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Menopausal symptoms, menopausal stage and cognitive functioning in black urban African women

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ABSTRACT

Objective: Studies, conducted largely in North America and Europe, demonstrate that menopausal symptoms and menopausal stage influence cognitive function. Here, we evaluate these associations in a large cohort of sub-Saharan African women, a population where these associations are understudied. We hypothesized that premenopausal women would show better cognitive performance than women later in the transition, and that menopausal symptoms would be inversely related to cognition.

Methods: This cross-sectional study included 702 black urban South African women between the ages of 40 and 60 years from the Study of Women Entering and in Endocrine Transition. Participants completed the Symbol Digit Modalities Test, a measure of processing speed and incidental recall. Menopausal stage was ascertained using the Stages of Reproductive Aging Workshop+10 criteria and symptoms using the Menopause Rating Scale. Multivariable linear regression analyses were used to examine adjusted associations between menopausal stage and menopausal symptoms on cognitive performance.

Results: In adjusted analyses, menopausal stage was not associated with processing speed ($p=0.35$) or incidental recall ($p=0.64$). However, more severe symptoms of hot flushes and anxiety were associated with slower processing speed (all $p < 0.05$), and more severe mood symptoms were associated with worse incidental recall ($p=0.008$).

Conclusion: Menopausal symptoms, but not menopausal stage, were associated with cognitive function in this cross-sectional study of sub-Saharan African women.

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Introduction

Applying a cross-cultural perspective^{1,2} to studies of menopause and cognition is important as characteristics that vary among women from different cultures (e.g. education; use of alcohol, tobacco, and illicit substances; diet; reproductive history; body mass index [BMI]; physical activity; socioeconomic status; and sources of stress) can modify neurobiology and the extent to which menopause and menopause symptoms are associated with cognitive function. Researchers have found it challenging to define a uniform experience of menopause amongst women of different cultures³, and care should be taken in using a standardized tool which takes into account the menopausal symptoms that are specific to different cultures and ethnicities³.

Studies show that the frequency and severity of vasomotor symptoms (VMS) may often be experienced and/or perceived differently by women in various population groups even though VMS are widely present^{1,4}, and studies have found that a clear understanding of the cultural imperative is

essential in understanding how different women experience menopause symptoms⁵. In addition, the differences in the understanding and perceptions of menopause symptoms between women from high-income and low-income countries may present challenges in research⁶, so providing women with culturally specific information on the menopause transition (MT) may be useful⁷. Midlife women in western cultures describe a 'mental fog' and 'slowness in thinking'^{8,9}. These constructs can be measured on neuropsychological tests of processing speed, like the Symbol Digit Modalities Test (SDMT)¹⁰, which measure the ability to concentrate on and quickly perform a cognitive task measuring the speed with which women can pair abstract symbols with numbers, as well as their memory for those pairs once the task is complete. As a non-verbal test, the SDMT can also be employed in populations of women whose primary language differs, such as black South African women, despite a shared culture where menopause and menopause symptoms are not widely recognized or discussed. Cognitive studies in such populations are needed to examine the universality of

cognitive symptoms of the menopause as such evidence would support the view that these symptoms reflect common neurobiological underpinnings.

To date, studies using neuropsychological tests to objectively assess cognitive symptoms of the menopause^{11–14} have not focused on women living in sub-Saharan Africa. In women living in the USA, the perimenopausal stage^{11–13} and severe menopausal symptoms^{15,16} are associated with worse cognitive functioning in the domains of processing speed and memory. Investigators from the Study of Women's Health Across the Nation (SWAN) conducted the only large-scale ($n = 1903$) longitudinal study (6-year follow-up) examining associations between menopause stage, menopause symptoms, and processing speed on the SDMT¹⁵. For menopause symptoms, high levels of anxiety (i.e. irritability/grouchiness, tense/nervous, pounding/racing heart, or feeling fearful for no reason) and depressive symptoms were associated with worse SDMT performance, after adjusting for other factors^{11,15}. Longitudinal studies in the SWAN also measure another aspect of impairment on the SDMT, the failure to show the expected improvement in test performance over repeated test administrations¹⁵. In unadjusted analyses, VMS were associated with less improvement in SDMT performance over time, but these associations were not significant in adjusted analyses. The longitudinal design appears to be important in detecting a relationship between menopausal stage and cognition; an earlier 2-year longitudinal study of 868 women from the Chicago SWAN site found no relationship between menopausal stage and SDMT performance¹⁷. Thus, longitudinal studies from the SWAN indicated that cognitive slowing in midlife women is associated with anxiety, depressive symptoms, and the late perimenopausal stage.

