# White Matter Status of Participants in Altitude Chamber Research and Training

Desmond M. Connolly; Vivienne M. Lee; Peter D. Hodkinson

**INTRODUCTION:** Magnetic resonance imaging (MRI) brain scans of U.S. Air Force (USAF) altitude workers show increased white matter hyperintensities (WMH) that appear related to decompression stress. Relevant exposure thresholds are unknown. This MRI survey compares the white matter status of UK participants (UKP) in altitude chamber research and training with USAF cohorts having background and increased WMH.

**METHODS:** UKP ($N = 20$) comprised 13 research subjects and 7 military altitude chamber instructors ages 33 to 50 yr (16 men, 4 women), encompassing 1417 decompressions over a 15,000-ft (4572 m) pressure altitude (range 11–189; median 50). High resolution MRI reproduced USAF sequences and data were analyzed at the University of Maryland to validate comparison with age-matched USAF control (DOC; $N = 85$) and aerospace operational physiologist (PHY; $N = 55$) cohorts.

**RESULTS:** UKP data are dichotomous: 17 subjects (85%) had normal scans (total 19 WMH) and three outliers had excess (>15) WMH (total of 83 lesions). WMH were not associated with metrics of decompression history (total exposures, rapid decompression, pressure breathing, hypoxia familiarization, decompression sickness, or exposure intensity). Ranked data indicate that UKP have fewer WMH than PHY but not DOC. UKP outliers' excess WMH are attributable to past mild traumatic brain injury.

**CONCLUSIONS:** WMH in UKP are unrelated to subjects' low intensity (brief, infrequent) experience of altitude chamber decompression, encompassing occasional hypobaric hypoxia and mild decompression sickness, even with cumulative experience over many years. Such low intensity hypobaric exposure appears 'subthreshold' for promotion of WMH.

**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 represent areas of neuronal injury that are progressive with age in later life, when they are associated with cognitive decline and poorer clinical outcomes.[5] Recently, excess WMH have been reported in younger U.S. Air Force (USAF) cohorts exposed occupationally to repetitive, nonhypoxic, hypobaric decompression, including U-2 pilots[12] and aerospace operational physiologists.[13] In U-2 pilots, severity of WMH may reflect cumulative hypobaric experience[11] and decompression is associated with decreased fractional anisotropy (FA), indicating global axonal stress.[10] An increased prevalence of WMH in healthy divers, relative to nondiver controls, supports an association between white matter injury and decompression stress.[4] Of concern, increased WMH in U-2 pilots may be associated with subtle, subclinical decrements in neurocognitive function,[14] consistent with reports in other healthy individuals with early white matter change.[2]

The nature of any relationship between subatmospheric decompression stress and white matter injury is unclear. No threshold magnitude or intensity of hypobaric exposure has been proposed above which white matter injury may be more likely to occur, either in terms of cumulative 'total dose' (total exposure numbers; cumulative hours of decompression), provocative decompression profiles (pressure differential; duration

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of exposure), or periodicity (exposure frequency; minimum recovery time).

Members of affected USAF cohorts are exposed routinely to considerable decompression stress over the course of their active duty careers, undertaking frequent or prolonged hypobaric decompression to ambient pressures that present a significant risk of decompression sickness (DCS) and necessitate prior denitrogenation breathing 100% oxygen (‘prebreathe’). Few UK personnel are exposed routinely or frequently to comparable levels of occupational decompression stress. However, hypobaric chambers are used to simulate altitude exposure for aircrew training at the Royal Air Force Centre of Aviation Medicine (RAF CAM, Henlow, Bedfordshire) and for research, test, and evaluation purposes at QinetiQ plc (previously at Farnborough, Hampshire, and now at Boscombe Down, Wiltshire). Training exposures include hypoxia familiarization at 25,000-ft (7620-m) equivalent pressure altitude (PA) and rapid decompression with pressure breathing at 45,000 ft (13,716 m) PA. Research exposures may include rapid decompression to high altitudes for life support system assessment, or extended decompression at medium altitude to assess risk of DCS.

Some participants in altitude chamber training and research accumulate numerous decompressions over time and the minimum exposure threshold necessary to promote WMH remains unknown. These individuals’ hypobaric exposures are documented in detail, so assessment of WMH burden in UK participants in past altitude chamber research and training (the ‘UKP’ cohort) can inform the association between decompression stress and white matter injury. A brain MRI survey conducted in accordance with the USAF method also enables comparison with USAF normative (control) and affected cohorts, respectively the ‘DOC’ cohort of healthy individuals with no known predisposing factors for WMH, and the ‘PHY’ cohort of aerospace operational physiologists with increased WMH. The outcome was anticipated to have direct relevance to ongoing altitude chamber research and training activities in the UK and potential relevance to others exposed occupationally to hypobaric decompression, e.g., aircrew and parachutists.

This study comprises a brain MRI survey of UKP using high resolution, volumetric, fluid-attenuated inversion recovery (FLAIR) sequences, in accordance with the USAF method, to quantify total subcortical WMH number and volume. WMH data are assessed in relation to detailed metrics of altitude exposure and personal factors known to predispose to WMH, and were compared with age-matched USAF DOC and PHY cohorts having normal and increased WMH, respectively. No neuro-cognitive assessments were conducted as no relevant control data are available.

