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.

Metformin

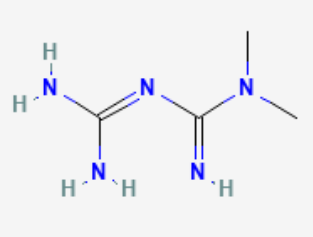
Evidence Summary

Metformin use is associated with decreased risk of dementia, mortality, cardiovascular disease, and cancer in diabetics. Long-term treatment may reduce vitamin B12 levels, so levels should be monitored.

Neuroprotective Benefit: Metformin use is associated with decreased dementia risk in people with type 2 diabetes, but results depend on dose, duration, APOE genotype, and other factors. In pilot trials in MCI, metformin improved a few cognitive functions.

Aging and related health concerns: Metformin treatment in people with type 2 diabetes is associated with decreased risk of mortality, cardiovascular disease, and various cancers, while decreasing bodyweight and improving lipid profiles.

Safety: Metformin is generally well-tolerated, with minor gastrointestinal side effects. People with renal failure should not use metformin as it increases the risk of lactic acidosis, a serious adverse event. Long-term use may reduce vitamin B12 levels.

Availability: Rx	**Dose**: For type 2 diabetes, metformin is often started at 500 mg once daily, orally, with dinner, and the dose is increased until the blood sugar is controlled, up to 2,000 mg per day.	**Chemical formula:** $C_4H_{11}N_5$ **MW**: 129.16  Source: PubChem
Common brand: Glucophage and Glucophage XR (Extended release) in the US		
Half-life: elimination half-life in plasma is ~6 hours	**BBB**: penetrant	
Clinical trials: Meta-analyses of randomized controlled trials have included tens of thousands of subjects total.	**Observational studies**: Numerous meta-analyses of observational studies have included millions of subjects.	

What is it? Metformin is a biguanide anti-hyperglycemic and first-line pharmacotherapy used together with diet and exercise for the management of type 2 diabetes mellitus. Metformin reduces gluconeogenesis in the liver, improves glucose uptake in peripheral tissues, and lowers blood glucose concentrations without causing hypoglycemia and increases the body's response to insulin (drugbank.com; medlineplus.gov). Metformin is also used off-label to treat polycystic ovary syndrome (PCOS)(drugs.com).

Metformin has many mechanisms, some of which include inhibition of hepatic gluconeogenesis (glucose production in the liver), slowing of mitochondrial respiration by inhibiting complex 1 of the electron transport chain, activation of the cellular energy sensor AMP-activated protein kinase (AMPK), and systemically increasing insulin sensitivity (reviewed in Liao et al., 2022). Metformin is often compared with rapamycin as both act on the same/similar pathways. Rapamycin is a direct inhibitor of mTOR (mammalian target of rapamycin) signaling (via inhibition of mTORC1), resulting in regulation of gene transcription, protein synthesis, mitochondrial biogenesis, and autophagy. Metformin also inhibits mTOR signaling, but through indirect pathways, via inhibition of complex I and activation of AMPK signaling (reviewed in Rotermund et al., 2018). Through complex I inhibition, metformin also reduces reactive oxygen species and regulates redox status.

Type 2 diabetes and Alzheimer's disease share certain characteristics, including impaired insulin signaling and oxidative stress. Because of this, metformin and other antidiabetic medications have been

extensively examined in preclinical and clinical studies in Alzheimer's disease and other neurodegenerative diseases.

Neuroprotective Benefit: Metformin use is associated with decreased dementia risk in people with type 2 diabetes, but results depend on dose, duration, APOE genotype, and other factors. In pilot trials in MCI, metformin improved a few cognitive functions.

Types of evidence:

- 2 systematic reviews of randomized controlled trials (RCTs) examining cognitive outcomes in patients with Alzheimer's or mild cognitive impairment
- 5 meta-analyses of observational studies examining associations between metformin use and risk of dementia or cognitive impairment
- 2 small randomized controlled trials in patients with mild cognitive impairment or mild dementia
- 1 randomized controlled trial in depressed patients with type 2 diabetes
- 1 clinical trial in patients with abnormal glucose metabolism and vascular cognitive impairment
- 4 observational studies examining cognitive or dementia outcomes
- Numerous reviews
- Numerous laboratory studies

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

Clinical trials and observational studies have shown mixed results with regards to metformin treatment and risk for (or incidence of) dementia and cognitive decline.

In a 2022 meta-analysis of 12 observational studies including a total of 194,792 subjects with type 2 diabetes, the pooled relative risk (RR) of neurodegenerative diseases was 0.77 (95% CI, 0.67 to 0.88) when comparing metformin users with non-users (Zhang et al., 2022). The effects were more prominent in long-term metformin users (over 4 years) (RR=0.29; 95% CI, 0.13 to 0.44) and studies from Asian countries (RR=0.69; 95% CI, 0.64 to 0.74). Though there was heterogeneity among studies and further research in randomized controlled trials are needed.

In a different 2022 meta-analysis of 19 studies (3 RCTs and 16 observational studies) enrolling people with or without diabetes who were taking metformin, there was no significant relationship between

metformin use (1500-2000 mg/day for 16-48 weeks in RCTs) and cognitive performance or protection against Alzheimer's disease, vascular dementia, all dementias, or cognitive impairment (Malazy et al., 2022). The odds ratio (OR) for dementia risk in cross-sectional studies was equal to 0.964 (95% CI, 0.7 to 1.23). The OR for 13 cohort studies was significant (OR=0.87; 95% CI, 0.82 to 0.93). In the subgroup analysis of cohort studies, a non-significant HR of 0.89 (95% CI, 0.77 to 1.01) was found for Alzheimer's disease. HRs for any dementia (0.90), vascular dementia (0.91), and cognitive impairment (1.51) were also non-significant in subgroup analysis of cohort studies.

In a 2020 meta-analysis of 10 observational studies including 254,679 subjects with type 2 diabetes, metformin treatment significantly reduced the occurrence of cognitive dysfunction (HR=0.90; 95% CI, 0.88 to 0.92) (Zhang et al., 2020). Compared with other antidiabetic medications, sulfonylureas also improved cognitive dysfunction (HR=0.92; 95% CI, 0.88 to 0.95), but metformin improved cognitive dysfunction slightly better, numerically, than sulfonylureas. In a subgroup analysis controlling for age, sex, education, diabetes course, complications, metformin dosage, and follow-up time, metformin significantly improved cognitive dysfunction in patients in the Americas (HR=0.69; 95% CI, 0.63 to 0.74) and Europe (HR=0.71; 95% CI, 0.66 to 0.76), while metformin did not significantly improve cognitive dysfunction in Asian patients (HR=0.99; 95% CI, 0.96 to 1.01).

