Odds Ratio Meta-Analysis and Increased Prevalence of White Matter Injury in Healthy Divers

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INTRODUCTION: Increased white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) brain scans of high altitude aircrew and altitude chamber workers indicate that exposure to low ambient pressure (hypobaria) promotes white matter injury. If associated with frequent decompression stress then experienced divers should also exhibit more WMH, yet published case-control studies are inconsistent. This meta-analysis evaluated the prevalence of WMH in healthy divers and controls.

METHODS: Eligible studies compared experienced divers (or hyperbaric workers) without neurological decompression illness with nondiving controls, identified from multiple database searches and reference list reviews. Studies were scored for sample size, recruitment bias, control matching, MRI sensitivity, and confounding factors before grading as low, medium, or high quality. Meta-analysis of odds ratios (OR) with 95% confidence intervals (CI) was conducted on all data using a random effects model and repeated after exclusion of low-quality studies.

RESULTS: There were 11 eligible studies identified. After data adjustment to exclude diving accidents, these encompassed 410 divers and 339 controls, of which 136 (33%) and 79 (23%), respectively, exhibited WMH (OR 1.925, 95% CI 1.088 to 3.405). Excluding four low-quality studies eliminated meta-analysis heterogeneity, with 98 of 279 divers (35%) and 44 of 232 controls (19%) exhibiting WMH (OR 2.654, 95% CI 1.718 to 4.102).

CONCLUSIONS: Results suggest that repeated hyperbaric exposure increases the prevalence of white matter injury in experienced healthy divers without neurological decompression illness. This is consistent with reports of increased WMH in asymptomatic altitude workers and an association with intensity of dysbaric exposure.

KEYWORDS: white matter hyperintensity, diving, altitude, magnetic resonance imaging, flying.

Connolly DM, Lee VM. *Odds ratio meta-analysis and increased prevalence of white matter injury in healthy divers.* Aerosp Med Hum Perform. 2015; 86(11):928–935.

Following an index case of severe neurological decompression illness (DCI) in a U-2 pilot,[11] the prevalence of subcortical white matter hyperintensities (WMH) evident on magnetic resonance imaging (MRI) brain scans was found to be increased in active duty U-2 pilots[15] and also in altitude chamber workers with a history of repetitive, nonhypoxic exposure to high altitude ($>$50 exposures to $\geq$25,000 ft).[16] The severity of WMH burden in U-2 pilots may be related to past DCI,[14] but remains significantly increased relative to nonaircrew controls even when past DCI is excluded.[16]

The long-term health consequences, if any, of developing altitude-related WMH at a relatively young age remain unknown, but WMH increase dramatically with age after 55 yr and 'are associated with an increased risk of stroke (meta-analysis hazard ratio 3.3, 95% confidence interval 2.6 to 4.4), dementia (1.9, 1.3 to 2.8), and death (2.0, 1.6 to 2.7).'[5] Progression of WMH is related to global cognitive decline, particularly attention and executive functioning.[12,23] An association of increased WMH with subclinical impairment of neurocognitive function has been reported in U-2 pilots,[17] consistent with subtle cognitive dysfunction seen in otherwise healthy individuals with punctate WMH.[1] Unsurprisingly, the increased prevalence of WMH in altitude workers is generating concern for their long-term health.

The causal relationship between WMH and hypobaric exposure is unclear. No relationship has yet been demonstrated between presence of WMH and total hypobaric 'dose'

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This manuscript was received for review in June 2015. It was accepted for publication in August 2015.

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DOI: 10.3357/AMHP.4392.2015

(numbers of exposures or total hours of exposure), but it is possible that periods of more intense hypobaric exposure may be important (absolute pressure differential, duration, and frequency of exposure). Divers, compressed-air tunnel (caisson) workers, and hyperbaric chamber attendants are exposed repeatedly to high pressure (hyperbaria) and must inevitably experience decompression stress upon return to the surface (normobaria). Thus, if intense periods of hypobaric decompression stress promote WMH in healthy altitude workers, then healthy divers exposed to frequent hyperbaria should also exhibit increased prevalence of WMH, even without past episodes of neurological DCI.

