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REVIEW

Metformin and cognition from the perspectives of sex, age, and disease

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Abstract Metformin is the safest and the most widely prescribed first-line therapy for managing hyperglycemia due to different underlying causes, primarily type 2 diabetes mellitus. In addition to its euglycemic properties, metformin has stimulated a wave of clinical trials to investigate benefits on aging-related diseases and longevity. Such an impact on the lifespan extension would undoubtedly expand the therapeutic utility of metformin regardless of glycemic status. However, there is a scarcity of studies evaluating whether metformin has differential cognitive effects across age, sex, glycemic status, metformin dose, and duration of metformin treatment and associated pathological conditions. By scrutinizing the available literature on animal and human studies for metformin and brain function, we expect to shed light on the potential impact of metformin on cognition across age, sex, and pathological conditions. This review aims to provide readers with a broader insight of (a) how metformin differentially affects cognition and (b) why there is a need for more translational and clinical studies examining multifactorial interactions. The outcomes of such comprehensive studies will streamline precision medicine practices, avoiding "fit for all" approach, and optimizing metformin use for longevity benefit irrespective of hyperglycemia.

Keywords Metformin · Cognition · Diabetes · Age · Sex · Gender · Brain function

Highlights
1. Metformin affects cognition.
2. Sex influences metformin pharmacokinetics and associated cognitive alterations.
3. Organic cation transporters and AMP-activated kinase might hold a key for metformin-associated cognitive alterations.
4. Age is a critical factor affecting metformin-associated cognitive alterations.
5. Metformin may inverse the pathological conditions induced cognitive variations.

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Introduction

In recent years, the prescription rate for metformin is increased to 235/1000 population for the FDA-approved indications and up to 20.3/1000 person for off-label use (Le and Lee 2019). Apart from the role in maintaining glucose homeostasis, metformin has several potential anti-aging properties. The longevity benefit was observed in diabetic patients taking metformin when compared with diabetic subjects on non-metformin protocols, as well as non-diabetic subjects not taking metformin (Bannister et al. 2014). Recently, metformin has been purported to have a detrimental effect on cognition in male mice, supported by findings in recent clinical

studies (Hervas et al. 2017; Kuan et al. 2017; Thangthaeng et al. 2017). Such surprising results that can affect the overall quality of life may outweigh metformin's longevity benefits, especially if the target population for such benefit is non-diabetic.

At NIH RePORTER (https://projectreporter.nih.gov/reporter.cfm), there are currently 85 projects funded for "metformin and aging" and 17 of these or other projects involved targeting metformin and cognition. Further, there are currently eleven registered clinical trials (https://clinicaltrials.gov/ct2/home) focused on metformin, aging, and longevity. Of the trials identified, eight are directly addressing the benefit of metformin on age-related problems and their underlying molecular mechanisms (Table 1). Six clinical trials included both men and women. There is no information regarding the assessment of beneficial or harmful effects of metformin across sexes in any of these clinical trials. None of these longevity studies has focused on cognition or psychomotor elements of brain functions.

As a near obligate glucose consumer, the brain is one of the most metabolically active organs in the body. Therefore, the brain is more susceptible to manipulation of energy metabolism by glucose-lowering medicines. It is unclear whether the beneficial or deleterious effects on brain function accompanies the improved longevity associated with metformin. It is also ambiguous whether the effects of metformin on brain function are universal across broad demographics, such as sex, age, and existing pathological conditions. We attempt to address this critical concern by considering the effects of sex, age, and pathological conditions on metformin-dependent changes in brain function. Previous findings from in vitro studies, in vivo studies in rodents, cross-sectional and longitudinal data analysis, and clinical trials relevant to these questions were scrutinized. The goal of this update is to provide precision medicine-based insight for metformin treatment, optimizing longevity and cognitive benefits, and mitigating risks.

Metformin increases lifespan

Barzilai et al. 2016 and Novelle et al. 2016, in two separate papers, discussed the detail mechanisms for the anti-aging benefit of metformin (Barzilai et al. 2016; Novelle et al. 2016). Metformin collectively influences inflammation, cellular survival, stress, autophagy, and protein synthesis, which are significant players in aging/longevity (Algire et al. 2012; Batandier et al. 2006; Bridges et al. 2014; Cho et al. 2015; Duca et al. 2015; Foretz et al. 2010; Jadhav et al. 2013; Kickstein et al. 2010; Lien et al. 2014; Liu et al. 2011; Lu et al. 2015; Moiseeva et al. 2013; Nair et al. 2014; Perez-Revuelta et al. 2014; Saisho 2015; Song et al. 2015; Xie et al. 2011; Zheng et al. 2012). There is mounting evidence to suggest that metformin prolongs the lifespan of many species, ranging from nematodes-to-rodents (Anisimov et al. 2008; Anisimov et al. 2011; Cabreiro et al. 2013; De Haes et al. 2014). This longevity benefit is dependent on genotype, age, sex, dose, and duration of metformin therapy. Metformin substantially prolonged lifespan in female outbred mice by nearly 40% (Anisimov et al. 2008). The longevity benefit is higher by 14% when metformin treatment was initiated earlier rather than later in old age (Anisimov et al. 2011). In 129/sv and R6/2 mice, metformin extended the lifespan in male mice with only a subtle effect in female mice (Anisimov et al. 2010b; Ma et al. 2007). Although this effect occurred across several mouse breeds, not all demonstrated consistent prolongation of lifespan (Martin-Montalvo et al. 2013). This disparity could be due to metformin dose or genetic variation across studies. Drosophila, mice, and rats treated with very high doses did not extend lifespan, suggesting the need to fine-tune the dosage scheduling for longevity benefits (Martin-Montalvo et al. 2013; Slack et al. 2012; Smith Jr. et al. 2010). The strain used by Smith et al. 2010 to understand metformin-associated longevity also failed to replicate the CR benefit on longevity, further emphasizing underlying genetics for longevity benefit and further need for precision medicine-based approach. It is often discussed that metformin both directly (by altering genetics) and indirectly (by lowering disease burden) provides longevity benefit. The NIA's intervention testing program (ITP) tested for longevity benefit in both male and female UM-HET3 mice using metformin (1000 ppm; 0.1%) alone or in combination with rapamycin (14 ppm) (Strong et al. 2016). Interestingly they observed metformin-associated 7% increase in longevity only in male mice (data pooled from all sites, statistically not significant, $p = 0.35$) and no such effect (0% change) in female mice irrespective of site. The major limitation of this study was site-specific variation in the benefit, which ranged from − 1 to 13%. While rapamycin alone treatment led to a uniform 10% increased longevity in both sexes. Further, the combination of metformin and rapamycin had synergistic longevity benefit up to 23% (statistically significant $p = 0$) in both male and female mice. These

