Additional Table 1 The positive effect of metformin on neurological diseases in humans and *in vivo*

Disease	Model	Treatment	Outcome	Specific outcome	Author	Year
AD, PD, HD	Human	T2D+	Improve	Lower risk of NDD (AD, PD, HD)	Shi et al.	2019
AD	APP/PS1-AD mouse model	200 mg/kg/day for 8 weeks	Improve	Alleviate behavioral changes	Lu et al.	2020
AD	APP/PS1-AD mouse model	4 mg/mL for 4 months	Improve	Metformin ameliorated the microglial autophagy impairment, reduced Aβ load, and tau pathology	Chen et al.	2021
AD	3xTg-AD mouse model	4 mg/mL for 6 weeks	Improve	Alleviates behavioral changes	Syal et al.	2020
AD	ApoE3-TR mouse model	300 mg/kg for 5 months	Improve	Improve the cognition	Zhang et al.	2019
AD	APP/PS1-AD mouse model	5 mg/mL for 8 months	Improve	Alleviates behavioral changes	Matthes et al.	2018
AD	APP/PS1-AD mouse model	3 mg/mL for 12 weeks	Improve	Alleviates behavioral changes and reduced the accumulated brain Aβ plaque	Xu et al.	2021
AD	APP/PS1-AD mouse model	200 mg/kg metformin for 14 days	Improve	Improved spatial memory deficit, neuronal loss, and enhanced neurogenesis	Ou et al.	2018
AD	APP/PS1-AD mouse model	200 mg/kg/day for 10 days	Improve	Decreased tau phosphorylation	Wang et al.	2020
AD	C57BL/6J mice	5 g/L metformin for 2 weeks	Improve	Decreased tau phosphorylation	Hettich et al.	2014
AD	Human	T2D+	Improve	Lower risk of AD	Sluggett et al.	2020
AD	Human	AD TD2-	Improve	Alleviates behavioral changes	Koenig et al.	2017
AD	Human	T2D+	Improve	Lower risk of dementia	Bohlken et al.	2018
AD	Human	General population	Improve	Lower risk of AD	Zheng et al.	2022

AD	Human	T2D+	Improve	Lower risk of AD	Torrandell-Haro et al.	2022
AD	Human	AD (MCI) T2D+	Improve	Improve cognitive performance	Pomilio et al.	2022
AD	Human	AD T2D+	Improve	Slower cognitive decline	Secnik et al.	2021
AD	Human	T2D+	Improve	Lower risk of dementia onset	Charpignon et al.	2022
AD	High-fat diet + Aβ	100 mg/kg for 8 weeks	Improve	Protective against Aβ	Asadbegi et al.	2016
AD	PS19 mice	4 mg/mL for 4 months	Improve	Improved learning and memory and decreased tau phosphorylation	Zhao et al.	2022
AD	SAMP8 mouse model	20 mg/kg/day or 200 mg/kg/day for 8 weeks	Improve	Improved learning and memory	Farr et al.	2019
AD	Streptozocin (STZ)-induced model	Post-STZ	Improve	Improved behavior	Pilipenko et al.	2020
AD	Streptozocin (STZ)-induced model	Post-STZ	Improve	Improved memory and decreased tau phosphorylation	Oliveira et al.	2021
AD	Streptozocin (STZ)-induced model	Post-STZ	Improve	Improved learning and memory	Nassar et al.	2020
AD	Streptozocin (STZ)-induced model	Post-STZ	Improve	Improved learning and memory	Kazkayasi et al.	2022
AD	Streptozocin (STZ)-induced model	Pre- and post-STZ	Improve	Improved inflammation and learning and memory	Saffari et al.	2020