Several relevant, peer-reviewed, case-control studies have been published over the last quarter century. Collectively, however, the available reports are inconclusive and contradictory, variously reporting increased WMH in divers,[20] fewer WMH in divers,[21] or no difference from controls.[29] This ambiguity extends to the wider diving literature. Well-referenced editorials conjecture on possible subtle, diffuse brain injury and an association with neuropsychological changes in divers,[2] or that covert neuropsychological deficit in divers may be related to a form of subclinical decompression sickness akin to multi-infarct dementia.[30] On the other hand, a more recent article states "At present there is no clear evidence that diving, in the absence of serious acute neurological decompression sickness, causes long-term neurological deficit."[4]

The proposition that altitude-related WMH are associated with intensity of decompression stress would be supported by increased prevalence of WMH in those exposed repeatedly to high pressures. Accordingly, a meta-analysis was undertaken of available case-control studies that report the prevalence of WMH in healthy, experienced divers (with no history of neurological DCI) relative to nondiver controls. In this context, the term 'diver' is taken to include military, commercial, and recreational divers, caisson workers, and hyperbaric chamber attendants. The inherent diversity of such studies (e.g., different 'diver' cohorts, nonstandard control groups, evolving MRI sensitivity over time, variability in excluding sources of bias) demanded that eligible studies be graded relative to contemporary criteria to assess the quality of their evidence so that poorer data could be excluded, as necessary, to reduce the anticipated heterogeneity in the meta-analysis.

METHODS

Repeated literature searches were conducted on PubMed, Scopus, and Google Scholar using various combinations of the terms 'diver' or 'diving,' 'white matter,' and 'MRI.' The reference lists of all eligible and many related but ineligible studies (e.g., cohort studies, case reports, or decompression illness papers) were reviewed in detail, as were Scopus lists of references citing each eligible and many ineligible studies. All searches were conducted in English.

Eligible studies reported the prevalence of WMH as the proportion of the total number of participants having any (≥ 1) WMH on MRI brain scan in a well-defined 'intervention' cohort of experienced divers and in a matched nondiver control group. To qualify as 'experienced,' the divers were either exposed routinely to hyperbaric environments during the course of their work (military and commercial divers, caisson workers, hyperbaric chamber attendants) or were experienced amateur divers with well-documented, extensive dive histories. Both divers and controls had to be essentially healthy, but unrelated medical conditions prompting MRI referral (e.g., for assessment of musculoskeletal limb injury or prior to maxillofacial surgery) were acceptable. Studies were ineligible if the diver cohort included those with past neurological DCI or diving accidents whose MRI data could not be excluded. In the event that a study included separate diver cohorts with and without past neurological DCI, in addition to a nondiving control group, only the data from the unaffected diver cohort were included.

Both authors independently assessed each study for eligibility and then for methodological quality with reference to five criteria, comprising sample size, recruitment bias, control matching, MRI sensitivity, and exclusion of confounding factors. Scores were awarded according to a three-point scale (0 = poor, 1 = fair, 2 = good) as detailed in **Table I**, giving a maximum score of 10. Discrepancies were resolved by consensus with reference to the original papers or by taking the mean

Table I. Criteria for Quality Assessment of Case-Control Studies Reporting Prevalence of White Matter Injury in Divers.