In a 2018 meta-analysis including 14 studies (7 cohort, 4 cross-sectional, 2 randomized controlled trials, and 1 case-control), dementia risk and cognitive impairment were compared between metformin users versus controls (not receiving metformin)(Campbell et al., 2018). Meta-analysis of 3 studies showed that cognitive impairment was less prevalent in diabetics taking metformin (OR=0.55; 95% CI, 0.38 to 0.78), and meta-analysis of 6 studies showed that dementia incidence was also significantly reduced (HR=0.76; 95% CI, 0.39 to 0.88; p=0.03). Cognitive function (measured by MMSE) was not significantly different between metformin and control groups, although both randomized controlled trials showed that metformin had a protective effect compared to placebo.

In a randomized controlled trial (RCT) of 58 patients with depression and type 2 diabetes, metformin treatment (up to 1.5-2.0 g/day) for 24 weeks significantly improved cognitive performance on all items of the Wechsler Memory Scale-revised (verbal memory, visual memory, general memory, attention/concentration, and delayed-memory indices), while lowering depression (Guo et al, 2014). The positive effects of metformin on cognitive function were correlated with HbA1c levels and improved depression.

In an observational study of 1,192 people with normal cognition and 807 people with Alzheimer's disease from the National Alzheimer's Coordinating Center database, metformin use was associated with better memory performance (better immediate memory and delayed memory, p=0.0202 and 0.0024, respectively) in people with normal cognition compared to non-metformin users (Wu et al., 2020). Among cognitively normal APOE4 non-carriers, metformin use was associated with better immediate and delayed memory over time, but these associations were not observed among APOE4 carriers. (The use of sulfonylurea, thiazolidinedione, or DPP4 inhibitor, showed no significant associations over time in cognitively normal individuals).

In a case control study of community-dwelling Finnish people with diabetes (7,225 Alzheimer's patients and 14,528 controls), metformin use (ever use) was not associated with incident Alzheimer's (adjusted OR=0.99; 95% CI, 0.94 to 1.05)(Sluggett et al., 2020). However, the adjusted odds of Alzheimer's were lower for people who used metformin for ≥ 10 years (aOR=0.85; 95% CI, 0.76 to 0.95), those dispensed cumulative defined daily doses (DDDs) of 1825-3650 (aOR=0.91; 95% CI, 0.84 to 0.98) and over 3650 DDDs (aOR=0.77; 95% CI, 0.67 to 0.88), and among participants dispensed an average of 2 grams of metformin daily (aOR=0.89; 95% CI, 0.82 to 0.96). People with Alzheimer's disease received a lower cumulative metformin dose over the study period (median of 875 versus 925). Data were adjusted for macrovascular complications (stroke, coronary artery disease, and peripheral arterial disease) and renal failure, but data on renal function (eGFR), glycemic control, lifestyle factors, BMI, and nonpharmacological approaches to diabetes management were not available, and therefore not adjusted for. Long-term and high-dose metformin use was associated with a lower risk of incident Alzheimer's in older Finnish people with diabetes.

In a retrospective longitudinal cohort study of 5,528 elderly US veterans with type 2 diabetes and insulin treatment followed for a median of 5.2 years, the incidence rate of neurodegenerative diseases was 11.48 per 1000-person-years among patients receiving metformin treatment, compared to 25.45 per 1000-person years for those not taking metformin (Shi et al., 2019). This study also showed that long-term metformin therapy was associated with lower incidence of neurodegenerative diseases, including Alzheimer's disease. Compared to people not taking metformin, 2-4 years and 4+ years of metformin use were significantly associated with lower risk of neurodegenerative diseases [adjusted HR (aHR)=0.62; 95% CI, 0.45 to 0.85; aHR=0.19; 95% CI, 0.12 to 0.31, respectively], while metformin exposure in the first 2 years showed no significant difference (though numerically higher risk of neurodegenerative diseases in people taking metformin for less than 1 year; aHR=1.16, 95% CI, 0.89 to 1.51). The incidence rate of dementia was 8.46 cases and 19.82 cases per 1000 person-years in metformin users vs non-users, respectively. Compared with the non-metformin treatment group, the

aHR was 0.55 (95% CI, 0.38 to 0.79) in the cohort receiving 2-4 years of metformin treatment. In the cohort with ≥4 years of metformin exposure, the aHR decreased to 0.22 (95% CI. 0.13 to 0.37). The incidence rates of Parkinson's disease and Alzheimer's disease were lower in the metformin treatment group (2.43 and 1.92, respectively) than in the non-metformin treatment group (5.9 and 3.92). For Alzheimer's disease, ≤1 year of metformin treatment was associated with a significantly higher risk (aHR=2.19; 95% CI, 1.21 to 3.94), while the cohort with ≥4 years of metformin treatment had a significantly lower risk (aHR=0.17; 95% CI, 0.04 to 0.70; non-metformin treatment as the reference group). Due to the limited number of mild cognitive impairment cases, no statistical significance was found between metformin-treated versus untreated cohorts.

Microvascular complications (diagnosis of neuropathy, nephropathy, or retinopathy), macrovascular complications (atherosclerosis, peripheral vascular disease, stroke, coronary artery disease, congestive heart failure), renal disease, tobacco use, and obesity at baseline were controlled for in the analysis. Interestingly, patients who took metformin were more likely to have worse glycemic control, less microvascular complications, and more macrovascular complications compared to those who never used metformin. Serum vitamin B12 levels, which can influence neurodegenerative disease risk, were not available in the Veterans Affairs electronic medical record database. More than 90% of the subjects in this study were men, and therefore, the results may not generalize to both sexes.

Human research to suggest benefits to patients with dementia or cognitive aging:

In a systematic review of 23 randomized controlled trials (RCTs) testing different antidiabetic drugs in patients with Alzheimer's, mild cognitive impairment, or subjective cognitive complaints, only 2 RCTs tested metformin and the authors noted that further research is needed (Munoz-Jiminez et al., 2020).

