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INVITED REVIEW

The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN)

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Abstract

Objective: Our initial understanding of the menopause transition (MT) has been framed by clinical samples of women seeking treatment rather than by population-based studies. The Study of Women's Health Across the Nation (SWAN) initiated in 1996 with an overall goal to define the MT, to characterize its biological and psychosocial antecedents and sequelae in an ethnically and racially diverse sample of midlife women.

Methods: This review summarizes the central findings of SWAN to date that can inform women and their healthcare providers about the impact of the MT and midlife aging on overall health and well-being.

Results: SWAN characterized changes in reproductive axis and menstrual cycle patterns that informed the development of the reproductive aging staging system Staging of Reproductive Aging Workshop+10; MT-related symptoms and mental health (vasomotor symptoms, sleep complaints, psychological symptoms, cognitive performance, and urogenital and sexual health); and physiological systems and functions (cardiovascular and cardiometabolic health, bone health, physical function performance) that are influenced by the MT. SWAN demonstrated substantial interrelations among these changes and significant racial/ethnic differences in the rate and magnitude of change in multiple health indictors in midlife women. The findings point to midlife as a critical stage for adopting healthy behavior and preventive strategies.

Conclusions: Over the past 23 years, SWAN has advanced our understanding of the impact of the MT and midlife aging on health and well-being in women. SWAN will be instrumental to determine whether MT-related changes during midlife are related to unfavorable health and well-being in early old age.

Key Words: Midlife – Menopause transition – Women – Aging – Symptoms.

T he menopause transition (MT) is a major health milestone for women with influences that extend far beyond reproduction. In addition to the symptoms that accompany menopause, concomitant biological, psychological, behavioral, and social changes shape women's midlife and future health. Much of what we now know about the MT, its characteristics, and its consequences is the product of a series of seminal cohorts that were established in the 1980s and 1990s.[1-6] These longitudinal studies broadened our understanding of the MT, which was formerly based on reports of women seeking clinical care and was not reflective of the more general MT experience.

Begun in 1996, the Study of Women's Health Across the Nation's (SWAN's) mission was to define the MT, to characterize its biological and psychosocial antecedents and sequelae, and to do so in an ethnically and racially diverse sample of women (Black, Chinese, Hispanic, Japanese, and White). The principal content areas in SWAN included the reproductive axis; menstrual cycle characterization; MT-related symptoms and mental health; sleep; bone health; body composition; cardiovascular risk factors and outcomes; physical function and performance; cognitive performance; and vaginal and urogenital health.

The goal of this article is to summarize central findings of SWAN to date that can inform women and their healthcare providers about the impact of the MT and midlife aging on overall health and well-being. First, we provide an overview of the design of the SWAN study including a description of relevant ancillary studies. Next, we summarize SWAN contributions to our understanding of changes in (1) reproductive axis and menstrual cycle patterns that informed staging of the MT; (2) symptoms and mental health; and (3) physiological systems and functions that are influenced by the MT. In each of these main areas, we provide, if known, how they are different (or similar) in each of the SWAN's racial/ethnic groups. We provide the clinical and research implications of the reviewed findings and conclude with the next steps SWAN will take to understand women's health in midlife and early old age (defined as the time when adverse changes in health and function start to accumulate[7]). To aid the use of the reviewed information for clinical care, teaching, and/or research, we include a ''take home messages box'' for each topic area and provide a central illustration figure that summarizes the impact of the MT and midlife aging on women's health and well-being.

OVERVIEW OF THE SWAN STUDY DESIGN

SWAN is a multisite, multiracial/ethnic, longitudinal cohort study.[6] Starting in 1996, SWAN enrolled 3,302 women at seven geographically distinct sites across the United States: Boston, MA; Chicago, IL; Pittsburgh, PA; Detroit, MI; Oakland, CA; Los Angeles, CA; Hudson County, NJ. The Coordinating Center is located at the University of Pittsburgh and the Central Laboratory is located at the University of Michigan. At enrollment, women were between 42 and 52 years of age, had an intact uterus and at least one ovary, were not receiving hormone therapy, were not pregnant or lactating, and had at least one menstrual period in the 3 prior months. Each site enrolled Non-Hispanic White women and women from one other predetermined racial/ethnic group. SWAN enrolled White (n = 1,550), Black (n = 935), Japanese (n = 281), Chinese (n = 250), and Hispanic (n = 286) women. Since enrollment, a baseline visit and 16 follow-up visits have been conducted through 2017.