The influence of menopausal stage on memory, particularly verbal memory, has been more widely studied. The two largest longitudinal studies – the SWAN and the Penn Ovarian Aging Study – found evidence that verbal memory decreases in the perimenopausal stage compared to the premenopausal stage^{11,13}. In the SWAN, the memory test assessed memory for a short story¹¹, and in the Penn Ovarian Aging study, the memory test assessed memory for a list of words¹³. Among cross-sectional studies, the Rochester Investigation of Cognition and Memory found that memory on a list-learning test was impaired¹². Using verbal memory tasks in black South African women is challenging because of the multiple languages spoken. A non-verbal, 'incidental' memory assessment can be conducted following the SDMT processing speed test by asking women to recall which numbers were paired with which symbols. The task is considered 'incidental' because, unlike most neuropsychological tests of memory, there are no specific instructions to try to remember the pairings; instead, the recall of the pairs is 'incidental' to the primary processing speed task. An advantage of this memory measure is that has been shown to be unrelated to education level¹⁸.

Menopausal symptoms, including VMS and mood, are also associated with cognition¹⁹. In a large longitudinal study, menopausal depressive and anxiety symptoms were associated with poorer cognitive performance¹¹. In a large

cross-sectional study of ethnically diverse midlife women where HIV infection was present in two-thirds of the cohort, VMS, depressive symptoms, and anxiety symptoms were all found to be inversely associated with cognitive function¹⁶.

As expected, data from the Study of Women Entering and in Endocrine Transition (SWEET) show that estrogen levels are lower in postmenopausal than premenopausal sub-Saharan African women²⁰. In this population, VMS were significantly higher in women in early postmenopause compared to women in the late reproductive stage. However, there is a paucity of data on the effect of the MT and menopausal symptoms on cognitive functioning in sub-Saharan African women.

There is a high prevalence of obesity and HIV infection in black South African women, and both of these factors are associated with impaired cognitive function²¹. In a prospective cohort study, greater BMI was associated with worse cognitive function²², and data from a large longitudinal study demonstrated that increased BMI was an independent risk factor for future cognitive decline²³. In a small prospective, randomized study in elderly men and women, where menopause was not staged, a decrease in BMI was positively associated with improved cognitive scores²⁴. Neurocognitive deficits are associated with HIV infection^{25,26}, and a comprehensive review suggests that HIV-infected women may be at greater risk for impaired cognitive function than uninfected women²⁷.

The aim of the present study was to examine the cross-sectional associations of menopausal stage and cognitive functioning on SDMT measures of processing speed in a population of black South African women. We hypothesized, based on findings from the SWAN, that anxiety and depression would be related to psychomotor slowing, but given the cross-sectional nature of the study we did not expect to find an association between menopausal stage and performance. We also explored associations between menopausal stage, menopausal symptoms, and performance on the SDMT incidental recall test to determine whether the measure is useful for detecting cognitive symptoms of the menopause.