SCORE (POINTS)	SAMPLE SIZE (DIVER/ CONTROL)	RECRUITMENT AND SELECTION	CONTROL GROUP MATCHING	MRI SENSITIVITY	CONFOUNDING FACTORS
Poor (0)	Either cohort $N < 24$	Probable bias, likely to be influential	Cohorts poorly matched for any factor likely to influence outcome	≤1T magnet OR no FLAIR sequence OR inconsistent procedure	Biased for age OR smoking OR possible neurological DCI
Fair (1)	Both cohorts $N \geq 24$, either cohort $N < 48$	Possible bias, unlikely to be influential	Sensible nondiving control group, reasonably matched for age, smoking, health	1.5T magnet AND consistent procedure AND FLAIR sequence but likely low resolution	Controlled for age AND smoking AND neurological DCI, but likely other influential source of bias
Good (2)	Both cohorts $N \geq 48$	Clear method, minimal bias, negligible influence	Cohorts well matched; any source of nondiving bias unlikely	>1.5T magnet AND consistent procedure AND FLAIR sequence AND good resolution (slice thickness <5 mm)	Well controlled for age, smoking, neurological DCI, and multiple other factors

MRI: magnetic resonance imaging; T: magnet strength in Tesla; FLAIR: fluid attenuated inversion recovery; DCI: decompression illness.

score when consensus could not be reached. Subsequently, the overall quality of each study was graded as either Low (total score ≤ 3), Medium (>3 to ≤ 6), or High (>6).

The scoring thresholds to achieve 'fair' and 'good' ratings for sample size were set at 24 and 48, respectively, for both the diver and the control cohorts. Studies varied widely in their qualitative description of recruitment and selection methods, with some paying greater care than others to avoiding bias. In particular, diver self-selection for research trials, on the basis of unreported past diving-related illness, is a recognized potential confounding factor. This element was difficult to grade for some reports, but, in general, those that provided reasonable detail of recruitment and selection processes were graded higher than those that did not. Studies also varied widely in how well they matched the control cohort to the diver cohort; where the control group clearly represented a sample of the general population that was likely to be quite different from the divers (e.g., with respect to background health, lifestyle, or occupation), then a lower score was likely.

Many and varied confounding factors are associated with WMH, e.g., age, smoking, alcohol, hypertension, lipids, cardiovascular disease, neurological disease, psychiatric disease, head injury, migraine, obstructive sleep apnea, sports, and lifestyle factors. Some studies controlled for many of these, but others hardly mentioned confounding factors; the latter were generally given a low score.

With regard to MRI sensitivity, fluid-attenuated inversion recovery (FLAIR) sequences are required to discriminate true WMH from artifacts (e.g., widened perivascular spaces), so studies that did not include FLAIR invariably received a low rating for MRI sensitivity, even if clear efforts were described to avoid inclusion of artifacts. Standard clinical MRI scans (5-mm slice thickness) will miss many smaller punctate WMH, so only higher resolution scans with greater magnet strength than 1.5 Tesla achieved the highest score.

It is important to acknowledge that some studies were conducted before many of the factors that influence propensity to WMH were recognized and that MRI sensitivity and capability have developed considerably in recent years. Furthermore, unbiased recruitment of divers, control group matching, and exclusion of numerous confounding factors present challenges that invariably demand compromise by researchers. Additionally, some studies only reported MRI data analysis as a secondary aim of the trial. Nonetheless, given the wide variety of diver and control cohorts, it was anticipated that meta-analysis of all eligible studies would exhibit marked heterogeneity with respect to study outcomes. Hence, the scoring system was intentionally demanding to ensure that less rigorous studies and poorer quality evidence (by contemporary standards) could be excluded in an effort to address this.

Abstraction of WMH data was simple. The total numbers of participants in the diver and control groups, and the numbers in each cohort with any WMH, were recorded for each eligible study. Reporting of WMH number, size, and location were highly inconsistent between studies, so no attempt was made to categorize the reported WMH in any greater detail. For these case-control studies the principal measure of effect is the odds ratio (OR), reported here with 95% confidence intervals (CI). Quantitative data synthesis was achieved by subjecting the amalgamated WMH data to OR meta-analysis (MedCalc Software, Version 14.12.0; Ostend, Belgium). A random effects model was adopted to reflect the disparate study cohorts, with statistical significance set at $P < 0.05$. In the event of excessive heterogeneity, as indicated by Cochran's Q test ($P < 0.05$) or I^2 (inconsistency) value $> 25\%$,[9] it was intended to repeat the meta-analysis following exclusion of data from low-quality studies.