Table 1 Clinical trials with a focus on metformin and aging

Sr.	Clinical trials identifier	Name of the study	Sample size	Sex	Sex-based analysis	Age (years)	Condition or disease	Metformin dose (mg/day)	Metformin duration	Evaluation	Outcome
1	NCT 03309007	A Double-Blind, Placebo-Controlled Trial of Anti-Aging, Pro-Autophagy Effects of Metformin in Adults With Prediabetes	30	Both	No details provided	30–70	Pre-diabetes	1500	12 weeks	Autophagy	Change in leucocyte LC3 score, at 0, 4, and 12 weeks
2	NCT 02432287	Metformin in Longevity Study (MILES)	15	Both	No details provided	35–85	Aging	1700	12 weeks	Longevity gene expression changes	Increase in gene expression in muscle and adipose tissue using RNA sequencing
3	NCT 03451006	Metformin and Aging Trial in the Elderly: A Pilot and Feasibility Study (MATE)	12	Both	No details provided	> 60	Aging, inflammation, frailty	2000	12 months	Effect of metformin in frailty	Change in frailty, balance score, gait speed, standing test from chair, change in senescent marker
4	NCT 02308228	Metformin to Augment Strength Training Effective Response in Seniors (MASTERS)	100	Both	No details provided	> 65	Aging	1700	16 weeks	Interaction with resistance training adaptations	Muscle size, biopsy and CT vastus lateralis, muscle strength, muscle macrophage, muscle inflammatory gene expression, insulin sensitivity
5	NCT 03072485	Phase 1 Study of the Effects of Combining Topical FDA-approved Drugs on Age-related Pathways on the Skin of Healthy Volunteers	10	Female	Not applicable	> 55	Aging	Topical application	4 weeks	Skin aging	Profile of gene transcript changes, Wrinkle score
6	NCT 01765946	Metformin and Longevity Genes in Prediabetes	38	Both	No details provided	40–75	Pre-diabetic, aging	1500	8 weeks (2 months)	Longevity gene expression changes	Longevity genes, Sirtuin-1, p66Shc, mTor, p53 in peripheral blood mononuclear cells, insulin sensitivity, monocyte polarization status
7	NCT 02745886	Metformin Induces a Dietary Restriction-like State in Human	60	Male	Not applicable	18–60	Aging, overweight subjects	1700	6 months	Calorie restriction like benefits	Gene expression profile, insulin sensitivity
8	NCT 03713801	Impact of Metformin on Immunity	50	Both	No details provided	63–90	Aging, vaccine response impaired	1500	12 weeks	Immune-response	Change in antibody response to PCV13 measurement of immune-phenotypes

findings from ITP studies could suggest that when metformin may have failed to increase longevity in female in one particular strain, combination with other modality might help to achieve the same amount of benefit as that of male.

In humans, there are indirect pieces of evidence for metformin-associated increased lifespan. Metformin early treatment can delay or prevent the onset of diabetes (Diabetes Prevention Program Research 2015). Metformin also improved health indicators for cardiovascular disease and atherosclerosis in males (Goldberg et al. 2013; Goldberg et al. 2017; Haffner et al. 2005). The cardiovascular risk reduction across the UK Prospective Diabetes Study (UKPDS) and the HOME Trial (NCT00375388) may justify the use of metformin as safe longevity-promoting therapy in patients with and without diabetes (Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group 1998; Kooy et al. 2009). To make this assertion, these findings will need to be reconciled with other studies conducted in non-diabetic subjects, such as the GIPS III study (NCT01217307), which demonstrated a little-to-no beneficial effect of metformin on cardiovascular health (Hartman et al. 2017; Lexis et al. 2014). In the CAMERA trial (NCT00723307), chronic metformin treatment for 18 months did not show any beneficial effect on cardiovascular health (Preiss et al. 2014). Interestingly, Han et al. 2019, meta-analyzed 40 studies comprising 1,066,408 patients and concluded that metformin reduced all-cause mortality and cardiovascular events in coronary artery disease patients. However, the authors also reported that overall, metformin did not effectively reduce the incidence of cardiovascular events in myocardial infarction and coronary artery disease patients in the absence of T2D (Han et al. 2019). There is a need to understand why metformin showed beneficial outcome in some studies and why showed no such effects in other studies. The answers to these questions could be deciding factors for precision medicine-based prescription of metformin for longevity benefits, especially in the absence of diabetes.

Metformin acts on neurons, astrocytes, and microglia (Fig. 1)

As the major cells of the brain, neurons are among the most metabolically active cells in the body. Energy regulator-AMP-activated protein kinase (AMPK) signaling is highly expressed in the neurons. Within neurons, metformin primarily acts via AMPK to maintain energy homeostasis (Hardie 2014). Many recent studies explored AMPK-dependent, AMPK-independent, and energy independent effects of metformin in neuronal activity, differentiation, toxicity, autophagy, and survival. These differential effects on neurons were dose, duration, and disease-dependent (Aatsinki et al. 2014; Bayliss et al. 2016; Canto et al. 2009; Fatt et al. 2015; Ge et al. 2017; Hawley et al. 2010; Isakovic et al. 2007; Jang and Park 2018; Katila et al. 2017; Khedr et al. 2018; Kickstein et al. 2010; Matthes et al. 2018; Ou et al. 2018; Potts and Lim 2012; Price et al. 2012; Sesen et al. 2015; Song et al. 2015; St-Pierre et al. 2006; Wang et al. 2012; Wang et al. 2018b; Yan et al. 2017; Zhang et al. 2016; Zhu et al. 2015).