One of the trials was a pilot randomized controlled trial (funded by ADDF) tested the safety and efficacy of metformin on cognitive function, brain imaging outcomes, and plasma Aβ42 levels in 80 elderly overweight patients with amnestic mild cognitive impairment (MCI) and without diabetes (Luchsinger et al, 2016). Metformin (up to 1000 mg, twice/day, orally) over 12 months improved scores on one of the primary outcomes--a memory test (selective reminding test; p=0.05) but did not improve the other primary outcome--ADAS-Cog scores—compared to placebo. Metformin treatment resulted in a non-significant increase in plasma Aβ42 levels. In the 40 participants who completed PET scans, there was a non-significant trend toward improved glucose uptake in all brain regions examined with metformin treatment. Secondary outcomes included the Clinical Global Impression of Change (for mild cognitive impairment), logical memory II delayed paragraph recall subtest of the Wechsler Memory Scale-Revised,

MMSE, Neuropsychiatric Inventory Questionnaire, and digit span backwards; however, no significant effects were observed.

The other RCT was a crossover RCT which investigated metformin's effect on cerebral spinal fluid (CSF) and neuroimaging biomarkers and cognition in 20 non-diabetic individuals with MCI or mild dementia due to Alzheimer's (Koenig et al, 2017). Metformin crossed the blood brain barrier and was present in the CSF (at 95.6ng/mL). Treatment with metformin (2000 mg/day) for 8 weeks caused no changes in CSF Aβ42, tau, or phosphorylated tau levels. Some improvements were seen in executive functioning, but not in other measures of cognition. Post-hoc analysis of patient who underwent analysis for cerebral blood flow before and after both the placebo and metformin treatments had increased blood flow in the orbitofrontal cortex, a region of the cortex involved in information processing that shows metabolic decline in individuals with Alzheimer's, but not in other brain regions.

In the Singapore Longitudinal Aging Study, metformin use in diabetics was inversely associated with cognitive impairment (OR 0.49; 95%CI 0.25-0.95), with >6 years of metformin treatment being associated with lowest risk of cognitive impairment (OR 0.27; 95%CI 0.12-0.60), after controlling for diabetes duration and fasting blood glucose (Ng et al, 2014). Another observational study of 67,000 participants who were non-demented and non-diabetic at baseline reported that of patients developing diabetes and taking only one medication during follow-up, those taking metformin were four-fold less likely to develop dementia than those taking thiazolidinediones (Cheng et al, 2014). A study using the Taiwan National Health Insurance database including a total of 127,209 people with type 2 diabetes reported decreased risk of dementia in subjects taking metformin compared to unmedicated type 2 diabetics (HR 0.76; 95%CI 0.58-0.98)(Hsu et al, 2011).

In an observational study of 1,192 people with normal cognition and 807 people with Alzheimer's disease from the National Alzheimer's Coordinating Center database, use of DPP4 inhibitors (e.g., sitagliptin, saxagliptin, etc.) was associated with a slower decline in delayed memory (RR=1.22; p=0.0055) in people with Alzheimer's disease, while metformin and sulfonylurea use were not associated with memory changes over time (Wu et al., 2020). However, in Alzheimer's patients who were APOE4 carriers, metformin use was associated with a greater decline in delayed memory. In people with amnestic mild cognitive impairment, none of the 4 antidiabetic drug classes were associated with differential memory changes.

Other population-based diabetic cohorts from Asia, Australia, and the UK have shown that long-term metformin increased the risk of AD, vascular dementia, and decreased cognitive performance (Imfeld et

al, 2012; Moore et al, 2013; Kuan et al, 2017). Importantly, though, Imfeld et al (2012) and Kuan et al (2017) did not analyze whether patients taking metformin were taking other anti-diabetics, whether their diabetes was under control, and did not adjust for vitamin B12 levels. Although Moore et al, (2013) reported decreased cognitive performance with metformin users, after adjusting for vitamin B12 levels, the association was no longer significant. In addition, patients taking metformin as well as calcium supplements (which can alleviate metformin-induced vitamin B12 malabsorption) had a reduced risk of impaired cognitive performance (OR=0.41; 95% CI, 0.19 to 0.92).

One meta-analysis on the impact of insulin sensitizers on the incidence of dementia from many of the previous studies revealed a trend for the reduction of dementia with metformin use in diabetics (RR=0.79, 95% CI 0.62-1.01) (Ye et al, 2016).

The Diabetes Prevention Program Outcomes Study (an RCT with placebo, metformin, and lifestyle intervention) showed that in 2,280 subjects, cumulative metformin exposure and diabetes status was not related to cognition (Luchsinger et al, 2017).

The fact that long-term metformin may reduce vitamin B12 levels and that most of the previous observational studies did not control for this makes it hard to come to any conclusions. Metformin is likely beneficial in diabetics, but vitamin B12 levels should be monitored closely.

A 2018 network meta-analysis included 19 RCTs testing 6 different antidiabetic drugs and enrolled a total of 4,855 people with Alzheimer's or mild cognitive impairment to determine if any of the antidiabetic drugs had an effect on cognitive function (Cao et al., 2018). There was overall improvement in cognitive performance in people receiving an antidiabetic agent compared with placebo ($p<0.001$). Only pioglitazone (15-30 mg) was more effective than placebo in improving cognitive performance, and it was also more effective than metformin (1000 mg), intranasal insulin (20 IU), and rosiglitazone (2, 4, and 8 mg). This study did not control for moderating factors including age, sex, and APOE genotype.

Vascular cognitive impairment is a syndrome in which there is evidence of clinical stroke or subclinical vascular damage, resulting in impairment of one or more domains of cognitive function. Insulin resistance, glucose metabolism defects, and atherosclerosis have been implicated in vascular cognitive impairment. In a clinical trial of 94 patients with abnormal glucose metabolism and non-dementia vascular cognitive impairment, adding metformin to donepezil for a year significantly improved several measures of cognitive function (ADAS-Cog, duration of Trail Making Test, and WHO-UCLA-Auditory Verbal Learning Test score; $p<0.05$ for all) compared to the comparator group where acarbose was

added to donepezil (Lin et al., 2018). For fasting insulin levels, insulin resistance index, and common carotid arteries intima-media thickness (CCA-IMT; measure of atherosclerosis), the metformin add-on group had significantly lower values compared to the acarbose add-on group ($p<0.05$). CCA-IMT was not changed from baseline with metformin add-on, but in the acarbose add-on group, CCA-IMT significantly increased. No significant differences with treatment or between treatments were observed in fasting blood glucose or HbA1c levels ($p>0.05$). The authors suggest that the improved cognitive function with metformin add-on may be related to the improvement in insulin resistance and decreased progression of the intima-media thickness, leading to less atherosclerosis and increased blood supply to brain tissue.

