Prospective Study of White Matter Health for an Altitude Chamber Research Program

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INTRODUCTION: Hypobaric decompression has been associated with brain white matter injury. Relevant exposure limits are unknown, raising ethical concerns over safety of volunteers for altitude chamber research. To inform this, a prospective study of white matter status using brain Magnetic Resonance Imaging (MRI) was conducted before and after a 9-mo program of hypobaric research.

METHODS: Volunteers underwent 3-D, volumetric, fluid attenuated inversion recovery (FLAIR) MRI at the University of Nottingham, UK, on study entry and again after their final exposure. MRI data were analyzed and reported independently at the University of Maryland, Baltimore, MD, USA. Entry criteria were $\leq$ 5 subcortical white matter hyperintensities (WMH) of total volume $\leq$ 0.08 mL.

RESULTS: One volunteer failed screening with 63 WMH (total volume 2.38 mL). Eleven individuals completed 160 short-duration ($<$ 1h) exposures (range 3 to 26) to $\geq$ 18,000 ft pressure altitude (maximum 40,000 ft), no more often than twice weekly. The cohort exhibited eight total WMH on study entry (total volume 0.166 mL) and five (mostly different) total WMH on exit (0.184 mL). Just one WMH (frontal lobe) was present on both entry and exit scans. Excess background WMH on MRI screening were associated with past mild traumatic brain injury (MTBI).

CONCLUSIONS: One hypoxia familiarization plus multiple, brief, infrequent, nonhypoxic hypobaric exposures (with denitrogenation) have not promoted WMH in this small cohort. Less intensive programs of decompression stress do not warrant MRI screening. A negative past history of MTBI has strong negative predictive value for excess WMH in young healthy subjects ($N = 33$).

KEYWORDS: white matter hyperintensity, altitude, decompression, magnetic resonance imaging, head injury, mild traumatic brain injury.

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Subcortical white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) brain scans provide evidence of white matter injury associated with nonhypoxic, decompression stress in altitude workers, including U-2 pilots,[10] aerospace operational physiologists,[11] and healthy frequent divers.[3] The long-term consequences, if any, of developing subclinical white matter injury at a young age (less than 50 yr) are unknown, but in later life such changes are progressive over time and associated with cognitive decline and poorer clinical outcomes.[5] In this context, U-2 pilots with increased WMH exhibit subtle, subclinical neurocognitive decrements,[12] consistent with reports in other healthy individuals with early white matter change.[1] Thus, any risk of predisposing to white matter injury cannot lightly be dismissed.

The lack of demonstrably "safe" hypobaric decompression exposure limits presented an ethical dilemma when planning a recent, manned, altitude chamber research program to assess various oxygen system configurations and regulator settings during multiple hypobaric exposures of research subjects, and accompanying inside observers, to a maximum 40,000 ft equivalent pressure altitude. Severity of WMH may reflect cumulative decompression experience,[9] but no evidence was available to support a safe level of exposure, or intensity of altitude decompression stress, at the time the study protocol was

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prepared for ethical review. Volunteers for these studies stood to gain no significant personal benefit from participating, beyond a very modest inconvenience payment, but were required to accept an unquantifiable risk of subclinical brain injury. The findings from a recent cross-sectional study of past UK subjects in altitude chamber research and training would have provided some reassurance, but these data were not available when the current study began.[4]

Ethical review endorsed the researchers' perceived requirement to satisfy their duty of care to volunteers to demonstrate absence of harm, or otherwise to document any harm that may have occurred during participation, by conducting brain MRI upon study completion. There was, therefore, a requirement for comparison baseline MRI scans on study entry, raising the possibility that volunteers could be found to have WMH on initial screening. The pathophysiology of WMH remains poorly understood. In particular, it is not known whether or not relatively young individuals with excess pre-existing WMH might be predisposed to further injury. Accordingly, it was necessary to screen out volunteers with elevated WMH relative to background levels for healthy individuals. This generated a further requirement to establish threshold criteria for acceptable "normal" total WMH number and total WMH volume on study entry.

