Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Intranasal Insulin

Evidence Summary

Initial evidence suggests that intranasal insulin may be beneficial for cognition, including in MCI/AD and for postoperative cognitive function. More robust studies with validated devices are needed.

Neuroprotective Benefit: Evidence thus far indicates that intranasal insulin may improve cognition in healthy individuals and MCI/AD patients, though more robust trials with validated devices are needed. Intranasal insulin appears to help prevent POCD.

Aging and related health concerns: There are some beneficial changes in biomarkers associated with intranasal insulin, though whether this would change clinical outcomes is not known.

Safety: Most studies find no increase in adverse events in patients who receive intranasal insulin compared to placebo at doses up to 160 IU; most side effects are related to intranasal delivery itself, including nasal irritation, rhinitis, and nose bleeds.

Availability: OTC in some states; available with prescription; device must be bought from manufacturer	**Dose**: Dose optimization is still under investigation. Many studies use up to 160 IU per day for healthy individuals and 20 to 40 IU per day for MCI or AD patients.	**Chemical formula:** $C_{256}H_{381}N_{65}O_{76}S_6$ **MW**: 5777.603g/mol Source: PubChem
Half-life: (In periphery): regular insulin (5-7 minutes), insulin detemir (5-7 hours)	**BBB**: Penetrant	
Clinical trials: The largest meta-analysis identified included 1,760 RCT participants.	**Observational studies**: No observational studies of intranasal insulin were identified.	

What is it?

Insulin is a critical peptide hormone that regulates levels of blood glucose and overall glucose metabolism. Cell types in many organ systems have insulin receptors, including neurons and glia; insulin in the brain is thought to affect aspects of neuronal communication, inflammatory responses, and glucose uptake across the blood-brain barrier (BBB), among other potential functions. Insulin signaling in the hypothalamus may also mediate peripheral metabolic responses (Arnold et al., 2018). Insulin is thought to be transported across the BBB via saturable transporters (Kellar & Craft, 2020).

Type 1 and type 2 diabetes are characterized by a lack of insulin and/or by a blunted response to insulin known as insulin resistance (Goyal et al., 2023). Type 2 diabetes (T2D) is a well-known risk factor for Alzheimer's disease (Livingston et al., 2024). Insulin resistance has been associated with aging, though maintenance of insulin sensitivity has been associated with longevity and centenarians (Kullmann et al., 2016). It is thought that chronic increased levels of insulin in the periphery due to an insulin-resistant state may cause insulin resistance in the central nervous system as well. Insulin resistance may cause cognitive impairment through other mechanisms such as damage to the cerebral vasculature, impaired insulin signaling in the brain, or glucose hypometabolism (Benedict & Grillo, 2015). Transport of insulin across the BBB can also be affected in AD, along with several other conditions. Intranasal administration of insulin bypasses this issue and delivers insulin directly to the brain. Moreover, intranasal

administration of insulin is thought to have low spillover to the periphery (Kellar & Craft, 2020). This method of delivery thus allows targeted administration without concomitant peripheral effects.

Insulin can also be delivered intranasally via different devices. There are different types of insulin available. These include:

- Regular (Humulin R, Novolin R, Velosulin R)
- Rapid-acting (Insulin glulisine – Aprida; insulin lispro – Admelog, Humalog; insulin aspart – Fiasp, NovoLog)
- Long-acting (degludec – Tresiba; detemir – Levemir, glargine – Basaglar, Lantus)

Intranasal insulin has been primarily explored for use in AD, but studies have also investigated its effects in cognitively unimpaired populations, including those with and without metabolic disease such as T2D. Some studies have also assessed intranasal insulin for potential efficacy in other neurodegenerative diseases or for postoperative cognitive delirium. Studies need to not just determine overall efficacy, but also which type(s) of insulin and device(s) are most associated with benefit for each individual condition and patient population.

Neuroprotective Benefit: Evidence thus far indicates that intranasal insulin may improve cognition in healthy individuals and MCI/AD patients, though more robust trials with validated devices are needed. Intranasal insulin appears to help prevent POCD.

Types of evidence:

- 7 meta-analyses and/or systematic reviews
- 23 clinical trials
- Multiple biomarker studies of insulin resistance
- 2 reviews
- Multiple preclinical studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

A 2023 systematic review and meta-analysis assessed the effects of intranasal insulin on cognition across a variety of patient populations. Their meta-analysis included 1,726 patients in total, all enrolled

in placebo-controlled RCTs. The authors pooled data from healthy, cognitively unimpaired patients (n=400) and found that there was no significant effect of intranasal insulin on global cognition in these participants. They did not identify any differences between studies that looked at acute dosing compared to long-term dosing in the healthy, cognitively intact population. When they looked at global cognition across all patient populations, including MCI and AD, they found that only long-term administration studies were associated with significant effects on global cognition; they did not see any significant effects in acute dosing studies (Wu et al., 2023).

A 2024 systematic review and meta-analysis specifically looked at the effects of intranasal insulin as compared to placebo on immediate and delayed recall. The meta-analysis included 5 studies, and included healthy participants, patients with obesity, and patients with MCI / AD. Their combined analysis found that there was a significant effect of intranasal insulin on delayed recall and overall cognition, but not on immediate memory (Gómez-Guijarro et al., 2024).

