# Diabetes as a disease of accelerated cognitive aging: role of diabetes interventions and implications for patient care

Tali Cukierman-Yaffe*

**Practice Points**

- People with diabetes have a greater risk of developing dementia and cognitive dysfunction. There is some evidence that people with diabetes experience an accelerated rate of cognitive decline.

- There is some evidence that cognitive dysfunction impedes diabetes self-care capacity and increases the risk of severe hypoglycemia.

- Diabetes-related cognitive dysfunction should be considered another complication of diabetes. Cognitive screening and cognitive surveillance should be part of routine care for older people with diabetes, just like the eye examination.

- There is some evidence regarding the effect of known dysglycemia interventions on diabetes-related cognitive dysfunction, although there is no unified way to assess this construct in trials of dysglycemia interventions.

- The ACCORD-MIND study and the ADVANCE study failed to show a role for glucose control in slowing the rate of cognitive decline in people with diabetes; however, sample size assumptions were not met in the ACCORD-MIND study so it is impossible to draw any definite conclusions.

- A substudy of ACCORD-MIND showed that people who were treated with an intensive glucose-lowering regimen experienced less of a decline in total brain volume than people who were treated with a standard glucose control regimen.

- There are some experimental data to support the role of the GLP-1 agonists in preservation of cognitive function.

- There are experimental and human data to support a cognitive protective role for insulin. The results of the ORIGIN cognitive substudy will shed some light on the effect of insulin on cognitive decline in people with diabetes.

- Physical activity and combined cognitive–physical activity hold promise in alleviating cognitive decline.

- Future trials of interventions in people with diabetes should include a cognitive assessment.

*Endocrinology Institute, Gertner Institute, Sheba Medical Center, Epidemiology Department, Tel Aviv University, Israel; tcukierm@gmail.com

**SUMMARY**   Diabetes may be viewed as a disease of accelerated cognitive aging. It is a risk factor for incident dementia, cognitive decline and cognitive dysfunction. Thus, 'diabetes-related cognitive dysfunction' may be viewed as another long-term complication of diabetes. This paper will briefly review the evidence supporting this, will elaborate on the implications for patient care and, finally, will describe what is known regarding the effect of existing diabetes interventions on this complication.

The population of people over the age of 60 years will represent 25% of the world's population by 2050 [1]. Thus, one of the major challenges that health systems are facing today is how to enhance successful/healthy aging. US data show that, among those fully independent at 60 years of age, less than 25% will reach 80 years without some form of disability [2]. One of the important determinants of successful/healthy aging is preserving cognitive function and prevention of cognitive decline. Studies have shown that cognitive function generally declines with age [3,4]; however, variability exists with respect to the degree and speed of decline. Evidence from the last decade has demonstrated that people with diabetes are more likely to experience an accelerated rate of cognitive decline and dysfunction, and are more likely to progress to dementia [5–10]. This review will provide a short summary of the evidence that 'diabetes-related cognitive dysfunction' is indeed another complication of diabetes. It will then elaborate in detail on the possible implications for everyday care of older patients with diabetes, and will finally describe what is known regarding the effect of diabetes interventions on this complication.

## Diabetes-related cognitive dysfunction: evidence supporting a relationship between diabetes, cognitive dysfunction & dementia

Type 2 diabetes is a disease that is characterized by hyperglycemia and is associated with a high risk of chronic diseases. It is a well-established risk factor for eye, kidney and neurological diseases, as well as for cardiovascular morbidity and mortality [11]. In the last decade, many prospective studies and several reviews have demonstrated that Type 2 diabetes is also a risk factor for cognitive dysfunction and dementia; with a 1.4–1.8-fold greater risk for minimal cognitive impairment (MCI), 1.5–2-fold greater risk for Alzheimer's disease (AD) and a 2–2.5-fold greater risk for vascular dementia [5,9,10,12–17]. The cognitive domains that have been reported to be more affected by this disease are psychomotor efficiency, learning, memory and executive function [6,18,19]. Some studies have also shown that it is a risk factor for an accelerated rate of cognitive decline [5,8,20–23], while others have found that although Type 2 diabetes patients have poorer scores, overall they exhibit a similar rate of cognitive decline to age-matched patients without diabetes [24].