## 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.

Past QinetiQ altitude chamber research participants and current/former instructors at RAF CAM were invited to join the study. Eligible candidates had undertaken at least 10 decompressions above 15,000 ft (4572 m) PA, thereby excluding those with very few decompressions or predominantly low altitude exposures. In consequence, as anticipated, the majority of all subjects’ decompressions were to ≥25,000 ft (7620 m) PA. An upper age limit of 50 yr was imposed to ensure valid age-matching with USAF cohorts and to avoid age-related WMH that accrue more rapidly after 55 yr.[7] Volunteers were briefed individually and provided written consent to participate.

Subjects completed a detailed questionnaire focusing on factors relevant to WMH encompassing biometric data, lifestyle factors, aspects of medical history, and recreational activities, particularly diving,[4] mountaineering,[16] and contact sports.[3,8] Metrics of past hypobaric decompression were collated in detail, with exposure numbers obtained from subject logbooks and chamber records. Decompression metrics encompassed total number, exposure frequency, personal hypoxia familiarization experiences at 25,000 ft (7620 m) PA, rapid decompressions (RD), occurrences of pressure breathing at altitude [>40,000 ft (12,192 m) PA], exposures lasting over 1 h, and occurrences of DCS.

### Procedure

Subjects attended the Sir Peter Mansfield Imaging Centre at Queen’s Medical Centre, University of Nottingham, UK, to undergo high resolution, 3-D volumetric 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.[12,13] 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. To assure valid comparison with USAF cohorts and minimize analyst bias, raw data and imagery were analyzed independently at the Centre for Brain Imaging Research, University of Maryland, by researchers supporting USAF studies. MRI scans were conducted through the period April 2016 to May 2017.

### Statistical Analysis

The key metrics of interest are total subcortical WMH count and total subcortical WMH volume. Using the current MRI method, up to five WMH are accepted as normal ‘background’ numbers, based on USAF DOC data obtained from healthy individuals (≤50 yr) not exposed routinely to decompression stress. No DOC subject had over 15 hyperintensities, so UKP subjects with more than this are considered to have ‘excess’ WMH.

WMH data are reported descriptively and presented in relation to metrics of decompression exposure using simple scatter plots and linear regression. UKP subjects’ experience of human centrifugation, G-induced loss of consciousness (G-LOC), and screening for patent foramen ovale (PFO) were assessed for relevance to WMH data using Fisher's exact test for 2 × 2 contingency tables (α = 0.05). A history of concussive head injury, consistent with a diagnosis of mild traumatic brain injury (MTBI), was evaluated in the same way.

USAF DOC and PHY cohorts' WMH data were age-matched to the UKP sample. Nonparametric analysis employed the Mann-Whitney (Wilcoxon rank sum) test to assess the equality of population medians between the UKP cohort and each of the age-matched USAF cohorts in turn (α = 0.05); single-tailed tests were employed to reduce outlier bias.

## RESULTS

### UKP Sample Characteristics

The UKP cohort of 20 medical, scientific, and technical subjects comprised 16 men and 4 women. Seven had undertaken military altitude chamber instructor duties at RAF CAM and 13 had participated in past QinetiQ research studies. Mean age at MRI was 42 yr. The cohort tended to be overweight with modestly elevated body mass index (BMI); biometric data are shown in **Table I**, the age distribution in **Fig. 1A**, and the BMI distribution in **Fig. 1B**.

UKP included 13 'never' smokers and just 1 current (occasional) smoker (3.75 pack years). Ex-smokers averaged only 2.5 pack years (range 0.25–5.5). The cohort's alcohol consumption was moderate (mean 8.7 units per week; range 0–21; median 8.0), with the majority drinking fewer than 10 units per week.

Eight subjects were recreational scuba divers with varying levels of experience. Three had completed over 100 dives and two had been deeper than 164 ft (50 m). Four had been diving for 15 yr or more and one had experienced diving-related neurological DCS requiring hyperbaric recompression. Two subjects had undertaken hyperbaric chamber duties as medical attendants.

Six had undertaken terrestrial ascents (mountaineering) above 10,000 ft (32,808 m) PA, two repeatedly, and four had experienced altitude sickness, one on several occasions. Two had general aviation flying experience and one had limited parachuting experience. Three had experienced G-LOC during human centrifugation; one of these, on another occasion, also experienced transient loss of consciousness (~5 s) due to pressure breathing syncope, with spontaneous complete recovery. Seven had engaged in various competitive contact sports, including rugby (five), soccer (three), field hockey (two), boxing (one), and karate (one).

Nine subjects reported past head injuries and seven of these were assessed as compatible with a likely diagnosis of MTBI. One subject experienced 'severe' back pain due to past spinal trauma and another had a 'moderate' tendency to vasovagal faints. Otherwise subjects had only 'slight' current symptoms, comprising limb sensory symptoms (two subjects), dizziness/vertigo (one), forgetfulness or loss of concentration (one), visual impairment (one), headaches (two), and neck pain or backache (five). The question on forgetfulness was used to segregate cohorts in an unrelated study of commercial diver health;[9] notably, the only respondent in the current study with forgetfulness was the scuba diver with past neurological DCS.

Family histories of neurological disease included seven of dementia, five of stroke, and two of motor neuron disease. Three subjects used nonpsychoactive medications (an antibiotic, simple analgesia, or inhalers for asthma).

### UKP Decompression Experience

Overall metrics of altitude exposure for the UKP cohort are shown in **Table II**. Subjects exhibited a wide range of altitude chamber experience (**Fig. 1C**). Only nine met eligibility criteria for the USAF PHY cohort having completed over 50 exposures above 20,000 ft (6096 m) PA. These nine contributed 1075 (~76%) of the 1417 UKP decompressions (mean 119 ± 45; range 68–189; median 104), including ~82% of the RDs, ~90% of the high altitude RDs with pressure breathing, and ~67% of the 93 decompressions lasting longer than an hour. The remaining 11 subjects were correspondingly less experienced.