RESULTS

Identified were 16 relevant case-control studies, comprising 15 peer-reviewed journal papers and one formal report.[13] One paper[27] was quickly excluded as the data were incorporated in a later extended analysis.[28] That and two further studies were later excluded for including divers with past neurological DCI.[21,24] These studies all exhibited obvious sources of bias, including inconsistent MRI procedures and past occupational MRI screening,[28] and poor case-control matching for age[21,24] and smoking.[21,24,28] As such, all would regardless have been graded low quality in accordance with Table I. The other significant exclusion concerns an extensive study of long-term diver health that included assessment of WMH prevalence in cohorts of 'forgetful divers,' 'nonforgetful divers,' and nondiving controls.[13] Unfortunately, discrete data could not be abstracted for just the nonforgetful divers without past neurological DCI, the only valid diver cohort that the current meta-analysis would allow.

The remaining 11 journal reports underwent methodological review and data abstraction for meta-analysis. Study cohort characteristics, diver recruitment criteria, and experience levels are summarized in **Table II**. They employ a diverse selection of healthy diver and control cohorts, yet, collectively, it is indisputable that the diver cohorts amassed an impressive record of hyperbaric exposure that contrasts dramatically with the pressure-naïve control group. Cautiously, however, it is not assumed that any differences in WMH prevalence between these cohorts will necessarily reflect a single (i.e., 'fixed') effect that is consistent between studies. Instead, the widely disparate natures of the diver and control cohorts support adoption of the more conservative (and statistically demanding) random effects model for odds ratio meta-analysis.

The outcome of methodological review of these studies is shown in **Table III**. With the lofty benefit of hindsight it is clear that the studies vary widely with respect to methodological rigor. In general, the four studies graded as low quality did not describe clear recruitment procedures, did not detail efforts to closely match the diver and control cohorts, and appeared vulnerable to obvious sources of bias. The four medium-quality studies were generally conducted satisfactorily. The high-quality studies tended to have larger sample sizes and went to greater effort to exclude confounding factors and ensure that controls were well-matched to their diver colleagues.

Table II. Eligible Studies: Cohorts, Inclusion Criteria for Divers, and Levels of Diving Experience.

STUDY (REFERENCE)	DIVERS	CONTROLS	DIVER INCLUSION CRITERIA	DIVER EXPERIENCE	NOTES
Fueredi 1991[7]	Caisson (pressure tunnel) compressed air workers	Tunnel miners/muckers not exposed to compressed air	Well documented dysbaric exposure (mean pressure * years of work)	Experienced (age range 30-67) but no exposure data given	Some 'divers' with past dysbaric osteonecrosis
Reul 1995[20]	Amateur scuba divers	Sports club members (runners, swimmers)	≥40 scuba dives per year for ≥4 yr	Not given beyond inclusion criteria	Three divers (two with WMH) reported diving accidents, one with transient neurological DCI; these data excluded
Yanagawa 1998[31]	Military (navy) divers	Military nondivers	Not given	Mean 14 yr diving (range 1-30)	
Sipinen 1999[25]	Military (navy) divers	Mixed military and civilian	"…very experienced…"	Age range 34-57 yr but no diving data	Third cohort of recreational divers with past DCI excluded
Tetzlaff 1999[26]	Commercial air divers	Commercial employees from military shipyard	≥2000 diving h logged	Mean 28 yr diving (range 10-43); 9700 h (2800-38,000); max depth 69 m (14-150), but majority (>80%) <20 m depth	Four divers with saturation dive experience; three retired; eight with non-neurological DCI
Hutzelmann 2000[10]	Mixed commercial and military (navy) air divers	Not detailed	"…experienced elderly divers…"	Mean (SD) 21.5 (0.2) yr diving; 5088 (6581) h; max depth 63 (16) m	Minority of divers (five) had experienced saturation diving
Cordes 2000[3]	Military (navy) compressed air divers	Nondiving military employees	Not given	Mean 17 yr diving (range 8-29); >1400 h (500-2777); >1650 dives (591-3170)	Majority (84%) of dives were shallow (0-20 m)
Tripodi 2004[29]	Professional scuba diving instructors	Healthy patients having MRI before facial surgery	>40 yr old and ≥10 dives per year to ≥20 m depth for ≥2 yr	Mean (SD) 984 (121) dives; mean dive depth 30 m	
Ors 2006[18]	Hyperbaric chamber inside attendants for HBOT	Not detailed	>6 mo in role and no recreational diving	Mean (SD) 4.3 (3.0) yr; 214 (292) 'dives', median 78, range 30-950	Typical HBOT at 14-20 msw for 90-120 min; two attendants to 50 msw had routine HBOT (no DCI)
Erdem 2009[6]	Military (navy) divers	Healthy patients with musculoskeletal disorders undergoing MRI	Not given	Mean (SD) 12 (6) yr diving (range 1-25); 857 (464) h (100-2100); max depth 53 (18) m (35-109); frequent depth 13 (8) m (6-51)	
Gempp 2010[8]	Military (navy) mine-clearance divers (120-140 dives yearly, often to 60 m)	Military hospital staff	Qualified mine clearance divers, <41 yr old and >500 logged dives	Mean (SD) 13 (0.5) years diving; 1659 (122) dives; 40–50% compressed air, remainder rebreather apparatus with nriched (30–60%) oxygen	Reports increased WMH in presence of significant right-to-left intracardiac shunts

