



*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 is a first line treatment for type 2 diabetes and shows potential benefit for dementia prevention, decreased mortality risk, decreased cardiovascular disease risk, and decreased cancer risk. Long-term treatment may reduce vitamin B12 levels which should be monitored if supplementation is needed.

**Neuroprotective Benefit:** Metformin crosses the blood brain barrier and may reduce the risk of dementia in type 2 diabetics. Research from non-diabetics is still uncertain.

**Aging and related health concerns:** Metformin delays the onset of many age-related diseases, possibly as a caloric restriction mimetic, with decreased risks for most age-related diseases (~10%-30%).

**Safety:** Metformin is well tolerated at physiologically relevant doses, with minor gastrointestinal side effects. However, long-term use may reduce vitamin B12 levels.



### **What is it?**

Metformin is the first-line treatment for type 2 diabetes (T2D), used for its glucose lowering effect and high safety profile in humans. It is a dimethylbiguanide, initially derived from *Galega officinalis* (French lilac). Although the exact mechanism of action of metformin is unknown, it inhibits hepatic gluconeogenesis, possibly by targeting mitochondrial respiratory chain complex 1, activating AMPK, and systemically increasing insulin sensitivity.

**Neuroprotective Benefit:** Metformin crosses the blood brain barrier and may reduce the risk of dementia in type 2 diabetics. Research from non-diabetics is still uncertain.

### Types of evidence:

- Two small randomized controlled trials in patients with MCI or mild dementia
- One randomized controlled trial in depressed patients with type 2 diabetes
- A meta-analysis of observational studies of insulin sensitizing drugs and T2D drugs on development of cognitive impairment or dementia
- Two observational studies not in the meta-analysis
- Multiple laboratory studies

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

No human studies have been conducted to assess the role of metformin in preventing dementia or age-related cognitive decline in healthy individuals. In one RCT of 58 patients with depression and Type 2 diabetes, 24-week metformin treatment (up to 1.5-2g/day) was shown to improve cognitive performance, specifically verbal, visual, general and delayed-memory indices, and lowered depression ([Guo et al, 2014](#)). The positive effects of metformin in improving cognitive function were correlated with HbA1c levels.

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

One pilot RCT (funded by ADDF) tested the safety and efficacy of metformin on cognitive function, biomarker imaging outcomes (CMRgl), and plasma A $\beta$ 42 levels in 80 elderly overweight patients with amnesic mild cognitive impairment and without diabetes ([Luchsinger et al, 2016](#)). Metformin (up to 1000 mg twice/day) over 12 months improved scores on a memory test but did not improve ADAS-Cog scores compared to placebo. Metformin treatment did not change plasma A $\beta$ 42 levels or a change in glucose uptake (only 40 participants completed PET scans and there were non-significant changes in



favor of metformin). A crossover RCT investigated metformin's effect on CSF and neuroimaging biomarkers and cognition in 20 non-diabetic individuals with MCI or mild dementia due to AD ([Koenig et al, 2017](#)). Metformin crossed the blood brain barrier and was present in the CSF (at 95.6ng/mL). 8-week treatment with metformin caused no changes in CSF A $\beta$ 42, tau or phosphorylated tau levels. Some improvements were seen in executive functioning, but not in other measures of cognition. Post-hoc analysis of patients on metformin who underwent analysis for cerebral blood flow 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.

Since metformin is a first line treatment for diabetes, most human observational studies that assess its role in prevention of dementia or cognitive impairment are carried out in diabetic or pre-diabetic individuals.

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 reported decreased risk of dementia in type 2 diabetics taking metformin compared to unmedicated type 2 diabetics (HR 0.76; 95%CI 0.58-0.98) ([Hsu et al, 2010](#)).

However, contradictory results are seen in other population-based diabetic cohorts from Asia, Australia and UK with long term metformin increasing 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 0.19-0.92).



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](#)).

Regardless of some contradictory results, 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 did not affect 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.