A 9-mo program of oxygen system assessments was subsequently conducted during 2017 in the QinetiQ-managed hypobaric chamber facility at MOD Boscombe Down, Wiltshire, UK. This involved 11 volunteers completing a total of 160 individual decompressions (range 3 to 26 per subject) to equivalent pressure altitudes of at least 18,000 ft, the majority of exposures requiring prior denitrogenation breathing 100% oxygen to mitigate the risk of decompression sickness (DCS). These individuals' MRI data represent the first prospective human study of white matter health to be reported in relation to a planned program of repeated, subatmospheric decompression stress. Study entry MRI data were later collated with previous UK survey data to re-evaluate the observation that excess WMH are associated with past mild traumatic brain injury (MTBI).[4]

METHOD

Subjects

This research was funded by the UK Ministry of Defense (MOD). The study adhered to the principles of the Declaration of Helsinki and the experimental protocol was approved, in advance, by the MOD Research Ethics Committee, an independent body constituted and operated in accordance with national and international guidelines. Five healthy volunteer QinetiQ employees were required to be altitude chamber research subjects and another five to be chamber inside observers (who fulfill the roles of safety person and assistant investigator). The first five volunteers to pass the stringent study entry screening criteria for high altitude research, and who wished to be research subjects, were allocated to those roles, with later volunteers being offered the inside observer vacancies.

Volunteers were briefed in person on the rationale for MRI screening and provided written informed consent to participate. They underwent detailed medical screening focusing on factors relevant to fitness for hypobaric decompression and hypoxia familiarization, suitability for MRI and factors predisposing to WMH, including past history of concussive head injury with disturbance or loss of consciousness. Study subjects were asked to declare any illnesses and injuries (e.g., from contact sports) that occurred during the research program and also to advise of any dysbaric exposures undertaken (e.g., flying, diving, parachuting, mountaineering) so that subsequent altitude chamber exposures could be scheduled after a suitable interval (generally 3 d). Otherwise no lifestyle restrictions were imposed.

Three volunteers were known to be acceptable for study entry on the basis of recent prior MRI data for total number and volume of WMH obtained during the previous retrospective survey, as their scans employed the same scanner, sequences and procedures, with quantitative WMH analysis at the Center for Brain Imaging Research, University of Maryland, Baltimore.[4] Owing to delays commencing the study, with loss of volunteers to relocation and other commitments, a total of 13 additional volunteers underwent entry screening MRI, the last of these to replace an inside observer who withdrew due to relocation after the study commenced. Thus, 11 individuals eventually participated in the altitude research program and these went on to have MRI scans on study exit, at least 4 wk after their final altitude exposure (mean 50 d, range 30–102 d). The five research subjects were all men, mean age 34 yr at study exit (range 23–44 yr); the six inside observers comprised three men (mean 34 yr, range 24–46 yr) and three women (mean 27 yr, range 26–29 yr). All were healthy, fit and well, with no comorbidities.

Procedure

Prior to any altitude chamber exposures, volunteers attended the Sir Peter Mansfield Imaging Centre at Queen's Medical Centre, University of Nottingham, UK, to undergo high resolution, 3-D volumetric, fluid attenuated inversion recovery (FLAIR) MRI for quantification of subcortical WMH using a contemporary GE MR750 machine with a 3.0 Tesla magnet (GE Healthcare, General Electric Company, Fairfield, CT) in accordance with the published USAF method.[10,11] Image analysis involves a sequence of steps including removal of nonbrain tissue, registration to a standard brain atlas, inhomogeneity correction and manual 3-D delineation of hyperintense lesions. Scans were repeated on study exit for the 11 subjects in the altitude chamber research program. To assure valid comparison with the USAF reference data used to establish study entry criteria, and also to avoid analyst bias when reporting exit data, all imagery was anonymized and was analyzed and reported independently at the Center for Brain Imaging Research, University of Maryland, Baltimore, MD, by the researchers supporting USAF studies.

Study entry criteria were based on the normative USAF control group dataset available at the time of protocol development.[10,11] The dataset comprised 162 healthy individuals

($\leq$ 50 yr) with no known predisposing factors for WMH and who were not exposed routinely to hypobaric decompression stress (**Fig. 1**). The near linear polynomial regression line and narrow 95% confidence intervals suggest that the majority of WMH in this cohort are of uniformly small volume, mean 0.0126 mL (12.6 mm^3). Using this high resolution MRI technique ("slice" width 1 mm), up to five WMH are acceptable as normal "background" numbers, encompassing just over 80% of this sample if total WMH volume is limited to no greater than 0.08 mL (80 mm^3). These conservative criteria were adopted for entry to the current study, anticipating a 20% rejection rate on the basis that up to one in five normal, healthy volunteers would have either $>$ 5 WMH and/or total WMH volume $>$ 0.08 mL. In practice, of 13 new volunteers who underwent screening MRI, 12 passed (92%). Only one volunteer failed screening, having 63 WMH with a total volume of 2.38 mL; this individual had a history consistent with past MTBI having slipped on ice, fallen backward and hit his head on a concrete surface with immediate, witnessed loss of consciousness.