Methods

Study population

Participants were black urban African women participating in the SWEET. They were the biological mothers and caregivers of the children in the Birth to Twenty Plus cohort, a longitudinal birth cohort study of child health and development in Africa²⁸. After 21 years, 2200 of these women remained in contact with the research staff. During a 3-year recruitment window for the SWEET, 902 of these 2200 women were randomly selected for recruitment to the SWEET. Of these 902 women, 200 women were excluded due to: age >60 years ($n = 35$), refusal ($n = 79$), death ($n = 37$), terminal illness ($n = 3$), or inability to contact ($n = 46$). In order to ensure that there was a more even distribution of premenopausal and postmenopausal women within the study cohort, only participants who were within 10 years of what was

hypothesized to be the age at final menstrual period (FMP) were included. Also, by excluding women aged >60 years it was hoped that age-related changes, as opposed to those that were specifically related to reproductive aging, would be attenuated. Thus, 702 women were enrolled into the study. All participants signed informed consent forms. The Human Research Ethics Committee (Medical) of the University of the Witwatersrand approved the study protocol (ethics certificate number M090620).

Key measures

Menopausal stage

The Stages of Reproductive Aging Workshop + 10 criteria²⁹ were used to ascertain the menopause stage²⁰ in five stages: late reproductive (stages –3b and –3a), menopausal transition (stages –2 and –1, early and late, respectively); early postmenopause (stages +1a, +1b, and +1c); and late postmenopause (stage +2).

Menopausal symptoms

On the Menopause Rating Scale (MRS)³⁰, participants rated the presence and intensity of 11 symptoms on a scale of 0–4, grading each symptom as absent=0, mild=1 or 2, severe=3, or very severe=4. A single interviewer administered the MRS, and, when necessary, trained team members interpreted the questions in the participant's native language. Consistent with the categorical approach used to measure menopausal symptoms in the SWAN¹⁵, six categorical outcome measures were calculated (i.e. severe, ≥ 3 vs. non-severe, < 3) for variables commonly examined in relation to cognition, including exhaustion, anxiety, irritability, depressed mood, sleep disturbance, and hot flushes, excluding five symptoms (sex problems, bladder problems, vaginal dryness, joint/muscle discomfort, and heart problems).

Cognitive measures

The SDMT served as a measure of processing speed¹⁰. The participant viewed a piece of paper with a key showing the numbers '1' to '9', each paired with a symbol. Below the key were rows of symbols and above each symbol was an empty box in which the participant was instructed to write in the particular number that was paired with the symbol. This measure primarily assesses speeded scanning and tracking aspects of attention³¹. The outcome was the number of boxes correctly filled in during a 90-second time limit, with a maximum score of 110. Incidental recall was measured by obscuring the key and previous answers, showing the nine symbols, and asking the participant to recall the numbers that matched each of the symbols. The maximum score was 9 points.

Additional measures and covariates

Questionnaires

A general questionnaire assessed reproductive health, menstrual history, educational level, and smoking and snuff use³². As previously described, menstrual history was determined where participants were asked close-ended questions about their bleeding patterns to determine their MT stage. These were followed by open-ended questions enabling a more accurate definition of the described bleeding patterns²⁰.

Body anthropometry

Blood pressure, height, weight, waist and hip circumference, and BMI were measured as described previously^{20,33}.

Hormonal assays

Fasting blood samples were obtained in the morning before 11 a.m. Serum and plasma samples were collected and immediately stored at -80°C . The assays for follicle stimulating hormone (FSH), estradiol (E2), and sex hormone-binding globulin have been described previously³³.

HIV serostatus

All participants were offered a voluntary HIV antibody test (Alere Determine™ HIV-1/2; Alere San Diego, Inc., San Diego, CA, USA). If the result was positive, referrals were made to a local HIV clinic for confirmatory serological testing and CD4 count and management. Both HIV-infected women being treated with antiretroviral medication and those who were not were retained in the study.