Only three subjects ever undertook eight or more exposures in a single calendar month, but this was exceptional; most achieved a maximum of four to seven exposures in one month. More typical exposure intensity was just two or three exposures per month. Some participated in intermittent altitude studies over many years, resulting in very low exposure rates per unit time. A better estimate of exposure intensity is reflected by each individual's average number of exposures per month of active chamber participation (between-subjects mean 2.7, range 1.1–4.7, median 2.5).

Older subjects accumulated more decompressions (**Fig. 1D**), reflecting, in some cases, intermittent participation in altitude research or training over many years. All had at least one personal training experience of hypobaric hypoxia at 25,000 ft (7620 m) PA, but most had received hypoxia familiarization on multiple occasions. There were 5 subjects who experienced a total of 10 discrete occurrences of subatmospheric DCS, with 1 having 4 episodes and 2 having 2 each. All were typical isolated limb pain 'bends' that occurred during prolonged exposure to assess DCS risk at medium altitudes and all resolved spontaneously upon immediate descent to ground level.

**Table I.** UKP Age at MRI (*N* = 20); Height, Weight, and Body Mass Index (*N* = 19).

| FACTOR | MEAN | STANDARD DEVIATION | RANGE (MIN–MAX) | MEDIAN |
|---|---|---|---|---|
| Age at MRI (yr) | 42.3 | 4.8 | 33.6–50.0 | 42.6 |
| Height (m) | 1.78 | 0.07 | 1.65–1.88 | 1.78 |
| Weight (kg) | 80.9 | 11.6 | 62.0–95.0 | 79.5 |
| BMI (kg · $m^{-2}$) | 25.7 | 3.4 | 20.7–32.9 | 25.1 |

UKP: UK participants.

### UKP Subcortical WMH

UKP exhibited a total of 102 discrete, punctate subcortical WMH. Of the subjects, 17 (85%) had normal scans (≤5 WMH), totaling just

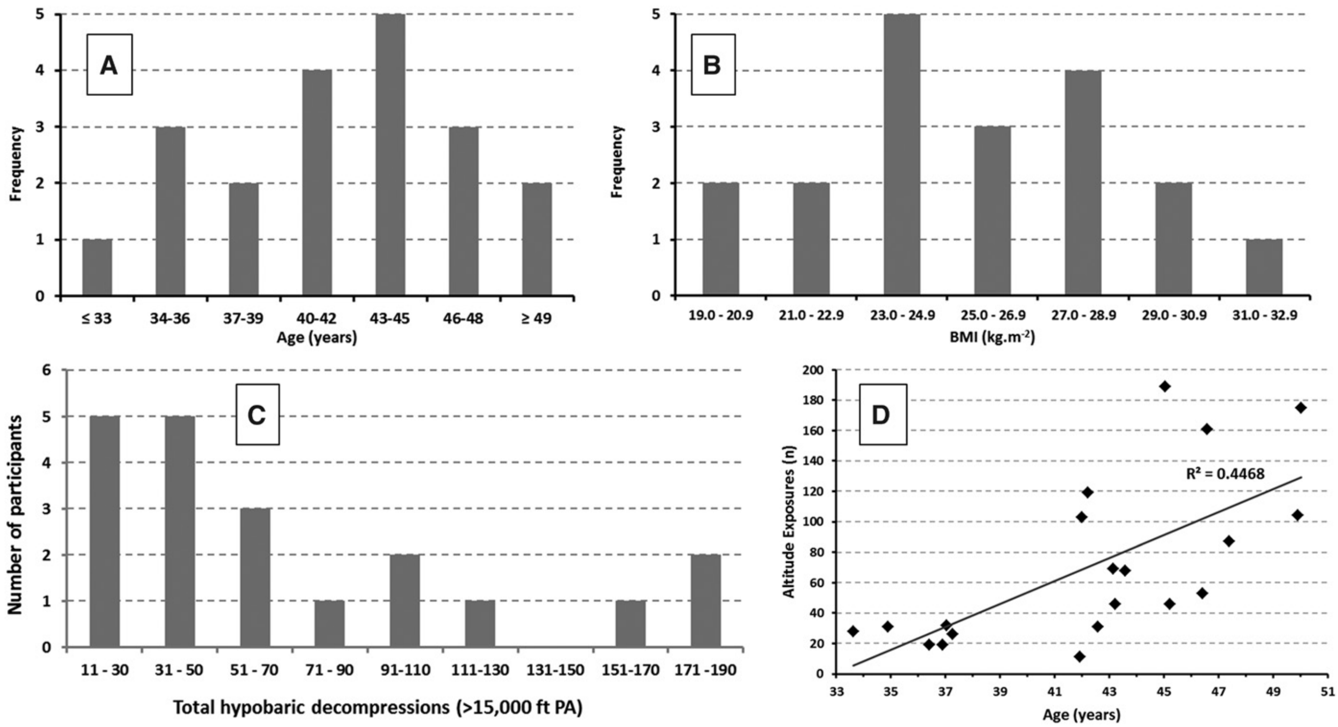


**Fig. 1.** UKP metrics: A) Age distribution; B) BMI distribution; C) Number of altitude chamber decompressions above 15,000 ft pressure altitude; D) Trend for decompression experience to increase with age.