Prospective studies with very long follow-up periods strengthen these observations. The Adult Health Study followed a cohort of atomic bomb survivors from Hiroshima and Nagasaki, and after approximately 35 years of follow-up, approximately 1800 participants were screened for dementia. Compared with nondiabetic individuals, diabetes increased the risk for vascular dementia and Alzheimer's dementia 1.3- and 4.4-fold, respectively [25]. The Israel Ischemic Heart Disease study demonstrated that people with diabetes in midlife had a 2.83-fold greater risk for the development of dementia three decades later versus those without diabetes [26].

## Implications for patient care

Diabetes is a disease that requires complex self-care behaviors and functional self-care capacity requires intact cognition. Several guidelines on the treatment of diabetes in the elderly have been published in the last year. All of these guidelines promote screening for cognitive dysfunction – the rationale being that cognitive dysfunction may impede self-care capacity [27,28].

One of the important aspects of diabetes self-care behavior is the treatment of hypoglycemic episodes in an adequate manner. This requires the individual to identify the symptoms of hypoglycemia, to measures blood glucose levels and react accordingly, thus preventing these nonsevere episodes from progressing to hypoglycemic events that require the aid of another. There is evidence that individuals with diabetes and cognitive dysfunction have a higher risk of developing severe hypoglycemia.

In the ADVANCE study, people with diabetes with severe cognitive impairment (Mini Mental State Examination [MMSE] ≤23) had a statistically significant greater risk for the development of severe hypoglycemia [29]. In the

ACCORD-MIND study, people who scored in the lower Digit Symbol Substitution (DSS) tertile had a 50% greater risk of developing severe hypoglycemia [30]. These data suggest that there is value to screening and perhaps also surveillance of cognitive function, and these should be part of the routine care of older people with diabetes, just as the yearly eye examination is.

In our institute, we recently founded the Center for Successful Aging with Diabetes, where people over the age of 60 years with diabetes undergo cognitive, physical and functional periodic assessment, creating a baseline measure for each individual (thus enabling the detection of an acceleration in decline during follow-up), enabling referral for further treatment, evaluation when needed and tailoring of diabetes treatment regimens.

## Treatment options for diabetes-related cognitive dysfunction

One of the major obstacles in finding treatment options for diabetes-related cognitive dysfunction is defining which outcomes we should be measuring when testing the effects of different interventions on the construct of 'cognitive dysfunction'. One possibility could be to use dementia as a major outcome, but the drawback of this is that the incidence of dementia is quite low in the younger age group, while it might be too late in the process to discern the effect of an intervention in the older age group. Thus, utilizing dementia as an outcome in trials would require either very long follow-up periods or large sample sizes. A second possibility could be to test the effect of an intervention on cognitive decline or, alternatively, on cognitive maintenance. A third possibility could be to use surrogates of cognitive function such as imaging, including total brain volumes, hippocampus volumes or developing functional MRI techniques. Finally, as cognitive function is cardinal for diabetes self-care behaviors, functional measures relating to diabetes self-care capacity could be used.

To date, there is no consensus regarding the tools/instruments that should be used. There is, however, no doubt that this whole field would benefit substantially from research aimed at elucidating the optimal instruments and unification of different tools used so that meaningful comparisons may be made.

In the following paragraphs I will present what is known regarding the effect of several known glucose-lowering interventions on diabetes-related cognitive dysfunction.

### ■ Effect of glucose control interventions on diabetes-related cognitive dysfunction
#### Glucose control
The first dysglycemia intervention that comes to mind for Types 2 diabetes is glucose control; this was tested in the ACCORD-MIND and ADVANCE trials.