A 2023 systematic review examined the effects of intranasal insulin administration on cognitive performance and also on cerebral blood flow in RCTs. The available studies suggested that acute administration of intranasal insulin was associated with improvements in spatial memory and executive function in healthy adults. In healthy adults, whole-brain cerebral blood flow was largely unaffected by intranasal insulin administration. However, there were regional changes, particularly in areas with higher densities of insulin receptors. The pattern of regional changes was different in patients with obesity, suggesting that existing insulin resistance may affect response to intranasal insulin. Repeated administration of intranasal insulin was associated with improvements in declarative memory in patients with obesity (Nijssen et al., 2023).

Another systematic review looked specifically at acute effects of intranasal insulin on a variety of outcomes, including cognitive outcomes, in open-label, observational, and randomized controlled trials. Of the 16 includes trials that assessed cognitive outcomes, 50% of the trials reported a significant effect of intranasal insulin on at least one cognitive domain (Tabassum et al., 2024).

The following chart summarizes the most relevant completed clinical trials using intranasal insulin in healthy individuals. A narrative review follows. Insulin refers to regular insulin unless otherwise stated (e.g. rapid-acting insulin).

Key: Significant Benefit; Significant Detriment; Unchanged / Not Significant (Black)

Study	Drug	Population	N	Length	Cognitive outcomes	Other outcomes
Acute administration						
Benedict et al., 2007	Insulin, rapid-acting insulin (4 x 40 IU)	Healthy young adult men (18-35)	36	1 week	Immediate word recall, delayed word recall	
Benedict et al., 2008	Insulin (160 IU)	Healthy young men and women (avg age 22)	32	Acute	Immediate recall (women), IR (men), verbal working memory (women), VWM (men), hippocampal-independent task	Plasma glucose, insulin
Krug et al., 2010	Insulin (160 IU)	Post-menopausal women	14	Acute	Immediate recall, verbal working memory, hippocampal-independent task	
Novak et al., 2014	Insulin (40 IU)	Healthy adults and T2D	29	Acute	Visuospatial memory, verbal fluency	Regional brain perfusion
Long-term						
Benedict et al., 2004	Insulin (4 x 40 IU/day)	Healthy young adults (18-34)	38	8 weeks	Immediate word recall, delayed word recall, attention, mood	Plasma glucose, insulin, cortisol
Benedict et al., 2007	Insulin, rapid-acting insulin (4 x 40 IU/day)	Healthy young adult men (18-35)	36	8 weeks	Immediate word recall, delayed word recall (DWR)	Plasma glucose, insulin

Hallschmid et al., 2008	Insulin (4 x 40 IU/day)	Obese men	30	8 weeks	Immediate word recall, delayed word recall	Plasma cortisol, ACTH, weight
Ritze et al., 2018	Insulin (160 IU evening vs. morning)	Healthy young adult men (avg age 27)	36	8 weeks	Immediate word recall (morning), IR (evening), delayed word recall (morning), DWR (evening)	
Novak et al., 2022	Insulin (40 IU)	Healthy controls and T2D	244	24 weeks	Healthy: Executive functioning, verbal memory, gait T2D: Executive functioning, verbal memory, gait	T2D: Cerebral blood flow, plasma insulin, insulin resistance, $HbA1_c$, weight, waist circumference, BMI

Acute treatment with insulin (160 IU) improved immediate recall and verbal working memory in healthy young women but not men. There were no improvements in a hippocampal-independent task. There were reductions in blood glucose but no increase in insulin (Benedict et al., 2008). In post-menopausal women, insulin (160 IU) improved verbal working memory but not immediate recall or performance on a hippocampal-independent task (Krug et al., 2010). In healthy young adult men, rapid-acting and regular insulin over one week had no effect on memory (Benedict et al., 2007). In healthy adults and adults with type 2 diabetes (T2D), acute administration of intranasal insulin (40 IU) was associated with improved visuospatial memory, and improvements in cognitive performance were associated with increases in vasoreactivity (Novak et al., 2014).

Benedict et al., 2008 speculate that different effects of intranasal insulin in women and men may be due to the fact that intranasal insulin has anorexigenic effects in men through its effect on the hypothalamus, whereas intranasal insulin has memory enhancing effects in women. This could be due to the differential effects of sex hormones and their interactions with insulin signaling.

Other studies tested longer treatment with intranasal insulin. In an RCT of 38 healthy young adults ages 18 to 34, intranasal insulin (4 x 40 IU/day) had no acute effects. An 8-week treatment improved delayed (but not immediate) word recall and had no effect on attention. Certain aspects of mood (e.g. self-confidence and well-being) also improved. There were no effects on plasma glucose or insulin levels,

though plasma cortisol levels were reduced. This could be due to intranasal insulin's effect on the hypothalamus (Benedict et al., 2004). Using data from the regular insulin-treated group from the previous study, Benedict et al., 2007 looked at the effects of rapid-acting insulin aspart (Insulin NovoLog, 4 x 40 IU/day) over 8 weeks in 36 healthy young adult men ages 18 to 35. Both regular and rapid-acting groups had improved scores on delayed, but not immediate, word recall after 8 weeks, with the rapid-acting insulin group performing even better than the regular insulin group. Similar cognitive results were also found in obese men after 8 weeks of regular insulin (4 x 40 IU/day) treatment, with additional reductions in serum cortisol and adrenocorticotropic hormone (ACTH). No changes were found for attention (Hallschmid et al., 2008). An RCT of a total of 244 individuals (129 healthy controls and 115 patients with T2D) tested 40 IU of regular insulin once per day compared to placebo for 24 weeks. Healthy controls who received intranasal insulin had better executive functioning and verbal memory compared to participants who received placebo; T2D participants who received intranasal insulin had better gait than patients who received placebo. The T2D cohort was underenrolled due to the start of the COVID-19 pandemic; when the authors compared all participants who received intranasal insulin to all who received placebo and adjusted for $HbA1_c$, they found that intranasal insulin treatment was associated with better executive function and verbal memory during and after treatment, and had better gait on treatment, as compared to those who received placebo (Novak et al., 2022).