19 lesions with mean WMH volume ~21 $mm^3$. There were 17 (89%) frontal lobe hyperintensities, the exceptions being isolated lesions in 2 individuals. Three subjects (two men, one woman) were 'outliers' with excess (>15) WMH, specifically 19, 29, and 35 lesions. Only 40 (48%) of these 83 WMH were frontal, with 22 (27%) parietal, 11 (13%) temporal, 6 (7%) sublobar, and isolated lesions elsewhere. Mean WMH volume for the outliers was ~43 $mm^3$. Of note, only 1 of the 10 most experienced UKP altitude chamber subjects had excess WMH. Two of the outliers had been research subjects at QinetiQ and one was an instructor at RAF CAM.

UKP age did not influence WMH number or volume (**Fig. 2**). Plots of total WMH volume are predictable from those of total WMH number, with three outliers instantly identifiable. For brevity, further graphs of WMH volume are omitted. The effect of the three outliers to bias the regression plots is clearly evident.

Plots of total WMH number against metrics of UKP decompression experience are shown in **Fig. 3**. Total WMH number is unrelated to total decompressions (Fig. 3A); hypoxia experience (Fig. 3B); rapid decompression (Fig. 3C); pressure breathing at high altitude (Fig. 3D); extended (>1 h) decompression (Fig. 3E); occurrences of DCS (Fig. 3F); or metrics of exposure intensity, including maximum exposures in 1 mo (Fig. 3G) or mean exposure frequency during active chamber participation (Fig. 3H).

### Consideration of Other Factors

The potential relevance of other factors to promote excess WMH was assessed using Fisher's Exact Test ($\chi^2$) for 2 × 2

**Table II.** UKP Decompression Experience (*N* = 20).

| METRIC | COHORT TOTAL (*N* = 20) | PER PARTICIPANT MEAN ± SD | RANGE (MIN–MAX) | MEDIAN |
|---|---|---|---|---|
| Total exposures >15,000 ft | 1417 | 71 ± 55 | 11–189 | 50 |
| Total Rapid Decompressions (RD) | 751 | 38 ± 41 | 0–150 | 25 |
| RD >40,000 ft (pressure breathing) | 326 | 16 ± 24 | 0–90 | 3 |
| Decompressions lasting >1 h | 93 | 5 ± 5 | 0–17 | 4 |
| Altitude DCS occurrences | 10 | 0.5 ± 1.1 | 0–4 | 0 |
| Personal hypoxia familiarizations | 46 | 2.3 ± 1.2 | 1–5 | 2 |
| Maximum exposures in one month | - | 6.4 ± 2.7 | 2–13 | 6 |
| Total years of chamber participation | 136 | 7 ± 5 | 0.5–18 | 6 |
| Mean exposures per month | - | 1.5 ± 1.3 | 0.2–4.7 | 1.1 |
| Total months chamber activity | 563 | 28 ± 24 | 6–89 | 17.5 |
| Mean exposures per active month | - | 2.66 ± 0.9 | 1.1–4.7 | 2.5 |

UKP: UK participants.

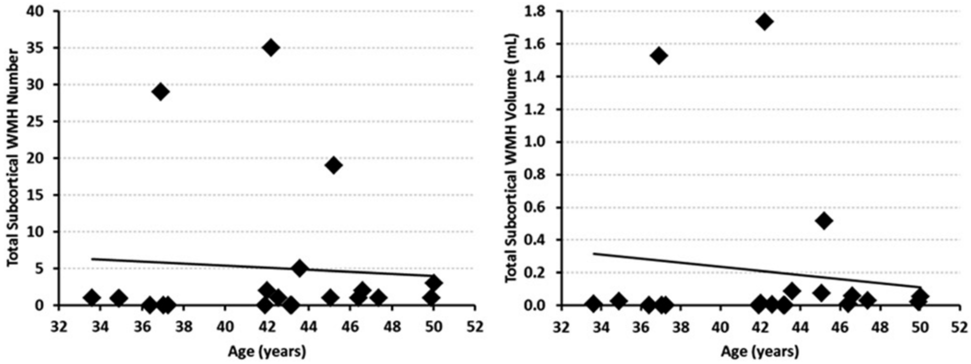


**Fig. 2.** UKP total subcortical WMH number and volume by age ($N = 20$).

contingency tables (**Table III**). Using transthoracic contrast echocardiography, 11 UKP members had previously undergone screening for PFO. Two were outliers in the current study with excess (>15) WMH; the remaining nine had from zero to two WMH. The only subject with a large PFO at rest had zero WMH. Another with a PFO that became 'substantial' upon Valsalva maneuver had just one WMH. The two with excess WMH both had small interatrial shunts of doubtful significance. The influence of PFO on excess WMH was not statistically significant.

Five subjects had experienced repeated exposure to sustained high $+G_z$ acceleration, of which two had excess WMH. These two were also known to have PFO. The influence of $+G_z$ acceleration was not significant in UKP, even when considered in conjunction with underlying PFO. Three subjects had experienced G-LOC, but only one of these had excess WMH; this was also not significant.

Nine UKP members described at least one episode of past head injury, many involving substantial energy transfer (including one blast trauma). Seven were judged consistent with MTBI, typically associated with loss of consciousness or disorientation, anterograde amnesia, persistent concussion symptoms, acute imaging, and hospitalization. These seven include all three with excess WMH (see Table III). The likely influence of MTBI on excess WMH in UKP is statistically significant ($P < 0.05$).