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

Preclinical studies have shown that metformin reduces insulin levels, inflammation, thrombosis, and metabolic syndrome, while improving insulin sensitivity (Zhang et al., 2020). With regards to neuroprotection, metformin exerts its effects through many mechanisms, but the one that has been studied the most is the AMPK signaling pathway. AMPK is an evolutionarily conserved cellular energy sensor. AMPK activation has wide-ranging effects, including inhibition of mTOR, inhibition of energy consumption, and stimulation of catabolic pathways (reviewed in Rotermund et al., 2018).

With regards to Alzheimer's disease, mechanistic studies have shown that metformin decreases neuronal loss/dysfunction (via decreased caspase-3/9 and inhibition of mitochondrial membrane permeability transition pore opening), Aβ depositions (through regulation of AMPK/mTOR/S6K/BACE1 signaling), tau phosphorylation (via activation of mTOR/PP2A pathway), chronic neuroinflammation (via AMPK activation-induced suppression of NF-kB pathway; decreased TNF-α, IL-1β, and IL-6; decreased microglial activation), insulin resistance, and impaired glucose metabolism, while promoting neurogenesis (increased AMPK/CREB-mediated neuroprotective gene expression, e.g., BDNF and synaptic markers), antioxidative properties (via increased Nrf-1, GSH, SOD, and MDA), autophagy (via increased Beclin-1 expression and LC3 conversion), mitochondrial biogenesis (by enhancing PGC-1α activity and Nrf-1) and cognitive functions (via inhibition of AChE activity)(reviewed in Liao et al., 2022, Madhu et al., 2022, Sanati et al., 2022, and Rotermund et al., 2018). However, some other studies have shown that metformin can increase tau phosphorylation (by increasing phosphorylation of GSK-3β) and Aβ generation (by increasing BACE1), impair autophagy (by causing abnormal autophagosome accumulation), and disrupt mitochondrial function (by impairing mitochondrial permeability transition pores and membrane channels).

APOE4 interactions: In an observational study of 1,192 people with normal cognition and 807 people with Alzheimer's disease from the National Alzheimer's Coordinating Center database, APOE4 genotype modified the relationships between metformin and cognitive outcomes (Wu et al., 2020). Among cognitively normal APOE4 non-carriers, metformin use was associated with better immediate and delayed memory over time, but these associations were not observed among APOE4 carriers. For APOE4 carriers with Alzheimer's disease, metformin use was associated with a *faster* rate of delayed memory decline.

Aging and related health concerns: Metformin treatment in people with type 2 diabetes is associated with decreased risk of mortality, cardiovascular disease, and various cancers, while decreasing bodyweight and improving lipid profiles.

Types of evidence:

- 3 meta-analyses of randomized controlled trials in people with type 2 diabetes
- 3 meta-analyses of randomized controlled trials examining cardiovascular risk
- 1 meta-analysis of randomized controlled trials examining the relationship between metformin use and inflammation biomarkers
- 1 meta-analysis of randomized controlled trials examining the effects of metformin on diabetes biomarkers
- 3 meta-analyses examining the association between metformin and all-cause or specific-cause mortality
- 1 meta-analysis examining the association between metformin use and mortality after surgery
- 3 meta-analyses examining cardiovascular risk, cholesterol, and other biomarkers
- 5 meta-analyses examining the association between metformin and cancer risk
- 1 meta-analysis of observational studies examining the association between metformin and risk for age-related macular degeneration
- 1 meta-analysis of observational studies examining the association between metformin and risk for vitamin B12 deficiency and prevalence of neuropathy
- 1 meta-analysis of observational studies examining the association between metformin and risk of fracture
- 1 clinical study of effects on microbiome
- 3 reviews of peripheral neuropathy risk
- Numerous laboratory studies

Lifespan: DECREASED ALL-CAUSE MORTALITY

In a 2021 meta-analysis of 13 randomized controlled trials (RCTs) including a total of 10,161 adult patients with type 2 diabetes, metformin treatment for 1 year or longer was associated with a non-significantly lower all-cause mortality compared to controls (placebo, no therapy, or active comparators)(Mantel-Haenszel OR; MH-OR=0.80; 95% CI, 0.60 to 1.07; p=0.14)(Monami et al., 2021). This association became statistically significant after excluding RCTs comparing metformin with sulfonylureas, SGLT-2 inhibitors, or GLP-1 analogues (MH-OR=0.71; 95% CI, 0.51 to 0.99). Metformin use was also associated with a lower risk of major adverse cardiovascular events (MACEs) compared with other anti-diabetic treatments, based on 2 RCTs (MH-OR= 0.52; 95% CI, 0.37 to 0.73; p<0.001).

In a 2019 meta-analysis of 40 studies comprising over 1 million patients with coronary artery disease (some RCTs, some observational studies), metformin treatment was associated with a significantly lower all-cause mortality (adjusted HR=0.67; 95% CI, 0.60 to 0.75; p<0.00001) compared to non-metformin therapy (Han et al., 2019).

In a subgroup analysis, metformin treatment was associated with a significantly lower all-cause mortality in patients who had myocardial infarction at baseline (aHR=0.79; 95% CI, 0.68 to 0.92; p=0.003) and in patients who had heart failure at baseline (aHR=0.84; 95% CI, 0.81 to 0.87; p<0.00001).

A 2017 meta-analysis reported that diabetics taking metformin had a lower all-cause mortality than non-diabetics (HR=0.93; 95% CI, 0.88 to 0.99), diabetics receiving non-metformin therapies (HR=0.72; 95% CI, 0.65 to 0.80), diabetics receiving insulin (HR=0.68; 95% CI, 0.63 to 0.75), and diabetics receiving a sulphonylurea (HR=0.80; 95% CI, 0.66 to 0.97)(Campbell et al, 2017). There are caveats to these analyses, because metformin is usually a first-line treatment for type 2 diabetes and patients taking other medicines may have more severe diabetes that cannot be controlled with metformin.

