

# Effects of Menstrual Cycle on Working Memory and its Correlation with Menstrual Distress Score: A Cross-sectional Study

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## ABSTRACT

**Introduction:** The menstrual cycle is a well-known physiological model for studying the effects of ovarian steroid hormones on cognitive functions, such as Working Memory (WM). Hormonal fluctuations during the menstrual cycle also affect menstrual distress related symptoms, which can independently affect cognitive functions. However, data regarding changes in WM functions during different phases of the menstrual cycle and the correlation of various WM functions with menstrual distress-related symptoms have been inconclusive.

**Aim:** To examine the verbal and visuospatial WM functions during the proliferative (day 10-14) and secretory phase (day 21-25) of the menstrual cycle and to correlate various WM functions with menstrual distress symptom scores.

**Materials and Methods:** A cross-sectional, observational study was carried out in the Department of Physiology at VMMC and Safdarjung Hospital, New Delhi, India, over a period of 18 months, from November 2020 to May 2022. A total of 40 young adult females with a history of regular menstrual cycles were selected for the study. Computerised software-based dual-task n-back WM tasks were given twice in the same menstrual cycle- first during the proliferative phase (day 10-14) and second during the secretory phase (day 21-25). In addition, a standardised Menstrual Distress Questionnaire (MDQ) based on various menstrual distress symptoms was administered to each subject after completion of the WM task, first during the proliferative phase (day 10-14) and second during the secretory phase

(day 21-25). Based on the MDQ, a Menstrual Distress Score (MDS) was calculated. Descriptive statistics, such as mean, median, standard deviation, and mode, were calculated, and Pearson's coefficient/Spearman's rank correlation coefficient was used to assess the correlation between WM parameters and MDS. Data were compiled and analysed using the statistical software Graph Pad Prism.

**Results:** The mean age of the study population was 23.4 years, with an average menstrual cycle length of 30 days. In the WM task, the overall proportion of correct responses across all tasks was significantly better in the secretory phase of the menstrual cycle than in the proliferative phase ( $p$ -value=0.040). Similarly, significantly improved performance in WM tasks during the secretory phase was also seen in the overall hit rate of the visual target ( $p$ -value=0.020) and auditory targets ( $p$ -value=0.044). On the other hand, the correlation of WM parameters with MDS did not show any statistical significance, except for a significant negative correlation ( $r$ -value -0.369;  $p$ -value=0.019) between the parametric sensitivity (subject's ability to correctly distinguish a target from a non-target) of auditory WM in the secretory phase and MDS in the proliferative phase.

**Conclusion:** The visual and auditory WM skills were significantly improved during the secretory phase compared to the proliferative phase of the menstrual cycle in terms of the target hit rate. However, increased MDS had no significant detrimental effect on the performance of WM tasks during the normal menstrual cycle.

**Keywords:** Follicular phase, Hormonal fluctuation, Luteal phase, Short term memory

## INTRODUCTION

The WM is a key cognitive function, that helps an individual's executive performance [1]. The term WM evolved from the concept of "Short-Term Memory (STM)," a cognitive system used for the retention of information over a short delay [2]. In contrast to STM, WM implies the capacity of an individual to simultaneously store some information, as well as, manipulate some other information for a short period [3]. Classically, two different types of WM have been described, auditory and visuospatial WM and two different systems in the brain process and maintain the information of the auditory and visuospatial WM [4]. Visuospatial WM is entrusted with temporary maintenance of an object's identity and spatial location, whereas, verbal WM temporarily maintains auditory (verbal) information such as words, letters and numbers [3]. In addition, various factors affect the WM capacity of an individual, including gender, age and personality [5]. Age-related impairment and decline in WM have been reported, and a well established fact [6]. It has also been reported that, oestrogen supplements in postmenopausal women improved WM functions [7]. This finding highlights a plausible link between WM capacity and the effects of sex steroid hormones (oestrogen and progesterone).

The menstrual cycle is a well known physiological model to study ovarian steroid hormones having an influence on emotion, behaviour, and cognitive functions like WM. Young females in their reproductive age experience dynamic changes in sex steroid hormones (oestrogen and progesterone) during the menstrual cycle. Along with hormonal changes, various premenstrual syndrome symptoms like alteration of mood, behavioural changes, pain and depression are also observed during the menstrual cycle [8].