Comparing the effects of morning versus evening intranasal insulin (160 IU in a single dose) over 8 weeks in 36 healthy men, Ritze et al., 2018 found that evening insulin improved delayed (but not immediate) recall compared to placebo at 5 weeks (but not 8 weeks).

Intranasal insulin has also been explored for its effects on perioperative cognitive impairment. Sun et al., 2024 describes a study of patients 65 years and older who were scheduled for orthopedic or pancreatic surgery under general anesthesia. The study enrolled 140 patients, 128 of whom completed the trial. The participants were randomized to receive either 40 IU insulin or matching placebo via an Aptar device 5 minutes before anesthesia induction and then once per morning on the three days following the surgery. Patients who received insulin had improvements in cognitive function as measured by MMSE from baseline to post-surgery, whereas patients who received placebo had decreases in MMSE score; the change from baseline was significantly different between groups (p=0.001). Post-operative cognitive function as measured by MoCA was also improved in the insulin group compared to placebo (p=0.001). There were significantly fewer cases of postoperative delirium in patients who received insulin (10.9%) compared to patients who received placebo (26.6%) (p=0.024). There were also

decreases in levels of certain inflammatory markers such as IL-6 in the insulin group compared to placebo group.

Other RCTs have also found that insulin treatment is associated with decreases in postoperative cognitive dysfunction (POCD) in patients after surgery compared to placebo treatment. Mi et al., 2023 found that of the patients given 7 days of treatment with 40 IU of insulin, 20.8% experienced POCD compared to 45.1% of patients who received placebo (p=0.008). The study involved older adults with metabolic syndrome. Zhang et al., 2024 reported that 13.3% of patients who received 3 days of 20 IU insulin 2 times daily had POCD, compared to 38.7% of the placebo group (p=0.024); this study involved older patients without metabolic syndrome. Huang et al., 2024 found that patients who received intranasal insulin had significantly reduced incidence of postoperative delirium within 3 days of surgery compared to placebo (p=0.011). This study enrolled patients 18 to 65 years of age. Huang et al., 2021 also found a significant decrease in postoperative delirium within 5 days of surgery (p=0.001) in elderly patients undergoing surgery who received intranasal insulin compared to those who received placebo. These studies enrolled patients of a variety of ages who had different indications for surgery, and many used different doses or different duration, but the available data show a clear trend towards benefit of intranasal insulin for postoperative cognitive function.

Human research to suggest benefits to patients with dementia:

A 2023 systematic review and meta-analysis assessed the effects of intranasal insulin on cognition across a variety of patient populations. Their meta-analysis included 1,726 patients in total, all enrolled in placebo-controlled RCTs. Eleven of the studies focused on patients with MCI or AD. When the authors pooled the data together from these 11 studies, they found that there was a significant improvement in global cognition following treatment with intranasal insulin compared to placebo, though there are substantial heterogeneity (SMD 0.22; 95% CI 0.05 to 0.38; I^2 = 69%). There were no significant effects identified for any individual cognitive domain (Wu et al., 2023).

Another 2023 systematic review and meta-analysis included a total of 12 studies comprising 620 patients with AD. They were able to meta-analyze seven of these studies, all of which were at least 4 months long, and found that patients treated with 20 IU of intranasal insulin had improved cognitive function as measured by ADAS-Cog compared to patients who received placebo (MD= −0.13; 95% CI −0.22 to −0.05, p=0.003). They did not see a statistical benefit of higher doses of intranasal insulin (AboEl-Asm et al., 2023).

A 2022 systematic review and network meta-analysis assessed the effects of several hypoglycemic drugs on cognitive function MCI and AD; they included 5 studies of intranasal insulin. The authors reported that 20 IU intranasal insulin was associated with significantly better cognitive function as measured by MMSE and on daily functioning as compared to placebo. Intranasal insulin was generally not significantly better than other hypoglycemic treatments, which included GLP-1 receptor agonists, DPP-4 inhibitors, metformin, pioglitazone, and rosiglitazone. Interestingly, the study found that 40 IU of intranasal insulin was superior in effect to 20 IU intranasal insulin as measured by benefits in daily functioning (Wang et al., 2022).

Another systematic review and meta-analysis of patients with MCI or dementia did not come to the same conclusions as other meta-analyses; they reported that they found no effect of intranasal insulin administration on cognition, though there was a statistical significant benefit for intranasal insulin treatment compared to placebo on activities of daily living (Long et al., 2022). However, it should be noted that this meta-analysis included two studies in which the patients did not have MCI or dementia; in one study, the patients were diagnosed with a major depressive episode, and in another, patients had HIV dementia. In the latter study, the results had not been published in a peer-reviewed journal, but rather on clinicaltrials.gov. Neither of these two studies were included by Wu et al., 2023, which may explain the discrepant findings.