Studies are listed in order of publication by first author. Scuba: self-contained underwater breathing apparatus; HBOT: hyperbaric oxygen therapy; MRI: magnetic resonance imaging; DCI: decompression illness; msw: meters of sea water pressure (equivalent depth).

There were no missing data, but one study identified zero WMH in the diver and control cohorts, likely attributable in part to low MRI sensitivity.[25] These data have been included to contribute to denominator numbers for the meta-analysis. A third cohort of divers with past DCI was excluded from the current study, but some of those participants did exhibit WMH.

One study reported that three of the divers experienced actual or near diving accidents, with one suffering neurological symptoms and two of the three having WMH.[20] The abstracted data from this study were therefore adjusted to reduce the total number of divers by three (from 52 to 49) and the number with any WMH by two from 27 to 25. Thus, the 11 eligible studies identified WMH in 136 of 410 divers (33%) and 79 of 339 controls (23%). An initial random effects odds ratio meta-analysis was conducted using the data from all 11 studies (**Fig. 1**). This indicated a statistically significant increased prevalence of WMH in divers (OR 1.925, 95% CI 1.088 to 3.405, $z = 2.249$, $P = 0.025$), but also confirmed statistically significant heterogeneity between the studies (Q value 20.59, $P < 0.05$), with substantial inconsistency (I^2 value > 56%).

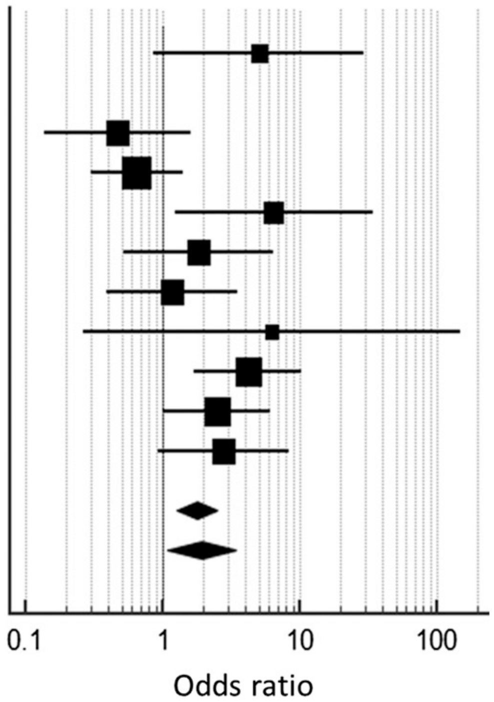
Accordingly, the data from the four low-quality studies were excluded. The remaining seven medium/high-quality studies

Table III. Assessment of Methodology of Eligible Studies, Scored in Accordance with Criteria in Table I.