Earlier studies have demonstrated an association of cognitive functions like WM with hormonal changes during the menstrual cycle [9-12] and behavioural symptoms in menstrual distress [13-15]. Hormonal fluctuation during the menstrual cycle also modulates the menstrual distressed symptoms apart from cognitive functions like WM discussed above [13-15]. Based on menstrual distress symptoms, the MDQ was developed as a standard method for measuring cyclical menstrual distress and perimenstrual symptoms [16]. The MDQ consists of various symptoms experienced during the menstrual cycle. In the questionnaire, 47 different symptoms are categorised into eight subcategories: pain, water retention, autonomic reaction, negative effect, impaired concentration, behavioural

change, arousal, and control [16]. The MDS was calculated based on this MDQ.

However, the data were inconclusive regarding the change in WM functions during different phases of the menstrual cycle and the correlation of various WM function with menstrual distress symptoms in terms of MDS during the regular menstrual cycles. The inconsistency of the data may be due to several reasons, including the different tasks used for assessing WM functions and diverse subject populations in various studies [17]. Also, there was a lack of data in the Indian population regarding the association of WM functions with the different phases of the menstrual cycle. Hence, the present study was planned to compare the visuospatial and verbal WM between the proliferative and the secretory phases of the menstrual cycle as primary objective and to correlate menstrual distress symptoms in the form of MDS with various WM parameters, if any as secondary objective. It had been hypothesised that, verbal and visuospatial WM function would be better in the proliferative phase of the menstrual cycle than in the secretory phase, and menstrual distress would have a detrimental effect on WM functions.

## MATERIALS AND METHODS

A cross-sectional, observational study was carried out in the Department of Physiology at VMMC and Safdarjung Hospital, New Delhi, India, over a period of 18 months, from November 2020 to May 2022. Ethical approval was granted by the Institutional Ethics Committee as per approval letter no. (IEC/VMMC/SJH/thesis/2020-11/CC-264).

**Sample size calculation:** The sample size was calculated using the study of Konishi K et al., as a reference [12]. The minimum sample size with 80% power and at 5% level of significance using the formula for comparison of matched pairs by Wilcoxon signed-ranked test was 40 based on the primary task. Simple random sampling method was used for selecting the subjects

**Inclusion criteria:** 48 right-handed, non obese Body Mass Index (BMI) <30 kg/m<sup>2</sup> female resident doctors of the hospital in the age group of 18-28 years, belonging to similar socioeconomic status (subjects self-judged their socioeconomic status) and without any history of significant medical or surgical disease included in the study.

**Exclusion criteria:** Subjects with irregular menstrual cycle, Polycystic Ovary Syndrome (PCOS), or similar endocrine problems were excluded from the study. Eight subjects, who could not complete the recording twice in both phases of the menstrual cycle were excluded, and the final study population was 40 subjects.

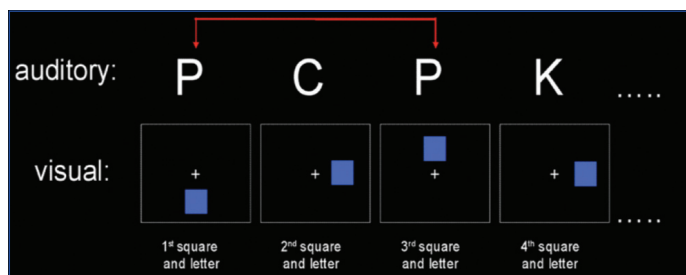
### Study Procedure

Two recordings were done from each subject: first on the day 10-14 of the menstrual cycle and second on the day 21-25 of the same menstrual cycle. Confirmation of the menstrual phase by counting the days, the first day of bleeding (menses) was called as day one of the menstrual cycle. After obtaining proper written consent, anthropometric measurements of height by using a stadiometer and weight using a standardised machine were recorded. Then, BMI was calculated using the above parameters. Thereafter, menstrual history in terms of age at menarche, length of the menstrual cycle, duration of bleeding in each cycle, and the approximate amount of blood loss was taken, and they were asked to fill out MDQ MDS was assessed on a four-point scale from 0 (no symptoms) to 3 (severe symptoms) and was expressed in mean and Standard Deviation (SD), based on Moos RH et al., [16].