At each visit, SWAN participants completed a standard protocol that included interview- and self-administered questionnaires focused on menstrual bleeding patterns, clinical health history, health behaviors, and psychosocial factors; sexual health, assessment of anthropometric measures, physical performance, and cognitive function; and provision of blood and urine samples. Self-administered monthly calendars for recording of menstrual flow heaviness as well as end-of-month questions on symptoms, gynecological surgery, and exogenous hormone use were collected through the MT. Each clinical site also elected to collect additional measures related to local scientific resources and interest at selected evaluations. Thus, some sites assessed body composition and bone density; radiographic knee osteoarthritis; subclinical cardiovascular atherosclerosis; and objective measures of sleep. At the most recent visit, a subset of women at all sites participated in protocols of accelerometer-assessed physical activity and measures of vaginal health.

The annual assessments of menstrual bleeding patterns and reproductive hormones—as well as monthly menstrual calendars—were of particular importance to the SWAN design because they allowed for precise identification of menopausal stages and the timing of the final menstrual period (FMP). SWAN defined the following stages: premenopausal (no change in bleeding patterns); early perimenopause (change in length of bleed or interbleed interval); late perimenopause (no bleeding in 3-11 months); natural postmenopause (no bleeding in 12 months not due to hysterectomy), surgical menopause (bilateral oophorectomy with or without hysterectomy), hysterectomy with one or two ovaries retained, and hormone use before FMP. To disentangle the effects of MT and chronological aging, analyses included measures of the MT and aging into the same models to identify independent effects. Because hormone use may mask the FMP, SWAN took into account hormone use in models at the various MT stages as well.

The depth and breadth of SWAN's contribution to understanding the MT and midlife aging extend through several existing sub- and ancillary studies. Of relevance to this report are the Daily Hormone Substudy (DHS) and the SWAN Sleep, the SWAN Mental Health, the SWAN Heart, and the SWAN Cardiovascular Fat ancillary studies. The DHS included a daily collection of first morning voided urine for an entire menstrual cycle or up to 50 days (whichever comes first) for 10 annual visits to characterize patterns of urinary hormone metabolites throughout menstrual cycles over the MT among a subset of SWAN participants (n = 848) across all clinical sites. The SWAN Sleep ancillary study collected in-home polysomnography (PSG) and actigraphy measures of sleep among a subset of SWAN participants (n = 370) across four clinical sites. The SWAN Mental Health ancillary study measured lifetime psychiatric diagnoses at baseline and occurrences of depression annually among SWAN participants from one site (n = 443). The SWAN Heart ancillary study measured subclinical markers of atherosclerosis over two visits among participants from two SWAN sites (n = 608) and the SWAN Cardiovascular Fat ancillary study quantified volumes of cardiovascular heart fat depots among SWAN Heart participants at one visit (n = 564).

WHAT WE HAVE LEARNED FROM SWAN

The reproductive axis, menstrual cycle patterns, and stages of the MT

As one of the largest and longest studies of the MT, SWAN has provided precise characterization of the main hormonal alterations and menstrual cycle changes that accompany the MT and define stages of reproductive aging (Box 1).[8]

The reproductive axis over the MT

Estradiol (E2) and follicle-stimulating hormones (FSHs) changed dramatically over the MT. Overall, E2 decreased across the FMP beginning at 2 years before the FMP and continuing for 2 years after the FMP, with a stabilization 2 years after the FMP. On the contrary, FSH increases across the MT with a gradual increase beginning 7 before the FMP and continuing until approximately 2 years before the FMP, followed by a remarkable increase in the time period of 2 years before to 2 years after the FMP, and finally a stabilization 2 years after the FMP.[9]

Interestingly, the *time course and pattern* of these hormonal changes across the MT did not vary by age at FMP or obesity, and they were conserved across racial/ethnic groups.[9] Instead, the *levels* of circulating E2 and FSH varied by body mass index (BMI) and race/ethnicity. Obesity markedly attenuated the rise in FSH level after FMP and was negatively associated with E2 level before FMP, but positively associated after FMP. Race/ethnicity was not associated with the span of FSH changes across the FMP, but Chinese and Japanese women had a shorter span of E2 changes and a slightly lower E2 levels than White or Black women.[9]