Altitude Chamber Program

Local risk assessment procedures were conducted to consider the possibility that participation might promote WMH. This outcome was categorized as "unlikely" but potentially "severe", thereby requiring further risk mitigation in addition to existing safety procedures. In consequence, the following precautions were implemented:

1. The upper age limit for volunteers was reduced to 45 yr;
2. Minimum recovery ("down") time between successive hypobaric decompressions was increased to approximately 3 d (minimum 68 h);
3. Exposure frequency was thereby limited to no more than two altitude chamber decompressions per working week;
4. Exposures were planned to minimize duration of decompression;
5. Conservative denitrogenation schedules were adopted;
6. Extended prebreathes on 100% oxygen were avoided by curtailing any experiment that was delayed.

All exposures were conducted in the QinetiQ-managed altitude chamber at MOD Boscombe Down, Wiltshire, UK. The test program encompassed a diverse range of oxygen system configurations, regulator settings, vent valve settings, supply hose configurations and ventilatory demands.

An overview of the scheduled hypobaric exposures is shown in **Table I**, indicating the total of each type planned for each research subject. Inside observers also completed the hypobaric exposures profiled in serials A, B and C but remained at base altitudes below 10,000 ft for serials D, E and F. For ease of understanding, profiles C and D are also represented in **Fig. 2**.

Rates of ascent and descent were ~4000 ft · min^{-1} except where stated. Subjects spent 5 min at base altitude prior to each rapid decompression in profiles E and F, the subsequent time spent above 10,000 ft being less than 10 and 15 min, respectively. Subjects' breathing gas was 100%