In a 2020 meta-analysis of 3 studies including people who underwent surgery, mortality rate within 30 days after surgery was similar between metformin-treated and non-treated individuals (risk ratio=0.86; 95% CI, 0.66 to 1.12; p=0.26)(Jones et al., 2022). For 2 of the studies reporting a 90-day outcome, metformin use was associated with a non-significantly reduced mortality (risk ratio=0.54; 95% CI, 0.46 to 0.64; p=0.19). In a sensitivity analysis using propensity-matched data, metformin use was associated with a significant reduction in mortality (risk ratio=0.79; 95% CI, 0.65 to 0.97; p=0.023). International guidelines and recommendations are mixed for metformin continuation/discontinuation before surgery. For minor ambulatory surgery, continuation of metformin was recommended unless there was renal

dysfunction, but for major procedures, metformin discontinuation before surgery has been recommended (Jones et al., 2022). The authors suggest that metformin's pleiotropic anti-inflammatory effects may confer protection in the perioperative period.

Several studies in model organisms show improvements in both lifespan and healthspan indices with physiologically relevant doses of metformin. Metformin increased lifespan of female, but not male SHR mice and C57BL/6 mice by 4-6% (Anisimov et al, 2008; Martin-Montalvo et al, 2013). On the other hand, a lifespan study from the NIA Interventions Testing Program that included data from multiple sites reported no increase in lifespan in metformin-treated mice, though there was a non-significant 7% increase in male mice (Strong et al, 2016). Transcriptomic data suggests that metformin mimicked caloric restriction interventions. Similar effects of metformin are observed in *C. elegans*, mediated through mitohormetic response or by altering microbial folate and methionine metabolism (Cabreiro et al, 2013; De Haes et al, 2014).

Cardiovascular disease: DECREASED CV MORTALITY AND INCIDENCE IN T2DM

In a 2021 meta-analysis of 2 RCTs including a total of 1,097 adult patients with type 2 diabetes, metformin treatment for 1 year or longer was associated with a lower risk of major adverse cardiovascular events (MACEs) compared with other anti-diabetic treatments, based on 2 RCTs (Mantel-Haenszel OR; MH-OR= 0.52; 95% CI, 0.37 to 0.73; p<0.001)(Monami et al., 2021).

In a 2020 meta-analysis of 16 observational studies including a total of 1 million patients with type 2 diabetes (and 701,843 patients taking metformin), metformin treatment (duration varied from 0.9-13 years) was associated with a significantly decreased risk of cardiovascular disease (OR=0.57; 95% CI, 0.48 to 0.68), including cardiovascular mortality (OR=0.44; 95% CI, 0.34 to 0.57) and incidence (OR=0.73; 95% CI, 0.59 to 0.90)(Zhang et al., 2020). In a subgroup analysis, metformin treatment showed significantly lower cardiovascular risk compared to treatment with sulfonylureas (OR=0.50; 95% CI, 0.38 to 0.64), including cardiovascular mortality (OR=0.34; 95% CI, 0.17 to 0.67) and incidence (OR=0.70; 95% CI, 0.55 to 0.89).

In a 2019 meta-analysis of 40 studies comprising over 1 million patients with coronary artery disease (some RCTs, some observational studies), metformin treatment was associated with a significantly lower cardiovascular mortality, all-cause mortality, and incidence of cardiovascular events, with adjusted hazard ratios (HR) of 0.81 (95% CI, 0.79 to 0.84; p<0.00001), 0.67 (95% CI, 0.60 to 0.75; p<0.00001), and 0.83 (95% CI, 0.78 to 0.89; p<0.00001), respectively (Han et al., 2019). Metformin treatment showed

significantly lower adjusted HR compared to sulphonylurea treatment (aHR=0.81; 95% CI, 0.77 to 0.85; p<0.00001) and non-medication (aHR=0.78; 95% CI, 0.66 to 0.92; p=0.002).

In the same meta-analysis, in people with myocardial infarction or coronary artery disease who did not have type 2 diabetes, metformin treatment did not have a significant effect on the incidence of cardiovascular events (Han et al., 2019). Metformin treatment was associated with lower creatine kinase MB levels, a cardiac marker used to diagnose acute myocardial infarction (standard mean difference=-0.11), but no effect on cardiac function (measured by left ventricular ejection fraction; mean difference=-2.91; 95% CI, -6.51 to -12.34), type B natriuretic peptide, a marker of cardiac/ventricular function (mean difference=-0.02), and LDL cholesterol (mean difference=-0.08).

The authors suggest that the cardiovascular protection conferred by metformin may be due to several mechanisms, including reduction of oxidative stress, inflammatory cytokines, and increased activity of endothelial nitric oxide synthase, promoting vascular endothelial function and angiogenesis (Han et al., 2019).

A meta-analysis of 13 RCTs in type-2 diabetic adults (>65 years old) taking physiologically relevant doses of metformin suggests that metformin monotherapy shows trends towards improvements in all-cause mortality (RR=0.96; 95% CI, 0.84-1.09), cardiovascular death (0.97; 95% CI, 0.80-1.16), myocardial infarction (RR=0.89; 95% CI, 0.75-1.06) and peripheral vascular disease (RR=0.81; 95% CI, 0.50-1.31), but not stroke (RR=1.04; 95% CI, 0.73-1.48) (Griffin et al, 2017).

Another meta-analysis of RCTs and observational studies comparing diabetic patients taking metformin versus those taking other drugs reported a slight decrease in the incidence of cardiovascular disease (HR 0.83; 95%CI 0.73-0.94) and a significant reduction in stroke (HR=0.70; 95% CI, 0.53-0.93) (Campbell et al, 2017).

The differences between these two meta-analyses could be that the first set were all randomized controlled trials while the second set were largely observational studies. Although RCTs are generally considered the 'gold standard' for reported outcomes, these studies are shorter in duration (between 6-79 months with most less than 3 years) while the observational studies tended to be longer (between 2.8-14 years with most around 5 years). Metformin's effects on cardiovascular disease may only be readily apparent with longer treatment.

The Diabetes Prevention Program Outcome Studies suggest that with a 3.2 year follow up, 1.7 g/day metformin treatment reduced severity and prevalence of coronary artery calcium in men, but not in women, and had favorable metabolic effects on lipoprotein subfractions mediated by changes in insulin resistance, BMI, and adiponectin (Goldberg et al, 2013, Goldberg et al. 2017).