#### *Mechanisms of action for neuroprotection identified from laboratory and clinical research*

Preclinical studies of metformin in AD rodent models report that metformin increases neurogenesis, is neuroprotective and has varying effects on cognition. In the leptin-resistant type-2 diabetes mouse model with lower synaptic proteins and higher phosphorylated tau and A $\beta$  levels, metformin attenuated tau and phosphorylated-tau levels and the reduction of hippocampal synaptophysin, but did not influence spatial learning and memory ([Li et al, 2012](#)). Interestingly, in an AD-mouse model (PDAPP), 8 weeks of metformin showed sexually dimorphic effects, improving metabolic variables in both sexes, but worsening AD-related cognitive phenotypes in males and improving cognitive phenotypes in females ([DiTacchio et al, 2014](#)). In scopolamine-induced memory deficit male Wistar rats and high-fat fed A $\beta$ -induced AD male Wistar rats, metformin rescued AD-like behaviors, reduced cognitive dysfunction, increased phosphorylated Akt, thereby decreasing phosphorylated tau levels and improving hippocampal long-term potentiation ([Asadbegi et al, 2016](#); [Mostafa et al, 2016](#)).

In contrast, other preclinical studies suggest that metformin may increase amyloid-beta peptides, increase beta-secretase, and induce metabolic stress and dendritic spine loss in hippocampal neurons ([Kuan et al, 2017](#)). It is not clear why there are variable results with metformin treatment in animal studies, but there are nearly as many negative, or harmful, results as there are positive results.

#### *APOE4 interactions:*

[Ng et al, 2014](#) reported benefits with metformin after controlling for ApoE4 status.



**Aging and related health concerns:** Metformin delays the onset of many age-related diseases, possibly as a caloric restriction mimetic, with decreased risks for most age-related diseases (~10%-30%).

Types of evidence:

- One meta-analysis of observational studies for decreased mortality risk
- Three mouse life-span studies
- Two meta-analyses of decreased cardiovascular risk
- Many studies in type-2 diabetics
- One meta-analysis of decreased cancer risk
- Multiple other studies for decreased cancer risk
- Three reviews of peripheral neuropathy risk
- One clinical study of effects on microbiome

*Details:* Metformin is hypothesized to be one of the top 'geroprotective' interventions that can mimic the beneficial effects of caloric restriction and improve multiple hallmarks of aging including metabolism (increase insulin sensitivity and decrease hepatic gluconeogenesis), epigenetics (DNA-repair), mitochondrial function and nutrient sensing ([Barzilai et al, 2016](#)). Moreover, recent meta-analysis suggested that metformin may reduce all-cause mortality and diseases of aging irrespective of its effect in diabetes ([Campbell et al, 2017](#)).

**Lifespan POTENTIAL BENEFIT**

No RCTs using metformin have been conducted in humans with lifespan modulation as the outcome. However, 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 includes 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](#)).

Observational studies corroborate these effects on model-system lifespan. A meta-analysis of four studies comparing diabetics taking metformin with non-diabetics reported a decreased risk of mortality (HR = 0.93; 95%CI 0.88-0.99). Additionally, a meta-analysis of nine studies of diabetic patients taking



metformin compared to diabetic patients taking other anti-diabetic drugs reported a decreased risk of mortality even after adjusting for diabetes control (HR = 0.75; 95%CI 0.69-0.82) ([Campbell et al, 2017](#)). Although there are caveats to these analyses (e.g. metformin is usually a first line treatment and patients taking other medicines may have diabetes that cannot be controlled with metformin), the data comparing diabetics on metformin with non-diabetics suggests an anti-aging effect with metformin – though there is a possibility that some diabetics who were undiagnosed and not taking medicine were in the non-diabetic group.

### **Cardiovascular disease (CVD): POTENTIAL BENEFIT**

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 non-significant benefits 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 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 CVD 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](#)).

**Type 2 diabetes and hyperglycemia: BENEFIT**

Multiple meta-analyses show 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](#)). Although the primary action of metformin as an anti-hyperglycemic agent is still debated, it is 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  $\alpha$ -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 sulphonylurea) but not rosiglitazone ([Sanchez-Rangel et al, 2017](#)).

Additive therapies of metformin with 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).

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](#)).

**Age-related cancers: SLIGHT BENEFIT**

Multiple meta-analyses of case-control and cohort studies report a potential 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 0.92-0.97) ([Campbell et al, 2017](#)). Metformin has also been shown to decrease the incidence of endometrial, breast, liver, pancreas, lung and colorectal cancers ([Perez-Lopez et al, 2017](#), [Ma et al, 2017](#); [Zhou et al, 2017](#); [Cai et al](#); [Dong et al, 2017](#); [Meng et al, 2017](#)). Results from randomized controlled trials are more variable, but these are confounded by the age of the treated individual and the short length of the studies ([Heckman-Stoddard 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](#)).

#### **Osteoarthritis NO EFFECT**

One observational study reported no effect on osteoarthritis in diabetic patients taking metformin ([Barnett et al, 2017](#)).

#### **Peripheral Neuropathy POTENTIAL DETRIMENT**

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 checked, even after supplementation, as it is hypothesized that metformin reduces the intestinal absorption of vitamin B12.

#### **Effects on microbiome SOME EVIDENCE**

Recent evidence suggests gut microbiome as a possible target of metformin action as an anti-diabetic ([Pollack, 2017](#)). In an RCT in type-2 diabetics, metformin altered the gut microbiome, with beneficial results seen in germ-free mice transferred with the altered human microbiota ([Wu et al, 2017](#)). Beneficial effects have been seen in metformin tolerance in a crossover study of 2-week metformin treatment with a GI microbiome modulator, indicating that metformin may rely on the gut microbiota in order to exert its effects ([Burton et al, 2014](#)).

**Safety:** Metformin is well tolerated at physiologically relevant doses, with minor gastrointestinal side effects. However, long-term use may reduce vitamin B12 levels.

#### Types of evidence:

- 2 long term safety trial in diabetics
- 2 secondary analyses after RCT.





Metformin has an excellent safety profile with over 60 years of use and there are no major side-effects or severe hypoglycemia in diabetics, except minor gastrointestinal discomfort ([DPP Research group](#)). Patients with severe diabetic ketosis or kidney disease may have major side effects and are not recommended to take metformin. No evidence is available for long term effects in healthy individuals. Major side effects including lactic acidosis occur in individuals with renal dysfunction taking metformin, and are generally very rare ([Aroda et al, 2016](#)). In an RCT, 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.

#### *Drug interactions:*

Interestingly, metformin has major drug interactions with X-ray contrast agents, such as diatrizoate and iohalamate, because of increased risk of lactic acidosis. Additionally, it should not be taken with the anti-biotic gatifloxacin ([major drug interactions here](#)). Moderate drug interactions include phenytoin, birth control pills, blood pressure medications, steroid medications including prednisone and dexamethasone and some thyroid medications ([moderate drug interactions here](#)). Metformin taken in conjunction with some pills may raise the chance of inducing hyperglycemia ([drugs.com](#))

#### **Sources and dosing:**

Metformin is sold as Glucophage and Glucophage XR (extended release) in the United States and is available at low-cost and has a good safety profile in healthy and diabetic individuals. Although inter-individual heterogeneity can determine pharmacodynamic responses to metformin, it is well-tolerated at clinically relevant doses of 1-2g/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 was shown to increase lifespan and healthspan benefits significantly. Micromolar concentrations of metformin in plasma may result in considerably higher quantities 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:**

Several clinical trials investigating the effects of metformin monotherapy in a variety of cancers and neoplasms and metformin combination therapy with other interventions in diabetes and metabolic disorders are underway. 5 clinical trials are investigating the effect of metformin on aging- one examining the effect of metformin on gene expression outcomes in muscle and adipose tissues



([NCT02432287](#)), one assessing the effect of metformin on sarcopenia and muscle metabolic health ([NCT03107884](#)), one testing if metformin can augment the effect of exercise in older individuals ([NCT02308228](#)), one studying the use of metformin as a topical agent for skin anti-aging ([NCT03072485](#)) and one comparing the effects of metformin with those of caloric restriction ([NCT02745886](#)).

The soon-to-be-launched TAME (Targeting Aging with Metformin) is the first multi-centered clinical trial to study the effects of metformin on improving human healthspan and delaying multiple age-related diseases in 3000 individuals between 70-80 years old ([Barzilai et al, 2016](#); [Hayden, 2015](#)).

#### Search terms:

Pubmed and Google: Metformin

- + neurodegenerative diseases, + Alzheimer's disease, + neuroprotection, + aging, + diabetes, + cardiovascular diseases, + cancer, + lifespan + aging + peripheral neuropathy + arthritis + hypotension

ClinicalTrials.gov

- Alzheimer's disease + Metformin, Aging + Metformin

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