Evaluating the effects of glucagon-like peptide-1 receptor agonists on cognitive function in Alzheimer's disease: A systematic review and meta-analysis

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Abstract

Background. Alzheimer's disease (AD) is the most common type of dementia. At present, some drug and non-drug therapies can be used to slow disease progression or prevent cognitive deterioration. More treatment options still need to be explored.

Objectives. A meta-analysis was performed to compile the relevant evidence for the use of glucagon-like peptide-1 (GLP-1) receptor agonists in preventing AD.

Materials and methods. We systematically searched English and Chinese databases, including Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, and Weipu website (VIP), based on the PICOS (Participants, Interventions, Comparisons, Outcomes, Study design) principles. The reviewers evaluated the search results and conducted the analysis; 5 articles with a total sample size of 184 patients were included. Changes in cognitive function, body mass index (BMI), blood glucose level, and insulin content were analyzed.

Results. A low risk of bias and no publication bias were found in these studies. The following results were obtained: 1) cognitive function: mean difference (MD) = 2.16, 95% confidence interval (95% CI): 1.45–2.88; 2) BMI change: MD = –1.16, 95% CI: –1.71––0.61; and 3) blood glucose change: standard MD (SMD) = –0.64, 95% CI: –1.21––0.88. No statistically significant difference was found in insulin content.

Conclusions. In this review, we showed that GLP-1 receptor agonists can effectively change cognitive function, BMI and blood glucose levels in patients with AD. This provides relevant clues for the prevention of AD. However, more studies are needed to refine these conclusions.

Key words: Alzheimer's disease, meta-analysis, cognitive function, hypoglycemic drugs, glucagon-like peptide-1 receptor agonists

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Introduction

The nervous system is a very important component of the human body, as it mediates many life activities. The available research has shown that cognition and emotion are regulated by the prefrontal lobe of the brain,[1] so when the nervous system is damaged, related functions are also affected. Several previous studies have revealed possible mechanisms for nervous system damage, including mitochondrial damage and associated inflammation in nerve cells[2,3]; therefore, neurologically related diseases need to be studied in depth.

Alzheimer's disease (AD), which is associated with progressive neurodegeneration, affects millions of people worldwide. The prevalence of AD is 10% in people over 65 years of age and 40% in people over 85 years of age. This amounts to a tremendous global health burden. Globally, there are nearly 46.8 million people suffering from AD, and treatment costs were estimated at USD 818 billion in 2015.[4] The main pathological features of AD include inflammation in the nervous system, amyloid plaques and neurofibrillary tangles in the brain.[5,6] Previous studies have shown that emotions such as fear are closely related to the central and peripheral nervous systems.[7] Synaptic dysfunction, neurotransmitter imbalance and neuroinflammation are closely related to the progression of AD.[8] Thus, homeostasis of the nervous system is essential for maintaining cognitive integrity. Thus far, only a few drugs that have been approved for the treatment of AD are being used in clinical environment, such as the acetylcholinesterase inhibitors and the non-competitive N-methyl-D-aspartate receptor antagonists. While these drugs can provide partial symptomatic relief, they cannot alter the progression of AD.[9] Although the U.S. Food and Drug Administration (FDA) approved aducanumab as the first disease-modifying therapy (DMT) for AD in June 2021,[10] there has been considerable medical and scientific controversy regarding its curative effect.[11] Two phase III trials of aducanumab have shown opposite results[12]; thus, currently available data do not provide sufficient evidence to support the clinical efficacy of aducanumab.[13] Therefore, the identification of a safe and effective DMT is a matter of critical importance.[14]

Diabetes is an endocrine disease characterized by abnormally high blood glucose levels.[15] There is a strong correlation between type 2 diabetes mellitus (T2DM) and AD[16]; the former is gradually being recognized as a risk factor for AD. There are many clinical and pathological similarities between T2DM and AD, including damage to the insulin signaling pathway.[17] In the central nervous system, insulin contributes to synaptic maintenance, neuron growth and survival, as well as maintenance and regulation of learning and memory[18]; therefore, insulin resistance becomes a potential risk factor for AD. Furthermore, hyperglycemia is strongly associated with the occurrence of AD. Karmi et al. conducted a magnetic resonance imaging (MRI) study and found that long-term chronic hyperglycemia can mediate hippocampal dysfunction,[19] and hyperglycemia inflammatory mediators, rheological factors, and dysregulation of the hypothalamic–pituitary–adrenal axis also may exacerbate cognitive decline.[20] In addition, some clinical evidence has found that diabetes patients with higher A1C levels are associated with diminished cognitive function.[21] Thus, it is believed that increasing insulin levels in the body may slow the progression of AD.

In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists have been used to control blood glucose levels in patients with diabetes. The pharmacological action of GLP-1 is to promote β-cell regeneration, growth and differentiation, and to inhibit β-cell apoptosis.[22] At the same time, GLP-1 can protect the nervous system, as it acts as a kind of growth factor.[23] A recent study found that GLP-1 improves the supportive ability of astrocytes to neurons, which explains the neuroprotective mechanism.[24] Importantly, GLP-1 can cross the blood–brain barrier, and it has also been reported that cells in the hypothalamus and hippocampus highly express GLP-1 receptors. However, abnormalities in the structure and function of the hippocampus and prefrontal cortex can cause cognitive impairment.[25] Thus, GLP-1 could help to slow the progression of AD. The GLP-1 can also induce neurite growth, thus achieving the effect of an AD intervention.[26,27] Animal studies have shown that the administration of a GLP-1 receptor agonist in rat ventricles can reduce nerve cell damage caused by neurotoxic stimulation, which may improve learning and memory function.[28] According to a mouse model of AD, treatment with the GLP-1 analog liraglutide can prevent the progression of memory decline.[29] Another recent study found that liraglutide can reduce associated brain complications when T2DM and AD occur simultaneously.[30] In 2019, Femminella et al. conducted the Evaluating Liraglutide in Alzheimer's Disease (ELAD) study to assess the effect of the novel GLP-1 analog liraglutide on AD, but they have not yet published their conclusions.[31] Therefore, relevant clinical evidence needs to be further studied.