Apart from neurons, metformin also affects astrocytes and microglia. A higher concentration at 10 mM metformin increased glucose consumption, lactate production, and decreased oxygen consumption leading the primary astrocytes toward more glycolytic metabolism. (Hohnholt et al. 2017; Westhaus et al. 2017) Similarly, ketogenic activation in terms of increased acetoacetate and β-hydroxybutyrate production occurred at 1 mM metformin concentration. (Takahashi et al. 2014) Despite these metabolic changes, metformin was found to be protecting the astrocytes against apoptosis and cell death induced by oxygen and glucose deprivation. (Gabryel and Liber 2018).

It is well known that AMPK regulates the energy balance as well as the functional phenotype of microglia. (Lu et al. 2010; Sag et al. 2008) The microglia are highly plastic in response to microenvironment changes. Metformin-induced AMPK activation changes the microglia polarization toward M2 phenotype, which helps in tissue repair following an injury such as middle cerebral artery occlusion. (Jin et al. 2014). Further detailed refining of the underlying mechanism of metformin in microglia indicated AMPK-dependent release of TNF-α and AMPK-independent regulation IL-1β, IL-6, IL-10, TGF-β, nitric oxide, reactive oxygen species, NF-κB, p65, and PGC-1α. Interestingly, sex of the species and location of microglia determine the impact of metformin on microglia, as shown by selective microglial activation and reversal of neuropathic pain in male mice. (Inyang et al. 2019).

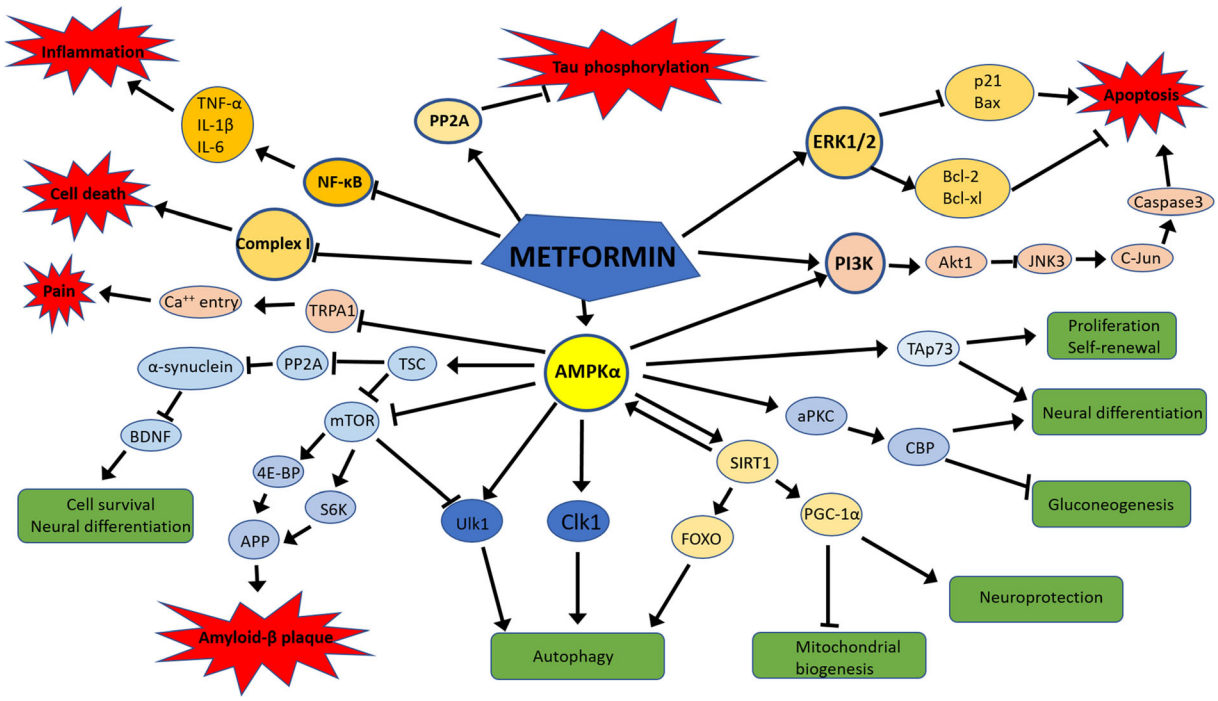

Fig. 1 Mechanisms of action of metformin in the neuro-glial environment. Metformin via AMPKα-dependent pathways promote cell survival, neural differentiation, autophagy, neuroprotection, proliferation, and self-renewal. Metformin inhibits amyloid-β-plaque formation via AMPKα. Metformin inhibits inflammation via inhibiting NF-κB. Metformin activates apoptosis via PI3K pathway and inhibits apoptosis via the ERK1/2 pathway. Metformin promotes Tau dephosphorylation via PP2A pathway

Metformin differently affects cognition (Table 2)

Human studies

Metformin has shown potential cognitive benefits in some disease conditions. There are very few preclinical or clinical studies, which have investigated the cognitive effect across age, sex, and blood glucose as individual factors or interfactorial interaction. Existing studies report changes across various cognitive evaluations, but with insufficient direct translational value to the broader population.

In a pilot cross-over study design using 2000 mg/day metformin for 8 weeks, Koenig et al. 2017 observed statistically significant favorable effect of metformin on executive function (Trail B test) and beneficial trends on measures of learning and memory (PAL total errors) and attention (DMS percent correct simultaneous) in non-diabetic MCI and AD patients. (Koenig et al. 2017) The study included 9 women and 11 men. The strength of the study was a cross-over design. The major limitation of the study was the pilot design with a small sample size. Similarly, in the Diabetes Prevention Program (DPP study), 2280 participants (776 on metformin, and 755 on placebo) were assessed for metformin and cognition relation. Overall this study observed no relation between metformin and cognition, which means that metformin was neither beneficial nor harmful in this study participants, and the authors concluded that metformin is cognitively safe. (Luchsinger et al. 2017) The cognitively safer outcome will support the use of metformin for longevity benefit. When looked at specific groups within the population, not all groups responded unequivocally. Especially the groups with higher hyperglycemia had worse cognition, and the aged population has consistently poor (non-significant) cognitive tests outcomes across all tests. (supplementary table 2 of the citation) Overall, men had significantly poor cognitive outcomes compared with women. (supplementary table 3 of the citation). Collectively, these factors indicate the role of hyperglycemia, age, and sex in cognitive outcomes in the presence of metformin.