Computerised software-based verbal and visuospatial WM test using Inquisit 6 software (milliseconds, USA. <https://www.millisecond.com/download/library/nback>). The task was known as the dual-task n-back task, a go/no go WM performance task with increasing difficulty levels. The implemented procedure in the software was initially described by

Jaeggi SM et al., [18]. In this task, the participants were presented with two sequences of stimuli in two modalities at the same time:

- Visual stimulus: a random sequence of blue squares that can be presented in eight different locations on the screen;
- Auditory stimulus: a random sequence of eight spoken roman letters [Table/Fig-1].



[Table/Fig-1]: Presentation of n-back WM trial on computer screen.

In each trial, one visual (blue square) and one auditory stimulus (random spoken letter) were presented simultaneously. Participants were asked to respond according to the following criteria: for 1-back (N=1) trials, if the location of the square was the same as the one in the previous trial, then it's a target (blue square), and the subjects had to press "A" on the computer keyboard; if not, then he/she did not have to press "A". Similarly, if the auditory letter was the same as the previous trial, then it's a target (random spoken letter), and press "L"; if not, he/she did not have to press "L". In the same way, for 2-back (N=2) trials, if the location of the square was the same as the one, two trials before, then it's a target, and the subject had to press "A"; and if the letter was same as the one, two trials before, then it was a target, and the subject had to press "L". This way 3-back (N=3) trial was also performed. Each dual n-task block consists of 20+ trials.+(plus) trials were the start trial given as a practice session to the subjects. The data of the start trials were not included in the performance of the subjects. Of the actual 20 experimental trials, 4 trials were only of a visual target (where the subject had to press "A" only), 4 trials were only of an auditory target (where the subject had to press "L" only), 2 trials presented both visual, as well as, auditory targets (where subject had to press both "A" and "L" simultaneously), and 10 trials were without any target (where subject didn't have to press "A" or "L").

Each trial presents the blue square and random spoken letter for 500 milliseconds, and the next blue square and random spoken letter were presented at an interval of 2500 milliseconds. Participants have the entire 3000 milliseconds to respond by pressing "A" or "L" if they detect a target or both "A" and "L" simultaneously, if they detect two targets. The total time required for the completion of the whole task (all trials) was approximately 25 minutes. Depending on the performance of the subject, the summary data file was collected during the dual-task n-back task. The summary data file contained various parameters of visuospatial and auditory WM such as 'overall proportion correct' responses across all trials, "hit rate overall" ('hit' means when the subject press 'A' for a visual target or 'L' for an auditory target) for visual and auditory targets across all trials, 'false alarm rate overall' ('false alarm' means when subject press 'A' or 'L' for a non target). 'Z-scores' of "hit rate" and "false alarm rate" were also calculated. 'Z-score' was an adjustment score calculated as per recommendation by Gregg AP and Sedikides C [19]. The adjustment was that, if the 'hit rate' or 'false alarm rate' was 0 then 0.005 was added to the value of 'hit rate' or 'false alarm rate', and if the 'hit rate' or 'false alarm rate' was 1 then 0.995 was added to the value of 'hit rate' or 'false alarm rate'. 'Parametric sensitivity (d)' of both visual and auditory WM was also calculated. A higher value of 'd' indicates better performance by correctly distinguishing a target from a non target. A value of d=0 suggests that it's a chance performance, whereas, a negative value of d' indicates that, non target was treated as target and target was treated as non target.

## STATISTICAL ANALYSIS

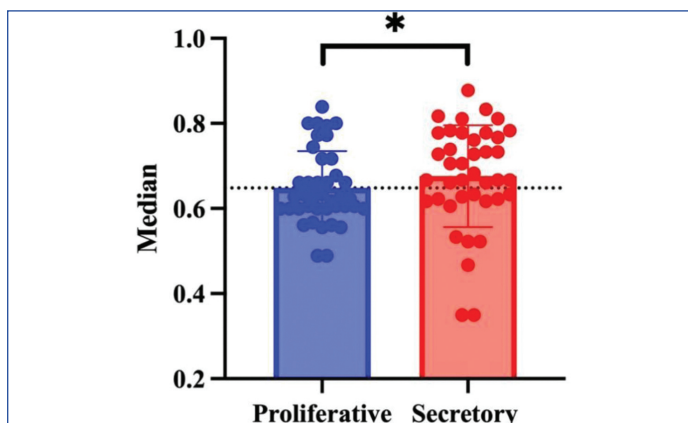
Data was compiled and analysed using the statistical software Graph PadPrism. Data were checked for normal distribution using the Kolmogorov-Smirnov test. Statistical significance of quantitative variables between the two groups was carried out by paired Student's t-test for Gaussian distributed parameters and Wilcoxon signed-rank test for non parametric parameters. Pearson's coefficient/Spearman's rank correlation coefficient was used to assess the correlation between WM parameters and MDS. The significance level was considered as p-value <0.05, Confidence interval as 95% and  $\beta=0.2$  and power was considered as 80%. Descriptive statistics such as mean, median, standard deviation and mode were calculated and represented with appropriate pictorial diagrams.