STUDY (REFERENCE)	COHORT SIZES (DIVER/CONTROL) N/N [SCORE]	RECRUITMENT [SCORE]	CONTROL MATCHING [SCORE]	MRI SENSITIVITY [SCORE]	CONFOUNDS [SCORE]	TOTAL SCORE	QUALITY GRADE
Fueredi 1991[7]	19/11 [0]	Included cases with past pressure injury and current neurological symptoms [0.5]	Relevant control group [1]	No FLAIR [0]	Alcohol excess both cohorts; divers past dysbaric injury (no DCI) [0]	1.5	LOW
Sipinen 1999[25]	29/24 [1]	Likely subject selectivity [0.5]	Diver cohort with past DCI excluded; mix of civilian and military divers and controls; no mention of smoking [0.5]	0.1T screening magnet, no FLAIR, insensitive scanning (WMH seen only in excluded DCI cohort) [0]	No efforts described to avoid likely confounds [0.5]	2.5	LOW
Hutzelmann 2000[10]	59/48 [2]	Mix of military and civil; recruitment methods unspecified and control group not described [0]	Fewer lighter smokers among divers – mean (SD) pack years 4 (8) relative to 9 (13) in controls [0]	1.5T + FLAIR (5 mm) [1]	No neurological DCI, but seven divers had some minor 'bends'; smoking bias [0]	3	LOW
Cordes 2000[3]	24/24 [1]	Not specified, probably fair [1]	Controls may have smoked significantly more: mean (SD) 17 (11) pack years compared to 9 (11) in divers [0]	1.5T with FLAIR, resolution not given [1]	Good effort to avoid confounds but smoking still an issue [0]	3	LOW
Yanagawa 1998[31]	25/25 [1]	Unclear, possible bias, but doubtful influence [1.5]	Both groups military, probably match well; possible excess alcohol in controls [1]	No FLAIR [0]	Well-controlled to exclude multiple confounds [2]	5.5	MED
Tetzlaff 1999[26]	20/20 [0]	Not well detailed, probably satisfactory [1]	Well-matched healthy shipyard workers [1.5]	FLAIR, low resolution [1]	No neurological DCI; eight divers had minor 'bends,' otherwise well controlled [1]	4.5	MED
Tripodi 2004[29]	30/30 [1]	First 30 divers from same club; possible self-selection bias; selection of controls unclear [0.5]	Scuba instructors versus healthy surgical patients, matched for age/gender, probably satisfactory[1]	FLAIR (5 mm) [1]	Exclusion of confounds not well documented, e.g., control group smoking [0]	3.5	MED
Ors 2006[18]	10/10 [0]	Small targeted pool of 'divers' recruited; control group not described [1]	Details of controls lacking; good matching for age and disease, fair for smoking [1]	FLAIR, resolution not given [1]	Two hyperbaric oxygen treatments? Control quality unclear [0.5]	3.5	MED
Reul 1995[20]	52/50 adjusted to 49/50 [2] (see confounds)	Well described; unclear how diving and sports clubs selected to recruit from; possible self-selection bias; important diseases excluded [1]	Well-matched control group [1.5]	No FLAIR obliges score of zero, but clear effort made to exclude artifacts and widened perivascular spaces [0]	Single diver had neurological DCI and two had diving accidents – these data excluded. Otherwise well controlled [2]	6.5	HIGH
Erdem 2009[6]	113/65 [2]	Control recruitment unclear (all have musculoskeletal disorder); possibly selective, but unlikely bias [1]	Good for age/gender, control background unknown; more controls smoked, but didn't affect outcome [1]	FLAIR, resolution not given [1]	Well controlled [2]	7	HIGH
Gempp 2010[8]	32/32 [1]	Well detailed; avoided self-selection bias [1.5]	Validity of control group unclear, but well matched for age and cardiovascular risk [1]	3T magnet, FLAIR and high resolution ($<$ 5 mm) [2]	Well controlled [2]	7.5	HIGH

Studies are listed by order of publication within each quality grading (final column). MRI: magnetic resonance imaging; DCI: decompression illness; WMH: white matter hyperintensities; scuba: self-contained underwater breathing apparatus; FLAIR: fluid-attenuated inversion recovery MRI.

