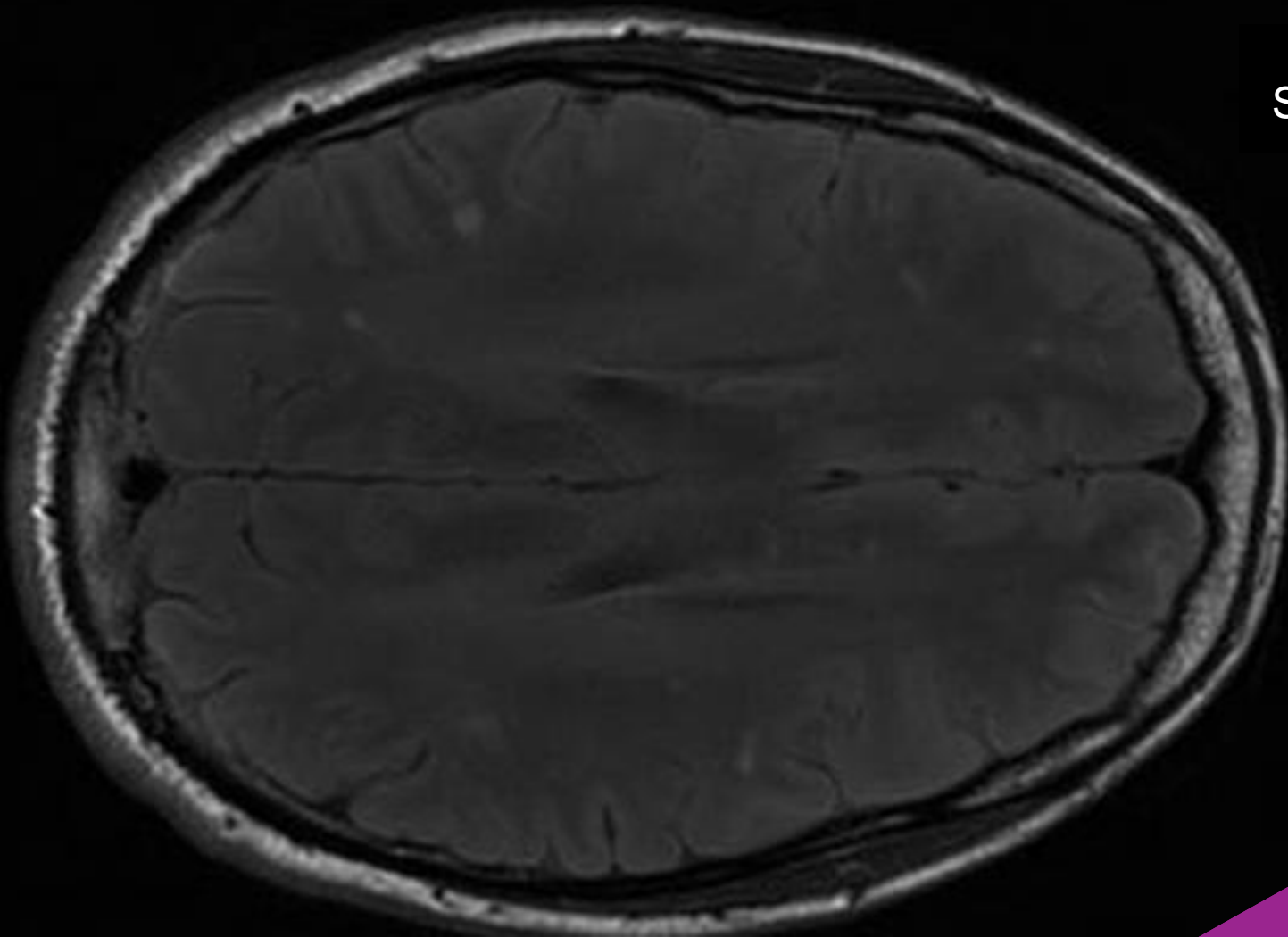


White Matter Hyperintensities and Implications for Future Altitude Chamber Research

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Dr Des Connolly



QINETIQ

Disclosure Information

Author's Declaration:

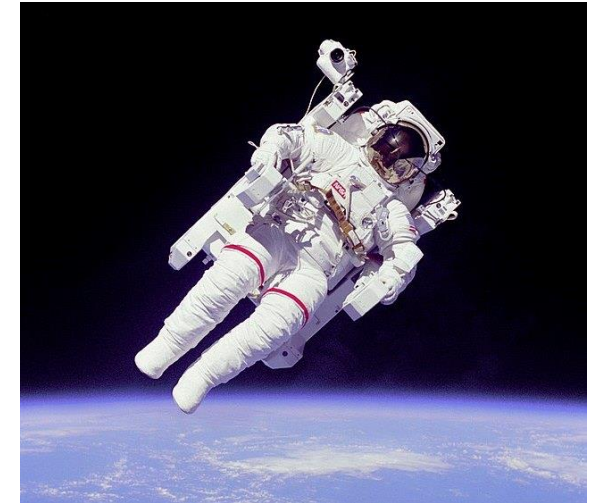
- I **have not** received Non-governmental or non-academic support or funding for the material which I intend to present.

Scope

-
- 1 Background
 - 2 Brief review of UK study outcomes
 - Retrospective survey
 - Prospective study
 - 3 Composite MRI dataset – influence of mild traumatic brain injury (concussion)
 - 4 Implications for future altitude chamber research at QinetiQ
-

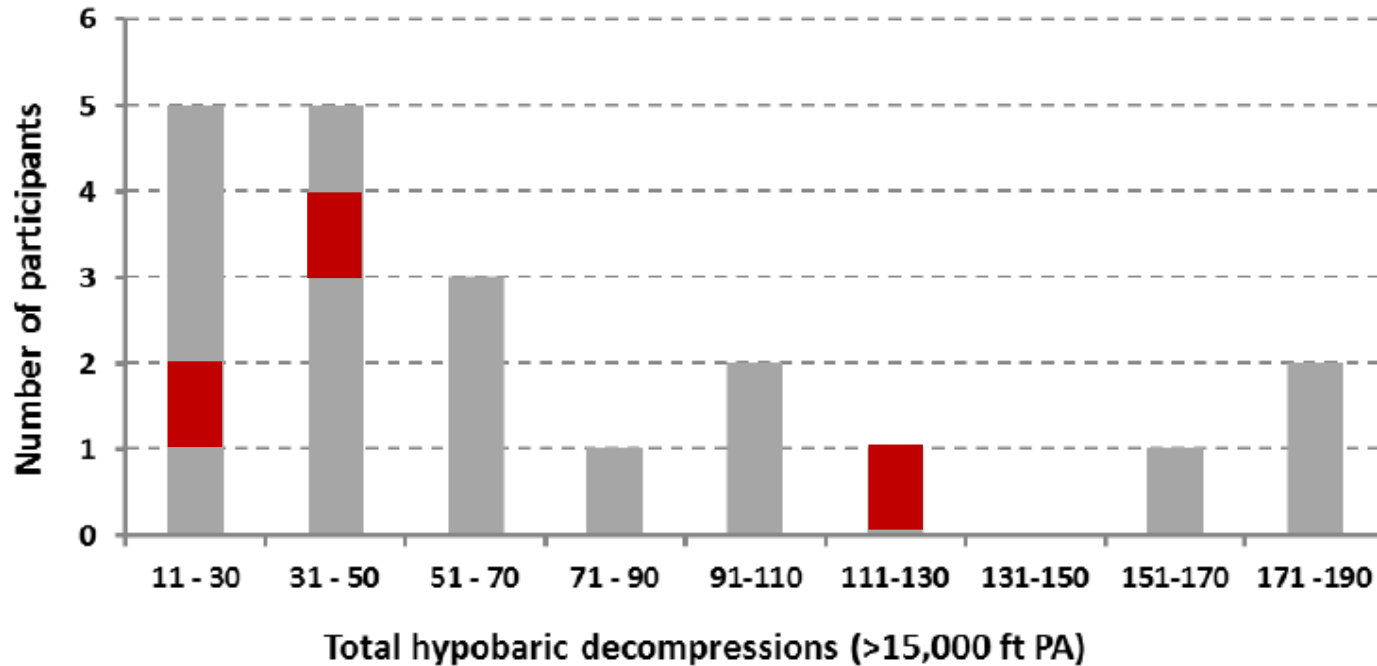
Background – Dysbaric White Matter Injury