The following chart summarizes the completed clinical trials using intranasal insulin. A narrative review is below.

Key: Significant Benefit; Significant Detriment; Unchanged / Not Significant (Black)

Study	Drug	Population	N	Length	Cognitive outcomes	AD biomarkers outcomes	Other outcomes
(Long-acting insulin)							
Claxton et al., 2015	Insulin detemir (10 IU bid or 20 IU bid)	aMCI/mild-moderate AD	60	21 days	E4+ verbal memory; E4- verbal memory; verbal/visuospatial memory		E4+ HOMA-IR; E4- HOMA-IR

Craft et al., 2017	Insulin detemir (20 IU bid)	aMCI/mild-moderate AD	36	4 months	ADAS-cog; DSRS; Memory composite	2/12 MRI Brain region volume; CSF Aβ42, tau, ptau, ptau/Aβ42	
Regular insulin							
Craft et al., 2012	Insulin (10 IU bid)	aMCI/mild-moderate AD	104	4 months	Memory; ADAS-cog; DSRS; ADCS-ADL	CSF Aβ40, Aβ42, tau; FDG-PET	
	Insulin (20 IU bid)		104		Memory; ADAS-cog; DSRS; ADCS-ADL	CSF Aβ40, Aβ42, tau; FDG-PET	
Craft et al., 2017	Insulin (20 IU bid)	aMCI/mild-moderate AD	36	4 months	ADAS-cog; DSRS; Memory composite	4/12 MRI brain regions; CSF Aβ42, tau, ptau, ptau/Aβ42; change insulin signaling from EV	
Craft et al., 2020	Insulin (20 IU bid)	MCI / AD	289 (49 device 1, 240 device 2)	12 months + 6-month OLE	Device 2: ADAS-Cog, CDR-SB, ADL-MCI, Memory composite Device 1: ADAS-Cog, ADL-MCI, CDR-SB, Memory composite	Device 2: Aβ42, Aβ40, total tau, ptau181, Aβ42/ Aβ40, Aβ42/tau Device 1: Aβ42, Aβ40, total tau, ptau181, Aβ42/ Aβ40, Aβ42/tau	Device 2: Hippocampal volume, entorhinal cortex volume Device 1: Hippocampal volume, entorhinal cortex volume

Reger et al., 2008	Insulin (20 IU bid)	aMCI/AD	25	21 days	Memory; Attention; DSRS – all compared to baseline		
Acute insulin treatment							
Reger et al., 2006	Insulin (20, 40 IU)	aMCI/AD	92	Acute	Story/word recall (ApoE4- patients); word recall (ApoE4+ patients), story recall (ApoE4+ patients)		
Reger et al., 2008	Insulin (10, 20, 40, 60 IU)	aMCI/AD	26	Acute	Story/word recall (in ApoE4-, not ApoE4+ at 20 IU)		
Rosenbloom et al., 2014	Rapid-acting insulin glulisine (20 IU)	Mild-moderate AD	12	Acute	Memory, attention, language, visuospatial function		
Rosenbloom et al., 2021	Rapid-acting insulin glulisine (20 IU bid)	MCI/AD	35	6 months	ADAS-Cog, CDR-SB, FAQ		

Acute treatment of individuals with aMCI/Alzheimer's with intranasal insulin improved delayed (but not immediate) story recall and delayed and immediate word recall in ApoE4- (but not ApoE4+) patients at 20 IU (other doses – 10, 40, and 60 IU – were largely ineffective) (Reger et al., 2008). These results were similar to a previous study where 20 IU and 40 IU improved story and list recall (40 IU only for list recall) in ApoE4- patients. Interestingly, 40 IU was detrimental to list recall in ApoE4+ patients (Reger et al., 2006). Another study tested the acute effects of rapid-acting insulin glulisine (20 IU) in ApoE4+ mild-moderate Alzheimer's patients and found no effect after treatment (Rosenbloom et al., 2014).

Other studies looked at longer term dosing. Craft et al., 2012 treated 104 patients with aMCI/mild-moderate Alzheimer's disease with insulin (10 or 20 IU bid) over 4 months. Patients treated with 20 IU

insulin, but not 40 IU insulin, had improved memory scores. In both groups there were improvements on the DSRS and ADAS-cog. There was less functional decline (measured with ADCS-ADL) in patients with Alzheimer's disease but not MCI. Although there were no significant changes in CSF markers (Aβ42, Aβ40, tau) in treated patients, CSF Aβ42 and tau/Aβ42 levels correlated with improved memory and function. Also, there was a reduction in the progression of hypometabolism (measured with FDG-PET) in five brain regions compared to placebo. Additionally, although there were no changes in markers for insulin resistance in neuronally-derived extracellular vesicles, in the 20 IU group, changes in insulin signaling from isolated serum extracellular vesicles correllated with cognition as a group and in ApoE4- (but not ApoE4+) patients (Mustapic et al., 2019).