Study	Quality	Divers n/N	Controls n/N	Odds ratio	95% CI	z	P
Fueredi 1991	Low	10/19	2/11	5.000	0.846 to 29.568		
Sipinen 1999	Low	0/29	0/24	-			
Cordes 2000	Low	6/24	10/24	0.467	0.136 to 1.596		
Hutzelmann 2000	Low	22/59	23/48	0.646	0.298 to 1.402		
Yanagawa 1998	Medium	9/25	2/25	6.469	1.230 to 34.013		
Tetzlaff 1999	Medium	12/20	9/20	1.833	0.522 to 6.435		
Tripodi 2004	Medium	10/30	9/30	1.167	0.393 to 3.467		
Ors 2006	Medium	2/10	0/10	6.176	0.260 to 146.786		
Reul 1995	High	25/49	10/50	4.167	1.709 to 10.157		
Erdem 2009	High	26/113	7/65	2.476	1.008 to 6.080		
Gempp 2010	High	14/32	7/32	2.778	0.933 to 8.270		
Total (fixed effects)		136/410	79/339	1.789	1.276 to 2.508	3.374	0.001
Total (random effects)		136/410	79/339	1.925	1.088 to 3.405	2.249	0.025



Test for heterogeneity	
Q	20.5902
DF	9
Significance level	P = 0.0146
I^2 (inconsistency)	56.29%
95% CI for I^2	11.35 to 78.45

Fig. 1. Forest plot of 11 case-control studies investigating prevalence of white matter hyperintensities (WMH) in divers. Outcome is presence of any WMH. Marker sizes shown relative to study weight with diamonds for pooled effects; 95% confidence intervals (CI) are shown; DF: degrees of freedom.

identified WMH in 98 of 279 divers (35%) and 44 of 232 nondiving controls (19%). Repeat meta-analysis exhibited limited heterogeneity (Q value 4.91, $P = 0.55$) with minimal inconsistency (I^2 value 0%) and demonstrated a highly statistically significant increase in prevalence of WMH in healthy divers compared to nondiver controls (OR 2.654, 95% CI 1.718 to 4.396, $z = 4.396$, $P < 0.001$).

DISCUSSION

Adequate data of sufficient quality are available to demonstrate that repeated diving (hyperbaric exposure) is associated with an increased prevalence of white matter injury in healthy individuals who have not experienced neurological DCI. This is consistent with the finding that experienced altitude workers also exhibit increased WMH[15,16] and supports the proposition that development of white matter injury may be related to intensity of dysbaric exposure (decompression stress). The studies in this meta-analysis report the presence of WMH inconsistently, but, as a generalization, the bulk of the increased burden in divers comprises fronto-parietal subcortical or deep white matter lesions. Relative to nondivers with WMH, some studies reported that divers had more numerous[8] and more extensive lesions.[20,31]

No consistent factors are identified between studies that relate metrics of diving intensity to occurrence of WMH. Individual medium/high-quality studies documented an association between WMH burden and years of diving,[31] hours of deep diving below 131 ft (40 m) depth,[26] or rate of decompression,[29] although others did not find an association with diving history.[6,20] The WMH load in divers was variably related to age, smoking and alcohol intake,[31] lipid status,[29] and presence of significant right-to-left intracardiac shunts.[8] Although not consistent between studies, such associations suggest a microembolic vascular etiology related to intensity of decompression stress and promoted by underlying cerebrovascular risk factors. A review of clinical, pathological, pathophysiological, and experimental findings has proposed that WMH are likely to result from transient but repetitive ischemic insults affecting small, intracerebral parenchymal vessels in watershed areas.[19] The predominantly fronto-parietal and subcortical pattern of altitude-related WMH also suggests a vascular origin related to the distribution of the internal carotid artery.[14] It is easy to imagine that a localized region of transient incomplete infarction would be vulnerable to more permanent damage in the event that a further insult occurred prior to complete resolution of the initial injury. Alternatively, a microvascular insult coinciding with a period of more generalized white matter metabolic stress might explain the focal nature of early, highly localized, punctate lesions. These are attractive models for dysbaric WMH arising during high intensity periods of repeated decompression stress, but must remain conjectural pending further research.