- USAF U-2 Pilots
 - Threefold increased incidence of neurological DCS from 2006-2009
 - Increased subcortical white matter hyperintensities (WMH)
 - Decreased global Fractional Anisotropy (loss of nerve fibre integrity)
- USAF Aerospace Operational Physiologists (altitude chamber instructors)
 - Increased WMH burden
- Healthy Divers (mostly military, commercial)
 - Increased prevalence of WMH (odds ratio meta-analysis of seven medium/high quality case-control studies, $P < 0.001$)
- NASA Astronauts
 - Increased WMH burden?
- **Environmental stress**
 - Non-hypoxic decompression stress (hyperoxic?)
 - Safe ('threshold') levels of exposure unknown



Retrospective Survey of Research and Training Participants

			<u>Total WMH</u>	<u>Mean WMH Volume</u>	<u>Frontal Lobe</u>
• Normal (≤ 5 WMH)	17	(85%)	19 (19%)	21 mm ³	89%
• Increased (6-15 WMH)	0		-	-	-
• Excess (>15 WMH)	3	(15%)	83 (81%)	43 mm ³	48%

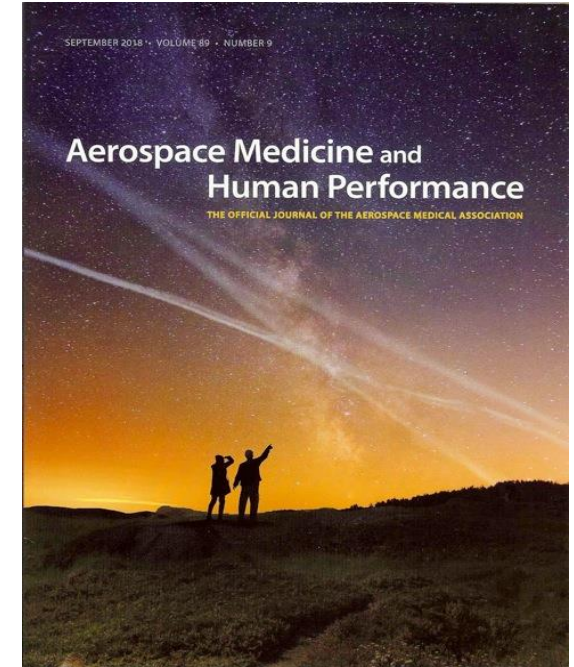


Total exposures (≥ 18 kft)	1417
Rapid decompressions	751
>40 kft (PPB)	326
Extended duration (>1 h)	93
Limb pain DCS	10
Hypoxia familiarisations	46

Interpretation of Retrospective Data (N = 20)

No association of WMH with altitude exposures:

- Total exposures
- Rapid decompressions +/- pressure breathing
- Hypoxia familiarisations at 25,000 ft
- Episodes of limb pain decompression sickness
- Prolonged exposures (>1h)
- Exposure intensity (decompressions per month)



2018; 89(9): 777-786

‘Low intensity’ decompression stress is sub-threshold for generating WMH (i.e. relatively infrequent, brief exposures)

Prospective Study - Ethics Dilemma (2015)

- No demonstrably 'safe' decompression exposure limits
 - Plan multiple varied exposures to maximum 40,000 ft



- **Duty of care to volunteers – do no harm**
 - Cannot document absence of harm unless perform 'exit' MRI
 - If perform 'exit' MRI then must have comparison 'entry' MRI
 - If do 'entry' MRI then what about pre-existing WMH?
 - Required MRI exclusion criteria (number/volume)
- **Additional mitigations:**
 - Upper age limit 45 years
 - Limit exposure frequency (max 2 per week at 3-day intervals)
 - Minimise duration of each decompression
 - Conservative denitrogenation schedules

(In effect, minimising risk of decompression sickness)

Outcome of 'Entry' MRI Screening (N = 13)

- 12 (92%) passed screening criteria (≤ 5 WMH with total volume ≤ 0.08 mL)
- Single exclusion with total 63 subcortical WMH with total volume 2.38 mL
 - Past history consistent with likely Mild Traumatic Brain Injury (MTBI)
 - Slipped on ice, fell backwards, hit head on concrete surface, immediate loss of consciousness
- N = 11 study participants
- 9-month work programme Feb - Nov 2017

Altitude Exposures Completed (≥ 18,000 ft)