This meta-analysis was conducted based on the P (Participants), I (Interventions), C (Comparisons), O (Outcomes), and S (Study design) (PICOS) principles. High-quality randomized controlled trials reported in both Chinese and English were included in this analysis. All patients had a clear diagnosis of AD or cognitive impairment. All the interventions in the trial were GLP-1 receptor agonist monotherapy, and the outcomes of all trials had clear data support.

Objectives

Although GLP-1 receptor agonists appear to be efficacious in treating AD, there is not yet enough clinical evidence to support this claim. Therefore, we conducted a meta-analysis to summarize what is known regarding the efficacy of these drugs in AD patients. We selected randomized controlled clinical studies on GLP-1 receptor

agonists in the treatment of AD to determine whether patients with AD can have changes in memory ability, skills and other dimensions of cognitive function after treatment, based on a scale test before and after the study. We evaluated changes in cognitive function and other indicators after GLP-1 receptor agonist interventions in patients with AD to provide a relevant basis for the prevention of the disease.

Materials and methods

Literature search and search strategy

Searches were conducted in a comprehensive manner for publications of relevant peer-reviewed papers and dissertations between 1990 and 2022 in the Embase, PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, and Weipu website (VIP) databases for all clinical studies on GLP-1 interventions in AD without language restrictions, using the Medical Subject Headings (MeSH) terms such as "glucagon-like peptide 1", "Alzheimer's disease" and "cognitive function". We also added all entry terms with the same meaning under all MeSH terms, such as "GLP-1", "AD" and "cognitions" into the search strategy. Then, the MeSH terms and entry terms of the same noun were connected by "OR", and words with different meanings were connected by "AND". Finally, the selection scope was limited to randomized controlled trials. The references of the included studies were searched manually as literature supplements.

Inclusion and exclusion criteria

The following criteria were used to determine which studies were eligible based on the PICOS principles[32]: 1) participants were aged ≥18 years with a diagnosis of AD or with cognitive impairment without a diagnosis of AD; 2) the intervention consisted of administration of a GLP-1 receptor agonist; 3) the outcome of the study included at least changes in cognitive function (not limited to type of cognitive function); 4) the study type was a randomized controlled trial; and 5) the baseline data were complete and included the number of observations, source of cases, follow-up time, and other indicators.

The exclusion criteria were as follows: 1) studies involving pregnant or breastfeeding patients; 2) studies on patients with other brain diseases or brain injuries; 3) review articles and animal or cell experiments; and 4) literature for which the outcome data could not be extracted.

Data extraction

An EndNote X9 (Clarivate Analytics, London, UK) library was initially created. A review of titles and abstracts was conducted. Based on the inclusion criteria, 2 researchers (ZB and WW) consulted the guidelines on data extraction for systematic reviews and meta-analyses, independently screened the literature, and extracted and cross-checked the data.[33] The basic information of the article was recorded, including the first author, publication date, sample size, average age, and sex of the patients, type of study design, diagnostic criteria for AD, intervention methods, and assessment methods of cognitive function. The 3rd investigator (LW) was consulted to resolve disagreements.

Quality assessment

A 5-dimensional evaluation of the included studies was conducted using the Cochrane Risk of Bias Assessment Tool (RoB v. 2.0; The Cochrane Collaboration, London, UK): 1) randomization process; 2) deviations from the intended interventions; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported result. When all the items of a dimension were satisfied, the quality level was considered low-risk; when some of the items were satisfied, the quality level was considered medium-risk; and when the reference did not meet the key requirements, the quality level was considered high-risk.

Statistical analyses

The STATA v. 16.0 (STATA Corp., College Station, USA) and Review Manager v. 5.4 (RevMan; The Cochrane Collaboration) were used to process the data. There was a single point representing each study connected to a forest plot with a regression line. After the effect size was log-transformed and divided by standard error (SE) (z-score), it was represented on the y-axis and expressed as the reciprocal of SE on the x-axis. Statistical heterogeneity across trials was assessed using the Cochran's Q test (with $p < 0.1$ indicating significance) and quantified using the I^2 statistic ($I^2 > 50\%$ for significant heterogeneity).[34,35] Considering that clinical heterogeneity and methodological heterogeneity could exist in any trial, we used the random effects model for the meta-analysis. Publication bias was assessed using funnel plots and Begg's test. In order to investigate publication bias, we constructed a funnel plot using Egger's test.[36]

Results

Search results and study characteristics

Based on the search strategy (Fig. 1), there were 427 articles in total; CNKI yielded 14 articles, Wanfang Data Knowledge Service Platform – 39 articles, VIP – 0 articles, PubMed – 316 articles, Embase – 31 articles, and Cochrane Library – 27 articles. We excluded 43 duplicate studies using EndNote X9.[37] In accordance with the title of the article, preliminary screening was conducted.

