once weekly for 22 weeks.<sup>98</sup>

#### **Benefits of intermittent fasting in cognitive function and Alzheimer's disease: empirical evidence**

*Animal studies* Fasting is an evolutionarily conserved adaptive behavior in the animal kingdom.<sup>13,16</sup> Animals, including humans, maintain a high level of cognitive function during fasting, which is adaptive upon facing food scarcity.<sup>16</sup> In line with these general presumptions, empirical evidence suggested that animals undergoing

long-term intermittent fasting had improved motor coordination, learning, and consolidation of memory in comparison with ad libitum-fed animals.<sup>99,100</sup> Furthermore, dietary restriction in animals was followed by an increase in newly generated cells in the dentate gyrus of the hippocampus and the expression of brain-derived neurotrophic factor (BDNF) and neurotrophin-3.<sup>101</sup> Intriguingly important is the role of BDNF given that the genes coding for BDNF and its receptor are present in vertebrates, not in worms, flies, or species lower on the evolutionary ladder.<sup>16</sup> In this way, intermittent fasting is arguably an intervention targeting the disease process from multiple angles in Alzheimer's dementia.

In mouse models, intermittent fasting from the age of 3 months was associated with improved exploratory behavior and performance in both the goal latency and probe trials when assessed at the age of 17 months in comparison with mice allowed ad libitum feeding.<sup>72</sup> In a similar study, mice maintained on intermittent fasting had enhanced learning and consolidation processes that were associated with facilitation of synaptic plasticity in the hippocampus, in comparison with mice allowed ad libitum feeding.<sup>100</sup> In mice subjected to alternate-day intermittent fasting, learning and memory performance were better than in control mice fed a high-fat diet.<sup>102</sup> Enhanced cognitive performance was associated with a thickened CA1 pyramidal cell layer in the hippocampus. Animal research suggests that BDNF contributed to neurogenesis induced by dietary restriction.<sup>48</sup> Contrary to other findings, authors of one study observed worsening of cerebral inflammation and cognitive function without significant changes in  $\beta$ -amyloid after 4 months of alternate-day fasting in mice.<sup>76</sup> In this study, alternate-day fasting began at the age of 2 months.

*Human trials* The effects of short-term fasting lasting a month have been typically studied in humans after Ramadan fasting. These real-world, prospective studies have involved participants of different ages and focused on the tolerability and adverse effects of fasting, rather than long-term cognitive benefits.<sup>103–106</sup> The results are heterogeneous: some findings suggest improvement in vigilance and processing speed with diurnal variation.<sup>103–105</sup> Although a few studies indicated an increased daytime drowsiness during Ramadan fasting, most studies did not show such an effect.<sup>103</sup> Taken together, data from these short-term studies do not suggest an overall significant adverse impact of fasting on sleep quality, daytime sleepiness, or cognitive function.<sup>103,105</sup> Studies of short-term fasting not associated with religion also showed inconsistent results regarding cognitive performance, with some studies showing deficits particularly in processing speed and executive

functions, whereas others showed no significant changes.<sup>107,108</sup>

Studies of long-term fasting have been limited in humans. Witte et al<sup>109</sup> demonstrated an improvement in verbal memory scores after 3 months of caloric restriction in healthy study participants with a mean age of 60 years. Leclerc et al<sup>110</sup> replicated the cognitive benefits after a longer period of regular caloric restriction for up to 24 months in a larger sample of 220 healthy participants (age range, 21–50 years). Improvement in working memory with caloric restriction was documented in comparison with an ad libitum diet.<sup>110</sup> Effects specific to fasting remained unknown, however. A longitudinal study of the neuroprotective model for healthy longevity, involving older adults, followed up 99 participants with mild cognitive impairment who were older than 60 years. Of the study participants, 37 practiced intermittent fasting 2 days/week from dawn to sunset, 35 observed fasting for 12 months, and 27 did not practice fasting.<sup>111</sup> The proportion of participants with successful aging (defined as being free of common chronic diseases, Mini-Mental State Examination score > 22, good functional ability, and good quality of life) was markedly higher in the regular fasting group (24.3%) compared with the non-fasting group (3.1%). This study was limited by small sample sizes.<sup>111</sup> Another trial showed the beneficial impact of externally administered ketone body, medium-chain triglycerides on cognitive performance in comparison with placebo in people with mild cognitive impairment.<sup>112</sup> Neurons involved in neurodegenerative diseases have common features such as mitochondrial dysfunction and oxidative damage, which result in energy crisis.<sup>113</sup> These selective neurons have a high energy demand, and when glucose metabolism is compromised, ketone bodies provide alternate energy sources. It is noteworthy that ketone metabolism remains unaltered in the early stages of neurodegenerative diseases.<sup>113</sup>