Statistical analysis

Group differences in continuous (e.g. age, hormone levels) and categorical (e.g. HIV status, menopausal symptoms) variables were examined using one-way analysis of variance and chi-square tests, respectively. A series of multivariable linear regression analyses was used to examine adjusted associations of menopausal stage and menopausal symptoms with cognitive performance. Relevant covariates included in multivariable models were age, education (no high school education vs. high school education or greater), employment status (employed vs. not), snuff use (vs. not), HIV serostatus (uninfected, infected on ARV, infected not on ARV, unknown status), and BMI. For analyses focusing on menopausal symptoms, menopausal stage was also included as a covariate. Significance was defined as $p < 0.05$ (two-tailed). Cohen's d effect sizes are also reported whereby a small effect is 0.2, a medium effect is 0.50, and a large effect is 0.8³⁴. Analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics by menopausal stage

On average, women were 49.6 years of age (standard deviation = 5.25), 43% were unemployed, and 21.5% were HIV infected. The majority of the sample did not complete high school (59%). Table 1 presents the characteristics of women as a function of the four menopausal stage categories: late reproductive ($n = 192$), menopausal transition ($n = 121$), early postmenopause ($n = 147$), and late postmenopause ($n = 130$). Overall, participant characteristics were comparable across menopausal stage except with respect to age, employment, and age at FMP. As expected, late postmenopausal women were the oldest, followed by early postmenopausal, transitioning, and late reproductive women (all $p < 0.05$). Late reproductive women also had the highest employment rate compared to all other women ($p < 0.05$). The age at FMP was higher for early postmenopausal women compared to late postmenopausal women ($p < 0.001$).

With respect to hormone levels, as expected, late reproductive women had higher E2 levels followed by transitioning, early postmenopausal, and then late postmenopausal women (Table 1). The sex hormone-binding globulin levels were also higher in late reproductive compared to early and late postmenopausal women (all $p < 0.05$), and in transitioning compared to late postmenopausal women ($p < 0.05$). Finally, FSH levels were highest in early and late postmenopausal women followed by transitioning and then late reproductive women (all $p < 0.05$).

Menopausal stage and cognitive performance

Table 2 presents the unadjusted association of menopausal stage and SDMT performance. In unadjusted analyses, late reproductive women performed significantly faster on the SDMT processing speed outcome than early and late postmenopausal women (all $p < 0.001$), and women transitioning performed significantly better than early ($p = 0.006$) and late ($p < 0.001$) postmenopausal women. However, in adjusted analyses, the menopausal stage was no longer associated with processing speed ($p = 0.35$) largely because of a strong relationship between performance and age ($r = -0.31$, $p < 0.001$). Menopausal stage was not associated with incidental recall on the SDMT in either unadjusted ($p = 0.05$) or adjusted ($p = 0.64$) analyses.

Menopausal symptoms and cognitive performance

Table 3 presents the unadjusted associations of menopausal symptoms and SDMT performance. In the overall sample, women reporting severe exhaustion performed worse on both the processing speed and incidental recall outcomes compared to women not reporting severe exhaustion (all $p < 0.05$). Women reporting severe anxiety and hot flashes performed significantly worse on the processing speed outcome compared to women not reporting these symptoms (all $p < 0.01$). Additionally, women reporting severe mood symptoms performed worse on incidental recall compared to women not reporting severe mood symptoms ($p < 0.01$).

Table 1. Characteristics of the study sample by menopausal stage.