The ACCORD-MIND trial tested the effect of very intensive glucose control (HbA1c of 6.4%) versus standard control (HbA1c of 7.5%) on cardiovascular outcomes. The cognitive substudy assessed the effect of these interventions on the rate of cognitive decline as measured by four cognitive instruments (MMSE, DSS, Stroop test and Rey Auditory Verbal Learning Test). It also included a substudy in which participants underwent structural MRI measurements. Unfortunately, the study was terminated early and, thus, sample size assumptions were not met. Therefore, there is a high chance that β-type errors existed (i.e., that no difference between the groups was detected despite the existence of such a difference). An analysis including the 20- and 40-month data failed to show an effect of treatment on changes in the cognitive test scores. However, in the subgroup that underwent brain MRI, a significant difference was noted in the change in total brain MRI volumes, with the intensively treated group experiencing less of a reduction than the conventional group. The ADVANCE trial also assessed the effect of an intensive glucose control regimen (HbA1c of 6.5%) utilizing gliclazide versus standard care (HbA1c of 7.3%) on cardiovascular outcomes. The MMSE was administered to participants and incident dementia was assessed. During a medium follow-up of 5 years, there was no difference between the groups in the rate of cognitive decline, as assessed by the MMSE, or in incident dementia rates [31].

#### GLP agonists
Data on the potential role of GLP agonists come mainly from experimental evidence. GLP-1 receptors are found in many brain areas related to memory and learning, and not connected to metabolic control (e.g., the dentate gyrus). They are also found on glial cells. Experimental studies in GLP-1 receptor knockout mice demonstrated that these animals exhibited an impairment in contextual memory and this was

reversible after GLP-1 receptor DNA transfer. This is also supported by studies showing that rats with overexpression of the GLP-1 receptor in the hippocampus show an improvement in learning and memory [32–34].

There is also experimental evidence linking the use of GLP analogs with improved cognitive function. Thus, in cell culture, GLP-1 analogs stimulate neurite outgrowth in a similar manner to NGF. In rats, intracerebroventricular administration of GLP-1 analogs enhanced learning and memory. There are also data showing that GLP-1 analogs cross the blood–brain barrier. In normal rats, exantide-4 improved hippocampus-based cognitive performance. Finally, in dysmetabolic animals and in animal models of AD, there is evidence that the GLP analogs may possess cognitive improvement properties. Thus, in experimental models of AD, GLP-1 cleavage products, liraglutide and exenatide have been shown to cause an improvement in learning and memory tasks. Lower memory and learning scores have been observed in mice with high-fat-diet-induced obesity and insulin resistance compared with controls; however, this effect was abolished by treatment with liraglutide [35–39].

To the best of my knowledge, there are currently no published studies linking the use of GLP analogs with improved cognitive function in humans. There are currently two randomized controlled trials (RCTs) underway looking at the effect of liraglutide and exenatide in people with AD/MCI [40]. The question of whether this class of drugs may have an effect on diabetes-related cognitive dysfunction remains unanswered.

## Insulin

Insulin receptors (IRs) are widely distributed in the brain, and the blood–brain barrier also contains many IRs. These have a role in transport (transport of amino acids and hormones) and functionality [11]. Higher concentrations of IRs are found in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus [41]. IR levels are higher in neurons than glial cells. IR levels decrease with age. In a rat hippocampus cell culture, IR signaling promoted cell survival under stress conditions (oxygen and glucose deprivation). IR signaling has also been shown to be involved in synaptic maintenance and dendrite formation [42,43].

Transportation of insulin into the brain occurs via a saturable system. In contrast to peripheral tissues in the CNS, insulin's main role is not in glucose acquisition, but in modification of feeding and cognitive behaviors. Thus, in animal models, administration of insulin into the cerebrospinal fluid resulted in improved memory. After memory formation, gene expression of IRs was upregulated [11,43–47].

Unlike for the GLP-1 analogs, we do have human data for insulin. There have been several small-scale, short-duration studies looking at the effect of a form of insulin that selectively enters the brain, intranasal insulin. These studies were summarized in a recent systematic review [48]. All studies were of a very short duration (up to 8 weeks) and showed some effect of a very high dose of insulin in people without cognitive dysfunction and in people with cognitive dysfunction on some of the cognitive domains [48]. Craft and colleagues recently published the results of a 4-month RCT of 104 participants with MCI/early AD. The patients were randomized to placebo, or 20 or 40 U of intranasal insulin. After a 4-month intervention period, subjects receiving intranasal insulin reported an improvement in delayed memory (p < 0.05) and in preservation of caregiver-rated functional ability (p < 0.01) [49].