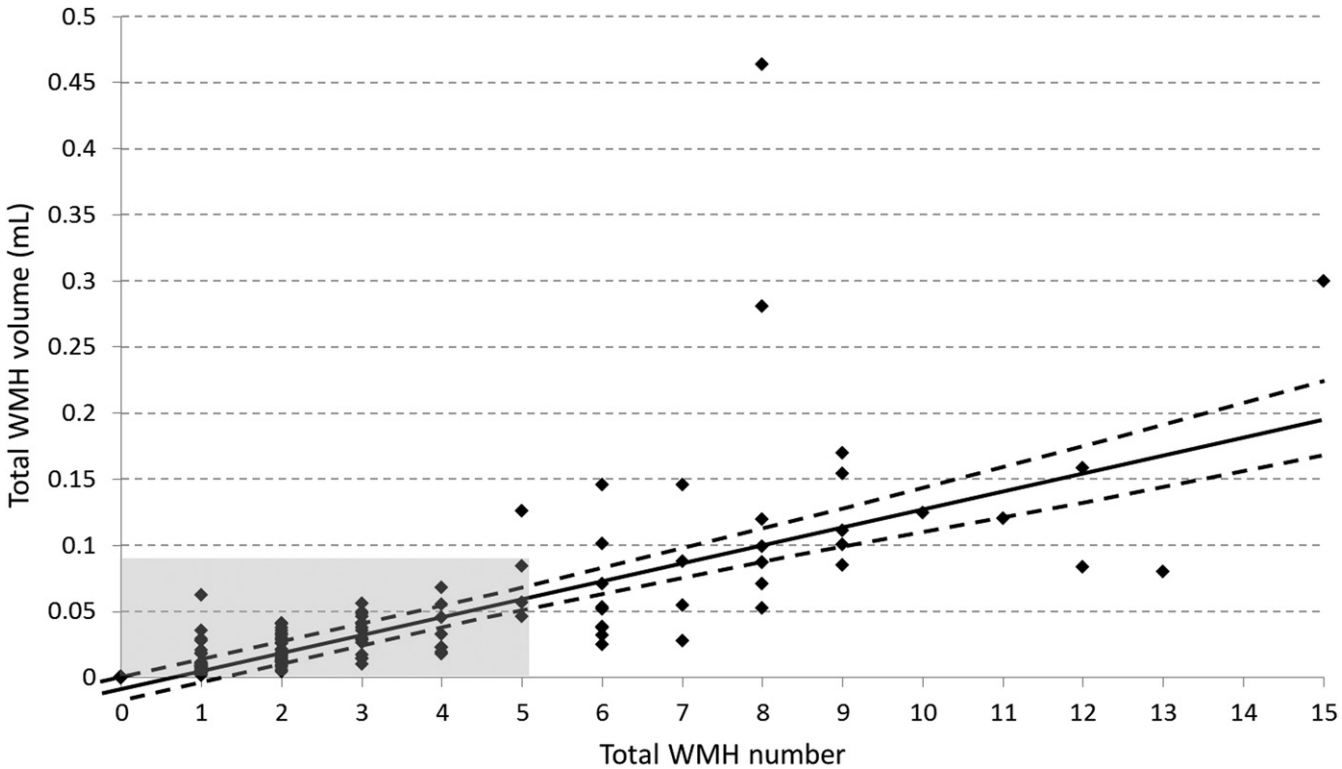

Fig. 1. Normative data for background total white matter hyperintensity (WMH) number and total WMH volume for the healthy USAF control cohort (N = 162) having no known factors predisposing to white matter injury (second order polynomial regression with 95% confidence intervals). Note multiple overlying data points especially for zero or very few WMH. The shaded area encompasses 80% of data points.

Table I. Planned Schedule of Hypobaric Chamber Exposures for Each Research Subject Undertaking Oxygen System Assessments.

SERIAL	ALTITUDE PROFILE	DURATION AT PLATEAU ALTITUDES (MINUTES)	MINIMUM OXYGEN CONCENTRATION (%)	DURATION OF 100% OXYGEN PREBREATHE (MINUTES)	TIME SPENT AT OR ABOVE 25,000 FT (MINUTES)	NUMBER OF EXPOSURES PER RESEARCH SUBJECT
A	Standard hypoxia familiarization at 25,000 ft	≤ 30	Ambient air	30	≤ 30	1
B	Steady exposure at 18,000 ft	≤ 20	60	None	0	2
C	Steady exposures in turn at 40,000 ft; 25,000 ft; 18,000 ft; 8000 ft	≤ 6 at each	60	90	≤ 20	5
D	Slow decompression from 24,000 ft to 35,000 ft	n/a	60	60	≤ 15	6
E	Rapid decompression (4 s) from 8000 ft to 25,000 ft	≤ 4	50	30	4	6
F	Rapid decompression (4 s) from 9000 ft to 40,000 ft	≤ 4	100	60	8	3

oxygen throughout except as shown in Fig. 2 for profiles C and D, and in profile E when breathing gas was switched to 50% oxygen for 5 min at the base altitude of 8000 ft prior to rapid decompression, whereupon it reverted to 100% oxygen. Inside observers also undertook 100% oxygen prebreathes when indicated and remained on 100% oxygen throughout decompressions above 18,000 ft. Thus, all exposures were nonhypoxic apart from the single initial hypoxia familiarization exposure. Hypobaric exposures began in February 2017 and were completed by November 2017. All exit MRI scans were completed by December 2017.

Statistical Analysis

The key metrics of interest are subcortical total WMH count and total WMH volume before and after participation in the altitude research program; these data are reported descriptively. The association between past MTBI and WMH in UK volunteers was reviewed using Fisher's exact test for 2×2 contingency tables ($\alpha = 0.05$) using a composite dataset that encompasses the entry screening data from the current prospective study and the cross-sectional retrospective study data reported previously.[4]

RESULTS

Hypobaric exposures to equivalent pressure altitudes ≥ 18,000 ft undertaken by each of the 11 eventual subjects are summarized in **Table II**.

Following consultation with the MOD Research Ethics Committee, three exposures were repeated due to technical issues during the original experiments (test equipment failure; difficulty with close control of a slow ascent rate; loss of data), such that, by chance, one research subject undertook three extra exposures while one inside observer conducted an extra profile C. Another 56 hypobaric decompressions were undertaken to < 10,000 ft pressure altitude, the majority by the first four inside observers, mostly in support of rapid decompression profiles.