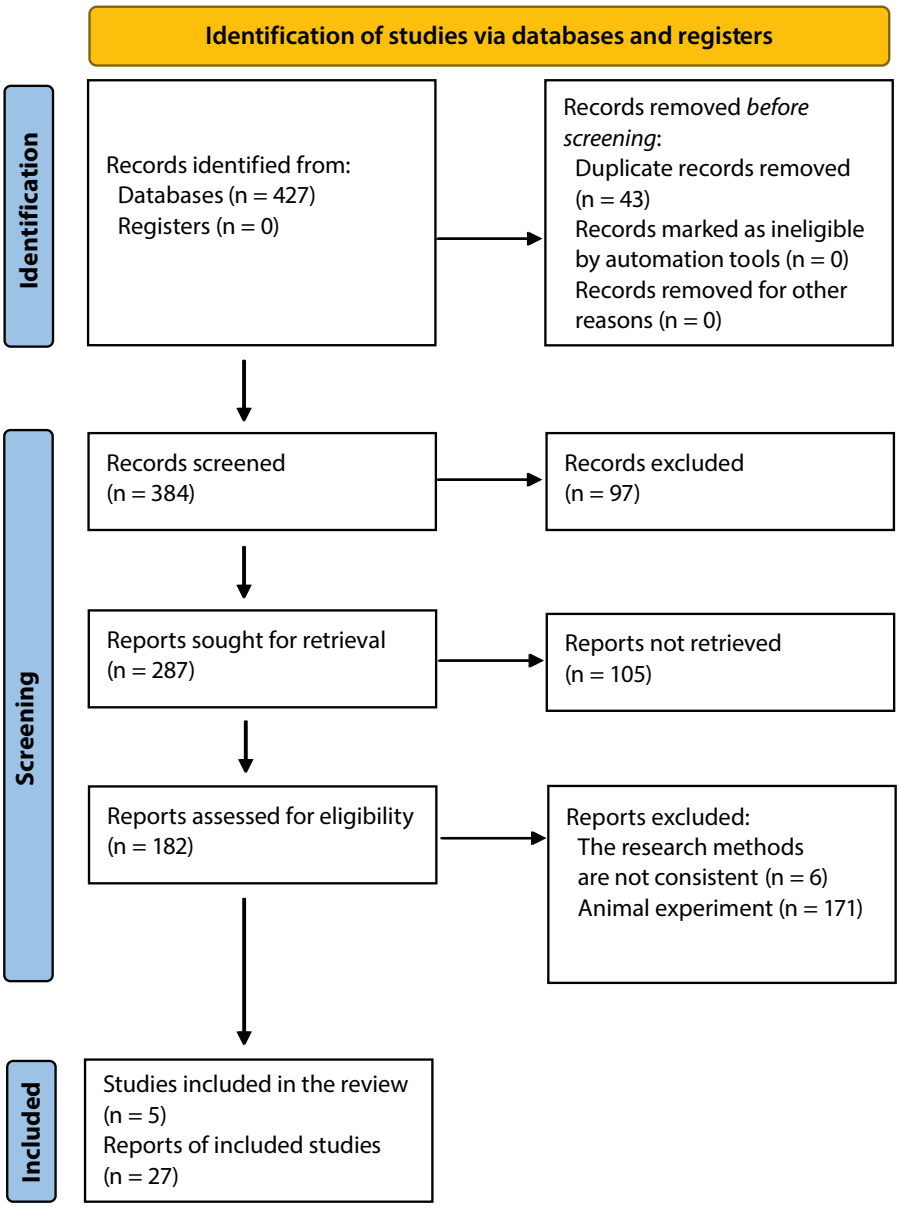

Fig. 1. Flow diagram of the literature search strategy used in this study

There were 97 exclusions after browsing the title, including 79 review articles or meta-analyses, and another 18 studies were excluded because their subjects were unrelated. Next, we reviewed the abstracts and excluded 105 studies that did not meet the study requirements. Of the remaining 182 articles, 171 were animal studies, and 6 studies had inconsistent methods, so they were excluded. Finally, 5 randomized controlled trials were included.

The inclusion and exclusion criteria were clearly stated in each of the 5 trials (Table 1). In all trials, the treated groups had similar baseline demographics, including age and gender. The total enrollment was 177. The mean patient age was 68 years. All patients were diagnosed with AD before the trial. In 3 of the studies, patients were treated with liraglutide, whereas exenatide was used in the other 2 studies. All cognitive function tests were conducted using a scale. The scales used were the Mini-Mental State Examination (MMSE) and the Wechsler Memory Scale–Fourth Edition (WMS-IV).

Study quality

The quality of all studies included in the meta-analysis was carefully evaluated using the Cochrane Risk of Bias Assessment Tool (RoB v. 2.0). The risk of bias was categorized as low, high or unclear, under the guidance of the Cochrane Handbook (https://training.cochrane.org/handbook). The risk of bias in all included studies is shown in Fig. 2,3. Overall, all 5 studies displayed a low risk of bias.

Results of GLP-1 intervention in AD

Four indicators were extracted from the 5 included studies,[38–42] all of which were randomized controlled trials. The major outcome included effects on cognitive function before and after the use of GLP-1 receptor agonists (Fig. 4). Additionally, insulin, blood glucose level and body mass index (BMI) were measured as secondary outcomes (Fig. 5–7).

Table 1. Characteristics of the selected studies

Author	Year	Randomization blinding	Study population	Diagnostic criteria for AD/MCI	Duration	Sample size, n	Cognitive measurement	Treatment	Sex (M/F)	Age (M ±SD)
Zheng[38]	2017	open-controlled	AD with DM	NINCDS-ADRDA	12 months	57	MMSE and ADL	exenatide + other	28/0	80.5 ±10.3
								placebo	29/0	
Mullins et al.[39]	2019	open-controlled	AD or MCI	CDR	6 months	21	MMSE and WMS-IV	exenatide	7/4	71.7 ±6.9
								placebo	4/6	74.0 ±6.4
Watson et al.[40]	2019	open-controlled	AD or MCI	MMSE	12 weeks	41	WMS-IV	liraglutide 1.8 mg	11/14	60.88 ±5.79
								placebo	5/11	59.56 ±5.69
Gejl et al.[41]	2016	double-blind	AD	MMSE	26 weeks	34	WMS-IV	liraglutide 1.8 mg	6/8	66.6
								placebo	15/5	63.1
Isik et al.[42]	2012	open-controlled	AD with DM	MMSE	6 months	24	MMSE	liraglutide 1.8 mg	–	71 ±6
								placebo	–	70 ±6

M – male; F – female; M ±SD – mean ± standard deviation; AD – Alzheimer's disease; DM – diabetes mellitus; MCI – mild cognitive impairment; NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; CDR – Clinical Dementia Rating; MMSE – Mini-Mental State Examination; WMS-IV – Wechsler Memory Scale–Fourth Edition; ADL – activities of daily living.