Variable	Menopausal stage (from STRAW + 10)				p-Value	Group differences
	Late reproductive (a) (stages -3b and -3a) (n = 192)	Menopausal transition (b) (stages -2 and -1) (n = 121)	Early postmenopause (c) (stages +1a, +1b, and +1c) (n = 147)	Late postmenopause (d) (stage +2) (n = 130)		
Age (years), mean (SD)	45.16 (3.30)	48.19 (3.73)	51.63 (3.85)	55.21 (3.50)	<0.001	a < b < c < d
Age of FMP (years), mean (SD)	–	–	47.59 (3.85)	43.86 (4.68)	<0.001	c > d
No high school education	118 (62)	65 (54)	85 (58)	81 (62)	0.45	
Employed	125 (65)	61 (50)	79 (54)	70 (54)	0.04	a > b, c, d
Snuff use	38 (20)	31 (26)	34 (23)	35 (27)	0.45	
Smoke status					0.61	
Never	178 (93)	110 (91)	137 (93)	116 (89)		
Former	8 (4)	5 (4)	8 (6)	9 (7)		
Current	6 (3)	6 (5)	2 (1)	5 (4)		
BMI (kg/m ²), mean (SD)	33.62 (7.61)	34.31 (7.96)	33.31 (7.28)	32.13 (6.26)	0.12	
Obese, BMI > 30 kg/m ²	129 (67)	83 (69)	103 (70)	84 (65)	0.80	
HIV serostatus					0.07	
Unknown	84 (44)	56 (46)	69 (47)	42 (32)		
Negative	77 (40)	49 (40)	65 (44)	75 (58)		
Positive, no ARV	13 (7)	8 (7)	5 (3)	4 (3)		
Positive, ARV	18 (9)	8 (7)	8 (6)	9 (7)		
Hormone levels (log), mean (SD)						
Estradiol	5.69 (0.98)	4.90 (1.31)	4.06 (1.11)	3.64 (0.73)	<0.001	a > b > c > d
DHEAS	0.42 (0.35)	0.41 (0.31)	0.39 (0.30)	0.39 (0.29)	0.81	
Total T	1.02 (0.25)	1.04 (0.24)	1.02 (0.22)	1.05 (0.27)	0.71	
Bioavailable T	2.42 (0.25)	2.44 (0.24)	2.43 (0.21)	2.44 (0.27)	0.86	
SHBG	1.78 (0.20)	1.73 (0.20)	1.68 (0.18)	1.66 (0.22)	<0.001	a > c, d; b > d
FSH	0.88 (0.40)	1.35 (0.50)	1.68 (0.36)	1.79 (0.19)	<0.001	a < b < c, d

Data presented as n (%). Subscripts differ at $p < 0.05$.

ARV, antiretroviral therapy use; BMI, body mass index; DHEAS, dehydroepiandrosterone; FMP, final menstrual period; FSH, follicle stimulating hormone; HIV, human immunodeficiency virus; SD, standard deviation; SHBG, sex hormone-binding globulin; snuff, smokeless tobacco; STRAW, Stages of Reproductive Aging Workshop; T, testosterone.

Table 2. Severe menopausal symptoms and cognitive performance on the Symbol Digit Modalities Test (SDMT) by menopausal stage.

Variable	Menopausal stage (from STRAW + 10)				p-Value	Group differences
	Late reproductive (a) (stages -3b and -3a) (n = 192)	Menopausal transition (b) (stages -2 and -1) (n = 121)	Early postmenopause (c) (stages +1a, +1b, and +1c) (n = 147)	Late postmenopause (d) (stage +2) (n = 130)		
Severe symptoms, n (%)						
Exhaustion	36 (19)	20 (17)	30 (20)	42 (32)	0.008	d > a,b,c
Anxiety	19 (10)	20 (17)	22 (17)	23 (18)	0.19	
Irritability	47 (25)	34 (28)	30 (20)	39 (30)	0.29	
Mood	36 (19)	27 (22)	32 (22)	32 (25)	0.65	
Sleep disturbance	39 (20)	24 (20)	37 (25)	31 (24)	0.64	
Hot flushes	32 (17)	32 (26)	40 (27)	33 (25)	0.08	
Cognition, mean (SD)						
SDMT						
Correct	31.00 (10.84)	30.04 (11.48)	26.41 (11.08)	23.69 (9.84)	<0.001	a > c,d; b > c, d
Incidental recall	5.05 (3.86)	4.97 (3.65)	4.14 (3.31)	4.27 (3.37)	0.05	

SD, standard deviation; STRAW, Stages of Reproductive Aging Workshop.

Table 3. Association between menopausal symptoms and cognitive performance on the Symbol Digit Modalities Test (SDMT).