#### Comparison with USAF Cohorts

The original USAF DOC ($N = 162$) and PHY ($N = 83$) samples were age-matched to UKP (33–50 yr), reducing these cohorts to DOC $N = 85$ and PHY $N = 55$. The age distributions of the resulting UKP, DOC, and PHY cohorts were broadly similar, although UKP had a slightly higher proportion of older members, with nearly half (47%) ages ≥43 yr compared to 35% of PHY and 25% of DOC. This does not appear to have biased against the UKP sample when comparing data between cohorts.

Summary data for total WMH number and volume for the three samples are shown in **Table IV**. Mean and SD of total WMH number are biased by outlier data which skew parametric measures of central tendency and variance, particularly for the smaller UKP sample. In contrast, for ranked data the median, first quartile (Q1), third quartile (Q3), and interquartile range (Q3–Q1) all suggest that UKP have fewer WMH than either DOC or PHY. The proportion of UKP with normal (≤5) WMH is similar to DOC, whereas the proportion of UKP with excess WMH is similar to PHY; however, the proportion with zero or very few (≤2 lesions) is greater for UKP (75%) than either the PHY (51%) or DOC (60%) cohorts (**Fig. 4A**). Overall, UKP data are heavily skewed by the three outliers with excess WMH.

The proposition that UKP have fewer WMH than either USAF cohort is supported by comparing ranked data for total WMH number normalized in proportion to sample size (**Fig. 4B**); UKP exhibit the fewest WMH until beyond Quartile 3. Mann-Whitney tests were conducted to assess the hypothesis that UKP have fewer WMH than either the PHY or DOC cohorts ($\alpha = 0.05$); these were single- (lower-) tailed to minimize the bias that outliers would introduce if using a two-tailed test, thereby enabling outcomes representative of the bulk of each cohort. Test results (adjusted for ties) were: UKP ($N = 20$), median 1.0, PHY ($N = 55$), median 2.0, $P = 0.045$; UKP ($N = 20$), median 1.0, DOC ($N = 85$), median 2.0, $P = 0.097$. Statistically, UKP have significantly fewer WMH than PHY, but not DOC. The WMH burden for UKP, therefore, appears lighter than PHY and consistent with DOC.

Considering metrics of total WMH volume for each of the cohorts (Table IV), once again the three outliers severely skew the UKP data, such that meaningful statistical comparison of volumetric data between the UKP and USAF cohorts is unachievable. Normalized ranked UKP volume data are consistently lower than PHY and similar to DOC until reaching the outlier data.

Comparison of the DOC, PHY, and UKP data using linear regression illustrates the effect of excluding the three UKP outliers on total WMH number (**Fig. 4C**) and total WMH volume (**Fig. 4D**). The large-dash regression lines include the UKP outliers and imply decreasing WMH number and volume with age, which is clearly nonsensical. Exclusion of outliers results in the solid UKP regression lines indicating gradual and slowly increasing WMH number and volume with age, as expected and consonant with the regression lines for the other cohorts.

## DISCUSSION

UKP data are dichotomous, comprising 17 individuals (85%) with normal scans (≤5 WMH), averaging just over 1 lesion each, and 3 outliers each with excess (>15) WMH (total 83 lesions). Almost all WMH on normal scans were frontal lobe lesions, whereas less than half of the 'excess' WMH were frontal (48%), with 27% parietal, 13% temporal, 7% sublobar, and scattered lesions elsewhere. Mean lesion volume for 'excess' WMH