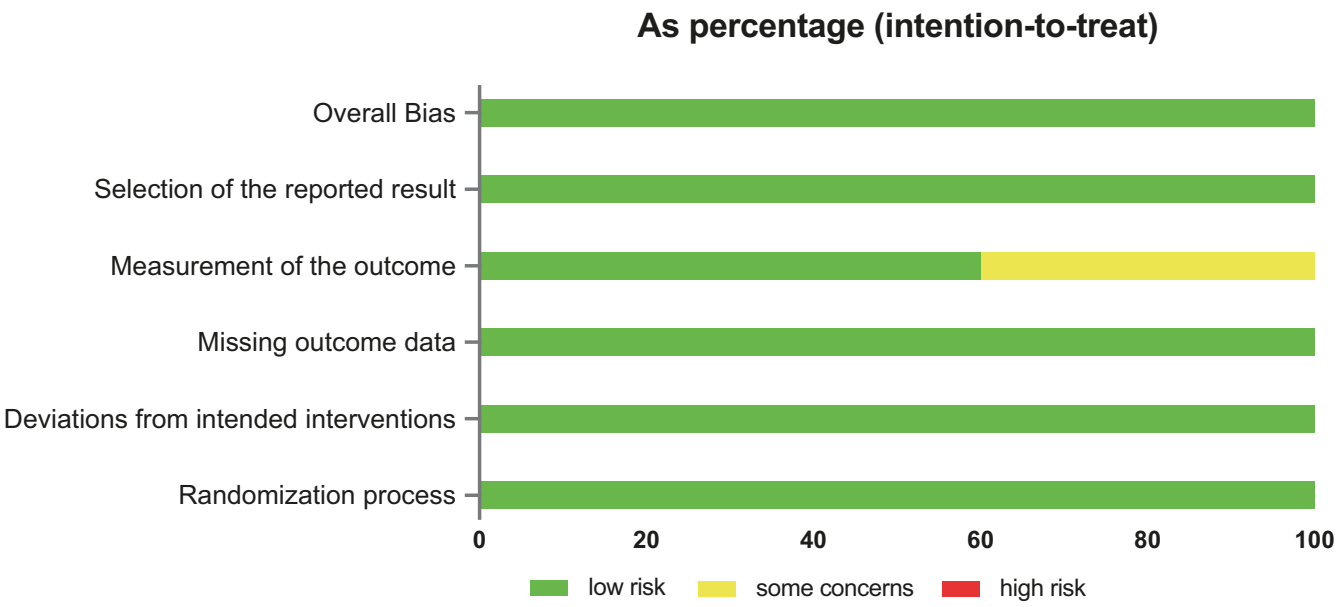

Fig. 2. Risk of bias graph

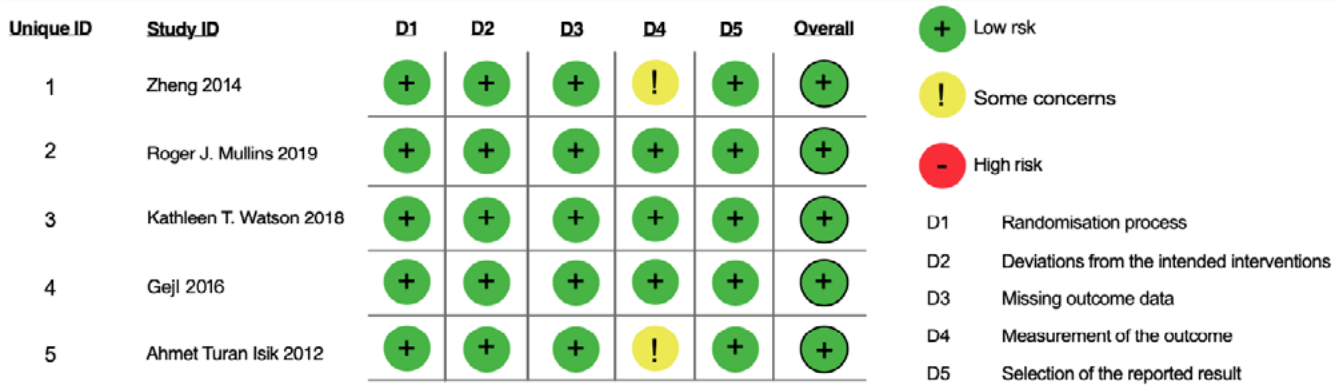

Fig. 3. Assessment of risk of bias

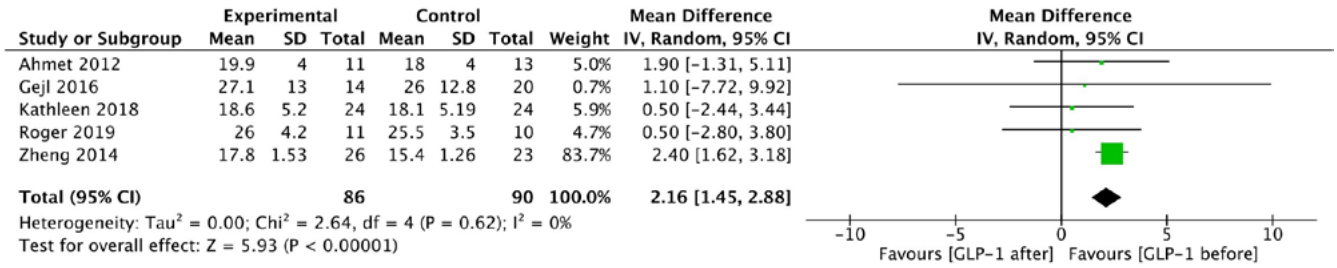

Fig. 4. Changes in cognitive function

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom; GLP-1 – glucagon-like peptide-1.