On the contrary, metformin treatment was also associated with cognitive decline in diabetic subjects receiving at least 1 g metformin per day for over 6 months

when compared with untreated, non-diabetic controls (Khattar et al. 2016). This study had several limitations. Firstly, the effects of age, sex, and disease severity were not controlled. Secondly, the controls used in this study were healthy, non-diabetic, age-matched subjects not receiving metformin medication, suggesting that cognitive effects observed in this study could be attributed to the severity of diabetes alone and may not be related to metformin. Future studies should consider using controls with pre-diabetic blood glucose levels with and without metformin treatment. Such an evaluation would provide a complete and more direct picture of the cognitive effects of metformin.

Similarly, the dementia screening program suggested an increased risk for cognitive impairment associated with diabetes and metformin, especially after adjustment for the age, sex, educational level, baseline test scores, hypertension, dyslipidemia, BMI, and baseline brain imaging abnormality (Koo et al. 2019). Kuan et al. (2017) used the Multivariate Cox proportional hazards regression model and supported the notion that metformin increased the risk for AD, vascular dementia, and Parkinson's disease (PD) (Kuan et al. 2017). The strength of this study was a large sample size (4651 patients), adjustment for several confounding factors, and 12-year follow-up. The authors reported that higher doses (> 385 g per year) and longer duration of metformin treatment increased the risk for developing PD (3.54 times) and dementia (1.97 times). Although this was a large sample size study, which controls for both age (54–75 years) and sex, the authors did not elucidate age-sex interaction effects in their data analysis.

In another study, the authors reported a higher risk of cognitive impairment in diabetic patients taking metformin (Moore et al. 2013). However, the authors also acknowledged study limitations, such as the lack of data on diabetes duration, severity, metformin treatment duration, and use of concomitant anti-diabetic agents. Careful consideration and further assessment of the study by Hervas et al. 2017 provide more insight into metformin's effect on cognition. The control group (without motor manifestation) showed cognitive impairment with metformin compared with the non-metformin group and beneficial effect of metformin on cognition in the Huntington's disease (HD) group (Fig. 1 in the citation) (Hervas et al. 2017). In a clinical cohort of 67,731 elderly patients (> 65 years old), the results demonstrated an association between diabetic status and dementia, which was mitigated with prolonged metformin therapy (Cheng et al. 2014). However, there was no consideration of metformin dose or sex-dependent analysis. Another two observational studies involving T2DM patients suggested that metformin was associated with impaired cognitive performance due to vitamin B_{12} deficiency (Biemans et al. 2015; Moore et al. 2013). However, Khattar et al. ruled out such a notion (Khattar et al. 2016).

Overall, there were mixed and complex reporting of metformin-induced alterations in cognition in human studies. This further provides strength to the argument that metformin may not be "fit for all" cognitively safe medication when under consideration for longevity benefits. Individual risk and benefit assessment are necessary for such utilization.

Animal studies

Often animal experiments are performed for better-controlled study design. In the adult, male Wistar rats, 100 mg/kg/day metformin reversed scopolamine-induced cognitive impairment (Mostafa et al. 2016). Metformin attenuated impairments of spatial learning and memory, as well as short-term working memory. This effect was associated with reduced inflammation and oxidative stress-mediated through Akt activation. Similarly, metformin (100 mg/kg) reduced cisplatin-induced cognitive impairment in young (8–10 weeks) female C57BL/6 mice during novel object recognition and social discrimination testing (Zhou et al. 2016). The positive aspect of this study was the use of female mice, as behavioral studies tend to neglect females due to phenotype variability across the estrous cycle. However, the authors failed to mention a possible trend of a deleterious effect of metformin compared with saline control in behavior tests (Fig. 1 in the citation) (Zhou et al. 2016).

Another study compared middle-aged male (12 months) C57BL/6 mice receiving chronic metformin treatment and chronic high-fat diet (HFD). Results suggested an improved spatial learning, coordinated running performance, and reduced memory impairments (Allard et al. 2016). However, this study lacks the inclusion of a "control+metformin" treatment group. Metformin treatment lowered body weight, which may confound the outcome of cognitive tests (latency to reach platform parameter). The coordinated running performance is negatively influenced by higher body weights (Cook et al. 2002; Mao et al. 2015; McFadyen

et al. 2003). The body weights of the mice in HFD with metformin treatment were significantly lower than HFD without metformin treatment (Allard et al. 2016). Similarly, in the Morris water maze test, the authors used latency to reach the platform, rather than path length as a learning measure. Higher body weight, reduced motor function, or slower swim speeds may influence escape latency, thereby skewing its utility as a learning measure in treatments that influence these variables.

These escape latency results were replicated in adult male Wistar rats receiving HFD and metformin treatment (Pintana et al. 2012). Alzoubi et al. reported similar preventative effects of metformin after chronic L-methionine-induced cognitive impairment using radial arm maze performance, spatial learning, and memory metric (Alzoubi et al. 2014). Metformin treatment at 100 mg/kg/day reversed the cognitive decline associated with HFD and chronic restraint stress in male Wistar rats (Khedr et al. 2018). However, the cognitive assessment parameter used in the Morris water maze testing was a latency to reach the escape platform. Since HFD, chronic restraint stress, as well as metformin treatment altered the body weight in these rats the latency, may not be an accurate estimate for cognition. This confound of weight can be removed by re-analyzing the data using body weights as co-variate. Contrastingly, another study using Wistar rats reported no influence of metformin fortified diet on cognition, despite improving insulin sensitivity (McNeilly et al. 2012). The study used Matched-the-Position tasks for cognitive assessment.

Overall, Table 2 B and C indicates cognitively beneficial effects of metformin in the presence of major disease models and possible deleterious effects in the absence of disease model. This further suggests that metformin could be useful, cognitively safer, and even beneficial as longevity medicine in the presence of certain disease conditions. However, caution needs to be taken in the absence of such major diseases when it could be possible that longevity benefit is accompanied by cognitive deterioration and reduced quality of life.