Symptom	SDMT score			
	Processing speed	p-Value	Incidental recall	p-Value
Exhaustion		0.008		0.04
Severe (n = 128)	25.73 (11.81)		4.07 (3.63)	
Not severe (n = 460)	28.65 (10.94)		4.79 (3.63)	
Anxiety		0.009		0.17
Severe (n = 84)	25.11 (12.29)		4.13 (3.33)	
Not severe (n = 499)	28.53 (10.96)		4.72 (3.65)	
Irritability		0.14		0.15
Severe (n = 150)	26.85 (10.94)		4.26 (3.45)	
Not severe (n = 438)	28.42 (11.27)		4.75 (3.64)	
Mood		0.34		0.007
Severe (n = 127)	27.22 (11.34)		3.87 (3.24)	
Not severe (n = 463)	28.28 (11.15)		4.84 (3.66)	
Sleep disturbances		0.28		0.26
Severe (n = 131)	27.12 (12.25)		4.33 (3.78)	
Not severe (n = 458)	28.32 (10.88)		4.73 (3.54)	
Hot flushes		<0.001		0.23
Severe (n = 137)	25.06 (11.64)		4.31 (3.62)	
Not severe (n = 452)	28.97 (10.91)		4.73 (3.59)	

Data presented as mean (standard deviation).

As shown in Table 4, in adjusted analyses, severe anxiety ($B = -2.66$, standard error [SE] = 1.23, $\beta = -0.08$, $p = 0.03$, Cohen's $d = -0.26$, 95% confidence interval [CI] = -0.49 to -0.03) and hot flashes ($B = -3.17$, SE = 1.01, $\beta = -0.12$, $p = 0.002$, Cohen's $d = -0.31$, 95% CI = -0.51 to -0.12) remained significant predictors of processing speed, and severe mood symptoms remained a significant predictor of incidental recall ($B = -0.96$, SE = 0.36, $\beta = -0.11$, $p = 0.008$, Cohen's $d = -0.27$, 95% CI = -0.47 to -0.07). In analyses simultaneously adjusting for menopausal stage and other menopausal symptoms, hot flashes remained a significant predictor of processing speed ($B = -2.91$, SE = 1.02, $p = 0.005$, Cohen's $d = -0.29$, 95% CI = -0.48 to -0.09), but not anxiety ($B = -2.17$, SE = 1.23, $p = 0.08$, Cohen's $d = -0.21$, 95% CI = -0.44 to 0.01).

Exploratory associations of cognition with hormone levels, BMI and HIV serostatus

In unadjusted analyses, higher E2 levels were associated with improved processing speed ($r = 0.16$, $p < 0.001$) and higher FSH levels were associated with decreased processing speed

Table 4. Multivariable model predicting cognitive performance on the Symbol Digit Modalities Test (SDMT).

Variable	SDMT	
	Scanning speed (n = 578)	Incidental recall (n = 586)
Age	-0.24 ^a	-0.12 ^c
Snuff user (vs. not)	-0.08 ^c	-0.04
No high school (vs. high school)	-0.12 ^b	-0.06
Unemployed (vs. employed)	-0.21 ^a	-0.08 ^c
BMI	0.02	0.02
HIV status (vs. HIV uninfected)		
HIV infected, no ARV	-0.05	-0.02
HIV infected, ARV	-0.04	0.00
Unknown status	-0.06	0.03
Menopausal stage (vs. late reproductive)		
Menopausal transition	0.05	0.02
Early postmenopausal	-0.01	-0.03
Late postmenopausal	-0.04	0.02
Severe hot flushes (vs. not)	-0.11 ^b	-
Severe mood symptoms (vs. not)	-	-0.11 ^b
Severe anxiety (vs. not)	-0.07 ^c	-
Adjusted R ²	0.18	0.03

Data presented as β -coefficient.

^a $p < 0.001$; ^b $p < 0.01$; ^c $p > 0.05$ and $p < 0.09$.

ARV, antiretroviral therapy use; BMI, body mass index.