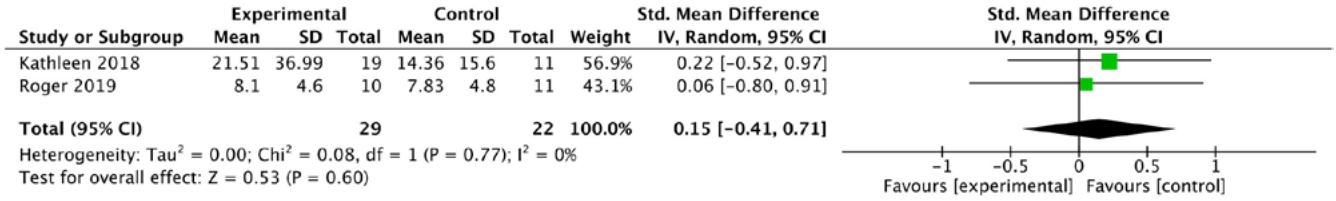

Fig. 5. Changes in insulin content

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

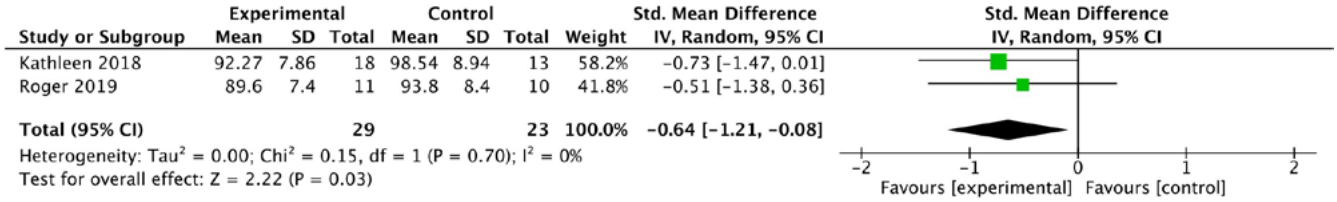

Fig. 6. Changes in blood glucose content

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

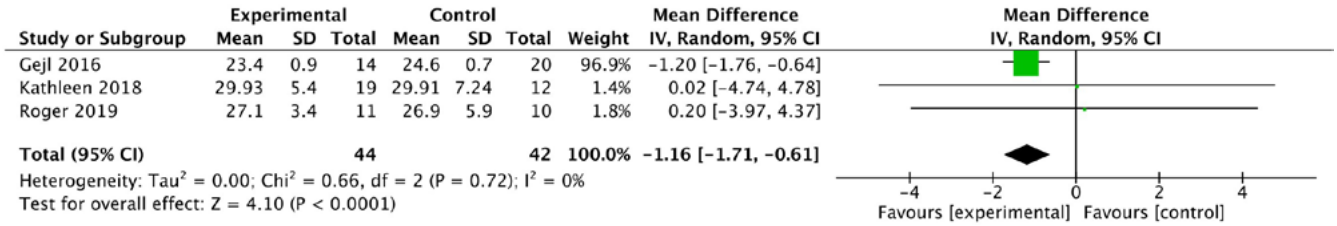

Fig. 7. Changes in body mass index (BMI)

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

Cognitive function was assessed using a random effects model that included 177 patients. In the test of heterogeneity, I^2 = 0% and p = 0.62, indicating low heterogeneity. After combining effect size, the meta-analysis showed that mean difference (MD) = 2.16, 95% confidence interval (95% CI): 1.45–2.88 and p < 0.05, and no publication bias was found (Begg's Test = 0.806, Egger's test = 0.153) after using STATA v. 16.0 to analyze the data.

Among the secondary outcomes, the results of insulin change concerned 51 patients, in which I^2 = 0% and p = 0.77 after the heterogeneity test. However, after combining the effect sizes, the p-value equaled 0.60, which indicated that there was no statistical significance; thus, there was no need to discuss this result in further detail. Owing to the different units in the included articles, a fixed-effect model was used to assess changes in blood glucose content. According to the heterogeneity test, I^2 = 0% and p = 0.7, indicating low heterogeneity, and the standard mean difference (SMD) = –0.64, 95% CI: –1.21––0.08, and p = 0.03, indicating statistical significance. The BMI changes were studied using a random effects model, and the results showed that heterogeneity was low (I^2 = 0%, p = 0.72), with MD = –1.16, 95% CI: –1.71––0.61 and p < 0.05. The results of the sensitivity analysis showed that all the studies had little influence on the total combined effect size, and the results were reliable and acceptable.

Discussion

Currently, clinical evidence regarding the efficacy of GLP-1 in treating AD patients is lacking. Therefore, we conducted a meta-analysis to summarize what is known about the effectiveness of this class of drugs in AD.

There is a strong link between cognitive dysfunction and obesity, hypertension, dyslipidemia, and T2DM.[43] There is extensive experimental evidence that patients with T2DM may suffer from cognitive decline accompanied by deterioration of memory, attention, intelligence, processing speed, and executive function. In addition, there are white matter abnormalities and brain atrophy (particularly in the cortical, subcortical and hippocampal regions).[44,45] Considering the pathologic similarities between T2DM and AD, and the characteristic effects of GLP-1 receptor agonists, treatment with enterosecretin analogs may be helpful in treating the cognitive deficits that occur in AD.[46] Therefore, a meta-analysis was conducted to address the efficacy of GLP-1 receptor agonists in patients with AD. The included studies reported changes in cognitive function before and after treatment in patients with AD, as well as BMI and levels of blood glucose and insulin after treatment. The following tools were used: MMSE, WMS-IV and Activities of Daily Living (ADL). The MMSE is a screening tool for detecting changes in cognitive skills, and WMS-IV and ADL are used to measure memory ability in patients with AD; all these tests are used to measure the cognitive function of AD patients. These results indicate that GLP-1 receptor agonist treatment can significantly improve the cognitive function of AD patients.

