**Table A1. Summary table of eligible publications exploring metabolomics in severe traumatic brain injury following selection process**

| Year of Study | Sample Type | Sample Size | Detection Technique | Study setting | Refs. |
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| (2006) | MRI | TBI patients=10, normal controls=10 | $^1$H-MRSI | $^1$H-MRSI examinations on patients to determine metabolite levels of N-acetyl aspartate, choline, creatine, and lactate post TBI | Marino et al. (25) |
| (2011) | Serum/Plasma | sTBI patients=19, healthy contols=44 | HPLC | Measured the effects of changes in branched-chain amino acids and plasma aromatic amino acid levels | Vuille-Dit-Bille et al. (35) |
| (2012) | Serum/Plasma | sTBI patients=20, mTBI patients=18, Orthopedic injury patients=15, Healthy volunteer=20 | LC-MS/GC-MS | Measured plasma levels of L-arginine and similar key metabolic products in patients post TBI and compared them to healthy volunteers and orthopedic controls | Jeter et al. (26) |
| (2013) | Serum/Plasma | sTBI patients=20, mTBI patients=18, Orthopedic Injury=15, Healthy volunteer=20 | LC-MS/GC-MS | Identified altered metabolic cascades and branched-chain amino acids in acute sTBI and mTBI patients | Jeter et al. (27) |
| (2013) | CSF | TBI patients (moTBI or sTBI only, 14 yrs or older)=44, non-injured controls=13 | $^1$H-NMR | Analyzed metabolites from the CSF of patients following TBI | Glenn et al. (37) |
| (2015) | CSF | sTBI patients=28, CSF control patients=11, serum control patients=20 | HPLC/GC-MS | Investigated the effect of the kynurenine pathway on brain damage post TBI | Yan et al. (62) |
| (2016) | Serum/Plasma | sTBI patients=20, mTBI patients=20, healthy volunteers=20 (ages ranged from 14 to 57) | LC-MS/GC-MS | Specifically examined methionine alteration and related metabolites following TBI | Dash et al. (29) |
| (2016) | Serum/ Microdialysate | TBI patients=144 (mTBI=108, moTBI=14, sTBI=22), acute orthopedic non-brain injury controls=28, validation study=67 TBI (mTBI=37, moTBI=7, sTBI=22, acute orthopedic non-brain injury controls=27 | GCxGC-TOFMS | Aimed to determine markers and outcome prediction for TBI patients by evaluating two independent cohorts using metabolic profiling. Combined results with clinical and CT data | Oresic et al. (33) |

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| (2016) | Microdialysate | sTBI patients=30, non-TBI neurosurgical patients =6 | HPLC | Analyzed the behaviour of extracellular NAA levels post sTBI | Shannon et al. (28) |
| (2017) | CSF | sTBI patients=20 (divided into non-survival=6 & survival=14), healthy controls=20 | HPLC | Assessed levels of glutamate, lactate, BDNF, and GDNF in sTBI patients between 2 and 4 h post injury to determine biomarker potential | Stefani et al. (38) |
| (2018) | Serum/Plasma/ Microdialysate | TBI patients=144 (sTBI patients=22, moTBI patients=14, mTBI patients=108), orthopedic injury controls=55, validation cohort=66 (sTBI=23, moTBI=7, mTBI=36) | GCxGC-TOFMS/GCxGC-MS | Explored if metabolites could validate the need for CT scans in TBI patients as well as predict the nature of brain injury | Dickens et al. (36) |
| (2019) | Serum/Plasma | sTBI patients=26, healthy controls=6 | LC-MS | Compared metabolite levels in arterial and jugular venous samples to determine changes post sTBI and study the effects on cerebral metabolism | Wolahan et al. (34) |
| (2019) | Microdialysate | TBI patients=26, validation cohort=12 | LC-MS | Combined clinical and cerebral microdialysis metabolomics data to investigate metabolites and associations with patient outcomes | Eiden et al. (63) |
| (2020) | Serum/Plasma | TBI patients=96 (mTBI=79, moTBI=10 sTBI=7) | GCxGC-TOFMS | Related circulating metabolites to findings from structural MRI post TBI | Thomas et al. (64) |
| (2020) | Serum/Plasma | TBI patients=29 (sTBI=12, moTBI=8, mTBI=9), control patients=10 | HPLC with UV-visible detection | Investigated the therapeutic potential of spermidine in TBI in humans and mouse models | Huang et al. (65) |
| (2021) | MRI | sTBI patients=10 | $^{31}$P-MRS | Tested the diagnostic potential of $^{31}$P-MRS to detect cerebral energy metabolism changes post TBI | Pinggera et al. (66) |
| (2021) | MRI | sTBI patients=26, control patients=20 | $^{31}$P-MRS | Performed 31P-MRS post TBI at two separate time intervals to detect alterations in cerebral energy metabolism | Pinggera et al. (67) |
| (2021) | Urine | TBI patients=8 (sTBI=2, moTBI=3, mTBI=3), no controls, | $^{1}$H-NMR | Analyzed urine samples in TBI patients to determine if metabolites changed during | Bykowski et al. (30) |

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| | | but incorporated a within-subject control design | | recovery, correlated to injury severity, and reflected TBI mechanisms | |
| (2022) | Serum/Plasma | TBI patients (sTBI and moTBI only)=51 | LC-MS | Investigation of serum glycome patterns following TBI to determine glyco-biomarker signatures and clinical relevance | Mondello et al. (31) |
| (2022) | Serum/Plasma | TBI patients=716, non-TBI patients=229 (orthopedic controls=40, internal medicine=96, other neurological patients=93). Samples collected from the Center-TBI, validation dataset=558 TBI patients | GC-QTOFMS/LC-QTOFMS | Intended to define and describe the metabolome related to acute TBI and investigate its effect on severity and patient outcome post TBI using metabolomics and lipidomics | Thomas et al. (32) |

*Note*. Abbreviations: $^{1}$H-MRSI, proton nuclear magnetic resonance imaging; $^{31}$P-MRS, phosphorous magnetic resonance spectroscopy; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; CT, computed tomography; GC-MS, gas chromatography-mass spectroscopy; GC-QTOFMS, gas chromatography coupled to quadrupole time-of-flight mass spectrometry; GCxGC-MS, 2D gas chromatography coupled to mass spectrometry; GCxGC-TOFMS, 2D gas chromatography coupled to time-of-flight mass spectrometry; GDNF, glial cell-derived neurotrophic factor; $^{1}$H-NMR, proton nuclear magnetic resonance; HPLC, high performance liquid chromatography; LC-MS, liquid chromatography-mass spectrometry; LC-QTOFMS, liquid chromatography coupled to quadrupole time-of-flight mass spectrometry; moTBI, moderate traumatic brain injury; MRI, magnetic resonance imaging; mTBI, minor traumatic brain injury; NAA, acetylaspartate; sTBI, severe traumatic brain injury; TBI, traumatic brain injury; UV, ultraviolet.