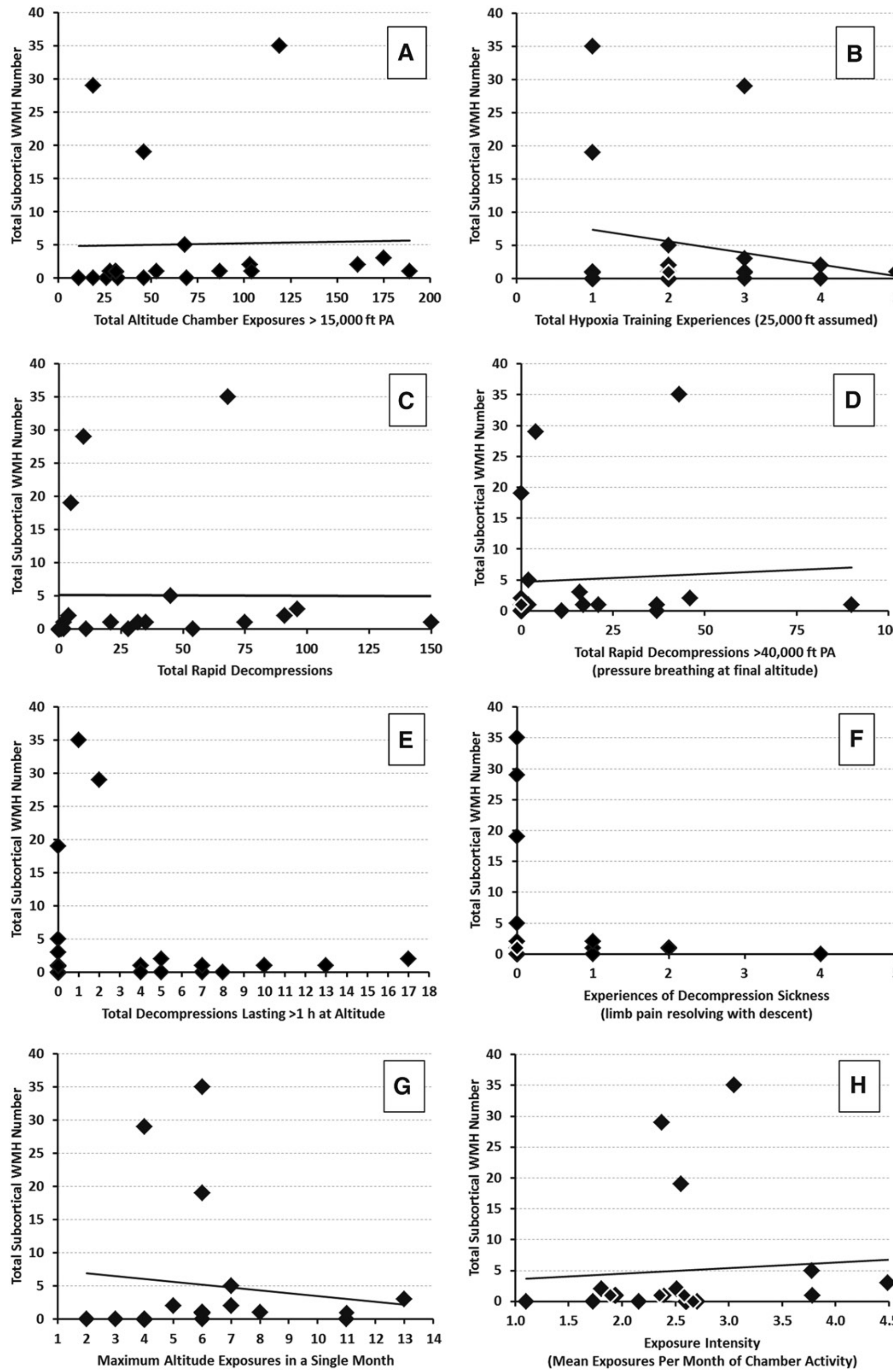


**Fig. 3.** Plots of total subcortical WMH number against metrics of decompression experience ($N = 20$); note numerous overlying data points. Graph F includes one episode of diving-related neurological DCS.

was twice that of WMH seen on normal scans. The three outliers account for over 80% of UKP subcortical WMH and exhibit a different anatomical distribution of larger lesions.

Thus, the three outliers are unrepresentative of the rest of the UKP cohort and their excess WMH are most readily associated with past concussive head injury consistent with possible MTBI.[15] Recent reports also suggest that white matter injury may result from repetitive subconcussive insults typical of some contact sports, manifesting as general loss of axonal integrity with decreased FA.[3,8] The three UKP outliers with excess WMH

**Table III.** 2 × 2 Contingency Tables for Evaluation of Potential Factors Predisposing to Excess WMH in UKP.

| | EXCESS (>15) WMH | | |
|---|---|---|---|
| | YES | NO | TOTALS |
| Patent Foramen Ovale (PFO) on TTCE | | | |
| Yes | 2 | 2 | 4 |
| No | 0 | 7 | 7 |
| Totals | 2 | 9 | 11 |
| Fisher exact test statistic ($\chi^2$) = 0.1091 (not significant at $\alpha$ = 0.05) | | | |
| Sustained +$G_z$ Acceleration | | | |
| Yes | 2 | 3 | 5 |
| No | 1 | 14 | 15 |
| Totals | 3 | 17 | 20 |
| Fisher exact test statistic ($\chi^2$) = 0.1404 (not significant at $\alpha$ = 0.05) | | | |
| Sustained +$G_z$ Acceleration with PFO | | | |
| Yes | 2 | 2 | 4 |
| No | 1 | 15 | 16 |
| Totals | 3 | 17 | 20 |
| Fisher exact test statistic ($\chi^2$) = 0.0877 (not significant at $\alpha$ = 0.05) | | | |
| G-induced Loss of Consciousness (G-LOC) | | | |
| Yes | 1 | 2 | 3 |
| No | 2 | 15 | 17 |
| Totals | 3 | 17 | 20 |
| Fisher exact test statistic ($\chi^2$) = 0.4035 (not significant at $\alpha$ = 0.05) | | | |
| Mild Traumatic Brain Injury (MTBI) | | | |
| Yes | 3 | 4 | 7 |
| No | 0 | 13 | 13 |
| Totals | 3 | 17 | 20 |
| Fisher exact test statistic ($\chi^2$) = 0.0307, which is statistically significant at $\alpha$ = 0.05 | | | |

UKP: UK participants; WMH: white matter hyperintensities; TTCE: transthoracic contrast echocardiography.

described: an unwitnessed fall from height onto a concrete floor and metal pipework, suffering two discrete blows to the head, disorientation, and likely anterograde amnesia; a fall down bare stairs sustaining multiple facial fractures, with witnessed loss of consciousness and persistent symptoms of concussion; and running "at full pelt" into a flailing arm with witnessed loss of consciousness, disorientation, and persistent symptoms of concussion, plus numerous subconcussive impacts ('headers') over many years of competitive soccer.

Other UKP lifestyle and recreational factors are unlikely to have contributed to the observed excess WMH. The outliers are all 'never' smokers and none regularly consumes more than 10 units of alcohol per week. None of the scuba divers, neither of the hyperbaric medical attendants, and none of the climbers had excess WMH.

No association is evident between numbers of WMH and any metric of past hypobaric decompression stress, including total exposures, hypoxia experiences, DCS occurrences, or metrics of exposure intensity. UKP have significantly fewer WMH than PHY and is consistent with the data of the DOC control group. Overall, UKP exhibit normal, background levels of WMH for a healthy sample up to 50 yr of age.