The interval between entry and exit scans ranged from 7–12 mo for new volunteers and 18–20 mo for the three volunteers who participated in the earlier MRI survey; this difference did not influence study outcomes. Data for these 11 subjects' total subcortical WMH number and total WMH volume on study entry and exit are shown in **Table III**.

The 13 volunteers who underwent entry screening for the current prospective study brought to 33 the total of UK

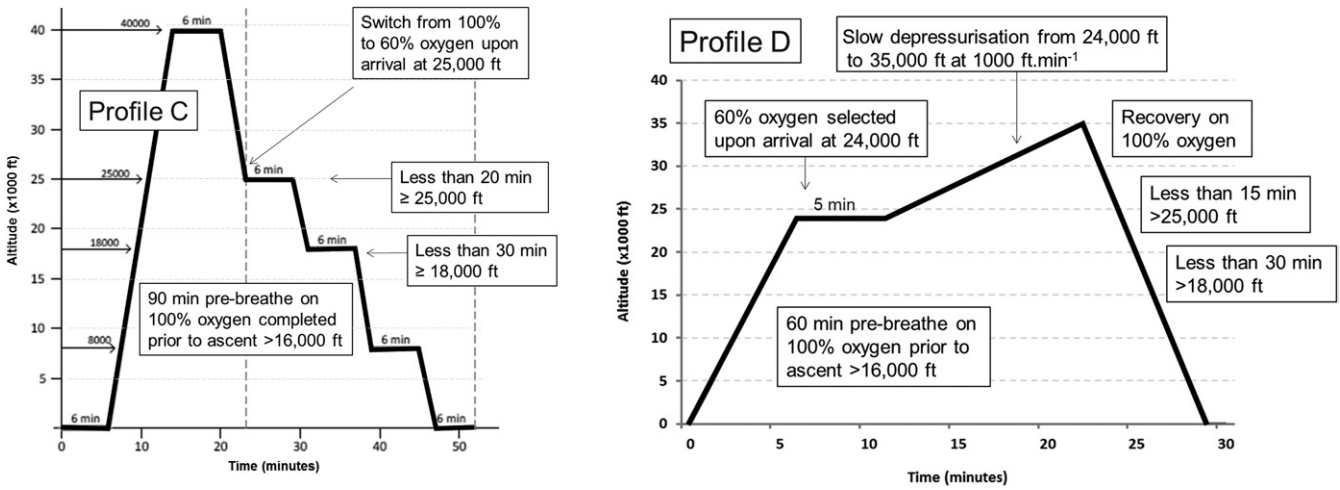

Fig. 2. Hypobaric chamber profiles C and D showing simulated altitude against time, oxygenation status and prebreathe schedules.

Table II. Hypobaric Exposure Profiles Experienced by Each of Five Volunteer Research Subjects and Six Volunteer Inside Observers.

		RESEARCH SUBJECTS					INSIDE OBSERVERS						
SERIAL	ALTITUDE PROFILE	1	2	3	4	5	A	B	C	D	E	F	TOTALS
A	Hypoxia at 25,000 ft	1	1	1	1	1	1	1	1	1	1	1	11
B	Steady at 18,000 ft	2	2	2	2	2	3	2	2	3	-	-	20
C	Profile C	5	6	5	5	5	5	-	5	6	5	5	52
D	Profile D	6	8	6	6	6	-	-	-	-	-	-	32
E	Rapid decompression to 25,000 ft	6	6	6	6	6	-	-	-	-	-	-	30
F	Rapid decompression to 40,000 ft	3	3	3	3	3	-	-	-	-	-	-	15
Totals		23	26	23	23	23	9	3	8	10	6	6	160

volunteers screened to date using 3-D FLAIR MRI. Of these 13, 2 gave a history of likely MTBI including the one screening failure. These additional data were used to reassess the association between past MTBI and a finding of "excess" WMH, where "excess" is $>$ 15 WMH and inconsistent with the normative USAF control sample. The updated 2 $\times$ 2 contingency table is shown in **Table IV**.

DISCUSSION

Across all 11 subjects in the current prospective MRI study, just one WMH lesion (frontal lobe) was reported on both entry and exit scans (inside observer "A" in Table III). This was assessed to have a volume of 74.2 mm^3 on entry and 105.5 mm^3 on exit, representing an increase in radius (for a spherical lesion) of ~0.3 mm. However, the lesion was easily identifiable on the raw axial FLAIR images and was unchanged in size and morphology between the entry and exit scans.