Considering the seven medium/high-quality studies, the 279 participating divers had a mean age of approximately 38 yr, with the vast majority in their 30s and 40s; only two studies (total 50 divers) reported the divers' mean age to be over 40 yr.[26,29] Thus, the finding of increased WMH prevalence in divers pertains to a younger population (i.e., under 55 yr) than would be expected to develop greater numbers of naturally occurring WMH. It should not, however, be assumed that female divers necessarily share the same propensity to develop WMH since the vast majority of divers participating in these studies were men.

This meta-analysis has limitations that flow from the studies that have been included as well as from the methodology of the meta-analysis itself. It is likely that some cases of undeclared DCI may have confounded the diver cohorts. Relative to contemporary standards, almost all studies used a relatively low MRI magnet strength and low resolution scanning protocol that would be likely to miss smaller punctate WMH. Volumetric data were not available and most studies did not report WMH in accordance with a published rating scale.[22] All studies failed to control for some confounding factors, e.g., none controlled for obstructive sleep apnea, although it is probably unrealistic to expect to exclude all potential sources of bias. The review was essentially limited to English language sources and it might be useful to extend the meta-analysis to include non-English language references if these are available and meet the inclusion and quality criteria. One final criticism that cannot be countered is that the grading of study eligibility and quality was conducted by only the two authors.

It could be argued that since two earlier and larger studies that included divers with DCI did not show increased WMH in divers,[21,28] DCI could not have biased the studies and that all case-control studies of asymptomatic divers should be included, regardless of past DCI. Even ignoring the other confounds in the excluded studies, it is noteworthy that including them on this basis in a meta-analysis of all 14 peer-reviewed reports results in 216 of 640 divers (34%) and 126 of 487 controls (26%) exhibiting WMH (random effects OR 1.692; 95% CI 1.018–2.813; $z = 2.029$; $P = 0.042$), continuing to suggest that diving increases prevalence of WMH. Unsurprisingly, a corresponding increase in meta-analysis heterogeneity suggests that this is inappropriate.

Small punctate subcortical WMH may be relatively static over time and clinically benign, whereas confluent lesions may be more likely both to progress and to be associated with cognitive decline.[23] Whether or not WMH associated with diving or altitude exposure behave similarly has yet to be determined, but given their inherently nonspecific character, it may be prudent, until proven otherwise, to assume that subcortical WMH of any origin have the same prognostic value. In the context of flying and diving this should encourage caution before authorizing periods of intense exposure to repetitive bouts of more severe decompression stress, unless operationally unavoidable.

To conclude, the outcome of this meta-analysis suggests that repetitive diving may be an independent risk factor for developing white matter injury in otherwise healthy individuals with no past history of neurological DCI or diving accidents. This finding is consistent with recent reports of increased WMH in altitude workers. WMH have not yet been associated with a single consistent metric of diving or altitude exposure history, but may instead reflect periods of more intense, repetitive dysbaric exposure and attendant decompression stress.

ACKNOWLEDGMENTS

This work was funded by the UK Ministry of Defence through the Defence Science and Technology Laboratory (DSTL) Aircrew Systems Research Programme. The authors would like to acknowledge recent collaboration and support from colleagues working at the U.S. Air Force School of Aerospace Medicine, Royal Norwegian Air Force Institute of Aviation Medicine, and Royal Air Force Centre of Aviation Medicine.

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