Based on this data, a larger, longer Phase 2/3 trial was initiated to test placebo compared to 20 IU intranasal insulin twice daily in 289 patients with MCI / AD. The trial had a 12-month RCT phase followed by a 6-month open label extension. However, this study was affected by an unexpected issue with the intranasal insulin device. The study initially used Kurve Technology's ViaNase device; this was the device used in Craft et al., 2012, and had been used in several studies of AD patients. The ViaNase device was altered for this Phase 2/3 trial to include an electronic timer, which unexpectedly malfunctioned in some devices and then required time and effort from trial staff and participants to replace the device. The malfunctions were occurring at an unacceptable frequency, and the decision was made to switch to a second device, NeuroPharma's Precision Olfactory Delivery device. This second device had shown good reliability in delivering specific doses of insulin to the olfactory cleft, which is thought to be an entry route for nose-to-brain delivery, though the device had not previously been used in patients with dementia. The study prespecified that the 240 patients who received device 2 would be the primary intent to treat population, and cognitive changes in these patients would be the primary outcome, whereas the 49 patients who received device 1 would be a secondary intent treat population.

The results were initially presented at the Clinical Trials in Alzheimer's Disease (CTAD) conference in 2018 (Alzforum). The overall findings were that there were no improvements in cognition or AD CSF biomarkers between groups, and treated patients had increased hippocampal shrinkage in the primary intent to treat group; that is, patients who received device 2. In secondary analyses of the group who received device 1, patients who received intranasal insulin throughout the study had better cognitive function at 12 months, and nominally significant better cognitive function at 6 months and during the 6-month open label study as compared to patients who initially received placebo. There were also improvements in measures of daily functioning and in AD biomarkers. As this was a small subgroup, though, the authors encouraged using caution to interpret these secondary analyses (Craft et al., 2020).

Further analyses of the device 1 cohort found that participants who received intranasal insulin via device 1 had better white matter health, as measured by reduced progression of white matter hyperintensity volume over the course of 12 months, as compared to placebo group patients (Keller et al., 2021). An exploratory analysis also found that patients who received intranasal insulin treatment via device 1 as compared to placebo had different profiles of markers of inflammation, immune function, and vascular health at 12 months (Keller et al., 2022). Larger trials with verified functional devices are needed to fully explore whether these effects of intranasal insulin reflect a biological truth.

According to Alzforum, a Phase 2 study was designed to assess how much insulin was delivered to the brain after intranasal delivery. This study confirmed that device 1 did increase levels of insulin in the CSF; the manufacturer of device 2 did not allow their device to be used in the study (Alzforum).

The same group ran another Phase 2 trial with a new device (Aptar CPS device) and presented their results at CTAD 2024. Before running a full trial, they first confirmed that the device delivered insulin to the brain in 16 adult participants who were either cognitively normal or had MCI. They confirmed an increase in insulin in the brain via PET scan. The four week Phase 2 study was a combination study of both intranasal insulin and an SGLT2 inhibitor called empagliflozin; the 47 enrolled participants had MCI or early AD and were not on diabetic medication. The participants were randomized to either placebo, intranasal insulin (40 IU four times a day), empagliflozin (10 mg once per day) or both insulin and empagliflozin. The primary outcome of the study was safety. Exploratory outcomes included measures of cognitive function and imaging and AD biomarkers. At the end of the trial, the authors found that cognitive function of the patients treated with intranasal insulin was significantly improved as compared to those who did not receive intranasal insulin. They also found that patients who received intranasal insulin had significantly better imaging measures of white matter health as compared to those who did not receive intranasal insulin. When they looked at immune and inflammation markers in the CSF of study participants, they found that intranasal insulin increased levels of BDNF and decreased certain inflammatory markers such as C1qa. Interestingly, they also saw significant changes in plasma markers of inflammation; treatment with intranasal insulin reduced levels of multiple inflammatory markers, including IFNs and chemokines. Such significant peripheral effects were not expected from intranasal administration; the authors theorized that this may be immune communication between the brain and periphery (Alzforum).

In an RCT of 60 patients with aMCI/mild-moderate Alzheimer's disease, 20 IU bid of intranasal insulin detemir (a long-acting insulin) over 21 days improved verbal and visual working memory. For verbal

memory, *A*poE4+ patients improved while ApoE4- were worse compared to placebo. These results reflected insulin resistance after the study with ApoE4+ patients becoming more insulin sensitive and ApoE4- patients becoming more insulin resistant as measured by HOMA-IR. No differences were seen with a lower dose (10 IU bid) (Claxton et al., 2015).

This study contrasts some of the studies of regular insulin in two ways: a higher dose was more beneficial, and ApoE4+ patients benefitted while ApoE4- patients were worse off. With regards to dosing, the authors speculate that as insulin detemir has greater cumulative exposure and has less affinity for the insulin receptor, the specific dose requirements might be different for this different form of insulin. With regards to ApoE4, insulin detemir has greater lipophilicity and albumin-binding, and ApoE4+ individuals with Alzheimer's disease have greater vulnerability to albumin nitration which may affect the binding of insulin detemir to albumin in the brain.

A clinical trial comparing regular insulin (20 IU bid), insulin detemir (20 IU bid), and placebo in 36 patients with aMCI/probable Alzheimer's disease over 4 months reported mixed results. Although there were no changes in global cognition (ADAS-cog) or daily functioning, individuals treated with regular insulin had improved memory scores compared to placebo. There were no changes in memory in patients treated with insulin detemir, though at 2 months, but not 4 months, ApoE4+ patients treated with insulin detemir had improved memory scores compared to ApoE4+ placebo patients. Regular insulin-treated patients had increased brain volume (by MRI) in 4 out of 12 brain regions compared to placebo while insulin detemir-treated patients had reduced volume in 2 out of 12 brain regions. CSF biomarkers (AB42, tau, ptau) did not change, though the ptau/AB42 ratio improved in patients treated with regular insulin (Craft et al., 2017). There were likely too few patients in this study to draw a conclusion. In a smaller study (n=25) using regular insulin (20 IU bid) in patients with aMCI/Alzheimer's disease, treated patients had improved memory, attention, and DSRS compared to baseline with no change in the placebo group (Reger et al., 2008).