The UK Prospective Diabetes Study showed that diabetic patients taking metformin had a risk reduction of 42% for diabetes-related death and 20% for cardiovascular disease (UKPDS group, 1998).

Metabolic and lipid profiles: DECREASED BODY WEIGHT, LDL, TOTAL CHOLESTROL, and TRIGLYCERIDES

In a 2021 meta-analysis of 6 randomized controlled trials including a total of 2,008 people with type 2 diabetes, metformin treatment significantly reduced mean body weight over time compared to placebo (-1.66 kg; 95% CI, -1.88 to -1.44; p<0.000; overall effect size z=5.40)(Gillani et al., 2021).

In the same meta-analysis, compared to placebo, metformin treatment significantly reduced mean total cholesterol (−0.24 mmol/L; 95% CI, −0.33 to −0.16; p<0.0001), mean LDL cholesterol (−0.38 mmol/L; 95% CI; −0.47 to −0.30; p<0.0001), and mean triglyceride levels (-0.24; 95% CI, -0.33 to -0.15; p<0.0001) (Gillani et al., 2021).

In an older 2018 meta-analysis of 6 randomized controlled trials including a total of 1,541 elderly people (over 60 years old) with type 2 diabetes, metformin treatment (variable doses across studies) for at least 12 weeks (and up to 3.2 years) resulted in a raw bodyweight difference of -2.23 kg (95% CI, -2.84 to -1.62 kg) compared to placebo groups (p<0.001)(Solymar et al., 2018). Both total cholesterol (-0.184 mmol/L; p<0.001) and LDL cholesterol levels (-0.182 mmol/L; p<0.001) decreased with metformin treatment. Five out of 6 studies reported changes in HbA1c and a meta-analysis showed a decrease in HbA1c with metformin treatment by an average of 0.49 (95% CI, -0.74 to -0.23; p<0.001). No significant difference was detected for fasting glucose.

Type 2 diabetes: BENEFIT; USED AS FIRST-LINE TREATMENT

In a 2022 meta-analysis of 37 randomized controlled trials including Japanese people with type 2 diabetes, metformin treatment (1500 mg/day) for 12 weeks or longer was significantly more effective in reducing HbA1c from baseline compared to 20 other anti-diabetic drugs, non-significantly more effective compared to 14 drugs, and non-significantly less effective compared to 2 drugs (glimepiride 2 mg/day and pioglitazone 45 mg/day)(Nishimura et al., 2022).

Older meta-analyses have also shown that metformin monotherapy is one of the most effective treatments for type 2 diabetes without increased risk of hypoglycemia (Hemmingsen et al, 2014; Palmer et al, 2016). Metformin has shown to have several benefits in diabetic individuals including improvements in circulating lipids, inflammatory markers, HbA1c, weight, and reduction of cardiovascular events (Marathur et al, 2016; Sanchez-Rangel et al, 2017). Comparative meta-analyses between metformin and other anti-diabetic drugs show that metformin has comparable glucose lowering effects to acarbose but better action than sulphonylureas, thiazolidinedione, DPP-4 inhibitors, and α-glucosidase inhibitors (McIntosh et al, 2012; Gu et al, 2015). A five-year clinical study from the Diabetes Outcome Progression Trial reported that metformin prevented progression to 'glycemic failure' better than glybenclamide (a sulfonylurea) but not rosiglitazone (Sanchez-Rangel et al, 2017).

A Cochrane meta-analysis reported that metformin consistently shows a strong benefit toward improving glycemic control with moderate benefits in weight, LDL and HDL levels, and diastolic blood pressure (Saenz et al, 2005) and may benefit LDL levels regardless of its effects on glycemic control (Wulffele et al, 2004).

Additive therapies of metformin with a SGLT-2 inhibitor or taspoglutide are more efficacious for HbA1c and blood glucose levels than monotherapy (Mologulu et al, 2017; Yang et al, 2017). Being the first line treatment, metformin (850 mg twice daily), primarily used as an anti-hyperglycemic agent and an insulin sensitizer in the Diabetes Prevention Program (DPP), reduced the incidence of type 2 diabetes by 31%, with a mean follow up of 3 years (Knowler et al, 2002). With an average follow-up of 2.8 years, metformin reduced glycated hemoglobin (5.9% as compared to 6.1% in placebo) and fasting plasma glucose (105 mg/dl as compared to 115 mg/dl in placebo).

***Cancers*:** DECREASED RISK OF MANY CANCERS IN T2DM

In a 2021 meta-analysis of 67 observational studies including over 10 million people with type 2 diabetes, metformin users had a significantly decreased risk of cancer compared to metformin never-users (OR=0.70; 95% CI, 0.65 to 0.76)(Zhang et al., 2021). The use of metformin was also found to be associated with a significantly decreased cancer risk compared to other anti-diabetic medications (OR=0.80; 95% CI, 0.73 to 0.87). Subgroup analyses revealed that the use of metformin was associated with a significantly decreased risk of bladder cancer (OR=0.76; 95% CI, 0.63 to 0.91), colorectal cancer (OR=0.73; 95% CI, 0.60 to 0.87), esophageal cancer (OR=0.72; 95% CI, 0.53 to 0.96), liver cancer (OR=0.61; 95% CI, 0.49 to 0.75), head and neck cancer (OR=0.55; 95% CI, 0.38 to 0.79), lung cancer

(OR=0.69; 95% CI, 0.60 to 0.80), pancreatic cancer (OR=0.62; 95% CI, 0.45 to 0.84), and prostate cancer (OR=0.74; 95% CI, 0.63 to 0.86). Similar results were found when metformin treatment was compared with other anti-diabetic medications.

In a 2022 meta-analysis of 5 phase II randomized controlled trials including 396 women with breast cancer (non-diabetic), add-on metformin treatment (500 mg TID, 850 mg BID, 1000 mg BID, or other) for 24-60 months was not associated with improved progression-free survival (HR=1.00; 95% CI, 0.70 to 1.43) or overall survival (HR=1.00; 95% CI, 0.71 to 1.39)(Wang et al., 2022).

In a 2020 meta-analysis of 18 observational studies in people with type 2 diabetes, metformin treatment was associated with a decreased lung cancer incidence (HR=0.78; 95% CI, 0.70 to 0.86) and increased lung cancer survival (HR=0.65; 95% CI, 0.55 to 0.77)(Xiao et al., 2020). In a subgroup analysis by type of lung cancer, metformin treatment showed a protective association for non-small-cell lung cancer (HR=0.68; 95% CI, 0.54 to 0.84) and small-cell lung cancer (HR=0.52; 95% CI, 0.39 to 0.69).