AD	Wild-type and human tau transgenic mice	5 mg/mL for 16–24 days	Improve	Decreased tau phosphorylation	Kickstein et al.	2010
HD	zQ175-HD mouse model	2 mg/mL for 3 months	Improve	Reduction of nuclear aggregates of mHtt and alleviates behavioral changes	Sanchis et al.	2019
HD	Human	T2D+	Improve	Improves cognition	Hervás et al.	2017
HD	Hdh150-HD mouse model	5 mg/mL for 3 weeks	Improve	Reduced mHtt protein production and alleviates behavioral changes	Arnoux et al.	2018
MS	Cuprizone model	Simultaneous administer cuprizone and metformin	Improve	Attenuates inflammation and demyelination	Abdi et al.	2021
MS	Cuprizone model	Simultaneous administer cuprizone and metformin	Improve	Protected oligodendrocytes	Largani et al.	2019
MS	Cuprizone model	Post-cuprizone	Improve	Lesion reduction and alleviates behavioral changes	Sanadgol et al.	2020
MS	Cuprizone model	Post-cuprizone	Improve	Promotes oligodendrocyte production	Houshmand et al.	2019
MS	EAE model	Post-EAE	Improve	Reduced EAE symptoms	Sun et al.	2016
MS	EAE model	Post-EAE	Improve	Reduced EAE symptoms and inflammation	Paintlia et al.	2013a
MS	EAE model	Post-EAE	Improve	Attenuates inflammation and demyelination	Paintlia et al.	2013b
MS	EAE model	During and post-EAE	Improve	Attenuates inflammation	Nath et al.	2009
MS	Ethidium bromide (EB) model	Post-EB	Improve	Promotes remyelination	Arabmoazzen and Mirshekar	2021
MS	Ethidium bromide (EB) model	Pre-EB	Improve	Improved remyelination	Neumann et al.	2019
MS	Human	MS TD2-	Improve	Attenuates inflammation	Negrotto et al.	2016
MS	Lysolecithin	Post-lysolecithin injection	Improve	Improved behavior	Kosaraju et al.	2020

MS	Lysophosphatidylcholine model	Post-lysophosphatidylcholine	Improve	Attenuates inflammation and demyelination	Esmaeilnejad et al.	2021
PD	6-OHDA model	Pre- and post-6-OHDA	Improve	Improves motor symptoms	Ryu et al.	2020
PD	BALB/c mice	Rotenone (brain slice)	Improve	Reduced apoptosis	Sardoiwala et al.	2020
PD	Haloperidol model	Pre-haloperidol	Improve	Attenuates behavioral changes and antioxidant activity	Adedeji et al.	2014
PD	MPTP model	Post-MPTP	Improve	Reduced neuron death	Katila et al.	2017
PD	MPTP model	Pre- and post-MPTP	Improve	Reduced neuron death and improved behavior	Kang et al.	2017
PD	MPTP model	Simultaneous administer MPTP and metformin	Improve	Protected dopaminergic neurons	Lu et al.	2016
PD	MPTP model	Pre- and during MPTP	Improve	Reduced neuron death and improved behavior	Yan et al.	2017
PD	MPTP model	Pre- and post-MPTP	Improve	Improved behavior and antioxidant activity	Patil et al.	2014
PD	MPTP model	Post-MPTP	Improve	Attenuates neuron loss	Bayliss et al.	2016
PD	Rotenone model	Simultaneous administered rotenone and metformin	Improve	Reduced neuron death and improved motor function	El-Ghaiesh et al.	2020
PD	Rotenone model	Simultaneous administered rotenone and metformin	Improve	Alleviates depressive behavior, and inflammation, and improves neurogenesis	Mendonça et al.	2022b
PD	Rotenone model	Simultaneous administered rotenone and metformin	Improve	Alleviates behavioral changes	Mendonça et al.	2022a
PD	Rotenone model	Pre- and post-rotenone	Improve	Improved behavior and inflammation	Wang et al.	2020
Stroke	Cerebral I/R	Pre-cerebral I/R	Improve	Alleviates behavioral changes and protected against apoptosis	Ge et al.	2017
Stroke	Cerebral I/R	Pre-cerebral I/R	Improve	Attenuated apoptotic cell death	Ashabi et al.	2014

Stroke	Cerebral I/R	Post-cerebral I/R	Improve	Improves antioxidants	Zeng et al.	2019
Stroke	Cerebral I/R	Post-cerebral I/R	Improve	Reduced neuronal damage, promoted neuroblasts proliferation and neuronal differentiation	Yuan et al.	2019
Stroke	Cerebral I/R	Post-cerebral I/R	Improve	Attenuates inflammation and lipid peroxidation	Abd-Elsameea et al.	2014
Stroke	Cerebral I/R	During and post-I/R	Improve	Improves behavior and antioxidant levels	Fatemi et al.	2020
Stroke	Global I/R	Pre-global I/R	Improve	Attenuates inflammation	Ashabi et al.	2015
Stroke	High-fat diet in spontaneous stroke mice	6 months old till 12 months old	Improve	Delayed stroke occurrence	Hollander et al.	2017
Stroke	Human	T2D+	Improve	Less severe stroke, lower fatality, and lower disability rates	Tu et al.	2022
Stroke	Human	T2D+	Improve	Less severe strokes and better functional outcome	Westphal et al.	2020
Stroke	Human	T2D+	Improve	Metformin improves post-stroke outcomes	Kersten et al.	2022
Stroke	Human	T2D+	Improve	Improved outcome	Wu et al.	2016
Stroke	Human	T2D+	Improve	Improve mortality	Horsdal et al.	2011
Stroke	Human	T2D+	Improve	Reduced neurological severity	Mima et al.	2015
Stroke	Hypoxia-ischemia (H-I)	Post-H-I	Improve	Alleviates behavioral changes	Bourget et al.	2022
Stroke	Hypoxia-ischemia (H-I)	Post-H-I	Improve	Alleviates behavioral changes, and inflammation, and promoted oligodendrogenesis	Livingston et al.	2020
Stroke	Hypoxia-ischemia (H-I)	Post-H-I	Improve	Inhibition of neuronal apoptosis and inflammation	Fang et al.	2017
Stroke	Hypoxia-ischemia	Post-hypoxia	Improve	Promotes NPC migration, and differentiation, and	Dadwal et al.	2015