The reduction in number of WMH between the entry and exit MRI in this sample is not considered meaningful. Two explanations are possible. The reported low levels of small background WMH may be transient foci of genuine white matter change that occur in daily life, coming and going for reasons unknown. Alternatively, they may represent low levels of background "noise" when conducting very high resolution 3-D FLAIR MRI, which is consistent with the acceptance of $\leq$ 5 WMH as normal using this technique. The latter explanation is considered more likely, as image processing is complex and likely to generate occasional contrast nonlinearities that may be interpreted subjectively as possible WMH. Similarly, manual delineation of 3-D lesions will inevitably introduce a small degree of subjective measurement error that will be influenced by lesion contrast. Thus, care must be taken not to over-interpret minor variations in either total number or volume of WMH reported on successive scans in the same individual. Accordingly, it is concluded that there is no meaningful difference in the entry and exit MRI data of the current study subjects and our duty of care to volunteers has been satisfied by demonstrating that no harm has occurred.

This manned program of altitude chamber research, incorporating a single hypobaric hypoxia familiarization exposure for each subject, has not promoted white matter injury. In this context, the current study has demonstrated a safe system of work using the procedures adopted for this research program with volunteers having normal white matter status. Altitude chamber studies comprising milder, briefer and/or fewer hypobaric decompressions may be considered highly unlikely to present any meaningful risk of long-term white matter change. On this basis, and given the existing MRI data on past UK participants in altitude chamber research and training,[4] it is not proposed to conduct postexposure MRI after future programs that are less extensive than the current study, providing the same constraints are observed with respect to intensity of altitude decompression stress (short exposure durations, no more frequently than twice per week at 3-d intervals), with minimum levels of exertion at altitude, following conservative denitrogenation schedules.

The question then arises as to whether prior MRI screening would still be required to exclude volunteers with pre-existing WMH. Of note, the current study provides evidence only that hypobaric decompression has not promoted white matter change in a small cohort having normal white matter status, i.e., having minimal or "background" levels of pre-existing WMH. While reassuring, this outcome provides no evidence regarding either safety or hazard to individuals who may have "excess"

Table III. Total Number and Volume of Subcortical White Matter Hyperintensities (WMH) on 3-D Volumetric Brain Magnetic Resonance Imaging at Study Entry and Exit (At Least 4 wk After the Final Hypobaric Exposure) for Five Research Subjects (1-5) and Six Inside Observers (A-F).

	RESEARCH SUBJECTS					INSIDE OBSERVERS						SAMPLE
	1	2	3	4	5	A	B	C	D	E	F	TOTALS
Total subcortical WMH number												
Entry MRI	0	1	0	0	0	1	1	2	0	3	0	8
Exit MRI	0	0	0	1	0	3	0	0	0	0	1	5
Change		-1		+1		+2	-1	-2		-3	+1	-3
Total subcortical WMH volume (mm^3)												
Entry MRI		26.1		0		74.2	9.2	18.4		38.4	0	166.3
Exit MRI		0		10.8		159.2	0	0		0	13.8	184.0
Change		-26.1		+10.8		+85.0	-9.2	-18.4		-38.4	+13.8	+17.7

Table IV. Revised 2 × 2 Contingency Table to Evaluate the Association Between Past Mild Traumatic Brain Injury (MTBI) and Finding of "Excess" (> 15) White Matter Hyperintensities (WMH) for all 33 UK Volunteers Who Have Participated in 3-D Volumetric Brain Magnetic Resonance Imaging for Evaluation of White Matter Status.

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

Fisher exact test statistic = 0.0031 (statistically significant at $\alpha = 0.05$).

pre-existing WMH, i.e., established underlying pathophysiology which remains poorly understood. Accordingly, it remains appropriate to screen out future volunteers for high altitude research who have "excess" WMH for their age. These individuals are not routinely exposed to occupational decompression stress and have nothing to gain personally from participating; their nonoccupational exposure to an optional, unquantifiable and avoidable risk may be considered ethically unjustifiable.