Thus, there is ample evidence that insulin may have a cognitive protective role; however, whether this is true in people with diabetes is unknown. The ORIGIN study was a 12,500-person, multicenter, international, randomized trial that studied the effects of insulin glargine-mediated normoglycemia versus standard care, and n-3 polyunsaturated fatty acid versus placebo on the risk of cardiovascular events in people with diabetes and prediabetes, with a median follow-up of 6.2 years. The MMSE and DSS were administered to participants at four time points throughout the study. In addition, data regarding incident dementia were collected. The results of this study will hopefully be published in the next several months.

## ■ Effect of lifestyle interventions on diabetes-related cognitive dysfunction

Physical activity is one of the only interventions that has been shown to delay age-related cognitive decline in individuals over the age of 50 years. In a Cochrane review, physical activity among individuals over the age of 50 years (with and without diabetes) was found to slow the rate of cognitive decline in certain domains: cognitive speed, visual auditory attention and motor function [50]. It is possible that the

combination of physical and cognitive training holds even greater promise. Indeed, in a recent multicenter cluster RCT of 3-month duration, individuals over the age of 70 years were randomized to cyber cycling (virtual reality tours and competitions) versus traditional exercise. After a short follow-up period, people who were randomized to the cyber cycling arm had significant gains in executive function. They also had a 23% reduction in predementia (MCI). The gains that were achieved by people with diabetes were greater [51].

## Conclusion

Diabetes may be viewed as a disease of accelerated cognitive aging; it is a risk factor for progression of cognitive impairment and future dementia. Thus, diabetes-related cognitive dysfunction should be considered another complication of diabetes. Cognitive dysfunction should be screened for, especially in the elderly, as it may affect the self-care capacity of the individual and increase his/her risk of hypoglycemia. More studies aimed at finding the optimal way to screen and measure progression of cognitive dysfunction in people with diabetes are needed as this may be a first step in aiding people with diabetes to age successfully and to elucidate new treatment options. There is some data to support the role of GLP-1 analogs in the prevention of cognitive decline. There are more data regarding the potential role of insulin in alleviating cognitive decline in people with diabetes. The results of the ORIGIN cognitive substudy will shed some light on this question. Finally, ongoing intervention studies in people with diabetes should include measures of cognitive function.

## Future perspective

Diabetes-related cognitive dysfunction is another complication of diabetes; with the rising number of older people with diabetes there is urgency to better understand this complication and to elucidate treatment options. Cognitive screening and surveillance should be part of the routine care of older people with diabetes. In our center, we have recently initiated the Center for Successful Aging with Diabetes, where older people with diabetes undergo periodic surveillance of cognitive, physical and functional capacities. It is cardinal that more research be focused on the optimal way to measure cognitive decline and cognitive dysfunction – this would be a first step in elucidating new treatment options. Future intervention trials in people with diabetes should include a cognitive assessment.

## References

1. Michel JP, Newton JL, Kirkwood TB. Medical challenges of improving the quality of a longer life. *JAMA* 299, 688–690 (2008).

2. Leveille SG, Guralnik JM, Ferrucci L, Langlois JA. Aging successfully until death in old age: opportunities for increasing active life expectancy. *Am. J. Epidemiol.* 149, 654–664 (1999).

3. Proust-Lima C, Amieva H, Letenneur L, Orgogozo JM, Jacqmin-Gadda H, Dartigues JF. Gender and education impact on brain aging: a general cognitive factor approach. *Psychol. Aging* 23, 608–620 (2008).

4. Proust-Lima C, Amieva H, Dartigues JF, Jacqmin-Gadda H. Sensitivity of four psychometric tests to measure cognitive changes in brain aging-population-based studies. *Am. J. Epidemiol.* 165, 344–350 (2007).

5. Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes – systematic overview of prospective observational studies. *Diabetologia* 48, 2460–2469 (2005).

6. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: a lifespan perspective. *Lancet Neurol.* 7, 184–190 (2008).