The treatment of T2DM with GLP-1 receptor agonists, such as liraglutide, has been approved. According to extensive animal studies, neuroprotection may be achieved with GLP-1 receptor agonists. It promotes the proliferation and differentiation of neurons, neurite outgrowth, synaptic plasticity, and memory formation, and reduces the toxicity of β-amyloid.[47] Furthermore, β-amyloid toxicity is mediated by insulin resistance.[48] Meanwhile, a recent in vitro model study found that as a result of reducing the activity of β-secretase 1 (BACE-1), an enzyme in insulin-resistant cells, liraglutide can decrease the production of β-amyloid.[49] Gejl et al. used positron emission tomography (PET) and found that glucose fluctuation levels in patients' brains can be reduced with GLP-1 receptor agonists.[50] Therefore, we hypothesized that GLP-1 receptor agonists could be used as potential drugs for preventing AD.

There is a strong association between unhealthy lifestyles, weight gain and obesity, and an increased risk of T2DM worldwide, as 60–90% of patients with T2DM are obese.[51] It has become a risk factor for AD, as a longitudinal study measured the sagittal abdominal diameter of 6583 individuals and found there is a nearly threefold risk of developing dementia for patients with the largest diameter compared to those with the smallest. Thus, they concluded that central obesity in midlife increased the risk of dementia.[52] Therefore, it is necessary to determine the effect of weight on T2DM patients. Liraglutide therapy has been reported to cause weight loss as an additional benefit. A higher dose formulation was developed specifically for obesity by the manufacturer in response to these findings. In December 2014, the FDA formally approved liraglutide 3 mg/day for this indication.[53] For BMI changes, the results of our study showed that MD = −1.16, 95% CI: −1.71−−0.61 and $p < 0.05$. This result was statistically significant and suggested that the BMI (or weight) of patients can be effectively changed after GLP-1 receptor agonist treatment, which is consistent with reports of relevant clinical trials. Ng and Wilding observed significant weight loss (1–3 kg) after 20–30 weeks of clinical liraglutide treatment in patients with T2DM.[54] Moreover, weight loss has been reported in T2DM patients treated with liraglutide (either monotherapy or combination therapy).[55] In patients with diabetes, there was a close correlation between BMI and GLP-1 receptor agonist use.[56] These results may be related to the mechanism underlying GLP-1 secretion. Kyriacou and Ahmed verified that exenatide can slow gastric emptying and reduce food intake.[57] Furthermore, the direct effect of GLP-1 on satiety signaling in the central nervous system, independent of vagal afferents, has been demonstrated to inhibit food intake.[58–60] The above studies indicate that GLP-1 can cause weight loss and reduce BMI. Meanwhile, Mansur et al. provided an explanation for the association between body weight and cognitive function, suggesting that the positive treatment effect on cognition may be partly due to the weight loss observed with liraglutide administration.[61]

We also analyzed changes in insulin and blood glucose levels after GLP-1 receptor agonist treatment in patients with AD. For the change in insulin content, the meta-analysis showed that $p = 0.60$ (>0.05), indicating no significant difference in the results. For the change in blood glucose, the meta-analysis showed that SMD = −0.64, 95% CI: −1.21−−0.08 and $p = 0.03$, which was statistically significant. The results showed that GLP-1 receptor agonists effectively reduced blood glucose levels in patients with AD. For changes in insulin level, although the result was not statistically significant, the effect size showed that GLP-1 receptor agonists could increase insulin content in vivo, which is consistent with the pharmacological effects of the drug.

Limitations

Meta-analyses review published literature to evaluate and quantitatively analyze the results of multiple studies in a comprehensive manner. This meta-analysis, however, has some limitations owing to the limited number of referenced studies. First, because of the small number of studies meeting the inclusion criteria, only 5 reports

were extracted and merged, which increased the uncertainty of the results. Second, the sample size of the study was small; therefore, verification of the results may be weak. More recent research reports should be included to supplement this meta-analysis. However, this study is the first to report the effect of GLP-1 receptor agonists during the treatment of AD, which is undoubtedly significant, and more research in similar direction should be conducted in the future.

Conclusions

Our study summarized current clinical studies and found that GLP-1 receptor agonists can effectively improve cognitive function, BMI and blood glucose levels in AD patients. There have been several previous animal studies demonstrating the effectiveness of GLP-1 receptor agonists on AD, based on neural or metabolic pathways. Therefore, we would suggest that GLP-1 receptor agonists may help slow the progression of AD. These findings provide a relevant basis for the prevention of AD. However, more clinical trials will need to be included to overcome the limited sample size and complement these findings.