SWAN demonstrated for *the first time* that not all midlife women experienced one pattern of E2 decline or FSH rise over the MT.[10] Among 31.5% of SWAN women, E2 rose around 5.5 years before the FMP with a steep decline almost 1 year before the FMP. A similar rise of E2 was observed among 13.1% of SWAN women, but with a slow decline over 2 years after the FMP. A third group of 26.9% experienced a slow-decline pattern with no E2 rise before FMP, and a last group of 28.6% followed a limited flat decline across FMP.[10] For FSH rise, three patterns were observed across the MT, with 40.7% of the evaluated participants followed a high FSH rise, 48.7% a medium rise, and 10.6% followed a low rise FSH pattern. Interestingly, the rise pattern of E2 before the FMP was mainly observed among non-obese women of all racial/ethnic groups, whereas the flat E2 and low rise FSH patterns were more pronounced among obese women of all racial/ethnic groups (Box 1).[10]

Menstrual cycle patterns

The menstrual calendar data showed that the menstrual cycle length increased beginning 7.5 years before the FMP, with the steepest increase starting 4 years pre-FMP, and increased variability in cycle length beginning 2 years pre-FMP.[11] Consistent with this finding, analyses of the SWAN DHS found cycle length increased primarily in cycles without evidence of luteal activity (ELA, presumed ovulatory) as determined by the Kassam algorithm,[12] whereas the mean cycle length in ELA cycles was highly stable over time at 27 to 29 days.[13] In turn, the percentage of ELA cycles declined from almost 100% 10 years pre-FMP to 88% 5 years later, followed by a sharper decline to 23% in the last year pre-FMP.[13] Chinese and Japanese participants had consistently longer cycle length than non-Hispanic Whites, as did women with an older age at MT onset, but these factors did not modify the time trends.[11] Black and Hispanic women had consistently lower percentages of ELA cycles (overall 73% and 66%, respectively) than non-Hispanic Whites, Chinese, and Japanese (81%-83%), with no racial/ethnic effect modification of MT-related declines (Box 1).[13]

MT stages: timing, duration, and correlates

SWAN participated in the ReSTAGE Collaboration—with the Melbourne Women's Midlife Health Project, the Seattle Midlife Women's Health Study, and the Treloar data—which investigated aspects of menstrual cycle regularity as potential markers of the early and late MT stages, proposed in the first Staging of Reproductive Aging Workshop (STRAW).[14] Pooled analyses of monthly menstrual calendar data suggested a persistent difference in consecutive menstrual cycle length of seven or more days as the optimal marker of entry into early stage of the MT, as this predicted subsequent FMP, was observed in a high proportion of women, and occurred before other candidate markers.[15] ReSTAGE recommended at least

60 days of amenorrhea as the marker of entry into late stage of the MT,[16] as both 60+ days and 90+ days—used by many past studies[17]—were similarly predictive of subsequent FMP, but 60+ days was observed in a higher proportion of women and is a more straightforward indicator for women and clinicians.[17]

Using the above STRAW criteria of early and late stages of the MT, analyses of menstrual calendar data showed that women who smoked had both an earlier onset of the MT and a shorter total MT duration (defined as time from the onset of the early MT to the FMP). Total MT duration was longer in those with earlier age at MT onset and in Black women. Shorter premenopausal cycle length was linked to shorter MT duration, consistent with faster follicle depletion, whereas women with irregular—and perhaps longer—cycles in mid-reproductive age had a longer early-stage duration.[18] Median age at natural menopause was 51.4 years in the cross-sectional screener data from SWAN[19] and slightly higher at 52.5 years among longitudinal cohort participants.[20] In multivariate modeling, race/ethnicity was not independently associated with age at natural menopause,[20] whereas time-varying current smoking—but not baseline smoking—was linked to an earlier age at natural menopause (Box 1).[20]