The sex-dependent actions of metformin

Despite a higher prevalence of type 2 diabetes in men (CDC 2015), women with T2DM have poorer glycemic control and underachievement of desired hemoglobin A_{1c} (HbA_{1c}) levels (Chiu and Wray 2011; Nilsson et al. 2004). Women with diabetes have higher mortality, reduced lifespan, and more complications compared with men (Deshpande et al. 2008; Gregg et al. 2007). The influence of sex steroids may underlie the sex-specific differences in disease progression and treatment responses (Arnetz et al. 2014). Hormone-based sex differences are evident in the most oral anti-hyperglycemic agents on the market today, including metformin (Arnetz et al. 2014).

Previous work demonstrates that metformin's bioavailability and glycemic control does not vary across sex or ethnicity in young adults (Karim et al. 2007). However, differences have been reported between sexes for metformin's non-diabetic effects on physiology. In men, metformin increased plasma fatty acid levels, myocardial fatty acid utilization, and oxidation, and lower myocardial glucose utilization, indicating decreased fatty acid clearance (Lyons et al. 2013). Despite similar glucose control, only in men with lower testosterone levels, metformin decreased thyrotropin levels, Jostel's thyrotropin index, and increased SPINA-GT when compared with normal testosterone level group (Krysiak et al. 2019). Another study found that men admitted to the intensive care unit for metformin-induced lactic acidosis had higher mortality compared with women (Biradar et al. 2010). Similarly, males with colorectal cancer had higher mortality when they were taking metformin compared with females colorectal patients on metformin (Park et al. 2017). On the other hand, in the Diabetes Prevention Program study, women receiving metformin to prevent T2DM were less adherent to treatment and reported a higher rate of adverse events (Walker et al. 2006). Metformin has also been associated with higher hospitalization and mortality rates in women (Pongwecharak et al. 2009).

Metformin exerted strong sex-dependent survival benefit in cases of colorectal cancer (CRC). This benefit was associated with longer duration of treatment with metformin (more than 22 months). After controlling for other clinically relevant factors, female diabetic patients with advanced stage CRC who had been treated with metformin had significantly lower CRC-related mortality, as compared with male counterparts (Park et al. 2017). In the Taiwanese population, Lee et al. (2011) reported similar findings with female CRC patients benefitting more than male CRC patients. However, the authors further reported the opposite sex effect with male hepatocellular cancer patients benefitting more than females (Lee et al. 2011). Interestingly, this differential effect on cancer-related mortality across sexes was

associated with lower dose metformin (500 mg/day) (Lee et al. 2011).

There are also potential sex-specific differences in the effect of metformin on longevity dependent on the strain of the mice. In female mice, the highest to lowest longevity benefit with metformin was reported in SHR (+ 37.9%) (Anisimov et al. 2008), FVB/N (+ 8.0% and + 6.7%) (Anisimov et al. 2005; Anisimov et al. 2010a), 129/Sv (+ 4.4%) (Anisimov et al. 2010b), and HD (0%) (Ma et al. 2007) strains, while in male mice, the high to low longevity effect was noted in HD (+ 20.1%) (Ma et al. 2007) and 129/Sv (− 13.4%) (Anisimov et al. 2010b) strains.

Few pre-clinical or clinical studies have investigated the effect of metformin on cognitive function. The available data shows mixed results of metformin-induced cognitive alterations. (Table 2 A, B, and C) (Guo et al. 2014; Kuan et al. 2017; Moore et al. 2013; Mostafa et al. 2016; Ng et al. 2014; Ying et al. 2014; Zhou et al. 2016). In our lab, we found learning and memory impairments in non-diabetic, young adult and aged C57BL/6 male mice after receiving metformin at human equivalent doses (1.5–2.0 g/day). Data analysis has suggested that this cognitive impairment was nearly exclusive to male mice, suggesting sex as a critical determinant for future investigation.

The role of organic cation transporters in the sex difference of metformin

The transport of metformin across organs occurs through organic cation transporters (OCTs). There is increasing evidence that sex steroids affect the expression and function of OCTs. OCT2 expression is lower in female rat kidneys compared with males, resulting in a lower urinary excretion rate for metformin (Ma et al. 2016). The reduced elimination of metformin could lead to higher metformin accumulation in other organ systems of females, underscoring some of the aforementioned sex-dependent complications. Daily administration of testosterone (10 mg/0.1 ml of olive oil) for 7 days increased OCT2 mRNA levels, OCT2 protein expression, and OCT2 transport activity in both males (significant $p < 0.05$) and females (not significant $p > 0.05$) in Wistar rats. Conversely, daily administration of 17β-estradiol (1 mg/0.1 ml of olive oil) for 7 days decreased transport activity of the OCT2 protein in male rats only (Urakami et al. 1999). Given that sex hormone levels vary among men and women across the lifespan, it is possible that metformin effects could be age-dependent. However, metformin is also the substrate for MATE1 and MATE2. Estrogen therapy in ovariectomized mice decreased the expression on MATE2 transporters (Meetam et al. 2009b). In contrary to above discussion, a recent study found no sex differences in metformin accumulation in the kidney, liver, brain, intestine, heart, and lung within 2 h after a single dose of metformin (Ma et al. 2016). However, the time point of 2 h may not be a good indicator for chronically prescribed drug like metformin.

We determined the expression of OCT2 in the hippocampus of young (3 months), middle age (12 months), and old (22 months) male mice. We observed that OCT2 expression decreased over age in the hippocampus (Supplemental Fig. 2). Further, we assessed the OCT2 mRNA expression variation using qPCR in adult male and female mice (6 months). We noticed that the female cortex and hippocampus had higher OCT2 mRNA expression compared with male. However, when checked the translation of this OCT2 mRNA to proteins, we observed that at the age of 6 months, the OCT2a and b protein expression in hippocampus did not vary in male and female. This could be due to the inhibition of translation of mRNA to protein by higher estrogen in female mice at a younger age when compared with age-matched male mice. However, the translation inhibition may be reversed in an older female with lower levels of inhibitory estrogen.