In contrast to affected USAF occupational cohorts with increased WMH, UKP have experienced comparatively low levels of decompression stress over the last two decades or so. In recent years, since the introduction of aircrew hypoxia familiarization using reduced oxygen breathing techniques, aircrew instructors have undertaken fewer hypobaric chamber exposures to 25,000 ft (7620 m) PA. Furthermore, military instructors at RAF CAM generally

**Table IV.** Metrics of Total WMH Number and Volume for UKP, DOC, and PHY Cohorts.

| | TOTAL WMH NUMBER | | |
|---|---|---|---|
| PARAMETER | UKP ($N$ = 20) | DOC ($N$ = 85) | PHY ($N$ = 55) |
| Mean | 5.10 | 2.94 | 6.71 |
| Standard Deviation | 10.15 | 3.11 | 11.18 |
| Range | 0 - 35 | 0 - 15 | 0 - 58 |
| Median | 1 | 2 | 2 |
| Quartile 1, Quartile 3 | 0, 2 | 1, 4 | 1, 6 |
| Interquartile Range (Q3-Q1) | 2 | 3 | 5 |
| **PROPORTION WITH NORMAL (BACKGROUND), INTERMEDIATE, OR EXCESS WMH** | **UKP (%)** | **DOC (%)** | **PHY (%)** |
| Normal (≤5) WMH | 85 | 81 | 67 |
| Intermediate (6–15) WMH | 0 | 19 | 18 |
| Excess (>15) WMH | 15 | 0 | 15 |

| | TOTAL WMH VOLUME (mL) | | | |
|---|---|---|---|---|
| | UKP ($N$ = 20) | UKP ($N$ = 17) EXCLUDING THREE OUTLIERS | DOC ($N$ = 85) | PHY ($N$ = 55) |
| Mean | 0.209 | 0.023 | 0.038 | 0.162 |
| Standard Deviation | 0.500 | 0.029 | 0.055 | 0.482 |
| Range | 0–1.734 | 0–0.087 | 0–0.300 | 0–3.405 |
| Median | 0.018 | 0.009 | 0.018 | 0.023 |
| Quartile 1, Quartile 3 | 0, 0.067 | 0, 0.043 | 0.005, 0.048 | 0.006, 0.084 |
| Interquartile Range (Q3-Q1) | 0.067 | 0.043 | 0.043 | 0.078 |

UKP: UK participants; DOC: USAF age-matched controls; PHY: aerospace operational physiologists.