## RESULTS

The mean age of the study population was 23.4 years and average menstrual cycle length was 30 days [Table/Fig-2]. The mean $\pm$ SD of the 'overall proportion of correct' response across all trials was 0.65 $\pm$ 0.09 during the proliferative phase and 0.68 $\pm$ 0.12 during the secretory phase of the menstrual cycle. The mean $\pm$ SD of MDS were 11.93 $\pm$ 9.49 during the proliferative phase and 17.45 $\pm$ 16.98 during the secretory phase of the menstrual cycle. Analysing the data of various WM parameters showed that, the overall proportion of correct responses (p-value=0.040) were significantly different between the proliferative and secretory phases of the menstrual cycle, with improved performance during the secretory phase [Table/Fig-3]. Similar, significantly improved performance in WM tasks during the secretory phase of the menstrual cycle was also seen in the overall 'hit rate' of visual targets (p-value=0.020) and overall 'hit rate' of auditory targets (p-value=0.044) [Table/Fig-4].

Parameters	Mean	Median	Mode
Age (in years)	23.4 $\pm$ 4.2	21	20
Height (in cm)	156.7 $\pm$ 5.9	155	155
Weight (in kg)	56.3 $\pm$ 9.8	54	52
BMI (in kg/m <sup>2</sup> )	22.9 $\pm$ 3.8	22.2	21.6
Age at menarche (in years)	12.9 $\pm$ 1.0	13	13
Length of each cycle (in days)	30.0 $\pm$ 3	30	30
Duration of bleeding in each cycle (in days)	4.8 $\pm$ 0	5	4
Blood loss per cycle (in no. of pads used)	9.5 $\pm$ 0	8.5	7

[Table/Fig-2]: Distribution of demographic data and menstrual history of the study population.



[Table/Fig-3]: Comparison of overall proportion of correct responses in WM task between proliferative and secretory phase of menstrual cycle. Wilcoxon signed-rank test was used. \*p-value <0.05

Calculated Z-score of the overall visual hit rate (p-value=0.044) and overall auditory hit rate (p-value=0.020) showed improved performance during the secretory phase of the menstrual cycle as compared to the proliferative phase [Table/Fig-4]. However, the false alarm rate, and Z-score of the overall false alarm rate of both visual, as well as, auditory WM tasks did not differ between the proliferative and secretory phases

S. No.	Parameters	Proliferative	Secretory	Significance
<b>Visual working memory parameters (overall)</b>				
1	Hit rate	0.54	0.69	$\wedge$ p=0.020*
2	False alarm rate	0.13	0.09	$\wedge$ p=0.577
3	Z-score of hit rate	0.09	0.51	$\wedge$ p=0.017*
4	Z-score of false alarm rate	-1.14	-1.36	$\wedge$ p=0.369
5	Parametric sensitivity	1.48 $\pm$ 0.52	1.77 $\pm$ 0.7	# p=0.042*
<b>Auditory working memory parameters (overall)</b>				
6	Hit rate	0.68 $\pm$ 0.12	0.74 $\pm$ 0.15	# p=0.044*
7	False alarm rate	0.17	0.16	$\wedge$ p=0.310
8	Z-score of hit rate	0.49 $\pm$ 0.35	0.72 $\pm$ 0.51	# p=0.020*
9	Z-score of false alarm rate	-0.97	-0.98	$\wedge$ p=0.301
10	Parametric sensitivity	1.44	1.6	$\wedge$ p=0.055

[Table/Fig-4]: Comparison of various Working Memory (WM) parameters between proliferative and secretory phase of menstrual cycle.