An older meta-analyses of case-control and cohort studies also reported a decrease in cancer incidence by 10-40% (Heckman-Stoddard et al, 2017). A meta-analysis of two studies comparing diabetics taking metformin compared to non-diabetics also reported a decreased risk of cancer (RR=0.94; 95% CI, 0.92 to 0.97) (Campbell et al, 2017).

Metformin is hypothesized to decrease cancer risk either through its insulin-lowering effect which may slow tumor proliferation or direct action against the mitochondrial respiratory complex 1 of the electron transport chain, thereby reducing energy consumption in the cell (Heckman-Stoddard et al, 2017). Other proposed anti-cancer mechanisms include AMPK activation leading to mTOR inhibition, resulting in downregulation of protein synthesis responsible for mitosis and cell division (Zhang et al., 2021).

Osteoarthritis: NO EFFECT

A cohort study using an electronic health record reported a lack of association between metformin use and osteoarthritis in diabetic patients (HR=1.02; 95% CI, 0.91 to 1.15)(Barnett et al, 2017).

Peripheral neuropathy: UNKNOWN; VITAMIN B12 LEVELS SHOULD BE MONITORED

In a 2022 meta-analysis that included 19 randomized controlled trials with a total of 18,181 subjects with type 2 diabetes, 5 studies reported neuropathic outcomes (paresthesia or pain in an extremity) but

due to the variable definitions of endpoints, a meta-analysis could not be performed (Gonzalez-Gonzalez et al., 2022). An older 2019 meta-analysis reported the same conclusion, where no significant association was seen between metformin use and prevalence of neuropathy (Yang et al., 2019).

Long-term metformin treatment may be associated with vitamin B12 deficiency which may increase the risk of peripheral neuropathy or exacerbate diabetic peripheral neuropathy (Ahmed et al, 2017). Although vitamin B12 deficiency is a well-known potential side effect of long-term metformin treatment, whether metformin increases the risk of peripheral neuropathy is unclear (Gupta et al, 2017; Russo et al, 2016). Individuals taking metformin should have vitamin B12 levels regularly monitored, as it is hypothesized that metformin reduces the intestinal absorption of vitamin B12.

Age-related macular degeneration: UNKNOWN; POTENTIAL BENEFIT

Age-related macular degeneration is the most common cause of blindness with prevalence increasing with age. In a 2021 meta-analysis of 5 retrospective studies, people with type 2 diabetes taking metformin were less likely to have age-related macular degeneration (pooled adjusted OR=0.80; 95% CI, 0.54 to 1.05), though the difference was not statistically significant (Romdhoniyyah et al., 2021). There are no published prospective studies that have investigated the association between metformin use and age-related macular degeneration. Because only 2 studies included people without diabetes, the association between metformin use and age-related macular degeneration could not be generalized to people without diabetes. The authors suggest that the mechanism of action for protection may be due to metformin's antioxidant, anti-inflammatory, anti-angiogenic, and anti-fibrotic effects.

Kidney function: POTENTIAL BENEFIT

In a 2022 meta-analysis that included 19 randomized controlled trials with a total of 18,181 subjects with type 2 diabetes, metformin treatment increased estimated glomerular filtration rate by a mean difference of 1.08 (95% CI, 0.84 to 1.33 ml/min/1.73 m^2) after 24 weeks (Gonzalez-Gonzalez et al., 2022). No metformin effects were found on urinary albumin-creatinine ratio, serum creatinine, and advanced kidney disease (OR=0.79; 95% CI, 0.28 to 2.21). Four studies evaluated outcomes including death from kidney causes, progression of nephropathy, and kidney adverse events, but there were no statistical effects with metformin on these outcomes.

Bone health: DECREASED RISK OF FRACTURE

In a 2019 meta-analysis of 6 observational studies, metformin use was associated with a significantly lower risk of fracture (RR=0.82; 95% CI, 0.72 to 0.93)(Salari-Moghaddam et al., 2019). OR/RR/HR ranged from 0.57 to 1.00 in the included 6 studies. The mechanisms are not well understood, but metformin has been shown to stimulate bone formation by inducing the differentiation and mineralization of osteoblasts through the activation of AMPK signaling and expression of the bone morphogenetic protein-2 (BMP-2)(Kanazawa et al., 2008).

Inflammation: DECREASED CRP LEVELS

In a 2021 meta-analysis of 13 randomized controlled trials including a total of 1,776 subjects with type 2 diabetes, metformin treatment (500-2,200 mg/day) was associated with a significantly lower CRP level (standardized mean difference; SMD= -0.76 mg/L; 95% CI, -1.48 to -0.049); p=0.036)(Karbalee-Hasani et al., 2021). However, circulating levels of TNF-α (SMD=-0.17 pg/mL; 95% CI, -0.55 to 0.20; p=0.37) and IL-6 (SMD=-0.06 pg/mL; 95% CI, -0.38 to 0.25; p=0.69) were not significantly lower with metformin treatment. Compared to treatment duration of less than 24 weeks, longer treatment duration was associated with a greater reduction of CRP levels. The anti-inflammatory effects of metformin are likely mediated through the inhibition of NFkB through AMPK-dependent and -independent pathways.

Effects on microbiome: SOME EVIDENCE

Recent evidence suggests gut microbiome as a possible target of metformin action as an anti-diabetic (Pollack, 2017). In a randomized controlled trial in people with type 2 diabetes, metformin mediated its action on HbA1c and fasting glucose concentrations by altering the gut microbiome (Wu et al, 2017). Germ-free mice receiving fecal transfer from metformin-treated people showed improvement in glucose tolerance.

Safety: Metformin is generally well-tolerated, with minor gastrointestinal side effects. People with renal failure should not use metformin as it increases the risk of lactic acidosis, a serious adverse event. Long-term use may reduce vitamin B12 levels.