In rats, metformin shows variable accumulation in the brain depending on the duration of metformin therapy (Labuzek et al. 2010—Table 2, columns 1 and 3) (Labuzek et al. 2010). At 2 h following a single dose of metformin, there was 2.5-fold increased concentration in the CSF, and 1.3-fold increased concentration in the cerebellum, as compared with plasma. Meanwhile, the hippocampus and frontal cortex had lower concentrations than plasma, with 0.3- and 0.5-fold differences respectively (Labuzek et al. 2010). At 3-week treatment, there was a 2.5- to 4-fold increased metformin concentration in the hippocampus, cerebellum, and frontal cortex, as well as a 14.5-fold increased concentration in the CSF, as compared with plasma (Labuzek et al. 2010). Regardless of the duration of metformin therapy, CSF always had the highest concentration of metformin, which is likely due to having the highest expression of OCT2 transporters. For diabetic and pre-diabetic patients, metformin is routinely administered chronically

Table 2 Studies with a focus on metformin and cognition

Sr.	Species	Sex	Sex-based analysis	Age (years/weeks/months)	Pathological conditions	Metformin dose	Metformin duration	Evaluation	Outcome	Reference
A. Human										
		57–58/42–43 (M/F)%	No	61–67 years	Diabetes and non-diabetic control not on metformin	No data	No data	Longevity	Longevity benefit over control	(Bannister et al. 2014)
		Both	No	40 and 65 years	T2DM	0.5–2.0 g/day	24 weeks	Cognition, anti-depressant effect	Better cognition, lessen depression	(Guo et al. 2014)
		60/40 (M/F)%	No	51–99 years	Alzheimer disease/mild cognitive impairment or cognitively normal	No data	No data	Cognition	Impairment of cognition	(Moore et al. 2013)
		Both	No	55 years and more	Diabetes and non-diabetic control not on metformin	No data	4–6 years	Cognition	Reduced risk of cognitive impairment	(Ng et al. 2014)
		Not disclosed	No	36–60 years	Diabetic vs healthy control	1 g/day	6 months	Cognition	Cognitive impairment	(Khattar et al. 2016)
		Both	No	67–80 years	Diabetes	No data	No data	Dementia	Lower association of dementia	(Cheng et al. 2014)
		Both	No	41–73 years	Diabetes	1.7 g/day	8–12 years	Cognition	No association with cognition	(Luchsinger et al. 2017)
		Both	No	54–75 years	Diabetes, Alzheimer disease, Parkinson disease	130 g–385 g/year	Up to 400 days	Cognition and neurodegenerative disease	Cognitive impairment	(Kuan et al. 2017)
		Both	No	30–72 years	Diabetes, Huntington's disease	No data, only intake association study	No data	Cognition and motor function	Cognitive impairment in control and cognitive benefit in HD	(Hervas et al. 2017)
		Female	No	56–70 years	Breast cancer survivor, obesity	500–1500 mg/day	6 months	Cognition	No effect on cognition	(Hartman et al. 2019)
		Male	No	25 and 30 years	Fragile X syndrome	500–2000 mg/day	1 year	Cognition and behavior	Improved cognition	(Protic et al. 2019)
		Both	No	55–80 years	Non-diabetic mild cognitive impairment and Alzheimer's disease	2000 mg/day	8 weeks	Cognition and biomarkers	Improved cognition	(Koenig et al. 2017)

Table 2 (continued)

Sr.	Species	Sex	Sex-based analysis	Age (years/weeks/months)	Pathological conditions	Metformin dose	Metformin duration	Evaluation	Outcome	Reference
		Both	No	> 60 years	Diabetic	NA	NA	Cognition	Higher risk for cognitive impairment	(Koo et al. 2019)
		Both	No	68.1 ± 7.8 years	Non-dementia vascular cognitive impairment	500 mg t.i.d.	1 year	Cognition	Improved cognition	(Lin et al. 2018)
		Both	No	> 65 years	Dementia	NA	NA	Cognition	Better cognition compared with sulphonylureas	(Orkaby et al. 2017)
B. Mice										
1	(129/Sv)	Male, female	Yes	3 months	Non-diabetic	100 mg/kg	18 months	Longevity	Decreased lifespan in male and increased lifespan in female	(Anisimov et al. 2010a)
2	C57BL/6	Male	No	6 and 11 months	Non-diabetic	0.1 to 1% metformin	Life-long	Longevity	Longevity benefit over control	(Martin-Montalvo et al. 2013)
3	C57BL/6	Female	No	8–10 weeks	cis-Diamineplatinum(II) dichloride (cisplatin)	100 mg/kg	7 days	Cognition	Prevention of cognitive impairment	(Zhou et al. 2016)
4	C57BL/6	Male	No	3, 12, and 24 months	Non-diabetic	297 mg/kg	3 months	Cognition	Cognitive impairment	(Thangthaeng et al. 2017)
5	C57BL/6J	Male	No	12 months	High-fat diet-induced diabetes	1% by weight	6 months	Cognition and psychomotor	Prevention of cognitive impairment	(Allard et al. 2016)
6.	C57BL/6	Male	No	3 months	Non-diabetic	181.8 mg/kg	3 months	Cognition and psychomotor	Impaired cognition	(Wenjun Li)
6	Outbred Swiss-derived female (SHR)	Female	No	3 months	Non-diabetic	100 mg/kg	No data	Longevity	Longevity benefit over control	(Anisimov et al. 2008)
7	Balb/c	Male	No	3 months	Non-diabetic	300 mg/kg	14 days	Cognition and neurogenesis	Reversed AlCl3·6H2O-Induced memory and neurodegeneration deficit	(Ahmed et al. 2017)
8	APP/PS1	Both	No	12–13 months	Non-diabetic, Alzheimer disease mouse model	5 g/l ad libitum in drinking water	8 months	Cognition	Improved memory	(Matthes et al. 2018)
9	APP/PS1	Female	No	26 weeks		200 mg/kg	14 days	Cognition	Improved cognition	(Ou et al. 2018)

Table 2 (continued)