Value is in Mean $\pm$ SD for parametric test and median for non parametric test. \*Paired t-test,  $\wedge$ Wilcoxon signed-rank test; #When p-value <0.05; significant, \*\*when it is <0.01; highly significant

of the menstrual cycle. Parametric sensitivity of overall visual responses was significantly better in the secretory phase (p-value=0.042) as compared to the proliferative phase, but 'parametric sensitivity' of the overall auditory responses did differ between the two phases of the menstrual cycle. The correlation of WM parameters with MDS showed a statistically significant (p=0.019) negative correlation (r-value=-0.369) between the parametric sensitivity of auditory WM of the secretory phase and MDS of the proliferative phase [Table/Fig-5]. All other parameters of WM were insignificantly correlated to the MDS of the menstrual cycle's secretory and proliferative phases.

Parameters	MDS secretory phase (p-value)	MDS proliferative phase (p-value)
MDS_S	1 (-)	0.117 (0.473)
MDS_P	0.117 (0.473)	1 (-)
Overall proportion of correct responses _S	-0.117 (0.472)	-0.288 (0.071)
Overall proportion of correct responses _P	-0.17 (0.293)	-0.282 (0.078)
v hit rate overall _S	-0.082 (0.614)	0.02 (0.909)
v hit rate overall _P	-0.144 (0.376)	-0.119 (0.463)
v false alarm rate overall _S	0.008 (0.963)	0.311 (0.051)
v false alarm rate overall _P	0.071 (0.664)	0.174 (0.282)
Z v hit rate overall _S	-0.092 (0.572)	0.024 (0.882)
Z v hit rate overall _P	-0.144 (0.376)	-0.119 (0.463)
Z v false alarm rate overall _S	0.019 (0.909)	0.303 (0.058)
Z v false alarm rate overall _P	0.09 (0.582)	0.178 (0.271)
v parametric sensitivity overall _S	0.027 (0.871)	-0.252 (0.116)
v parametric sensitivity overall _P	-0.202 (0.21)	-0.152 (0.351)
a hit rate overall _S	-0.229 (0.154)	-0.132 (0.417)
a hit rate overall _P	0.123 (0.451)	-0.02 (0.903)
a false alarm rate _S	0.011 (0.949)	0.257 (0.109)
a false alarm rate _P	0.207 (0.199)	0.232 (0.149)
Z a hit rate overall _S	-0.241 (0.134)	-0.11 (0.501)
Z a hit rate overall _P	0.132 (0.415)	-0.015 (0.926)
Z a false alarm rate _S	0.021 (0.899)	0.257 (0.109)
Z a false alarm rate _P	0.207 (0.199)	0.232 (0.149)
a parametric sensitivity overall _S	-0.142 (0.382)	-0.369 (0.019)*
a parametric sensitivity overall _P	0.015 (0.926)	-0.125 (0.441)

[Table/Fig-5]: Correlation among Working Memory (WM) parameters and Menstrual Distress Score (MDS).

Non parametric test, Spearman's correlation has been used. Mean value of different WM parameters and MDS score has been used for correlation study. S: Secretory phase parameters; P: Proliferative phase parameters; v: Visual parameter; a: Auditory parameters; r=Correlation Coefficient; p-value=2-tailed significance; #When p-value <0.05; significant, \*\*when it is <0.01: highly significant

## DISCUSSION

The WM is a cognitive system for temporarily storing and manipulating remembered information. Intact WM is essential for many higher order cognitive tasks, like reasoning, explanation, and mathematical computation [2]. The influence of sex hormones such as oestrogens, progesterone, and testosterone on cognitive functions was established as a reason for sex differences in cognitive tasks, including WM [20,21]. The menstrual cycle is a natural model for understanding these hormonal influences on WM because hormonal flux, particularly oestrogen and progesterone, occur naturally along the menstrual cycle [17,22]. However, the data were inconclusive regarding the change in WM functions during proliferative and secretory phases of the menstrual cycle [12]. Moreover, the correlation of various WM function with menstrual distress symptoms in terms of MDS during the regular menstrual cycles were also lacking, particularly in the Indian population. So, in the present study, assessment of the WM functions in two distinct phases of the menstrual cycle (follicular or proliferative phase and secretory, or luteal phase) was done from 40 normally menstruating (average length  $30.0 \pm 3$  days) healthy young adult women in age group of 20-24 years, with a BMI of  $22.9 \pm 3.8$  kg/m<sup>2</sup>. All women included in the study were right-handed to avoid hemispheric effect of brain on cognition.