($r = -0.19$, $p < 0.001$), but these associations were no longer significant in adjusted analyses (all $p > 0.72$). Neither BMI nor HIV serostatus was associated with SDMT performance (all $p > 0.89$).

Discussion

The primary aim of this study was to examine whether processing speed and incidental recall varied by menopausal stage and menopausal symptom severity in black urban mid-life women from South Africa. Adjusted results showed no association between menopause stage and SDMT performance. However, the hypothesis that menopausal symptoms would be associated with processing speed was supported by findings that anxiety and hot flashes were significantly associated with decreased psychomotor speed, and that severe mood was a significant predictor of incidental recall.

Broadly, these results demonstrate that associations between menopausal symptoms and cognitive performance may be observed in cultures where knowledge of

menopause and menopausal symptoms is limited²⁰. There was generally a lack of understanding about the MT in the SWEET participants²⁰, which may be as a result of a poor primary health care system with limited access to gynecologists, suggesting that black urban South African women are not generally questioned about menopause. In addition, their economic position and their cultural perspective on menopause and aging may also have played a role in the women in the study²⁰. However, although more than two-thirds of the SWEET participants had a very low educational level and nearly half of the cohort did not understand the meaning of the term menopause²⁰, the women were able to give reasonably precise information about changes in bleeding patterns, such that their reproductive aging could be staged using Stages of Reproductive Aging Workshop + 10 criteria. This correct staging was confirmed by the FSH and E2 trends. These findings suggest that such associations are observed cross-culturally, perhaps reflecting a common underlying neurobiology.

The lack of association between menopause stage and processing speed in the present study is similar to findings from a cross-sectional study of 1657 SWAN participants³⁵, but differs from a longitudinal study of 2362 SWAN women where those in the late MT stage performed worse on SDMT processing speed compared with premenopausal and postmenopausal women¹¹. While this may be due to the greater sensitivity of the longitudinal design over the cross-sectional design, it may also reflect a limited window during the late MT/very early postmenopausal stage when processing speed is slowed. In the present study, early and late were combined into one transition group because of small sample sizes. A smaller cross-sectional study ($n=117$) found that late reproductive women had slower processing speed than those in early menopause¹².

Our findings for the association between processing speed and menopausal symptoms are consistent with previous large scale cross-sectional studies in US and UK women demonstrating an inverse association between menopausal anxiety and processing speed^{15,16,36}. Indeed, in the present study, the relationship between processing speed and menopausal symptoms was considerably stronger for hot flushes than for anxiety. The difference in findings from the SWAN and the SWEET may reflect cohort differences in the severity of hot flushes in relation to obesity, as 67.8% of women in the SWEET²⁰ were obese compared with 21.7% of women in the SWAN³⁷, and cultural differences may play a role in the manner in which the SWEET participants described their hot flushes²⁰. However, BMI is positively associated with VMS^{20,38} in both cohorts. In the SWAN it was found that obesity is a strong risk factor for VMS, especially in the late MT and early postmenopause stage³⁹, and women with a BMI of 31 kg/m² had more frequent VMS⁴⁰. In the SWEET participants, VMS were strongly associated with the early MT, late MT, and early postmenopause stage, and it was found that very obese women had a significantly higher prevalence of severe/very severe VMS²⁰. Lastly, in the present study, severe depressed mood was unrelated to processing speed, whereas

the longitudinal SWAN study found a statistically significant, albeit small, association¹⁵.

Finally, we examined the association of a measure of incidental recall with menopausal stage and menopausal symptoms. To our knowledge, this is the first assessment of this cognitive ability in relation to menopausal stage and symptoms. This measure is of interest because of its ecological validity; memory function in everyday life typically requires incidental recall of information as opposed to intentional encoding of information for later recall. In the present study, the only significant finding on the incidental recall measure was that severe depressed mood was associated with decreased incidental recall⁴¹. This finding is interesting because it suggests that incidental recall may be more sensitive to depressed mood in midlife women than processing speed.