For the UK cohort of 33 young individuals screened with MRI to date (Table IV), the prevalence of "excess" WMH is ~12%. These volunteers all had past MTBI, suggesting that a screening question for past MTBI would have high sensitivity and negative predictive value for excluding excess WMH (both 100% in this small series). The compromise is that this would also exclude ~15% of volunteers who would otherwise be acceptable by not having excess WMH despite having past MTBI. Additionally, this would not exclude other less common causes of white matter change in a young population, discussed further below.

The statistical confidence that a screening question for MTBI may offer in excluding excess WMH may be evaluated using the data in Table IV. Those with no past MTBI all had normal white matter status and may be considered the denominators in a small series of 24 consecutive negative outcomes, i.e., none exhibited excess WMH (zero numerators). The derivation of confidence intervals from small series with zero numerators is well documented.[6] 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:

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

Hence:

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

Fig. 3 plots R_{max} for values of n up to 30, showing the upper 95% confidence limit (credible maximum future risk) of an event (in this case, a false negative screening outcome) based on zero previous occurrences in a series; the lower limit remains zero for as long as there are zero numerators. For $n = 24$, we can have > 95% confidence that R_{max} is < 11% (and > 99% confidence that it is < 18%). It is also clear from Fig. 3 that extending the series by small increases in n (i.e., further MRI screening of volunteers with no past MTBI) is unlikely to inform the true rate characteristic of our population or substantially improve the confidence limits. Nonetheless, occasional false negatives