7. Gregg EW, Yaffe K, Cauley JA *et al.* Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. *Arch. Intern. Med.* 160(2), 174–180 (2000).

8. Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K. Change in cognitive function by glucose tolerance status in older adults: a 4-year prospective study of the Rancho Bernardo study cohort. *Arch. Intern. Med.* 164(12), 1327–1333 (2004).

9. Yaffe K, Blackwell T, Kanaya AM, Davidowitz BA, Barrett-Connor E, Krueger K. Diabetes impaired fasting glucose and development of cognitive impairment in older women. *Neurology* 63, 658–663 (2004).

10. Yaffe K, Blackwell T, Whitmer RA, Krueger K, Barrett Connor E. Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. *J. Nutr. Health Aging* 10, 293–295 (2006).

11. Havrankova J, Roth J, Brownstein M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature* 272, 827–829 (1978).

12 Reijmer YD, van den BE, Ruis C, Kappelle LJ, Biessels GJ. Cognitive dysfunction in patients with Type 2 diabetes. *Diabetes Metab. Res. Rev.* 26, 507–519 (2010).

13 McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet* 379, 2291–2299 (2012).

14 Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch. Neurol.* 64, 570–575 (2007).

15 Luchsinger JA. Type 2 diabetes and cognitive impairment: linking mechanisms. *J. Alzheimers Dis.* 30(Suppl. 2), S185–S198 (2012).

16 Vagelatos NT, Eslick GD. Type 2 diabetes as a risk factor for Alzheimer's disease: the confounders, interactions, and neuropathology associated with this relationship. *Epidemiol. Rev.* doi:10.1093/epirev/mxs012 (2013) (Epub ahead of print).

17 Cheng G, Huang C, Deng H, Wang H. Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern. Med. J.* 42, 484–491 (2012).

18 Biessels GJ. Sweet memories: 20 years of progress in research on cognitive functioning in diabetes. *Eur. J. Pharmacol.* doi:10.1016/j.ejphar.2013.04.055 (2013) (Epub ahead of print).

19 Small GW, Bookheimer SY, Thompson PM *et al.* Current and future uses of neuroimaging for cognitively impaired patients. *Lancet Neurol.* 7, 161–172 (2008).

20 Fontbonne A, Berr C, Ducimetiere P, Alperovitch A. Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study. *Diabetes Care* 24(2), 366–370 (2001).

21 Ott A, Stolk RP, Hofman A, van HF, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 39(11), 1392–1397 (1996).

22 Cerhan JR, Folsom AR, Mortimer JA *et al.* Correlates of cognitive function in middle-aged adults. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Gerontology* 44(2), 95–105 (1998).

23 MacKnight C, Rockwood K, Awalt E, McDowell I. Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging. *Dement. Geriatr. Cogn. Disord.* 14(2), 77–83 (2002).

24 van den Berg E, Reijmer YD, de BJ, Kessels RP, Kappelle LJ, Biessels GJ. A 4 year follow-up study of cognitive functioning in patients with Type 2 diabetes mellitus. *Diabetologia* 53, 58–65 (2010).

25 Yamada M, Kasagi F, Sasaki H, Masunari N, Mimori Y, Suzuki G. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. *J. Am. Geriatr. Soc.* 51(3), 410–414 (2003).

26 Schnaider BM, Goldbourt U, Silverman JM *et al.* Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology* 63, 1902–1907 (2004).

27 Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. *Diabetes Res. Clin. Pract.* 50(3), 203–212 (2000).

28 Bayer AJ, Johnston J, Sinclair AJ. Impact of dementia on diabetic care in the aged. *J. Royal Soc. Med.* 87(10), 619–621 (1994).

29 de Galan BE, Zoungas S, Chalmers J *et al.* Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with Type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial. *Diabetologia* 52, 2328–2336 (2009).

30 Punthakee Z, Miller ME, Launer LJ *et al.* Poor cognitive function and risk of severe hypoglycemia in Type 2 diabetes: *post hoc* epidemiologic analysis of the ACCORD trial. *Diabetes Care* 35, 787–793 (2012).