Symptoms and mental health
Vasomotor symptoms

Up to 80% of SWAN women reported vasomotor symptoms (VMS), defined as hot flashes and night sweats occurring during the past 2 weeks, at some point during the MT, with the highest reporting occurring during the transition from early to late perimenopause.[21] In contrast to long-held beliefs that VMS last only a few years, frequent VMS persisted for a median of 7.4 years, with even longer durations for some women.[22] Analyses examining individual trajectories of VMS over the MT found four trajectories, with women falling into approximately equal proportions across four groups.[23] An early onset group of women had VMS early in the transition that continued after the FMP, but then declined. A later onset group had VMS peaking at the FMP and continuing, though declining, into their postmenopausal years. A third group had few or no VMS throughout the MT, and a fourth group of women, which we dubbed the ''super flashers,'' started VMS well before their FMP that continued well into the postmenopause. These findings provide insight into different patterns of VMS experienced by women.

SWAN's diverse cohort has provided additional insight into racial/ethnic differences in VMS. Black women had the highest prevalence and longest duration of VMS, and were most bothered by their VMS.[21,22,24] Asian women had the lowest VMS prevalence, whereas Hispanic and White women fell between the Black and Asian groups. Women in lower socioeconomic positions were more likely to have VMS, independent of race/ethnicity.[21]

Several other demographic and psychological factors were associated with VMS. Less education, smoking, greater depressive symptoms, greater anxiety, and more symptom sensitivity were all significantly related to greater subsequent reporting of VMS.[21] Depressed mood and anxiety were also associated with greater perceived bother of VMS, independent of VMS frequency.[24] Women with a history of childhood abuse or neglect were more likely to report VMS over the MT.[25]

SWAN has elucidated and helped resolve a complex relation between VMS and body weight/adiposity. In SWAN, higher adiposity was a risk factor for VMS early in the transition,[26] but this relation reversed after women became postmenopausal, with greater adiposity associated with lower VMS.[27] A similar reversal by menopause stage was noted between VMS and adipokines or inflammatory substances released by body fat.[28]

Although the physiology of VMS is not fully understood, reproductive hormones likely play an integral role. In serum samples from the full SWAN cohort and urine samples from the DHS, lower E2 (or estrone conjugates in the case of urine samples) and higher FSH levels were associated with VMS reporting, particularly in the setting of non-ELA cycles.[29] Variants in genes that encode for estrogen receptor alpha and enzymes involved in synthesis and conversion of estrogens predicted greater likelihood of VMS (Box 2).[30]

Sleep

Sleep is a multidimensional concept. Major dimensions of sleep include duration, continuity, timing, regularity, and satisfaction, in addition to sleep disorders. Some theorists include daytime sleepiness and napping as indicators of poor nighttime sleep in their models. Sleep dimensions can be assessed by self-report (questionnaire, interview, diary), behavioral movement (actigraphy), and PSG (multichannel physiological recordings, including electroencephalogram [EEG]). Not surprisingly, different measures of the same dimension do not yield the same results. Thus, it is necessary to take a comprehensive approach to understand the impact of the MT on sleep.

In the SWAN initial cross-sectional survey, late perimenopause and natural postmenopausal women reported more sleep difficulties than did premenopausal women, regardless of the occurrence of VMS. Postmenopausal hormone therapy users had similar rates of sleep difficulties to premenopausal women.[31] A longitudinal analysis of the first 7 years of SWAN showed a similar pattern of MT for self-reported sleep disturbance, defined as trouble falling asleep, waking up several times, and waking up earlier than planned at least three nights weekly in the last 2 weeks, with several exceptions. Early perimenopause was also associated with more sleep disturbance and hormone therapy use did not protect postmenopausal women from sleep disturbance. Frequent reporting of VMS, E2 decline, and FSH rise were also associated with sleep difficulties.[32] Waking up several times at night showed the most pronounced association with menopause stage.

Most studies of menopause and sleep complaints report averages across women by menopausal stage, which does not address whether a subset of women is especially vulnerable to the development of sleep disturbance near the FMP. Using group-based trajectory modeling, four different patterns of

Vasomotor symptoms
- Up to 80% of midlife women experience vasomotor symptoms during the menopause transition, with the patterns of vasomotor symptoms heterogeneous across time.
- Vasomotor symptoms can last more than 8 years, with a longer duration if experienced early in the transition.
- Black women have the highest prevalence, longest duration, and are most bothered by their vasomotor symptoms, whereas Asian women have the lowest vasomotor symptoms prevalence.
- Adiposity could be a risk factor for vasomotor symptoms early in the transition but appears to be protective at later stages of the menopause transition.