*Adverse effects of intermittent fasting: limitations, challenges, and barriers* Authors of a systematic review and meta-analysis observed that intermittent fasting is largely safe.<sup>114</sup> Nonetheless, lack of energy, headaches, feeling cold, constipation, bad breath, lack of concentration, and bad temper have been reported.<sup>114</sup> The practice of intermittent fasting needs careful preparation after considering physical and psychological health (Table 2). Because diabetes mellitus involves substantial alterations in insulin levels and sensitivity and, hence, glucose levels, safety and tolerability of intermittent fasting in this condition, particularly in those receiving insulin and oral hypoglycemic agents, warrant more trials.<sup>115</sup> Although largely protective of neuronal health

**Table 2 Precaution and adverse effects of intermittent fasting**

Condition	Complications
Type 1 and 2 diabetes mellitus	Paucity of evidence on safety Extra caution such as frequent self-monitoring of capillary glucose required. Continuous glucose monitoring and flash glucose monitoring with alarm systems are now widely available, enabling safe adoption of intermittent fasting.
Anorexia nervosa (study subjects with BMI <25)	Potential worsening of anorexia nervosa and excess weight loss
Amyotrophic lateral sclerosis	Motor neurons may be vulnerable to prolonged fasting. Enhanced neurodegeneration in the inherited form of amyotrophic lateral sclerosis.
Loss of lean body mass	Resistance training required

and neuroplasticity, fasting promoted neurodegeneration in the inherited models of amyotrophic lateral sclerosis and did not offer protection against the progression of the disease, suggesting that motor neurons involved in this disease may not be able to adapt to the stress of intermittent fasting.<sup>116,117</sup> A few reports indicate that intermittent fasting could be associated with loss of lean body mass in addition to fat mass.<sup>118,119</sup> Available evidence shows that loss of appendicular muscle mass, however, can be prevented, including in older people, by resistance training and incorporating protein-rich food into the meal regimens.<sup>120–122</sup> Fasting may not be advisable for patients with advanced or rapidly progressing dementia. Although a high body mass index is associated with an increased risk of AD in midlife, reduced appetite, weight loss, and malnutrition may occur in the late phase of dementia.<sup>92,123</sup> Likewise, recent unintentional weight loss should alert the clinician to the risk of malnutrition or emergence of new medical issues, and fasting is not recommended in such instances.

In 2021, authors of a Cochrane review found that intermittent fasting was superior to ad libitum diet in reducing weight, albeit not statistically significantly so.<sup>124</sup> There is paucity of data on outcomes such as all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, or heart failure. There was no significant difference between intermittent fasting and caloric restriction without intermittent fasting in cardiometabolic risk factors, an observation replicated in a recent trial.<sup>125</sup> The evidence base indicating beneficial effects of fasting on Alzheimer's pathology, such as  $\beta$ -amyloid deposition, is preliminary and derived from animal studies. Additionally, findings regarding the effect of

intermittent fasting on AD pathology, such as  $\beta$ -amyloid deposition, are inconsistent.<sup>72,76,126</sup> Human trials in which outcomes related to AD were assessed are limited.

One of the limitations in the RCTs of intermittent fasting was poor adherence to interventions.<sup>127,128</sup> Self-reported adherence to an intervention regimen varied widely from 29% to 92%, with better adherence to 16 hours of daily fasting and a reminder through an app than to 5 days of normal eating and a twice-weekly calorie restriction regimen.<sup>118,127</sup> Previously published reports from RCTs of intermittent fasting showed a dropout rate that varied from 18% to 34% over 12 months, whereas the dropout rate for the control groups was 26%.<sup>11,118,127,128</sup> In the study by Trepanowski et al,<sup>128</sup> the dropout rate was attributed more to the alternate-day fasting group than the daily fasting group. Moreover, alternate-day fasting was not superior to the daily fasting regimen.<sup>128</sup> With a completion rate of 88%, Ravussin et al<sup>11</sup> demonstrated the feasibility of a 2-year RCT of caloric restriction compared with an ad libitum diet in 218 people aged 21–51 years. In a meta-analysis, authors found an overall adherence of 60.5% in intervention trials for weight loss.<sup>129</sup> Adherence to the interventions improved with social support and dietary intervention relative to exercise alone.