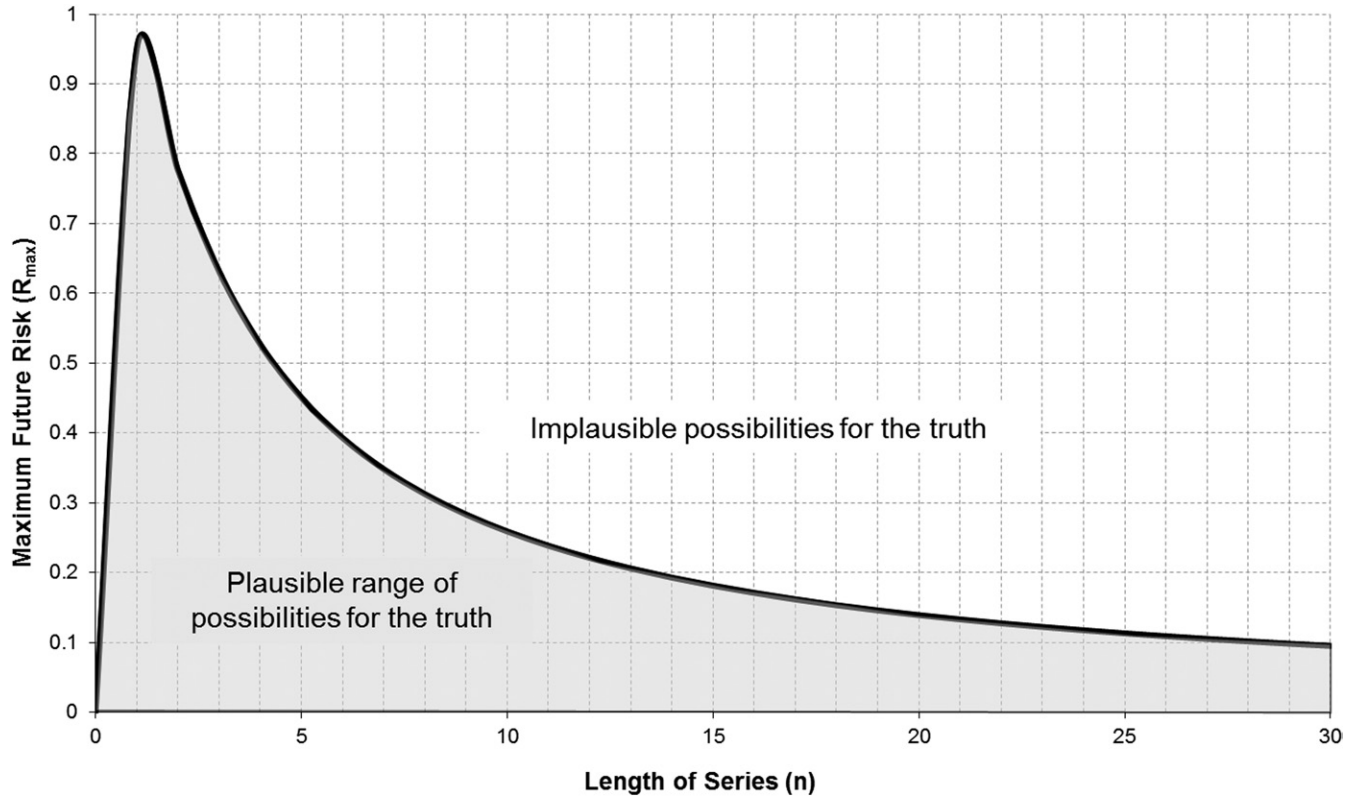

Fig. 3. Maximum future risk for zero numerators in a series (95% confidence limits shaded).

should be expected, since white matter change may result from other (e.g., infectious or inflammatory) causes at a relatively young age, although these may also be sought with appropriate screening questions (e.g., for past episodes of possible viral encephalopathy or diagnoses of optic neuritis).

Accordingly, for future programs of human high altitude research that are no greater in scope or risk than the current study, we propose to screen out volunteers most likely to have excess WMH by questionnaire rather than using MRI. The questionnaire will include asking about past head injury consistent with MTBI, in addition to other factors known to predispose to white matter injury under the age of 50 yr (e.g., cardiovascular risk factors, neuropsychiatric disease, past episodes of illness that might indicate infectious or inflammatory neurological involvement, migraine, etc.). Consideration will also be given to excluding participants in (particularly contact) sports, and activities requiring use of head protection, at a competitive level likely to be associated with occasional concussive or repetitive subconcussive head injury.[2,7] These measures are expected to substantially reduce the likelihood of hypobaric exposure of research volunteers having excess pre-existing WMH.

Some altitude research studies, most obviously those simulating extended operational exposure, or investigating risk of DCS or physiological responses to more intensive subatmospheric decompression stress, will require more prolonged, frequent or repetitive hypobaric exposure. The reassurance gained from the current study should not be extended to such research. Examples might include simulation of prolonged high altitude flight in a low differential pressure cabin, or repeated "bounce" profiles to simulate payload delivery at medium altitudes. Such profiles will necessarily incur greater risk of DCS than the current study (where it was rated as "negligible") and may therefore warrant volunteer screening with MRI. However, it is emphasized that WMH are not pathognomonic of DCS and, while both DCS and WMH are independently associated with intensity of hypobaric decompression stress, any relationship between them has yet to be established. Nonetheless, the current study implies again that more intensive (frequent, prolonged or exertional) altitude decompression stress, thereby presenting greater risk of DCS, must be necessary to promote WMH.[4]

Unlike DCS, WMH do not appear as an acute response to hypobaric decompression stress, although hypobaric exposure is associated with decreased fractional anisotropy in U-2 pilots, indicating an acute white matter response consistent with global axonal stress.[8] To conjecture, under these conditions a focal subcortical "hit" in the watershed regions of the cerebral circulation might result in a localized, subclinical insult promoting permanent white matter change or, if transient, predispose to permanent injury in the event of local recurrence upon subsequent hypobaric decompression. Such a "hit" might then be considered a subclinical manifestation of DCS with a common etiology, becoming more likely as evidence accrues of common provocative subatmospheric decompression profiles.

Limitations of the current study obviously include the small sample of predominantly male, Caucasian, civilian subjects; widely varying hypobaric exposure profiles; and different exposure schedules and cumulative altitude decompression experience of the 11 subjects. Accordingly, it is not at all clear that the current findings should yet be extended to other cohorts, UK military personnel, or even to samples other than volunteers for studies in this laboratory; caution is advised. Nonetheless, this is the first prospective MRI study to report human white matter status in relation to repetitive, nonhypoxic, subatmospheric decompression stress and clearly demonstrates that human hypobaric exposures may be undertaken without causing permanent white matter change. Thereby, it provides a baseline level of altitude chamber research participation that may be considered "subthreshold" for risk of white matter injury and against which proposals for future work may be assessed, e.g., with regard to cumulative hypobaric decompression stress and scheduling of exposures. However, it is emphasized that this approach to management of research volunteers and establishing a safe system of work for altitude chamber research is not designed or intended to translate directly to assessment of occupational fitness for altitude exposure or associated medical employment policies, e.g., for aircrew or parachutists.

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