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References

1. Battaglia S, Cardellicchio P, Di Fazio C, Nazzi C, Fracasso A, Borgomaneri S. Stopping in (e)motion: Reactive action inhibition when facing valence-independent emotional stimuli. *Front Behav Neurosci*. 2022; 16:998714. doi:10.3389/fnbeh.2022.998714
2. Tanaka M, Toldi J, Vécsei L. Exploring the etiological links behind neurodegenerative diseases: Inflammatory cytokines and bioactive kynurenines. *Int J Mol Sci*. 2020;21(7):2431. doi:10.3390/ijms21072431
3. Tanaka M, Szabó Á, Spekker E, Polyák H, Tóth F, Vécsei L. Mitochondrial impairment: A common motif in neuropsychiatric presentation? The link to the tryptophan–kynurenine metabolic system. *Cells*. 2022;11(16):2607. doi:10.3390/cells11162607
4. Prince MR, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. World Alzheimer Report 2015. The global impact of dementia: An analysis of prevalence, incidence, cost and trends. 2015. https://www.alzint.org/u/WorldAlzheimerReport2015.pdf. Accessed April 1, 2022.
5. Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018; 25(1):59–70. doi:10.1111/ene.13439
6. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–1590. doi:10.1016/S0140-6736(20)32205-4
7. Battaglia S, Orsolini S, Borgomaneri S, Barbieri R, Diciotti S, di Pellegrino G. Characterizing cardiac autonomic dynamics of fear learning in humans. *Psychophysiology*. 2022;59(12):e14122. doi:10.1111/psyp.14122
8. Khan S, Barve KH, Kumar MS. Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. *Curr Neuropharmacol*. 2020;18(11):1106–1125. doi:10.2174/1570159X18666200528142429
9. Olivares D, Deshpande VK, Shi Y, et al. N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. *Curr Alzheimer Res*. 2012;9(6):746–758. doi:10.2174/156720512801322564
10. Dhillon S. Aducanumab: First approval [published correction appears in *Drugs*. 2021;81(14):1701. PMID:34324167]. *Drugs*. 2021;81(12):1437–1443. doi:10.1007/s40265-021-01569-z
11. Tampi RR, Forester BP, Agronin M. Aducanumab: Evidence from clinical trial data and controversies. *Drugs Context*. 2021;10:2021-7-3. doi:10.7573/dic.2021-7-3
12. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. *Alzheimers Dement*. 2021; 17(4):696–701. doi:10.1002/alz.12213
13. Vaz M, Silva V, Monteiro C, Silvestre S. Role of aducanumab in the treatment of Alzheimer's disease: Challenges and opportunities. *Clin Interv Aging*. 2022;17:797–810. doi:10.2147/CIA.S325026
14. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: Few candidates, frequent failures. *Alzheimers Res Ther*. 2014;6(4):37. doi:10.1186/alzrt269
15. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol*. 2020;16(7):377–390. doi:10.1038/s41581-020-0278-5
16. Schnaider Beeri M, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology*. 2004;63(10):1902–1907. doi:10.1212/01.WNL.0000144278.79488.DD
17. Verdile G, Fuller SJ, Martins RN. The role of type 2 diabetes in neurodegeneration. *Neurobiol Dis*. 2015;84:22–38. doi:10.1016/j.nbd.2015.04.008
18. Bassil F, Fernagut PO, Bezard E, Meissner WG. Insulin, IGF-1 and GLP-1 signaling in neurodegenerative disorders: Targets for disease modification? *Prog Neurobiol*. 2014;118:1–18. doi:10.1016/j.pneurobio.2014.02.005
19. Karmi A, Iozzo P, Viljanen A, et al. Increased brain fatty acid uptake in metabolic syndrome. *Diabetes*. 2010;59(9):2171–2177. doi:10.2337/db09-0138
20. Strachan MWJ, Reynolds RM, Marioni RE, Price JF. Cognitive function, dementia and type 2 diabetes mellitus in the elderly. *Nat Rev Endocrinol*. 2011;7(2):108–114. doi:10.1038/nrendo.2010.228
21. Cukierman-Yaffe T, Gerstein HC, Williamson JD, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors. *Diabetes Care*. 2009;32(2):221–226. doi:10.2337/dc08-1153
22. Nauck MA. Glucagon-like peptide 1 (GLP-1) in the treatment of diabetes. *Horm Metab Res*. 2004;36(11/12):852–858. doi:10.1055/s-2004-826175
23. Hölscher C. The incretin hormones glucagonlike peptide 1 and glucose-dependent insulinotropic polypeptide are neuroprotective in mouse models of Alzheimer's disease [published correction appears in *Alzheimers Dement*. 2015;11(11):1395. PMID:24529525]. *Alzheimers Dement*. 2014;10(1 Suppl):S47–S54. doi:10.1016/j.jalz.2013.12.009
24. Zheng J, Xie Y, Ren L, et al. GLP-1 improves the supportive ability of astrocytes to neurons by promoting aerobic glycolysis in Alzheimer's disease. *Mol Metab*. 2021;47:101180. doi:10.1016/j.molmet.2021.101180
25. Battaglia S, Thayer JF. Functional interplay between central and autonomic nervous systems in human fear conditioning. *Trends Neurosci*. 2022;45(7):504–506. doi:10.1016/j.tins.2022.04.003
26. Gengler S, McClean PL, McCurtin R, Gault VA, Hölscher C. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. *Neurobiol Aging*. 2012;33(2):265–276. doi:10.1016/j.neurobiolaging.2010.02.014
27. Perry T, Greig N. Enhancing central nervous system endogenous GLP-1 receptor pathways for intervention in Alzheimer's disease. *Curr Alzheimer Res*. 2005;2(3):377–385. doi:10.2174/1567205054367892
28. During MJ, Cao L, Zuzga DS, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat Med*. 2003;9(9): 1173–1179. doi:10.1038/nm919
29. Hansen HH, Fabricius K, Barkholt P, et al. The GLP-1 receptor agonist liraglutide improves memory function and increases hippocampal CA1 neuronal numbers in a senescence-accelerated mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2015;46(4):877–888. doi:10.3233/JAD-143090
30. Carranza-Naval MJ, del Marco A, Hierro-Bujalance C, et al. Liraglutide reduces vascular damage, neuronal loss, and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. *Front Aging Neurosci*. 2021;13:741923. doi:10.3389/fnagi.2021.741923
31. Femminella GD, Frangou E, Love SB, et al. Evaluating the effects of the novel GLP-1 analogue liraglutide in Alzheimer's disease: Study protocol for a randomised controlled trial (ELAD study) [published correction appears in *Trials*. 2020;21(1):660. PMID:30944040]. *Trials*. 2019;20(1):191. doi:10.1186/s13063-019-3259-x
32. Muka T, Glisic M, Milic J, et al. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *Eur J Epidemiol*. 2020;35(1):49–60. doi:10.1007/s10654-019-00576-5