Altitude Profile	Subjects					Inside Observers						Totals
	S1	S2	S3	S4	S5	A1	A2	A3	A4	A5	A6	
Hypoxia training @ 25 kft	1	1	1	1	1	1	1	1	1	1	1	11
18 kft steady (≤ 20 min)	2	2	2	2	2	3	2	2	3			20
40/25/18/8 kft steady (≤ 6 min each)	5	6	5	5	5	5		5	6	5	5	52
24 to 35 kft slow (1 kft / min)	6	8	6	6	6							32
8 to 25 kft rapid decompression (4 s)	6	6	6	6	6							30
9 to 40 kft rapid decompression (4 s)	3	3	3	3	3							15
Total Exposures ≥18 kft	23	26	23	23	23	9	3	8	10	6	6	160
Exposures to <10 kft			1			11	13	14	15		2	56
Grand Totals	23	26	24	23	23	20	16	22	25	6	8	216

MRI Entry / Exit WMH Data (University of Maryland)

Total subcortical WMH number

MRI	S1	S2	S3	S4	S5	A1	A2	A3	A4	A5	A6	Total
Entry	0	1	0	0	0	1	1	2	0	3	0	8
Exit	0	0	0	1	0	3	0	0	0	0	1	5
Change	0	-1	0	+1	0	+2	-1	-2	0	-3	+1	-3

Total subcortical WMH volume (mm³)

MRI	S1	S2	S3	S4	S5	A1	A2	A3	A4	A5	A6	Total
Entry	-	26.1	-	-	-	74.2	9.2	18.4	-	38.4	-	166.3
Exit	-	-	-	10.8	-	159.2	-	-	-	-	13.8	184.0
Change	0	-26.1	0	+10.8	0	+85.0	-9.2	-18.4	0	-38.4	+13.8	+17.7

Interpretation of Prospective Data (N = 11)

Subcortical WMH number	0	1	2	3
Entry	6	3	1	1
Exit	8	2	0	1
Change	Increase	Decrease	Decrease	No change

- Interpreted as ‘no change’ in underlying normal WMH burden
- Satisfies duty of care: ‘no harm’
- May reflect limit of reproducibility inherent in high resolution MRI technique or reporting of transient white matter change in normal life

Composite MRI Dataset – Influence of Past MTBI (N = 33)

- History of concussion consistent with mild traumatic brain injury (MTBI)

		Excess (>15) WMH?		Totals
		Yes	No	
MTBI?	Yes	4	5	9
	No	0	24	24
Totals		4	29	33

- 2 x 2 contingency table: Fisher Exact Test (χ^2) statistic = 0.0031

MTBI “no”

Sensitivity 100%

Negative predictive value 100%

(statistically significant at $\alpha = 0.05$)

$$= 4 / (4 + 0)$$

$$= 24 / (24 + 0)$$

Zero Numerators i.e. If Nothing Goes Wrong, Is Everything All Right?

- The maximum risk (R_{\max}) for which a finding of zero numerators from a series (n) is compatible to a 95% confidence limit ($P < 0.05$) is given by:

$$(1 - R_{\max})^n = 0.05$$

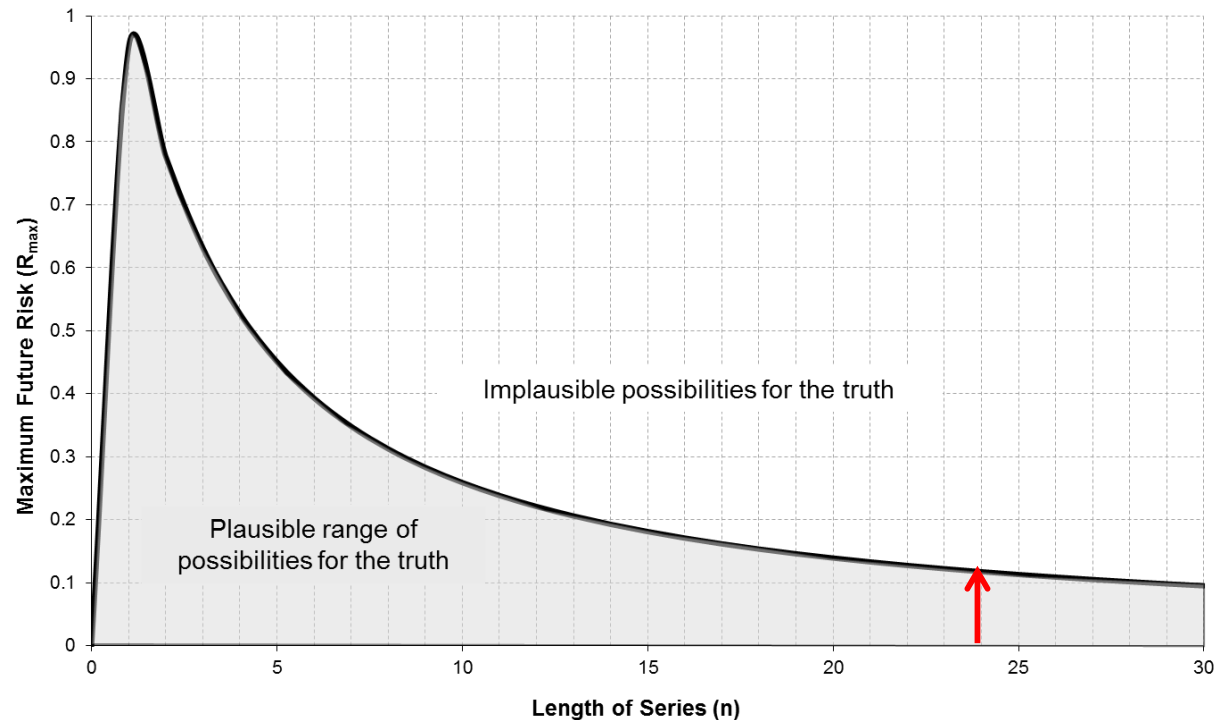
So: $R_{\max} = 1 - 0.05^{(1/n)}$

Hanley JA, Lippman-Hand A.
If nothing goes wrong, is everything all right? Interpreting zero numerators.
JAMA 1983; 249(13): 1743-1745.

For $n = 24$:

The 95% confidence limits are 0 – 0.11

The 99% confidence limits are 0 – 0.18



Maximum future risk for zero numerators in a series
(95% confidence limits shaded)

Way Forward?

MINIMAL RISK

Brief exposures (< 1h)

Infrequent exposures (max 2/week)

Recovery time 3 days +

Limited total exposure burden (<25 ascents)

Low risk DCS (altitude, duration, activity, pre-ox)

'Research' (conservative) profiles

No requirement for exit MRI

Entry screen by questionnaire for MTBI

(and other predisposing factors)

UNKNOWN RISK

Prolonged exposures (> 1h)

Frequent exposures (and 'bounce' profiles)

Shortened recovery times (1-2 days)

Cumulative exposure (>25 ascents)

Increased risk DCS (esp long duration, exertion)

'Operational' profiles (e.g. to assess DCS risk)

Requirement for exit MRI

Requirement for entry (screening) MRI

What do these studies add?

- Basis for conducting small/medium altitude research projects without requirement for screening MRI:
 - Programmes that present negligible or low risk of decompression sickness
 - Using young (UK) volunteers (<50y)
- Help to establish a *minimum* 'safe' threshold level of hypobaric exposure (cumulative dose, exposure duration, exposure frequency, recovery time) below which white matter injury should not occur.

Caution

- **This reassurance does not extend to:**
 - Exposures presenting greater decompression stress (altitude, duration, exertion, compromised pre-breathe)
 - Exposures intended to study risk of decompression sickness:
 - Frequent, repetitive or 'bounce' profiles
 - Prolonged exposure at provocative altitudes, especially with physical exertion
 - Occupational cohorts (exposed repeatedly to decompression stress on an indefinite basis)

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- Royal Air Force Centre of Aviation Medicine, RAF Henlow, Bedfordshire, UK
- Colleagues at QinetiQ plc

COMMERCIAL IN CONFIDENCE

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Questionnaire Screening for MTBI

– ***Have you ever suffered a head injury that resulted in:***

- Loss or disturbance of consciousness?
- Loss of memory for events before or after the event?
- Persistent symptoms of concussion (e.g. headache, nausea, difficulty concentrating etc)?
- Attendance at hospital for imaging (e.g. MRI or CT scans)?
- Admission to hospital (e.g. for overnight observation, sedation or surgery)?