Altered Central and Blood Glutathione in Alzheimer Disease and Mild Cognitive Impairment: a Meta-Analysis

Jenny Jinghan Chen, Mathura Thiyagarajah, Jianmeng Song, Clara Chen, Nathan Herrmann, Damien Gallagher, Mark J. Rapoport, Sandra E. Black, Joel Ramirez, Ana C. Andreazza, Paul Oh, Susan Marzolini, Simon J. Graham, and Krista Lanctôt

Sunnybrook HEALTH SCIENCES CENTRE

UHN Toronto General Toronto Western Princess Margaret Toronto Rehab

UNIVERSITY OF TORONTO

Introduction & Background

- Glutathione (GSH) - primary brain antioxidant
- Oxidative Stress (OS) seen in Alzheimer Disease (AD) and Mild Cognitive Impairment (MCI)
- Depletion of GSH linked to OS-mediated neurodegeneration

Objectives & Hypotheses

- Aim: to quantitively review the body literature of in vivo GSH in brain and blood using meta-analytic methods in those with AD and MCI
- **Hypothesis: GSH will be lower in AD and MCI compared to controls**

Methods

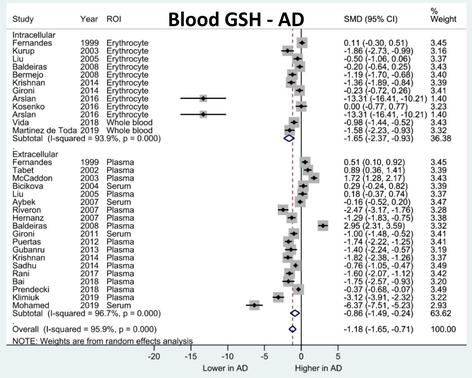
- Searched Medline, PsychInfo, and Embase (1947-June 2020) for studies with *in vivo* brain or blood GSH in MCI or AD with a healthy control (HC) group
- Standardized mean differences (SMD) and 95% confidence interval (95CI) calculated using random effects models
- A-priori subgroups:
  - Meshcher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) vs. non in brain GSH
  - Intra- vs. extra-cellular in blood GSH
- Q statistic and Egger's test were used to assess heterogeneity and risk of publication bias

Sample Search Strategy (PRISMA guidelines)	
Population	"Alzheimer Disease" OR "Dementia" OR "Dementia, Vascular" OR "Dementia, multi-infarct" OR "cognitive dysfunction" **Note MCI is indexed under these terms
Method of measurement	"Magnetic resonance spectroscopy" OR "Proton Magnetic Resonance Spectroscopy"
Comparison	AD or MCI vs. Controls
Outcomes	"Glutathione" OR "Oxidative Stress" OR "Antioxidants"
Type of question	Screening/diagnosis/prognosis
Type of Study	Randomized control trials, controlled trials, prospective/cohort/longitudinal follow-up studies, cross sectional studies, case control studies Exclude: case reports, research in progress, conference abstracts, dissertations, books, scientific meeting reports

Summary of Included Studies (Blood GSH)

- AD: lower intracellular and extracellular blood GSH overall
- Heterogeneity observed throughout (I2 >85%)

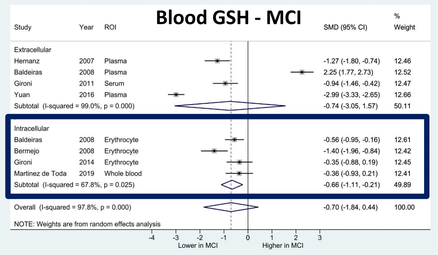
First Author, Publication Year	Tissue	Analysis Method	N (Case/HC)	MMSE of Case	Mean Age	% Male
Blood GSH studies – AD						
Arslan, 2016	Erythrocyte	DTNB	24/15	N/A	73.5	77%
Aybek, 2007	Serum	DTNB	62/56	17.8	72.1	47%
Bai, 2018	Plasma	DTNB	16/16	13.1	N/A	N/A
Baldeiras, 2008	Plasma and erythrocyte	OPA	42/37	20.9	70.8	39%
Bermejo, 2008	Erythrocyte	OPA	45/28	N/A	80.0	N/A
Bicikova, 2004	Serum	HPLC	21/40	N/A	72.5	44%
Fernandes, 1999	Plasma and erythrocyte	OPA	74/35	N/A	67.2	45%
Gironi, 2011	Serum	HPLC	25/66	18.9	72.5	36%
Gironi, 2014	Erythrocyte	HPLC	37/28	N/A	76.1	40%
Gubandru, 2013	Plasma	DTNB	21/10	10.51	79.9	52%
Hernanz, 2007	Plasma	HPLC	25/44	N/A	73.4	52%
Kliumiuk, 2019	Plasma	DTNB	15/50	13.4	80.9	30%
Kosenko, 2016	Erythrocyte	DTNB	12/14	N/A	76.1	35%
Krishnan, 2014	Plasma and erythrocyte	DTNB	30/40	4	66.3	54%
Kurup, 2003	Erythrocyte	DTNB	15/15	N/A	N/A	N/A
Liu, 2005	Plasma and erythrocyte	HPLC	33/20	17.7	75.9	45%
Martinez de Toda, 2019	Whole blood	OPA	20/30	N/A		55%
McCaddon, 2003	Plasma	HPLC	50/57	18	79.0	37%
Mohamed, 2019	Serum	ELISA	50/25	19.2	69.8	50%
Prendecki, 2018	Plasma	HPLC	88/80	15.3	73.9	73%
Puertas, 2012	Plasma	DTNB	46/46	22	74.2	39%
Rani, 2017	Plasma	DTNB	45/45	3.5	69.6	N/A
Riveron, 2007	Plasma	DTNB	25/30	N/A	N/A	N/A
Sadhu, 2014	Plasma	DTNB	104/93	6.4	N/A	54%
Tabet, 2002	Plasma	Commercial Assay Kit	31/30	13.9	N/A	46%
Vida, 2018	Whole blood	OPA	44/38	19.3	75.9	41%
Blood GSH studies – MCI						
Baldeiras, 2008	Plasma and erythrocyte	OPA	85/37	27	70.3	39%
Bermejo, 2008	Erythrocyte	OPA	34/28	27	78.3	N/A
Gironi, 2011	Serum	HPLC	20/66	N/A	71.4	33%
Gironi, 2014	Erythrocyte	HPLC	26/28	21.5	76.5	43%
Hernanz, 2007	Plasma	HPLC	26/44	N/A	74.4	51%
Martinez de Toda, 2019	Whole blood	OPA	20/30	25	N/A	50%
Yuan, 2016	Plasma	Commercial assay kit	138/138	N/A	64.5	51%