Sr.	Species	Sex	Sex-based analysis	Age (years/weeks/months)	Pathological conditions	Metformin dose	Metformin duration	Evaluation	Outcome	Reference
					Non-diabetic Alzheimer disease mouse model					
10	C57/129j	No detail	No	2 months	Non-diabetic	200 mg/kg	38 days	Cognition and neurogenesis	Improved memory and increased neurogenesis	(Wang et al. 2012)
11	ApoE TR	Male	No	13 month	Alzheimer disease risk model	300 mg/kg	5 months	Cognition	Improved in ApoE3 TR mice only	(Zhang et al. 2019)
12	No	Female	No	No age (22–27-g body weight)	Ovariectomy	7–15 mg/kg	21 days	Cognition	Improved cognition	(Fatemi et al. 2019)
13	C57BL/6J	Male	No	8–10 weeks	Streptozotocin-induced diabetes	200 mg/kg	6 weeks	Cognition	Improved cognition	(Wang et al. 2018a)
14	C57BL/6J	Male	No	6 weeks	High-fat diet-induced diabetes	0.2% w/w	6 months	Cognition	Improved cognition	(Mamo et al. 2019)
C. Rats										
1	Wistar	Male	No	Adult (180–200 g)	Scopolamine insult	100–300 mg/kg	14 days	Cognition	Prevention of cognitive impairment	(Mostafa et al. 2016)
2	Wistar	Male	No	5 weeks (180–200 g)	High-fat diet-induced diabetes	30 mg/kg	21 days	Cognition and mitochondrial function	Prevents brain mitochondrial dysfunction and ultimately restores learning behavior	(Pintana et al. 2012)
3	Wistar	Male	No	200–250 g	L-Methionine induced cognitive impairment	30 mg/kg/	4 weeks	Short-term and long-term memory	Prevents short- and long-term memory	(Alzoubi et al. 2014)
4	Wistar	Male	No	125–150 g	High-fat diet-induced diabetes	1800 ppm (144 mg/kg diet)	10 weeks	Cognition	No effect	(McNeilly et al. 2012)
5	Wistar	Male	No	150–200 g	High-fat diet-induced stress and depression	100 mg/kg/day	4 weeks	Cognition Lipid profile	Reverted stress and high-fat diet-induced cognitive decline	(Khedr et al. 2018)
6	Wistar	Male	No	250–300 g	Methamphetamine induced anxiety, depression, cognition impairment and neurodegeneration	50–150 mg/day	21 days	Cognition, anxiety, depression, neurodegeneration	Dose dependent improved in cognition	(Keshavarzi et al. 2019)

Table 2 (continued)

Sr.	Species	Sex	Sex-based analysis	Age (years/weeks/months)	Pathological conditions	Metformin dose	Metformin duration	Evaluation	Outcome	Reference
7	Sprague-Dawley	Mae	No	8 weeks	Hypobaric hypoxia induced cognitive impairment	100 mg/kg	21 days	Cognition	Prevented impairment in cognition	(Zhao et al. 2019)

for months to years. It is possible that the long-term use could likely lead to rising accumulation of metformin in the brain, ultimately impacting the brain function in a time-dependent manner (Thangthaeng et al. 2017; Wenjun Li et al. 2019). We observed sex-dependent negative impact of metformin on short-term memory, cognitive flexibility, and delayed reversal in non-diabetic young adult C57BL6 male mice only and no such effect in females (Supplemental Fig. 3). In the male mice, although metformin enhanced locomotor, balanced performance, and induced anxiolytic effect, metformin impaired both short-term cognition, cognitive flexibility, and long-term spatial cognitive function (Wenjun Li et al. 2019).

Aging affects metformin

Aging is associated with a physiological functional decline in various organ systems, including the hepatorenal metabolic-excretory system, psychomotor, and cognitive brain function (Costa et al. 2013; Shetty et al. 2014). With aging, sex hormonal decline occurs in both men and women (Bungum et al. 2011; Resnick et al. 2017). Sex hormones affect the expression and function of OCTs. Castrated rats showed OCT function loss, which is restored with the administration of testosterone (Meetam et al. 2009a). In male C57BL6 mice, OCTs are downregulated in the aging brain, as shown by lower mRNA and protein expression and activity (Wu et al. 2015). Contrastingly, the OCT function in ovariectomized mice was higher when compared with control and estrogen supplementation (Meetam et al. 2009b). In females, the sex hormone profile changes drastically across the lifespan. Near menopause initiation, there is a sudden drop in the estrogen:androgen ratio. This phase is dubbed as post-menopausal hyperandrogenism as characterized by higher levels of dehydroepiandrosterone and testosterone. This would necessarily mean that peri- and post-menopausal females may have a sudden increase in OCT expression and activity, further leading to significant differences in metformin bioaccumulation throughout the body and urinary excretion rates. Therefore, the age-associated altered sex steroids might affect the pharmacokinetics of metformin differently in men versus women requiring the specific calculation of the optimum dose to avoid any deleterious effects.

The direct action of metformin versus secondary glucose-lowering effect on cognition

Are the effects of metformin on longevity-related benefits universal? This critical question is thoroughly discussed by Konopka et al. 2019 and further supported by other studies (Konopka and Miller 2019). Metformin exerts antagonistic pleiotropy dependent on the presence or absence of pre-existing disease conditions such as T2DM, Alzheimer's, aging, Huntington's, Parkinson's disease, or cancers or concomitant interventions such as exercise (Table 2A) (Konopka et al. 2019; Konopka and Miller 2019; Walton et al. 2019). The impact of metformin, whether it is due to control of sugar levels or more direct, is ambiguous.

Alteration in glucose levels has an impact on cognition in both males and females across the lifespan. Both acute and chronic blood sugar aberrations lead to cognitive impairment (Davis et al. 1996; Draelos et al. 1995; Frier 2001; Gonder-Frederick et al. 1994; Ryan and Geckle 2000; Sheen and Sheu 2016; Sommerfield et al. 2004). A homeostatic normoglycemic range between 4 and 15 mmol/l is necessary to achieve optimum cognitive and psychomotor function (Cox et al. 2005). This range could represent an analog similar to routine physiological parameters, such as blood pressure and body temperature. Thus, a metformin-induced normoglycemic range higher or lower than the endogenous, homeostatic limits may be a critical determinant of altered cognitive function observed in previous studies.