Sleep
- Self-reported sleep complaints increase across the menopause transition.
- During midlife, sleep duration and deep sleep measured objectively do not worsen and may improve.
- Black and Hispanic women have shorter sleep duration and less efficient sleep relative to White women.
- Poor sleep may have an adverse impact on women's cardiovascular health at midlife.

Depressive symptoms and anxiety
- Depressive symptoms and anxiety are somewhat higher during late peri- and postmenopause than premenopause.
- Other factors such as stressful life events, financial strain, low social support, sleep problems, and low physical activity are important contributors to depressive symptoms and/or anxiety, independent of the menopause transition.
- Of those examined in SWAN, testosterone is the only hormone related to depressive symptoms.
- Black women are less likely to experience increases in depressive symptoms, whereas Hispanic women are more likely to consistently experience depressive symptoms over midlife.

Cognitive performance
- Menopause-related cognitive performance difficulties are characterized by a temporary absence of learning during perimenopause that resolves in postmenopause (when learning resumes).
- Age-related cognitive performance decline starts later after menopause and is related to chronological age but not to time since the final menstrual period.

Genitourinary and Sexual Health
- Decline in intercourse frequency does not lead to vaginal dryness or pain with intercourse.
- Urinary Incontinence is a frequently reported symptom among midlife women that is not related to menopause or estradiol decline.
- Sexual functioning declines become apparent 20 months before the final menstrual period and slows after the final menstrual period.
- Compared to White, Black women show a smaller decline in sexual function over the menopause transition, whereas Japanese women show a larger decline.

SWAN, Study of Women's Health Across the Nation.

in FSH in the 7 years before the sleep protocol was associated with longer sleep time and more deep sleep, but consistent with the self-reported sleep disturbance, less favorable self-reported sleep quality.[34] A spectral analysis of non-rapid eye movement sleep showed that beta EEG power, a measure of cognitive arousal, was greater in late perimenopausal and postmenopausal women than in pre- and early perimenopausal women, with hot flashes explaining part of this relationship of cognitive arousal with menopausal status.[35]

Race/ethnic differences in sleep characteristics and their determinants are substantial. White women reported the most sleep complaints and Hispanic women the fewest in the full SWAN cohort.[32] US-born Hispanic, Chinese, and Japanese women had more sleep complaints compared to their first-generation immigrant ethnic counterparts.[36] On the contrary, Black women had shorter sleep duration, longer sleep latency, and lower sleep efficiency measured by PSG compared to both White and Chinese women in the SWAN Sleep ancillary study.[37] In addition, EEG beta power was higher and delta power lower in Black compared to White women. Actigraphy measures of sleep in the SWAN cohort show similar results: Black and Hispanic women had shorter sleep and lower sleep efficiency than White women.[38] The major factors that mediated race/ethnic differences in actigraphy were financial hardship and increasing health problems, and for Black women, VMS.

The associations of sleep at midlife with health outcomes have focused thus far primarily on cardiovascular health. In the SWAN Sleep ancillary study, women who had the metabolic syndrome had less PSG-assessed sleep efficiency, more beta power, and greater apnea/hyponea scores (an indicator of sleep disordered breathing), compared to those who did not.[39] Women with multiple indicators of sleep disordered breathing had elevated inflammatory and coagulation biomarkers.[40] In addition, Black women who had higher levels of C-reactive protein also had shorter PSG sleep duration and those who had higher levels of fibrinogen had lower sleep efficiency. Women with lower total delta power showed increased diastolic blood pressure over time.[41] A delayed bedtime, relative to keeping one's usual bedtime, was related to increased insulin resistance, but not to change in BMI over time (Box 2).[42]

Depressive symptoms and anxiety

A long-held belief is that women experience increased depression and anxiety during the MT. Researchers continue to evaluate the scientific evidence for this belief and whether VMS, sleep disruption, and other stressful factors contribute to negative moods at midlife.