Abbreviations: AD - Alzheimer Disease, DTBN - 5,5'-dithio-bis(2-nitrobenzoic acid), ELISA - Enzyme-linked immunosorbent assay, GSH – Glutathione, HC - Healthy control, HPLC – High performance liquid chromatography, MCI - Mild Cognitive Impairment, MMSE - Mini-Mental State Examination, N/A – not available, OPA - O-Phthalaldehyde

- Egger's test indicated risk of publication bias in AD studies (bias [95%CI] = -7.04 [-11.49, -2.95], p=0.003)

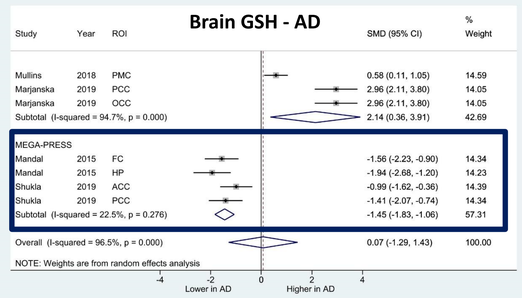
- MCI: no difference overall, in subgroup analysis, intracellular GSH lowered vs. HC



Summary of Included Studies (Brain GSH)

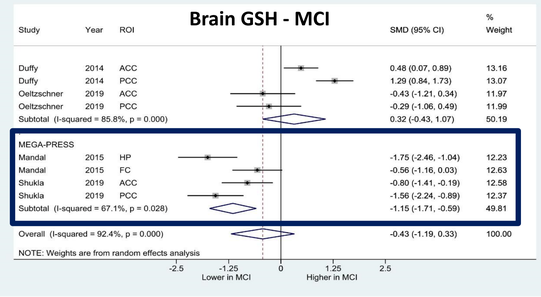
- Subgroup of studies using MEGA-PRESS reported lower brain GSH in AD and MCI
- Heterogeneity observed throughout (I2 >85%)

First Author, Publication Year	Tissue	Analysis Method	N (Case/HC)	MMSE of Case	Mean Age	% Male
Brain GSH studies – AD						
Mandal, 2015	Brain: hippocampus, frontal cortex	MEGA-PRESS, reference: water	19/28	23.6	66.2	68%
Marjanska, 2019	Brain: posterior cingulate, occipital cortex	STEAM, reference: water	16/33	19	73.2	82%
Mullins, 2018	Brain: posteromedial cortex	J-PRESS, reference: creatine	27/54	25.4	72.2	57%
Shukla, 2019	Brain: anterior and posterior cingulate	MEGA-PRESS, reference: water	18/27	N/A	69.4	70%



Abbreviations: AD - Alzheimer Disease, GSH – Glutathione, HC - Healthy control, MCI – Mild Cognitive Impairment, MEGA-PRESS - Meshcher-Garwood Point-Resolved Spectroscopy, MMSE - Mini-Mental State Examination, N/A – not available, PRESS – Point-Resolved Spectroscopy, SMD - Standardized mean difference, STEAM - STimulated Echo Acquisition Mode

First Author, Publication Year	Tissue	Analysis Method	N (Case/**HC**)	MMSE of Case	Mean Age	% Male
Brain GSH studies – MCI						
Duffy, 2014	Brain: anterior and posterior cingulate	PRESS, reference: creatine	54/41	28.7	68	52%
Mandal, 2015	Brain: hippocampus, frontal cortex	MEGA-PRESS, reference: water	22/28	24.2	66	65%
Oeltzschner, 2019	Brain: anterior and posterior cingulate	STEAM, reference: creatine	13/26	28.1	69	65%
Shukla, 2019	Brain: anterior and posterior cingulate	MEGA-PRESS, reference: water	19/28	N/A	66.6	71%



- Egger's test indicated risk of publication bias in MCI studies (bias [95%CI] = -11.28 [-20.6, -1.95], p=0.03)

Conclusion

- Blood GSH: intracellular GSH may be more sensitive to early stages of disease (MCI); extracellular changes become apparent in more severe stages of cognitive impairment (AD)
- Brain GSH: need for measurement standardization and studies to explore sources of heterogeneity, sub-group analysis suggest decrease in brain GSH in MCI and AD (MEGA-PRESS)

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PI: K. Lanctôt, **QI:** D. Gallagher | Contact: Dr. Krista Lanctôt Email: krista.lanctot@sunnybrook.ca

alzheimer's association

CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada