

Cerebral blood flow decline in neurodegeneration using a healthy reference normative model

Mathijs Dijsselhof^{1,2}, David R. Van Nderpelt^{2,3}, Wibeke Nordhøy⁴, Ole A. Andreassen^{5,6}, Lars T. Westlye^{5,7}, Luigi Lorenzini^{1,2,8}, Leo Pieperhoff^{1,2}, Alle Meije Wink^{1,2}, Floor Duits^{9,11}, Alun D. Hughes¹², Jonathan M. Schott¹³, Menno Schoonheim¹⁴, Eva Strijbis¹⁵, Joost Kuijer^{16,17}, Bert-Jan H. Van den Born^{18,19}, Mervin Tee²⁰, Saima Hilal^{20,22}, Christopher Chen^{21,22}, Frederik Barkhof^{1,2,23}, James Cole²⁴, Jan Petr^{1,25}, Henk-Jan Mutsaerts^{1,2}

1. RING, AUMC, NL 2. Brain Imaging, Amsterdam Neuroscience, NL 3. RING, MS Center Amsterdam, NL 4. Physics and Computational Radiology, Oslo University Hospital, NO 5. Precision Psychiatry, Oslo University Hospital, NO 6. Psychology, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, NO 7. KG Jebsen Centre for Neurodevelopmental Disorders, NO 8. Neuroscience, University of Genova, ITA 9. Alzheimer Center Amsterdam, Neurodegeneration, NL 10. Neurodegeneration, Amsterdam Neuroscience, NL 11. Neurochemistry lab, Amsterdam Neuroscience, NL 12. Unit for Lifelong Health & Ageing, UCL, UK 13. DRC UCL Queen Square Institute of Neurology, UK 14. Anatomy and Neurosciences, MS Center Amsterdam, NL 15. Neurology, MS Center Amsterdam, Amsterdam Neuroscience, NL 16. Department of Radiology & Nuclear Medicine, AUMC, NL 17. Amsterdam Neuroscience, MS Center Amsterdam, NL 18. Internal Medicine, AUMC, NL 19. Public and Occupational health, AUMC, NL 20. Saw Swee Hock School of Public Health, National University of Singapore, SGP 21. Pharmacology, National University of Singapore, SGP 22. Memory Aging and Cognition Centre, National University Health System (NUHS), SGP 23. Queen Square Institute of Neurology, UCL, UK 24. UCL, UK 25. Helmholtz-Zentrum Dresden-Rossendorf, GE

- ### Introduction

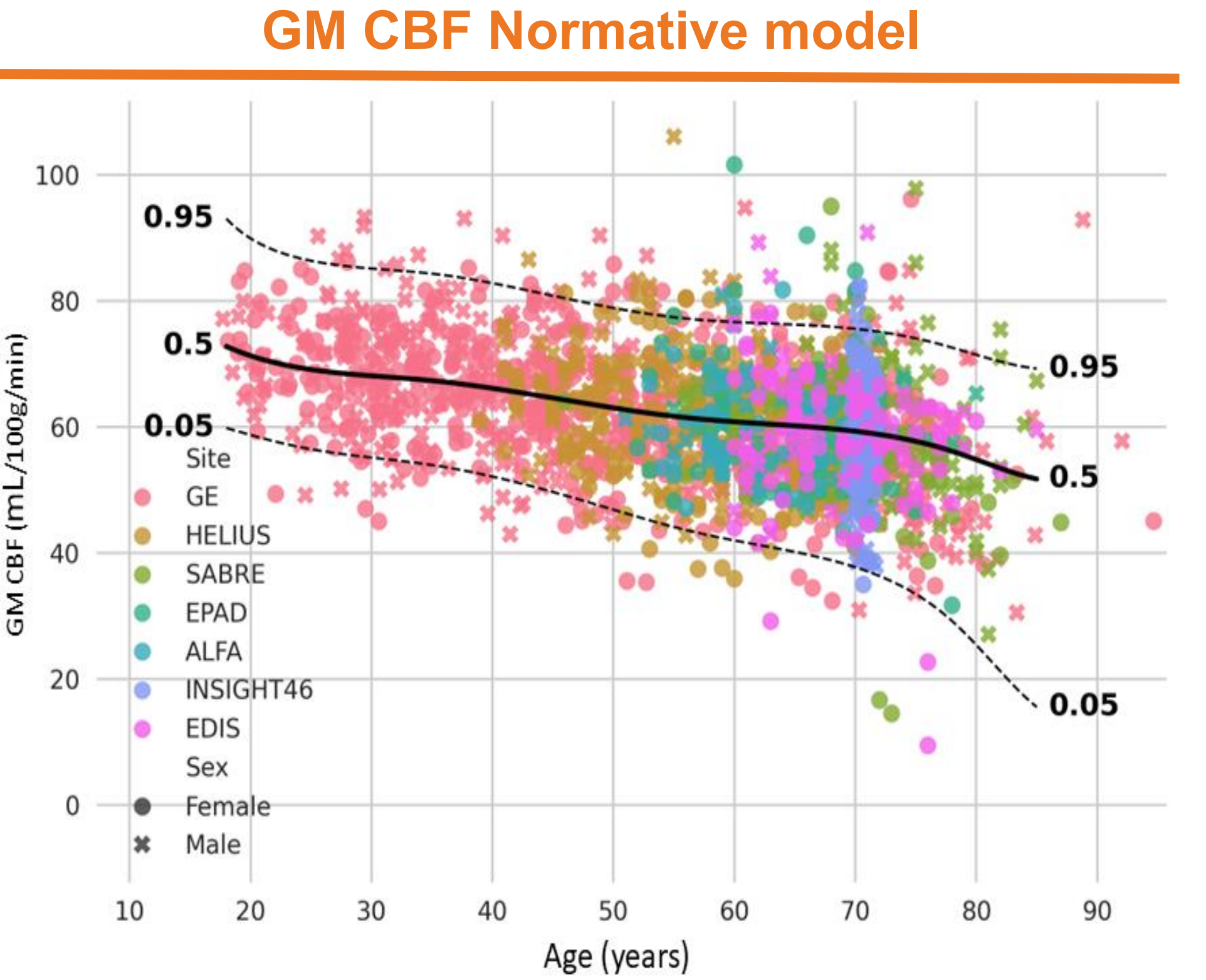
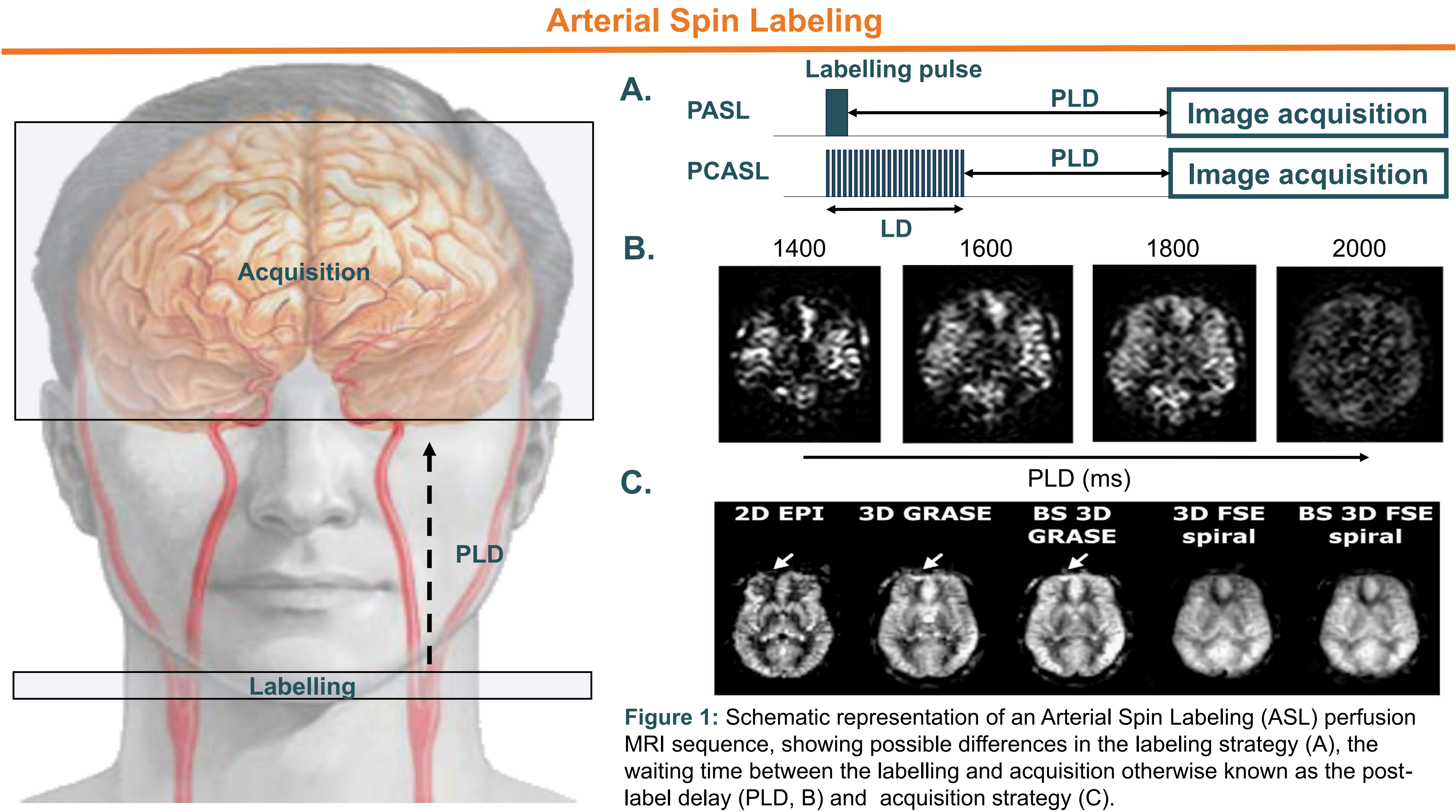
 - Arterial Spin Labelling (ASL)-measured Cerebral blood flow (CBF) is:
 - Associated with Alzheimer's Disease (AD)¹ and multiple sclerosis (MS)²
 - Affected by cardiovascular risk factors (CVRF)³
 - Increased CBF, via CVRF management⁴, improves cognition⁵
 - Therefore, CBF is a promising biomarker for early-stage diagnosis, disease monitoring, treatment stratification, and secondary prevention
 - However, CBF alterations across the full neurodegenerative continuum are unclear, and conflicts arise due to:
 - Use of single, older, heterogeneous cohorts at late stages of disease
 - ASL MRI sequences **differ** substantially between vendors
 - Labelling technique (LD, **Figure 1A**)
 - Post-label delay (PLD, **Figure 1B**)
 - Acquisition strategies (**Figure 1C**)
 - Normative modelling** methods offer individualised deviations scores, while accounting for ASL sequence differences
 - Thus, healthy reference CBF charts can be created by pooling many differing datasets, necessary to study CBF change in brain pathology
 - Therefore, we created a uniquely large combined ASL dataset of **4368 subjects** across **11 cohorts** and **6 ASL** sequences to
 - Develop normative grey matter (GM) CBF charts, using non-Gaussian Bayesian regression
 - Assess CBF deviations in **AD, MS, and hypertension**
- ### Results

 - Normative model performance (Figure 2,3)**
 - Pearson's correlation between true and predicted CBF = 0.6
 - Standardised mean squared error = 0.65
 - Explained variance = 0.36
 - Dataset comparability**
 - Without** normative models
 - GM CBF of 13 out of 15 were different (p<0.05)
 - With** normative models
 - Only GM CBF of Insight 46, SABRE, HELIUS differed from combined StrokeMRI and TOP hold-out set (p<0.02)
 - GM CBF in pathology (Figure 4)**
 - Without** normative models
 - Hypertension** (55.6±15.2 mL/100g/min) and **AD** (57.6±13.1 mL/100g/min) were lower (p<0.03) compared to **HC** (62.2±12.2 mL/100g/min).
 - SCD** (60.5±13.3 mL/100g/min), **MCI** (61±14.3 mL/100g/min), and **MS** patients did not differ (65.1±11.0 mL/100g/min, p>0.94, Figure 4A)
 - With** normative models
 - HC** (61.2±10.4 mL/100g/min) was higher than **MCI** (58±13.6 mL/100g/min), **AD** (56.6±12.8 mL/100g/min), and **hypertension** (56.7±10 mL/100g/min) patients (all p<0.03)
 - SCD** (59.7±13.2 mL/100g/min) was higher than **AD**, and **MS** patients did not differ (61.1±9.7 mL/100g/min, p=0.22, Figure 4B) from **HC**.

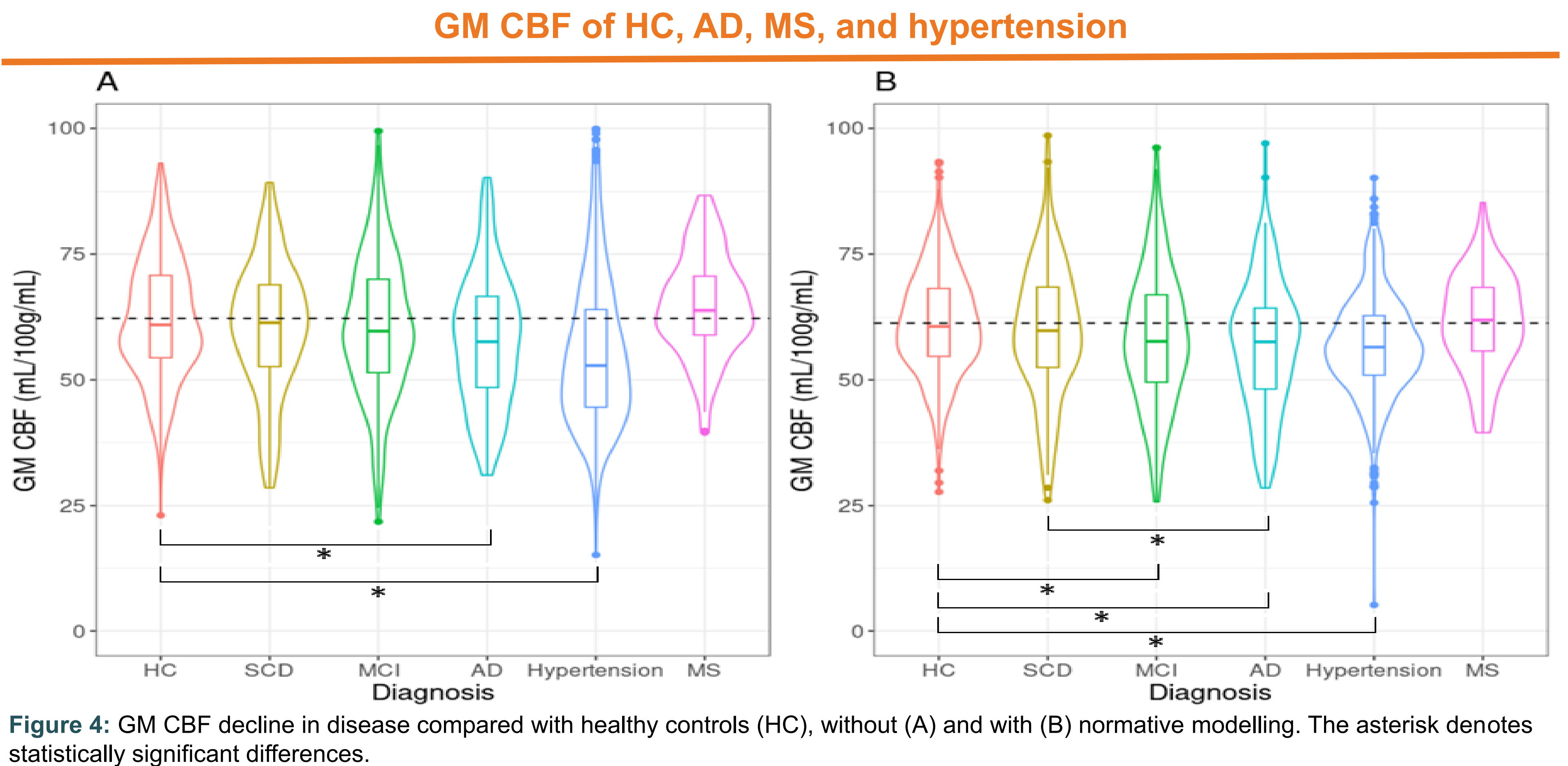
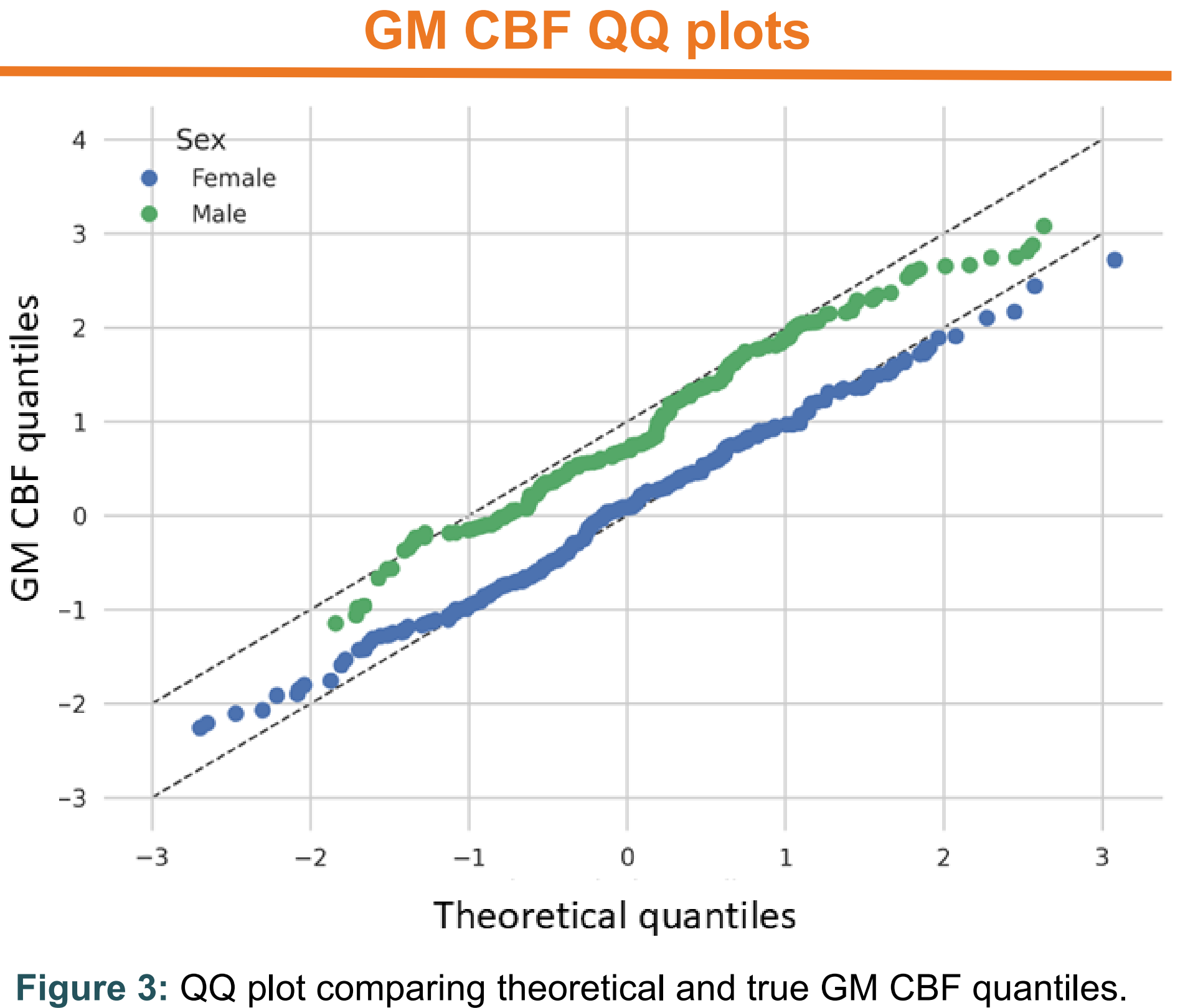
- ### Conclusion

Normative GM CBF reference charts can pool heterogeneous ASL datasets and could improve the disentanglement of CBF changes across the spectrum of neurodegenerative pathology.
- ### Discussion

 - ASL-CBF is affected by physiology⁶, which could explain the model's low explained variance
 - Normative modelling reduced site- and sequence-level effects across cohorts
 - Able to combine different ASL sequences
 - Increasing differences between patients and HC
 - Lower normative GM CBF was found in the MCI vs HC and SCD vs AD groups, which was obscured without normative modelling
 - CBF could be altered in preclinical AD phases already
 - highlighting the potential of CBF-modifying treatments in preventative strategies
 - Similar HC and MS CBF could be explained by pooling and potentially mixing patients with higher CBF⁷ and lower CBF², depending on disease stage
 - Future studies should assess associations among clinical measures (cognitive tests, SBP, MS disease duration) to improve normative CBF reference models and disentangle CBF change in neurodegeneration



Vendor	GE						Philips			Siemens	
	StrokeMRI	TOP	DemGen	Amsterdam dementia cohort	ADNI	MS cohort Amsterdam	SABRE	EPAD/ALFA	HELIUS	EDIS	Insight46
Cohort											
Dataset	Training/hold-out	Training/hold-out	Patient	Patient	Patient	Patient	Training/hold-out	Training/hold-out	Training/hold-out	Training/hold-out	Training/hold-out
Healthy controls (n)	566	528			33	26	263	204	411	159	169
Patients (n)			SCD (60) MCI (109) AD (65)	SCD (148) MCI (196) AD (154)	MCI (22) AD (7)	MS (94)	HT (380)	HT (99)	HT (121)	HT (187)	HT (113)
Age (years) [range]	60 ± 14 [20 – 85]	38 ± 10 [18 – 59]	67 ± 10 [38 – 85]	63 ± 8 [43 – 80]	74 ± 7.4 [58 – 85]	47 ± 9 [29 – 69]	71 ± 7 [37 – 85]	65 ± 7 [51 – 88]	59 ± 8 [39 – 76]	69 ± 6 [60 – 65]	71 ± 1 [69 – 72]
Females (%)	63	47	49	47	50	68	44	66	45	66	53
Labelling type	PCASL	PCASL	PCASL	PCASL	PCASL	PCASL	PCASL	PASL/PCASL	PCASL	PCASL	PCASL
LD (ms)	1450	1450	1450	1450	1450	1450	2000	1650	1800	1500	1800
PLD (ms)	2025	2025	2025	2025	2025	2025	1800	2025/1800	1800	1500	1800
Readout	3D Spiral	3D Spiral	3D Spiral	3D Spiral	3D Spiral	3D Spiral	2D EPI	2D EPI	2D EPI	2D EPI	3D GraSE



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