Intranasal insulin has been explored for other neurodegenerative diseases. A proof of concept RCT tested 40 IU of intranasal insulin once daily or matching placebo for 4 weeks in 15 patients with Parkinson's disease (PD). The researchers found that at the end of the trial, patients who received intranasal insulin had improved verbal fluency and improved motor symptoms compared to the placebo, though these benefits were not quite statistically significant, perhaps due to the small size of the trial (Novak et al., 2019). A clinicical trial was designed to explore the effects of intranasal insulin (20 IU twice

daily) or placebo in patients with fronto-temporal dementia (FTD); unfortunately, the study was prematurely terminated due to COVID-19, with only 3 participants completing the trial (NCT04115384).

Overall, there are several studies that suggest there could be a benefit of intranasal insulin for patients with dementia, but longer, larger trials with validated devices are necessary to confirm these benefits; more work is also needed to identify best dose and type of insulin.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Insulin is a peptide hormone primarily produced by pancreatic β-cells; insulin is responsible for regulation of glucose levels in the periphery. Unlike other tissues, cells in the central nervous system are generally not as reliant on insulin for glucose utilization. However, insulin crosses the blood-brain barrier (BBB) via receptor-mediated transport under physiological conditions. Insulin can also reach parts of the brain that are not protected by the BBB. Insulin receptors are ubiquitous in the brain, though there is regional variability in expression levels (Kellar & Craft et al., 2020; Milstein & Ferris, 2021).

Insulin signaling in the brain is complex. Insulin binds to insulin receptors (IRs) and sets off a complex signaling cascade, including downstream activation of the PI3K / Akt / mTOR pathway. Insulin signaling can also lead to induction of a pathway targeting Ras, ERK, and MAPK. Thus, insulin signaling can affect a broad range of cellular functions, from cell growth, proliferation, and survival to neurotransmitter homeostasis, synaptic plasticity, and lipid synthesis. While glucose uptake is largely insulin-independent in the brain, insulin can nonetheless impact metabolism, such as through modulation of mitochondrial homeostasis. Insulin receptors are found on glia as well and impact their metabolism (Milstein & Ferris, 2021). Appropriate insulin signaling is important for brain health.

Diseases that involve dysregulation of insulin signaling such as type 2 diabetes are risk factors for AD, particularly when they are not appropriately controlled (Livingston et al., 2024). Multiple post-mortem studies suggest impaired insulin signaling in the brains of patients with Alzheimer's disease. In 54 patients, Steen et al., 2005 reported reduced levels of insulin growth factor (IGF)1-R, IGF2-R, IR, IGF-1, IGF-2, IRS-1, IRS-2, and insulin mRNA in multiple brain regions. In contrast, Moloney et al., 2010 reported an increase in IGF1-R *protein* expression in Alzheimer's patients, though IGF1-R protein was highly expressed in astrocytes and colocalized with amyloid plaques and tau tangles. Although Moloney et al., 2010 found similar expression of the IR protein in Alzheimer's and control brains, in control neurons IR was expressed throughout the cell soma while in Alzheimer's neurons it was largely localized

around the nucleus. They also reported an increase in molecular hallmarks of insulin resistance. Talbot et al., 2012 found an increase in markers of insulin resistance in hippocampal CA1 neurons in postmortem tissue from AD patients compared to healthy controls.

Impaired insulin signaling was also reported in post-mortem tissue from patients with Alzheimer's, T2DM, and Alzheimer's with T2DM, with the greatest effect in patients with both Alzheimer's and T2DM. There was an inverse correlation between expression of many proteins involved with insulin signaling and tau phosphorylation, suggesting reduced insulin signaling in areas with increased p-tau (Liu et al., 2011). In addition, *ex vivo* studies suggested that hippocampal and cerebellar tissue from Alzheimer's patients show reduced responsiveness to insulin and IGF-1 and an inverse correlation between episodic memory and markers of insulin resistance in hippocampal neurons (Talbot et al., 2012).

In a cross-sectional study of 62 patients with either aMCI/AD, T2DM, FTD, or controls, Kapogiannis et al., 2015 reported increased insulin resistance in neuronally-derived extracellular vesicles (EVs) in patients with Alzheimer's disease and T2DM, but not other conditions. Furthermore, in a retrospective analysis of blood samples collected up to 10 years before the diagnosis of Alzheimer's, insulin resistance increased in EVs, suggesting that insulin resistance in the brain occurs before the onset of clinical symptoms. Mullins et al., 2017 reported that in 24 patients with biomarker supported aMCI/Alzheimer's disease, brain volume in the right middle/superior temporal gyri positively correlated with markers of effective insulin signaling in neuronally-derived blood exosomes, suggesting that improved insulin sensitivity was correlated with increased brain volume.

Insulin is also thought to impact AD pathology. Insulin may modulate toxicity of both tau and Aβ, in addition to its effects in promoting neuronal health and functions such as neurotransmission. In patients with T2D and AD, those who receive T2D treatment have been shown to have reduced Aβ pathology compared to those with T2D and AD who are not treated for their T2D. There may also be altered transport of insulin into the central nervous system in several conditions, including in AD (Kellar & Craft et al., 2020). Taken together, it appears that there is insulin deregulation in AD. Restoring some level of insulin signaling may therefore be beneficial, and intranasal insulin offers a direct way to impact brain health without peripheral side effects, provided the dose of intranasal insulin is not too high (see Safety section for more discussion).

In animal studies, intranasal insulin has improved markers of insulin signaling, reduced levels of amyloid (but not tau), increased levels of synaptic proteins, and reduced inflammation (Bedse et al., 2015; Chen et al., 2014).

APOE4 interactions:

It is possible that APOE4 status interacts with the effects of intranasal insulin, but more work is needed in this area to fully explore this interaction.

A 2023 systematic review and meta-analysis noted that 4 of their 11 included studies of MCI/AD stratified their patients by APOE status. In three of the four studies, intranasal insulin was associated with memory improvements in APOE4 non-carriers, while APOE4 carriers either showed no benefit or decline in memory. The fourth study did not find an impact of APOE4 status on response to intranasal insulin. However, three of the four studies also tested only an acute dose of intranasal insulin rather than chronic dosing (Wu et al., 2023). The one study that did use chronic dosing also saw a sex effect with higher doses of intranasal insulin, with APOE4 non-carrier men showing improved cognitive performance and APOE4 negative women showing declined cognitive performance, while their APOE4 positive counterparts were stable (Claxton et al., 2013). There may be a relationship between the specific type of insulin used (e.g. regular insulin compared to long-acting insulin like insulin detemir) as well as dose with APOE4 (Reger et al., 2006; Reger et al., 2008; Claxton et al., 2015). Larger studies are needed to fully delineate the interactions of APOE status, sex, and intranasal insulin administration.

Aging and related health concerns: There are some beneficial changes in biomarkers associated with intranasal insulin, though whether this would change clinical outcomes is not known.

Types of evidence:

- 6 clinical studies on peripheral biomarkers
- 2 reviews

Most studies have examined the effect of intranasal insulin on the CNS. However, intranasal insulin may also act on the hypothalamus, causing peripheral effects. Insulin action in the brain may also change eating patterns, which could theoretically affect overall health (Milstein & Ferris, 2021). However, one 24-week clinical trial of 89 participants with type 2 diabetes randomized to either placebo or 40 IU of

intranasal insulin daily found that intranasal insulin treatment did not affect food intake, body weight, or body composition (Becerra et al., 2023); whether other studies would replicate these results with different doses or patient populations is not yet known.

No studies have looked at lifespan. However, multiple studies reported that sub-chronic (8-week) intranasal insulin reduced blood levels of cortisol (Hallschmid et al., 2008; Benedict et al., 2004 – 40 IU, four times daily). Acute intranasal insulin (160 IU) was reported to reduce circulating levels of free fatty acids (but not triglycerides) and improve peripheral insulin sensitivity in lean, but not obese, men (Iwen et al., 2014; Heni et al., 2014). A 4-week treatment with intranasal insulin (40 IU, 4 x day) had no effect on hepatic lipid content but reduced circulating levels of branched chain amino acids (Scherer et al., 2017).

Safety: Most studies find no increase in adverse events in patients who receive intranasal insulin compared to placebo at doses up to 160 IU; most side effects are related to intranasal delivery itself, including nasal irritation, rhinitis, and nose bleeds

Types of evidence:

- 4 systematic reviews
- 2 clinical trials

One advantage of intranasal insulin is that it largely does not enter the periphery and is therefore thought to generally not affect systemic markers. However, spillover is possible at higher doses and may be influenced by the specific patient population.

Wu et al., 2023 reported on the results of a systematic review and meta-analysis of placebo-controlled RCTs of intranasal insulin used for cognitive function in diverse patient populations, including patients with MCI, AD, psychiatric conditions, metabolic syndrome, and healthy, cognitively intact individuals. The study comprised a total of 1,726 individuals. The review of the 22 included studies that had adverse event reporting found that common side effects included nasal irritation and rhinitis, light-headedness / dizziness, nausea, and nosebleeds. There were no significant differences between placebo and treatment group in total number of adverse events, and no significant difference in frequency of reports of any one type of adverse event. Another systematic review and meta-analysis from AboEl-Azm et al.,

2023 similarly found that there was no difference in the risk of adverse events between groups (RR=1.28; 95% CI: 0.75 to 2.21, p=0.36).

A recent review looked at all the intranasal insulin clinical trials among all indications (18 studies, 832 people, duration generally between 2-12 months). Although some studies reported slight reductions in serum glucose levels, no cases of symptomatic hypoglycemia were reported. No adverse events were reported to be greater in the insulin group. The most common adverse events were due to the route of administration and included slight burning in the nasal cavity after administration and some cases of nasal cavity infections (Schmid et al., 2018). The largest, longest trial of intranasal insulin identified included 289 individuals and lasted for 12 months, with a 6-month open label extension. There were equal numbers of adverse events in the placebo and intranasal insulin group, and most adverse events were mild (Craft et al., 2020).

One systematic review assessed the amount of peripheral 'spillover' of intranasal insulin in different patient populations. The authors found that in healthy adults, peripheral insulin concentrations did not appear to change at doses of 40 IU or under but did increase with doses of 80 IU or 160 IU, with concomitant decreases in glucose concentrations. These changes were small compared to administration of subcutaneous insulin or after food intake. There were more mixed results in patients with obesity, type 2 diabetes, or MCI/AD, with many studies finding no changes or only changes at doses of 160 IU. Chronic administration did not affect fasting insulin or glucose levels in any group studied. There did not appear to be any effects on blood pressure or heart rate with acute administration; there was one study that found decreased heart rate in adults with overweight or obesity when they received doses of 160 IU daily for 8 weeks (Nijssen et al., 2023).

An open-label dose-escalation study of intranasal insulin in patients undergoing cardiac surgery found that while there were no cases of hypoglycemia at 40 IU, 80 IU, or 160 IU intranasal insulin or with saline, there were two cases of hypoglycemia out of three total patients given 240 IU insulin. While there were no cases of hypoglycemia at 160 IU, serum insulin was transiently increased in this group (Nakadate et al., 2023).

Taken together, these results suggest there can be peripheral effects in healthy adults at higher doses, but that they are typically small and transient. There can be peripheral effects in surgical patients, and those at very high doses can be undesirable.

One hypothesis on how insulin resistance can increase the risk of Alzheimer's disease is the fact that insulin degrading enzyme (IDE) degrades both insulin and amyloid. It is thought that chronically high levels of insulin may saturate IDE, thereby causing higher levels of amyloid. Therefore, hypothetically, chronic use of intranasal insulin in healthy individuals may increase the level of amyloid (Qiu & Folstein, 2006). At this point, however, this is speculation, and other groups cite the fact that insulin levels are much lower in the brain than the saturation constant for IDE, and thus, competitive inhibition is unlikely (Corraliza-Gomez et al., 2023).

Drug interactions:

Although little intranasal insulin enters the periphery, it may hypothetically interact with other glucose-lowering drugs. Major drug interactions for insulin include many antibiotics, though it is unclear if the same interactions occur with intranasal insulin (Drugs.com).

Research underway:

There are 20 ongoing studies of intranasal insulin registered on clinicaltrials.gov. Many of these studies involve using intranasal insulin for psychiatric conditions or exploring the physiology of the neurological reaction to intranasal insulin. Four of the registered trials are examining the effects of intranasal insulin on cognition or in MCI or dementia.

NCT06072963 is a 12-month combination trial study of intranasal insulin plus semaglutide, a GLP-1 receptor agonist. The study aims to enroll 80 patients with metabolic syndrome and MCI who are enriched for cerebrovascular disease and at high dementia risk. The patients will be randomized to one of four groups: intranasal insulin + semaglutide, intranasal insulin + placebo semaglutide, placebo intranasal insulin + semaglutide, or placebo intranasal insulin + placebo semaglutide. This study utilizes ViaNase; Kurve Technology for intranasal insulin administration, and patients will receive 20 IU twice per day, or matching placebo. The dosing for oral semaglutide will start at 3 mg once per day and titrate up to a maximum of 14 mg once per day, depending on tolerability, or matching placebo. The primary outcomes are the change in cognitive function, change in cerebral blood flow, and change in brain glucose uptake. Secondary measures include change in daily functioning, blood biomarkers of AD, gray matter and hippocampal volume, and physical capacity. This study is expected to be completed in December 2028.

NCT04251585 is a study of intranasal insulin in patients with Parkinson's disease (PD). This study enrolled 30 patients with PD and randomized them to either placebo or one of three dose groups of Novolin-R intranasal insulin: 20 IU, 40 IU, or 80 IU. All doses were given twice daily for 21 days. The primary outcome is safety. The secondary outcomes include a variety of measures of cognitive function, mood, and motor function. This study is predicted to be completed at the end of 2024.

NCT06391853 aims to assess the effects of intranasal insulin on neurometabolic and neurovascular coupling, as well as on cortical activity, in individuals who are cognitively intact, have MCI, or have AD. The study plans to enroll 120 participants. The study has a crossover design; patients will receive either intranasal insulin (160 IU) or matching placebo. 30 minutes after study drug administration, they will receive a PET scan; fMRI and EEG recordings will also be collected during the scan. They will also undergo neuropsychological testing after the scans and again a week later. At the next study visit the participant will undergo the same protocol but will receive the opposite study drug. The primary outcomes are effects of intranasal insulin administration on fMRI, FDG PET, and EEG. Secondary outcome measures include the impacts of sex and APOE status on response to intranasal insulin administration, as well as impacts of study drug administration on cognitive performance. This study is expected to be completed in October 2026.

NCT03857321 plans to enroll 30 individuals who are cognitively normal or who have MCI. The study has a crossover design; patients will be randomized to receive either placebo or insulin (20 IU) and then receive the other study drug at the next visit. The primary outcome is levels of CSF insulin 30 minutes after administration. Secondary outcomes include a measure of immediate and delayed memory recall and levels of AD biomarkers 30 minutes after study drug administration. This study is expected to be completed in August 2025.

There is also one trial (NCT03943537) that is exploring the acute effects of intranasal insulin on cognitive function and metabolism on patients with certain psychiatric disorders compared to healthy control participants.

Search terms:

Pubmed, Google: intranasal insulin

- Alzheimer's, memory, cognition, longevity, aging, Parkinson's, aging, postoperative cognitive delirium

Websites visited for intranasal insulin:

- Clinicaltrials.gov
- Examine.com
- Drugs.com (Insulin)
- WebMD.com
- PubChem
- DrugBank.ca