It is possible that the metformin-associated increased risk of dementia, cognitive loss, and AD progression is not related to glucose controlling effect. In a mechanistic study using cell line and primary neurons, Chen et al. 2009 found that metformin increased Aβ generation by upregulating beta-secretase 1 (BACE1) promoter activity in an AMPK-dependent manner (Chen et al. 2009). Similar studies performed on non-diabetic AD mouse models (APP/PS1) found the opposite effect by improving cognition and memory benefits of short-term and long-term metformin therapy. These cognitive benefits were unrelated to glycemic control and were due to the prevention of both amyloid plaque formation and tau phosphorylation via multiple AMPK-dependent

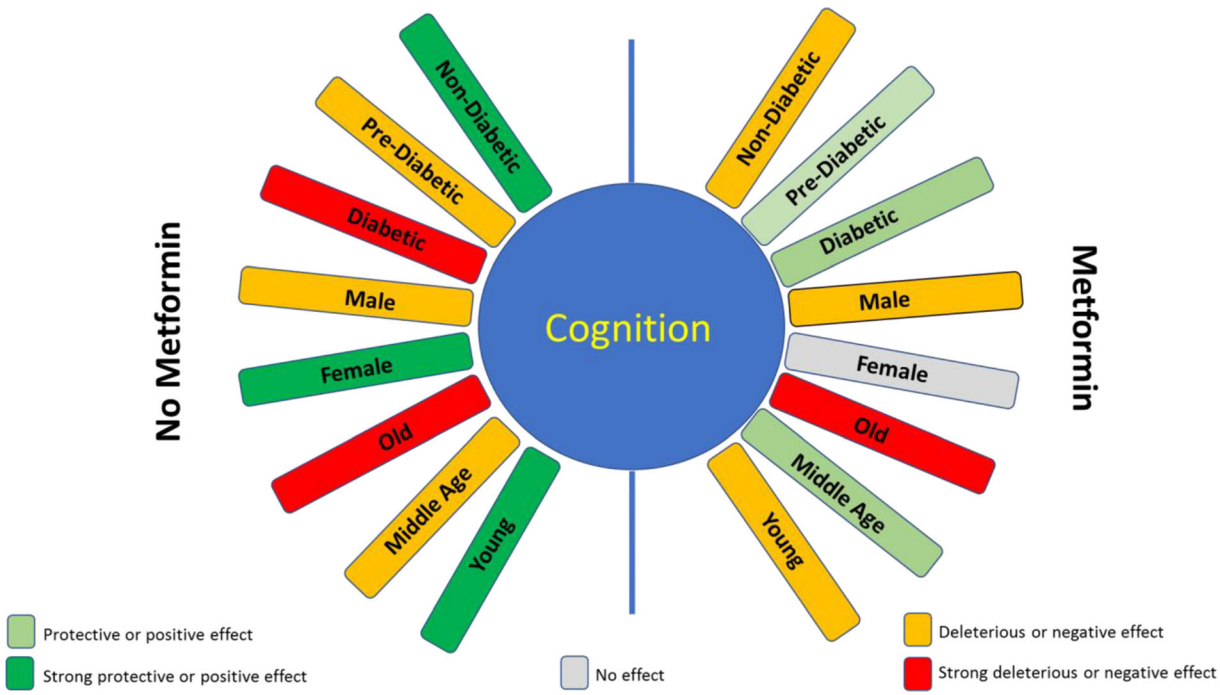

Fig. 2 Multifactorial interaction on the effect of metformin on cognition. The effect of metformin on cognition is mediated by a variety of factors, including age, sex, blood sugar levels, and associated disease condition. The color-coding in this predictive model is a summary of existing evidence on known mediators of metformin-induced cognitive changes. A more substantial clinical investigation should aim to extend these data to achieve a more accurate precision medicine approach to metformin pharmacotherapy

pathways (Matthes et al. 2018; Ou et al. 2018), which suggest that the experimental design and model plays a critical role in outcome and conclusion.

Microvascular injury can lead to cerebrovascular inflammation and lead to vascular cognitive impairment (Fulop et al. 2018). Co-existing conditions such as hypertension might induce microvascular injury leading to an acceleration of AD pathophysiology as well as VCI (Csiszar et al. 2017). Metformin has been found to improve cognitive function in patients with non-dementia VCI, abnormal glucose metabolism by improving insulin resistance index (Lin et al. 2018). Similarly, cerebral ischemia leads to cognitive alterations by fluctuating brain energy metabolism via AMPK activation. It is currently unclear whether this activity is protective or deleterious for neural tissues, and if AMPK manipulation could be helpful (Pineda-Ramirez et al. 2017). Metformin has been examined as a means to affect the ischemia-related cognitive decline. One study found that sub-chronic metformin pre-treatment enhanced novel object recognition performance in a rat model of forebrain ischemia (Ashabi et al. 2014). Another study demonstrated that long-term pre-treatment with metformin in global cerebral ischemia-induced upregulation of the AMPK-BDNF-P70S6K pathway, subsequently enhancing learning and memory (Ghadernezhad et al. 2016). It was also shown that 7-day metformin pre-treatment (10 mg/kg) significantly reduced AMPK activation in ischemic brains. This effect was not observed with other dosages or duration of administration. These findings suggest an association between metformin, AMPK, and neuroprotection in cerebral ischemia, but also demonstrate a need to optimize intervention initiation time, duration, and the dose of metformin (Deng et al. 2016).

Conclusion: (Fig. 2)

Based on this available information, it is clear that metformin affects longevity and neuro-cognition via AMPK-dependent and -independent mechanisms. Although various AMPK-independent mechanisms have been described over many years, these have not been well scrutinized in relation to cognition (Viollet et al. 2012). These effects of metformin were inconsistent and varied depending upon species (mice, rat, and human), sex, age, metformin dose, treatment duration, and associated pathological conditions (diabetes, stroke, AD, etc.). Figure 2 is not perfect and perhaps at the most primitive state just to put forth an idea that such a design and some form of the equation involving multiple factors may be useful in the future. There is a need for more translational studies that address these factors, to develop a comprehensive metformin dosing formula to achieve optimum anti-aging benefits and mitigate side effects. The differential and controversial impact of metformin on brain function described across the literature warrants a precision medicine-based approach to establish novel individualized therapy guidelines.

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