33. Taylor KS, Mahtani KR, Aronson JK. Summarising good practice guidelines for data extraction for systematic reviews and meta-analysis. *BMJ Evid Based Med*. 2021;26(3):88–90. doi:10.1136/bmjebm-2020-111651
34. Higgins JPT. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327(7414):557–560. doi:10.1136/bmj.327.7414.557
35. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statist Med*. 2002;21(11):1539–1558. doi:10.1002/sim.1186
36. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002. doi:10.1136/bmj.d4002
37. Bramer WM, Milic J, Mast F. Reviewing retrieved references for inclusion in systematic reviews using EndNote. *J Med Libr Assoc*. 2017;105(1): 84–87. doi:10.5195/jmla.2017.111
38. Zheng JY. Effect of GLP-1 analogs on improving cognitive function in patients with diabetes mellitus and Alzheimer's disease [doctoral dissertation]. Shandong First Medical University, Taian, China; 2017.
39. Mullins RJ, Mustapic M, Chia CW, et al. A pilot study of exenatide actions in Alzheimer's disease. *Curr Alzheimer Res*. 2019;16(8):741–752. doi:10.2174/1567205016666190913155950
40. Watson KT, Wroolie TE, Tong G, et al. Neural correlates of liraglutide effects in persons at risk for Alzheimer's disease. *Behav Brain Res*. 2019;356:271–278. doi:10.1016/j.bbr.2018.08.006
41. Gejl M, Gjedde A, Egefjord L, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: Randomized, placebo-controlled, double-blind clinical trial. *Front Aging Neurosci*. 2016;8:108. doi:10.3389/fnagi.2016.00108
42. Isik AT, Soysal P, Yay A, Yildiz GB, Kiskac M, Kazancioglu R. P4-214: Can sitagliptin, a GLP-1 inhibitor, improve cognitive function in elderly diabetic patients with Alzheimer's disease? *Alzheimers Dement*. 2012; 8(4S Part 19):P710. doi:10.1016/j.jalz.2012.05.1919
43. van den Berg E, Kloppenborg RP, Kessels RPC, Kappelle LJ, Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim Biophys Acta Mol Basis Dis*. 2009;1792(5):470–481. doi:10.1016/j.bbadis.2008.09.004
44. Bordier L, Doucet J, Boudet J, Bauduceau B. Update on cognitive decline and dementia in elderly patients with diabetes. *Diabetes Metab*. 2014;40(5):331–337. doi:10.1016/j.diabet.2014.02.002
45. Correia SC, Santos RX, Carvalho C, et al. Insulin signaling, glucose metabolism and mitochondria: Major players in Alzheimer's disease and diabetes interrelation. *Brain Res*. 2012;1441:64–78. doi:10.1016/j.brainres.2011.12.063
46. Candeias EM. Gut-brain connection: The neuroprotective effects of the anti-diabetic drug liraglutide. *World J Diabetes*. 2015;6(6):807. doi:10.4239/wjd.v6.i6.807
47. Salcedo I, Tweedie D, Li Y, Greig NH. Neuroprotective and neurotrophic actions of glucagon-like peptide-1: An emerging opportunity to treat neurodegenerative and cerebrovascular disorders. *Br J Pharmacol*. 2012;166(5):1586–1599. doi:10.1111/j.1476-5381.2012.01971.x
48. Neth BJ, Craft S. Insulin resistance and Alzheimer's disease: Bioenergetic linkages. *Front Aging Neurosci*. 2017;9:345. doi:10.3389/fnagi.2017.00345
49. Jantrapirom S, Nimlamool W, Chattipakorn N, et al. Liraglutide suppresses tau hyperphosphorylation, amyloid beta accumulation through regulating neuronal insulin signaling and BACE-1 activity. *Int J Mol Sci*. 2020;21(5):1725. doi:10.3390/ijms21051725
50. Gejl M, Egefjord L, Lerche S, et al. Glucagon-like peptide-1 decreases intracerebral glucose content by activating hexokinase and changing glucose clearance during hyperglycemia. *J Cereb Blood Flow Metab*. 2012;32(12):2146–2152. doi:10.1038/jcbfm.2012.118
51. Heppner KM, Perez-Tilve D. GLP-1 based therapeutics: simultaneously combating T2DM and obesity. *Front Neurosci*. 2015;9:92. doi:10.3389/fnins.2015.00092
52. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology*. 2008;71(14):1057–1064. doi:10.1212/01.wnl.0000306313.89165.ef
53. Nuffer WA, Trujillo JM. Liraglutide: A new option for the treatment of obesity. *Pharmacotherapy*. 2015;35(10):926–934. doi:10.1002/phar.1639
54. Ng SYA, Wilding JPH. Liraglutide in the treatment of obesity. *Exp Opin Biol Ther*. 2014;14(8):1215–1224. doi:10.1517/14712598.2014.925870
55. Fadini GP, Rigato M. Comparative effectiveness of liraglutide in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes*. 2014:107. doi:10.2147/DMSO.S37644
56. Toft-Nielsen MB, Damholt MB, Madsbad S, et al. Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J Clin Endocrinol Metab*. 2001;86(8):3717–3723. doi:10.1210/jcem.86.8.7750
57. Kyriacou A, Ahmed AB. Exenatide use in the management of type 2 diabetes mellitus. *Pharmaceuticals*. 2010;3(8):2554–2567. doi:10.3390/ph3082554
58. Kanoski SE, Fortin SM, Arnold M, Grill HJ, Hayes MR. Peripheral and central GLP-1 receptor populations mediate the anorectic effects of peripherally administered GLP-1 receptor agonists, liraglutide and exendin-4. *Endocrinology*. 2011;152(8):3103–3112. doi:10.1210/en.2011-0174
59. Rüttimann EB, Arnold M, Hillebrand JJ, Geary N, Langhans W. Intrameal hepatic portal and intraperitoneal infusions of glucagon-like peptide-1 reduce spontaneous meal size in the rat via different mechanisms. *Endocrinology*. 2009;150(3):1174–1181. doi:10.1210/en.2008-1221
60. Baggio LL, Huang Q, Brown TJ, Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1–albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor–dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes*. 2004;53(9):2492–2500. doi:10.2337/diabetes.53.9.2492
61. Mansur RB, Ahmed J, Cha DS, et al. Liraglutide promotes improvements in objective measures of cognitive dysfunction in individuals with mood disorders: A pilot, open-label study. *J Affect Disord*. 2017;207:114–120. doi:10.1016/j.jad.2016.09.056