	(H-I)			restores sensory-motor function		
Stroke	Intraventricular hemorrhage (IVH)	Post-IVH	Improve	Alleviates behavioral changes	Cao et al.	2022
Stroke	Middle cerebral artery occlusion (MCAO)	Post-MCAO	Improve	Promoted functional recovery	Jin et al.	2014
Stroke	Middle cerebral artery occlusion (MCAO)	Pre-MCAO	Improve	Decreased neurobehavior scores, infarct area, and apoptosis	Wang et al.	2021
Stroke	Middle cerebral artery occlusion (MCAO)	During and post-MCAO	Improve	Promoted focal angiogenesis and neurogenesis	Liu et al.	2014b
Stroke	Middle cerebral artery occlusion/reperfusion (MCAO/R)	Post-MCAO	Improve	Attenuates neurological deficits and neuronal apoptosis	Ruan et al.	2021
Stroke	Middle cerebral artery occlusion/reperfusion (MCAO/R)	Post-MCAO	Improve	Alleviates behavioral deficits and enhanced angiogenesis	Venna et al.	2014
Stroke	Permanent middle cerebral artery occlusion (pMCAO)	Pre-MCAO	Improve	Reduced infarct volume, neurological deficits and cell apoptosis	Jiang et al.	2014
Stroke	Permanent middle cerebral artery occlusion (pMCAO)	Pre-MCAO	Improve	Reduced infarct volume and neurological deficits	Zhu et al.	2015

Stroke	Permanent middle cerebral artery occlusion (pMCAO)	Pre-MCAO	Improve	Decreased neurological score, infarct area, and apoptosis	Deng et al.	2016
Stroke	Permanent middle cerebral artery occlusion (pMCAO)	Post-MCAO	Improve	Improves neurological state and reduces infarct size	Zemgulyte et al.	2021
Stroke	Permanent middle cerebral artery occlusion (pMCAO) in spontaneously hypertensive rats	Pre-MCAO	Improve	Increased life span and reduced the infarct area	Guo et al.	2017
Stroke	Transient forebrain global cerebral ischemia	Pre-GCI	Improve	Improved memory and neurological scores	Ghadernezhad et al.	2016
Stroke	Transient forebrain global cerebral ischemia	Pre-GCI	Improve	Alleviates behavioral changes	Sarkaki et al.	2015
Stroke	Transient forebrain global ischemia	Pre-transient forebrain global ischemia	Improve	Alleviates behavioral changes	Ashabi et al.	2016
Stroke	Transient global cerebral ischemia (tGCI)	Pre-tGCI	Improve	Attenuated BBB disruption	Farbood et al.	2015
Stroke	Transient middle cerebral artery occlusion (tMCAO)	Post-MCAO	Improve	Reduced cerebral infarction volume, improved the neurological deficit score, and ameliorated neuronal apoptosis	Liu et al.	2022

	mouse model					
Stroke	Transient middle cerebral artery occlusion (tMCAO) mouse model	Post-MCAO	Improve	Alleviates BBB disruption and caused protected against apoptosis	Liu et al.	2022
Stroke	Transient middle cerebral artery occlusion (tMCAO) mouse model	Post-MCAO	Improve	Improved neurobehavioral outcomes, reduced infarct volume, and attenuated inflammatory	Liu et al.	2014a

AD: Alzheimer's disease; Aβ: amyloid beta; BBB: blood-brain barrier; EAE: experimental autoimmune encephalomyelitis; GCI: global cerebral ischemia; HD: Huntington's disease; I/R: ischemia/reperfusion; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS: multiple sclerosis; NDD: neurodegenerative diseases; NPC: neural progenitor cell; PD: Parkinson's disease.