In the present study, the WM task parameter 'overall proportion of correct' response was significantly better in the secretory phase (day 21-25) of the menstrual cycle than the response in the proliferative phase (day 10-14). Furthermore, audio-visual WM tasks in the form of visual 'hit rate' and auditory 'hit rate' were also better in the secretory phase in comparison to the proliferative phase, and the difference was statistically significant. These findings indicated improved visual and auditory WM skills in terms of the target 'hit rate' during the secretory phase as compared to the proliferative phases of the menstrual cycle. However, the 'overall false alarm rate' of both visual and auditory WM was not different between the proliferative and secretory phases. This effect was probably due to the higher progesterone level in the secretory phase of the menstrual cycle because in a normal menstrual cycle, the oestrogen level is low, and the progesterone level is high during the secretory phase [23]. The present study's findings were similar to a study conducted by Hidalgo-Lopez E and Pletzer B. In their study, women performed WM tasks significantly faster during the luteal phase than in the pre-ovulatory phase [24]. Similarly, a study by Simic N and Santini M also demonstrated that, the best performance of verbal WM and verbal fluency were seen during the menstrual and mid-luteal phases in comparison to the proliferative phase of the menstrual cycle [25]. Another study by Maki PM et al., also showed that, the performance task of implicit memory was better at the mid-luteal than the follicular phase, but performance on a test of explicit memory did not vary across the menstrual cycle [26]. The present study also concluded that, improved performance of WM tasks during the proliferative phase was attributed to progesterone but not estradiol [26]. It has been shown that, estradiol produces greater activation in the left prefrontal cortex, a region associated with verbal processing and encoding, while progesterone was associated with changes in regional brain activation patterns during a visual memory task (left prefrontal cortex and right hippocampus) [27].

However, Leeners B et al., described a negative association between progesterone level and change in WM from the pre-ovulatory to mid-luteal phase of the menstrual cycle. Although, when the same subjects were followed-up for the consecutive second menstrual, a negative association didn't replicate [10]. Hampson E and Morley EE also demonstrated that, higher oestrogen level rather than progesterone level was associated with better WM performance [28]. Along with WM functions, MDS was also assessed for each subject. The central hypothesis of the present study was that, the MDS during different phases of the menstrual cycle had a

detrimental effect on verbal and visuospatial WM in young adult females. However, the data didn't support the above hypothesis. Statistically significant correlations between WM parameters and MDS in both the secretory and proliferative phases of the menstrual cycle were not found in the study. However, a negative correlation of statistically significant between the 'parametric sensitivity' of the auditory WM parameter of the secretory phase and MDS of the proliferative phase ( $p=0.019$ ,  $r=-0.369$ ). The result was similar to a study by Sundstrom Poromaa I and Gingnell M; and Hartley LR et al., [17,29]. These findings indicated that, the higher MDS in terms of menstrual distress had no detrimental effect on WM performance in young adult women. However, auditory WM performance of secretory phase negatively correlates with MDS of proliferative phase, indicating menstrual distress of proliferative phase may affect auditory WM performance during the secretory phase of menstrual cycle.

## Limitation(s)

In the present study, data of only one menstrual cycle at two time points had been collected and hormonal assays was not done. It would be better if follow-up of the same subjects could be done for consecutive 3 to 4 menstrual cycles and data collection could be done at multiple time points within the same menstrual cycle, rather than only in the proliferative and the secretory phases of the menstrual cycle along with hormonal measurement, preferably on a large population. Additionally, in the present study, only subjects with normal menstrual cycle have been used, however, the results from the present study may be compared with the subjects having abnormal mensuration cycle to yield better comparison.

## CONCLUSION(S)

The present study found that, young female subject's visual and auditory WM skills improved during the secretory phase as compared to proliferative phases of the normal menstrual cycle in terms of 'target hit rate'. However, the overall 'false alarm rate' of both, visual and auditory WM was not different between the proliferative and secretory phases. In addition, increased MDS had no significant detrimental effect on WM tasks in young adult women.

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