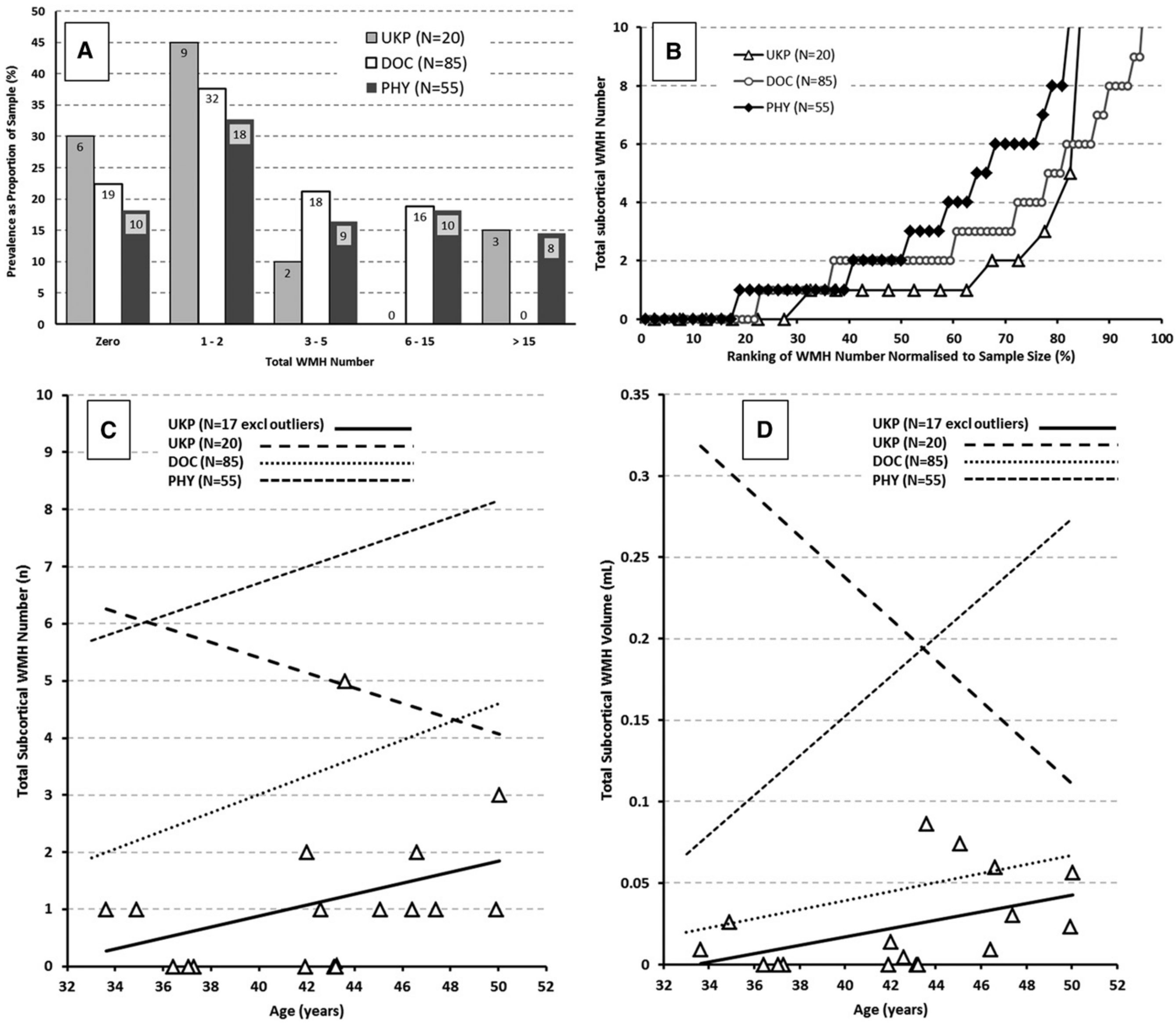


**Fig. 4.** Comparison of UKP, DOC, and PHY cohorts: A) Prevalence of WMH number normalized to sample size; B) Ranked WMH number normalized to sample size; C) Linear regression of WMH number with age; D) Linear regression of WMH volume with age.

undertake this role for a single tour of duty rather than as a career-long activity. Subjects in altitude research at QinetiQ may be exposed repeatedly to medium or high equivalent altitudes, but these decompressions are usually brief and sporadic. Only ~6.5% of UKP hypobaric exposures lasted longer than an hour. Typical UKP exposure intensities involve just two or three decompressions per month of active chamber participation. Even during busier spells, it is very unusual for an individual to undertake more than five or six decompressions per month. Accumulated decompression experience is also limited; only nine UKP volunteers exceed the minimum eligibility criteria of the PHY cohort. Thus, UKP represents a comparatively 'low intensity' decompression stress sample compared to affected USAF cohorts.

Even so, the UKP cohort has accumulated a substantial decompression record over time, particularly the nine most experienced individuals. This experience encompasses prolonged decompressions for up to 4 h at altitudes over 20,000 ft (6096 m) PA to assess DCS risk, rapid decompressions to a maximum 60,000 ft (18,288 m) PA, hypobaric pressure breathing, multiple hypoxia familiarizations, and occurrences of limb pain DCS. Regardless, these do not appear to have predisposed to WMH across the cohort as a whole, although it is impossible to state unequivocally that decompression has not contributed to evolution of specific lesions in any given individual. Nonetheless, on balance, it seems that procedures for conducting altitude chamber research and training in the United Kingdom over the last two decades have not promoted white matter injury, so it appears reasonable to infer that UKP experience of low intensity decompression stress is subthreshold for promoting WMH.

This survey has only considered the relevance of past decompressions above 15,000 ft (4572 m) PA. Since these have not caused WMH, even frequent decompression to lesser altitudes must be very unlikely to promote WMH. On this basis, flight at airliner cabin altitudes should not pose any meaningful risk. Furthermore, it may be inferred that more intensive (frequent and/or prolonged) high altitude exposures would be more likely to promote WMH, which is to say that decompressions presenting greater risk of DCS are implicated.

The relevance of underlying PFO to risk of decompression sickness and white matter injury remains controversial, with studies reporting conflicting outcomes.[1,6] While PFO does not appear to have influenced the MRI findings in the current survey, the small numbers involved do not support wider interpretation.

Limitations of the current study include the cross-sectional design, limited UKP sample size, practical difficulties with recruitment, widely varying past decompression experience, highly skewed nature of WMH datasets, and numerous confounding factors with potential to promote WMH in different individuals, particularly cardiovascular risk factors that evolve with middle age. Age-matching has also decreased substantially the DOC and PHY sample sizes. Fortunately, UKP data constitute clearly dichotomous subsets with either normal or excess WMH, facilitating data interpretation and consideration of potential contributory factors, with past MTBI most readily implicated. Nonetheless, care should be taken not to rely too heavily on data from such a small sample. For example, the contingency matrices are easily biased and their significance readily altered by just a few data points.

In summary, 'low intensity' decompression stress, with occasional hypobaric hypoxia familiarization at 25,000 ft (7620 m) PA, is not associated with WMH in healthy UK participants in altitude chamber research and training up to age 50 yr. Their experience reflects a subthreshold level of decompression stress for promoting white matter injury. Hence, current protocols for repeated altitude chamber exposure remain appropriate for UK altitude research, test and evaluation, and aircrew training.

The results have been considered for inferences relevant to those occupationally or operationally exposed to low ambient pressures (e.g., aircrew, parachutists). While acknowledging the highly variable susceptibility to decompression stress within and between individuals, for personnel undertaking relatively brief and infrequent decompressions consistent with those described for UKP, including occasional hypobaric hypoxia refresher training, these data suggest that there is no increased likelihood of developing WMH. This reassurance may not extend to personnel undertaking more intensive (repetitive, frequent, and/or prolonged) decompressions that present greater risk of DCS or for those occupationally exposed to repetitive decompression as a career-long activity. Examples might include repeated, frequent, and/or prolonged high altitude flight in fast jet cabins with low differential pressurization systems, or periods of frequent, repeated cabin decompression at medium/high altitude for payload delivery from tactical air transport. Finally, it is possible that the UKP cohort may not be representative of military personnel exposed operationally to hypobaria and that additional unknown factors may act to increase their occupational risk; role-specific MRI surveys may be necessary to eliminate this possibility.

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