*Intermittent fasting in the older population* Several studies investigated the effects of intermittent fasting in the older population.<sup>109,121,130–132</sup> Ooi et al<sup>111</sup> prospectively studied intermittent fasting in older individuals with mild cognitive impairment for 3 years and assessed the cognitive outcomes. A pilot study of 10 participants aged  $\geq 65$  years suggested that the older population could tolerate 14–18 hours of daily fasting for 4 weeks, with 84% adherence.<sup>130</sup> Another randomized trial investigated the effects of a hypocaloric diet in older obese individuals for 13 weeks.<sup>121</sup> In a controlled trial, 45 women older than 60 years participated in 16 hours of daily fasting for 6 weeks and achieved significant weight reduction.<sup>131</sup> Response to caloric restriction in 50 healthy, normal weight to overweight older individuals was a decrease in plasma insulin and C-reactive protein levels and improved verbal memory performance at the end of 3 months.<sup>109</sup> In an RCT pilot study, older male veterans successfully completed 5 days of normal eating and a twice-weekly fasting regimen that lasted for 6 months.<sup>132</sup>

## DISCUSSION

There are no definite treatments or preventive drugs for dementias arising from Alzheimer's and other

neurodegenerative diseases. Notably, the pathological processes in AD are complex and extend beyond  $\beta$ -amyloid and tau.<sup>133</sup> Our current understanding of AD is likely to reflect a proximate etiology rather than the original cause. Vascular diseases play a critical role in late-onset AD. Oxygen free radicals and genomic mutations are also implicated in AD.<sup>134,135</sup> In this context, it is worth considering intermittent fasting, given its favorable impact on vascular endothelium, cellular metabolism, production of oxygen free radicals, and consequent diminished risk for genome mutations.

Intermittent fasting for 12–24 hours appears to be a promising approach to reduce the risk of AD pathology and its clinical manifestation of dementia. Two sets of empirical findings support this hypothesis, one from animal studies demonstrating a favorable impact of intermittent fasting on AD pathology and the other derived from human studies showing the benefits of fasting in reducing the risk of cardiovascular disease, inflammatory conditions, and obesity, which are associated with AD pathology.<sup>32,90,93–95,136</sup> This heterogeneity of pathological processes implies the need for interventions that have broad actions. Intermittent fasting may meet these requirements, with its profound and widespread cellular and metabolic effects.

Human trials of the effects of intermittent fasting on cognitive function and dementia are limited, presumably because of trial adherence and difficulties in maintaining a fasting regimen. However, other lifestyle interventions, such as exercise, were studied and found to reduce cognitive decline in older people. A YouGov poll among more than 1200 US adults in 2020 showed that 24% of the surveyed population practiced intermittent fasting at some stage in their lives, a figure consistent with systematic data from the US Healthy Minds Study.<sup>137,138</sup> Reports from Australian media suggest a growing enthusiasm for the practice of intermittent fasting.<sup>139</sup> Possibly enrichment trials targeting the population at risk of dementia can address the challenges in intermittent fasting trials.

## CONCLUSIONS

Intermittent fasting may be tested in clinical trials of AD for safety, feasibility, and efficacy given the broad cellular and metabolic impact of intermittent fasting that can favorably affect AD pathology from multiple angles. In particular, the beneficial effects of intermittent fasting in promoting vascular health and reducing oxidative damage provide empirical support for such trials.

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*Author contributions.* A.E. contributed to the work's conception and design; data search and data extraction from the existing literature, and data interpretation; writing the article, and reading and approving the version submitted. N.P. contributed to the conception of the study, and to data interpretation, and reviewed, edited, and approved the final version of the article. N.L. contributed to the conception of the study, and to data interpretation, and reviewed and approved the final version of the article.

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