There were several limitations of our study. Firstly, the cross-sectional design limited sensitivity to potential menopausal stage effects. Secondly, we could not assess verbal memory performance, which appears to be especially sensitive to menopausal stage¹³, because English was not the first language of the participants and there are 11 different official languages in South Africa. It was decided to use a non-verbal measure of processing speed and incidental recall, the SDMT. A pilot study showed that this measure functioned well, and the participants were able to complete this neuropsychological test without difficulty. The SDMT has been used in South African populations in studies of HIV⁴², and in assessing cognitive abilities in South African primary school children in rural KwaZulu Natal⁴³. Thirdly, as in the SWAN^{15,44}, we did not use a formal tool to measure anxiety, but instead assessed anxiety-based items in a menopausal symptom inventory, in this case the MRS where anxiety is included in the psychological domain³⁰. A pilot study undertaken in March 2011, before data collection commenced, showed that the participants in the pilot study found some terminology in the MRS difficult to understand. Therefore, permission was obtained from the authors of the MRS to simplify certain terminology in order to clarify the responses. Each participant in the SWEET was questioned during one-on-one interviews, by a single interviewer, who had a clinical background of dealing with women in the MT. The interviewer used open-ended questions to clarify the responses. This mixed approach to self-reported VMS has been recommended in studies and reviews where cultural differences are apparent^{3,45}. Although the key comparator in the current study was the SWAN, they did not use the MRS but used a similar list of symptoms in the SWAN questionnaire⁴⁶. However, we decided to use the MRS because it is cross-culturally applicable, has been internationally validated, and has been translated into nine different languages³⁰; thus, we felt that it would be best suited to our study cohort. In addition, strengths of the MRS include its ability to assess quality of life⁴⁷ and its reliability⁴⁸. Difficulty in scoring has been found in some population groups due to lower education levels and inability to understand the values of the scale, but this disadvantage can be addressed if a single member of the research team administers the scale⁴⁹. Studies in the

following population groups have used the MRS, and found it to be reliable and valid in describing severity and prevalence of symptoms: Latin America^{50,51}, Oman⁵², Nigeria⁵³, Malaysia⁴⁹, and Sri Lanka⁵⁴. Fourthly, the cross-sectional analysis may account for the differences in age at FMP between early and late menopausal women. It appears that age at FMP may be more accurately predicted in longitudinal studies, where the participants use menstrual calendars⁵⁵. The difficulty in accurately ascertaining age at FMP when it is self-reported has been widely discussed. Studies have shown that recalling this many years after it occurred is not always accurate⁵⁶. It seems that number of years since FMP may therefore have affected accurate recall of FMP among SWEET participants. Thus, a previous study in this same study population demonstrated that women 3 years or less from FMP reported a higher mean age at FMP than those who were interviewed more than 9 years after FMP²⁰. A lack of understanding about the MT and a poor primary health care system with limited access to gynecologists may also affect this recall, because the participants in the current study would not have been routinely questioned about their FMP and may therefore have found it hard to recall such information. In addition, cultural values regarding menopause may also have played a role in the poor recall of FMP, and further examination of whether the MT has the same level of importance for black urban South African women as it seems to have in western women is needed. Finally, assessment of HIV was voluntary, and therefore our finding of no association between HIV serostatus and SDMT performance must be taken with caution, especially given the robust associations of HIV with SDMT performance in well-characterized cohorts of HIV-infected women²⁶.

Conclusion

These findings in a large cross-sectional cohort study of black urban South African women examined the extent to which cognitive symptoms of the menopause, objectively measured by the SDMT, were related to menopausal stage and menopausal symptoms. Findings demonstrate associations of anxiety and hot flashes with processing speed, and incidental recall with depressed mood. The demonstration of these associations in a population of women living in a culture with very limited recognition of the menopause suggests that cognitive symptoms of menopause are not related to cultural expectations or assumptions of the menopause and may, instead, reflect a common underlying neurobiological substrate

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