Types of evidence:

- Numerous meta-analyses in people with type 2 diabetes
- 2 meta-analyses comparing different formulations of metformin (e.g., immediate-release vs extended-release vs slow-release, etc.)
- 2 secondary analyses after RCT

Metformin has had a good safety profile for over 60 years, with a common side effect of gastrointestinal discomfort; severe hypoglycemia is rare (DPP Research group). Chronic renal failure is one of the main contraindications for metformin use and metformin can be used safely when the estimated glomerular filtration rate is at least 45 ml/ min/1.73 m^2 (Hur et al., 2020; Orloff et al., 2021). The risk of lactic acidosis (resulting in death, hypothermia, hypotension, etc.), while rare, increases with renal or hepatic impairment, age 65 years or older, having a radiological contrast agent, having surgery, being in hypoxic states, and excessive alcohol intake (Drugs.com; Aroda et al, 2016). People with severe diabetic ketosis or kidney disease should not take metformin.

In a randomized controlled trial, mild anemia occurred in 12% of metformin treated diabetics, compared to 8% in placebo-treated, and vitamin B12 deficiency occurred in 7% of metformin-treated patients as compared to 5% in placebo-treated (Lalau et al, 1990). Monitoring of vitamin B12 is recommended in patients taking metformin.

In a 2022 network meta-analysis of 37 randomized controlled trials, metformin treatment (1500 mg/day) versus other oral antidiabetic drugs were compared, and metformin had a significantly lower incidence of hypoglycemia compared to 23 other treatments; only pioglitazone (30 mg/day) showed a lower relative risk compared to metformin (Nishimura et al., 2022).

In a 2021 meta-analysis including 15 randomized controlled trials that compared the "extended-release" formulations of metformin (including slow-release, extended-release, controlled-release, and delayed-release) to "immediate-release" metformin reported that gastrointestinal side effects were non-significantly lower in people randomized to the extended-release formulation compared to the immediate release metformin (OR=0.69; 95% CI, 0.45-1.07, p=0.10), based on 9 studies including 2,164 participants (Tarry-Adkins et al., 2021). Gastrointestinal side effects were significantly lower in patients

randomized to the delayed-release metformin compared to immediate-release metformin (OR=0.45, 95% CI, 0.26 to 0.80; p=0.006), though this is based on a single study including 472 participants. Efficacy (measured by fasting plasma glucose) was not significantly different across immediate-release, extended-release, or delayed-release metformin. Individuals randomized to extended-release versus immediate-release had lower LDL cholesterol levels (-5.73 mg/dl; 95% CI, -7.91 to -3.56; p<0.00001). No significant differences in total cholesterol, HDL, or triglycerides were observed across the different formulations.

In a different 2021 meta-analysis of 9 randomized controlled trials including a total of 2,609 people with type 2 diabetes, the effect of extended-release metformin treatment (for at least 12 weeks) was compared with immediate-release at equal doses (Abrilla et al., 2021). Immediate-release metformin was statistically better, but clinically similar, at lowering HbA1c compared to extended-release metformin (mean difference, 0.09%; 95% CI, 0.01-0.17%). Extended-release metformin had a significantly lower rate of dyspepsia (RR=0.58, 95% CI, 0.34 to 0.98) and both formulations were associated with a similar cumulative incidence of other key gastrointestinal symptoms.

Drug interactions: Metformin interacts with 353 drugs, 19 of which are major drug interactions, 305 are moderate drug interactions, and 29 are minor drug interactions (see full list at Drugs.com). Metformin has major drug interactions with X-ray contrast agents, such as diatrizoate and iothalamate, because of increased risk of lactic acidosis. Additionally, it should not be taken with the antibiotic gatifloxacin (Drugs.com; major drug interactions). Moderate drug interactions include phenytoin, birth control pills, blood pressure medications, steroid medications including prednisone and dexamethasone, and some thyroid medications (Drugs.com; moderate drug interactions). Metformin taken in conjunction with some pills may raise the chance of inducing hyperglycemia (Drugs.com)

Sources and dosing:
Metformin is marketed as Glucophage and Glucophage XR (extended-release) in the US and is available at low-cost and has a good safety profile. Although inter-individual heterogeneity can determine pharmacodynamic responses to metformin, it is well-tolerated at clinically relevant doses of 1-2 g/day (Pawlyk et al, 2014). Most *in vitro* assays suggest that metformin in mM concentrations is sufficient for its pharmacological action. In murine lifespan models, 0.1% w/w dose of metformin increased lifespan and healthspan significantly. Micromolar concentrations of metformin in plasma may result in considerably higher levels of metformin in mitochondria of hepatocytes (Chandel et al, 2016). However, in the first human RCT in pancreatic cancer, micromolar levels of plasma metformin levels did not show survival endpoint benefits (Kordes et al, 2015).

Research underway: Based on ClinicalTrials.gov, there are 377 active clinical studies testing metformin across a variety of disease indications, including many types of cancer, heart failure, coronary artery disease, macular degeneration, osteoarthritis, obesity, schizophrenia, multiple sclerosis, Huntington disease, and many others (ClinicalTrials.gov). A phase 2/3 randomized controlled trial is ongoing to test long-acting metformin (Glucophage XR, titrated up to 2,000 mg/day) versus matching placebo in 370 people with early and late amnestic mild cognitive impairment without diabetes (NCT04098666). The intervention lasts for 24 months. This clinical trial has an estimated study completion date of April 2025. ADDF is funding a prevention trial led by Miia Kivipelto, MD, PhD, at the Karolinska Institute and Imperial College London. Dr. Kivipelto is combining the multi-domain lifestyle intervention from her FINGER trial with metformin to examine whether it can prevent cognitive impairment and disability in cognitively healthy people (NCT05109169).

The idea for the Targeting Aging with Metformin trial (the TAME trial) was formed by Dr. Nir Barzilai and his colleagues in 2014. Fundraising has been underway for many years, with a goal of $42M, and currently raised amount of $11M, as of April 2022 (afar.org). This multi-center trial plans to recruit 3,000 individuals between the ages of 65-79 to determine whether metformin treatment slows aging in people. The dose for metformin to be tested is 1,500 mg, slow-release, once daily, based on a slide deck by Jamie Justice, PhD, Wake Forest School of Medicine, from the 2019 State of the Science Symposium.

Search terms:

Pubmed and Google: Metformin

- + neurodegenerative diseases
- + Alzheimer's disease
- + neuroprotection
- + aging
- + diabetes
- + cardiovascular diseases
- + cancer
- + lifespan
- + peripheral neuropathy
- + arthritis
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Websites visited:

- ClinicalTrials.gov
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- WebMD.com
- PubChem
- DrugBank.ca

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