31 Patel A, Macmahon S, Chalmers J *et al.* Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358, 2560–2572 (2008).

32 Perry TA, Greig NH. A new Alzheimer's disease interventive strategy: GLP-1. *Curr. Drug Targets* 5, 565–571 (2004).

33 During MJ, Cao L, Zuzga DS *et al.* Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat. Med.* 9, 1173–1179 (2003).

34 Hamilton A, Patterson S, Porter D, Gault VA, Holscher C. Novel GLP-1 mimetics developed to treat Type 2 diabetes promote progenitor cell proliferation in the brain. *J. Neurosci. Res.* 89, 481–489 (2011).

35 Porter DW, Kerr BD, Flatt PR, Holscher C, Gault VA. Four weeks administration of liraglutide improves memory and learning as well as glycaemic control in mice with high

fat dietary-induced obesity and insulin resistance. *Diabetes Obes. Metab.* 12, 891–899 (2010).

36 Porter D, Faivre E, Flatt PR, Holscher C, Gault VA. Actions of incretin metabolites on locomotor activity, cognitive function and *in vivo* hippocampal synaptic plasticity in high fat fed mice. *Peptides* 35, 1–8 (2012).

37 Lennox R, Porter DW, Flatt PR, Gault VA. (Val(8))GLP-1–Glu–PAL: a GLP-1 agonist that improves hippocampal neurogenesis, glucose homeostasis, and β-cell function in high-fat-fed mice. *ChemMedChem* 8, 595–602 (2013).

38 Huang HJ, Chen YH, Liang KC *et al.* Exendin-4 protected against cognitive dysfunction in hyperglycemic mice receiving an intrahippocampal lipopolysaccharide injection. *PLoS One* 7, e39656 (2012).

39 McClean PL, Parthsarathy V, Faivre E, Holscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. *J. Neurosci.* 31, 6587–6594 (2011).

40 Egefjord L, Gejl M, Moller A *et al.* Effects of liraglutide on neurodegeneration, blood flow and cognition in Alzheimer's disease – protocol for a controlled, randomized double-blinded trial. *Dan. Med. J.* 59, A4519 (2012).

41 Unger JW, Livingston JN, Moss AM. Insulin receptors in the central nervous system: localization, signalling mechanisms and functional aspects. *Prog. Neurobiol.* 36, 343–362 (1991).

42 Zhao WQ, Chen H, Quon MJ, Alkon DL. Insulin and the insulin receptor in experimental models of learning and memory. *Eur. J. Pharmacol.* 490, 71–81 (2004).

43 Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. *Pharmacol. Ther.* 136, 82–93 (2012).

44 Banks WA. The source of cerebral insulin. *Eur. J. Pharmacol.* 490, 5–12 (2004).

45 Carro E, Torres-Aleman I. The role of insulin and insulin-like growth factor I in the molecular and cellular mechanisms underlying the pathology of Alzheimer's disease. *Eur. J. Pharmacol.* 490(1–3), 127–133 (2004).

46 de la Monte SM, Wands JR. Alzheimer's disease is Type 3 diabetes – evidence reviewed. *J. Diabetes Sci. Technol.* 2, 1101–1113 (2008).

47 Sabayan B, Foroughinia F. Role of insulin metabolism disturbances in the development of Alzheimer disease: mini review. *Am.*

*J. Alzheimers Dis. Other Demen.* 23, 192–199 (2008).

48   Shemesh E, Rudich A, Harman-Boehm I, Cukierman-Yaffe T. Effect of intranasal insulin on cognitive function: a systematic review. *J. Clin. Endocrinol. Metab.* 97, 366–376 (2012).

49   Craft S, Baker LD, Montine TJ *et al.* Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch. Neurol.* 69, 29–38 (2012).

50   Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database Syst. Rev.* 2, CD005381 (2008).

51   Anderson-Hanley C, Arciero PJ, Westen SC, Nimon J, Zimmerman E. Neuropsychological benefits of stationary bike exercise and a cybercycle exergame for older adults with diabetes: an exploratory analysis. *J. Diabetes Sci. Technol.* 6, 849–857 (2012).