SWAN has measured depressive symptoms using the Center for Epidemiological Studies of Depression (CES-D) scale at baseline and at all subsequent visits. At baseline, 23% of SWAN women scored 16 or higher on the CES-D, the cut-point for indicating potential clinical depression.[43] In longitudinal analyses,[44] the odds of having high depressive symptoms were significantly greater in the early peri-, late peri-, or postmenopause, as compared to the premenopause, with

sleep complaint trajectories were apparent over the MT. Only 15% reported increasing sleep complaints with the MT; specifically, waking up frequently around the time of the FMP. The other groups showed stability over the transition or a linear increase consistent with aging-related increases in sleep problems not specific to the MT.[33] Black and White women were more likely to experience an increasing prevalence of waking up frequently around the FMP, relative to the other racial/ethnic groups.

Sleep data gathered by PSG within the SWAN Sleep ancillary study paint another picture. More rapid increases

highest odds in the late perimenopause.[43,44] However, stressful life events, being Hispanic, and having low education conveyed greater risk for high depressive symptoms than did menopausal status.[44] Testosterone was the only reproductive hormone related to depressive symptoms and was positively related to higher odds of depressive symptoms.[44]

Most studies of menopause and depression report mean levels of depressive symptoms over the MT, which does not address the heterogeneity of patterns of depressive symptoms experienced by women. Using group-based trajectory modeling, five different trajectories of depressive symptoms over midlife aging were identified. Half (50%) of the women had very low CES-D scores (scores <5), 29% had scores less than 16 over the entire time, 11% of women initially had high CES-D scores that decreased over time, and small groups of women showed an increasing trend over time (5%) or consistently high scores (5%) over time.[45] Black women were less likely to be in the increasing group and more likely to be in the decreasing symptom trajectory. Hispanic women were more likely to be in the consistently high group. The group with increasing scores was characterized by lower physical activity, an increase in sleep problems, a smaller reduction in stressful life events, and a decrease in social support. Baseline menopausal status (ie, pre- or early perimenopausal) was not associated with trajectory group membership.

In the SWAN Mental Health ancillary study, women were two to four times as likely to experience a major depressive episode in the MT or early postmenopause than in premenopause,[46] although menopause status was not a significant predictor of first episode of major depression.[47]

Although anxiety symptoms are highly prevalent among midlife women and may precede the onset of depressive symptoms, they have received much less attention than depression or depressive symptoms. SWAN has examined anxiety longitudinally using a measure of anxiety based on a composite of four anxiety symptoms: irritability, nervousness or tension, feeling fearful for no reason, and heart pounding or racing. Internal consistency of these items is good (Cronbach alpha of 0.77) and the scores are highly correlated with the Generalized Anxiety Disorder-7 (Spearman $r = 0.71$), a commonly used measure of anxiety. The odds of high anxiety symptoms were significantly greater for early peri-, late peri-, and postmenopause compared to premenopause, and peaked in the late perimenopause.[48] However, menopausal stage was no longer significantly related to anxiety when analyses were adjusted for frequent VMS. Among women who did not have anxiety before the MT there was a greater likelihood of reporting anxiety over the MT compared to when premenopausal, independent of multiple risk factors, including upsetting life events, financial strain, fair/poor perceived health, and VMS.[48] Odds ratios for anxiety symptoms increased from early peri- to late peri-, but then declined in postmenopause, suggesting that increased levels of anxiety may be a temporary occurrence. Perceived health less than very good and at least one upsetting event in the past year conveyed greater risk of anxiety symptoms than did menopause stage (Box 2).

Cognitive performance

Approximately 60% of midlife women report problems with memory during the MT, yet studies of measured cognitive performance during the transition are rare.[49-52] To address unanswered questions about midlife cognitive function, the SWAN protocol included in-person serial tests of cognitive processing speed, verbal episodic memory, and working memory. SWAN's initial, 4-year longitudinal analysis of the relation between the MT and cognitive performance disclosed a *temporary* decrement in both processing speed and verbal episodic memory during the perimenopause; the decrement resolved in postmenopause.[51] The negative perimenopause effect was subtle, manifest as the *absence of a learning effect*, meaning that cognitive test scores *did not get better* with repeated administrations. Improvement with repeated testing is normative in this age range.[53] But even in perimenopause, test scores did not drop—they simply did not improve during this MT stage. It is important to make the distinction between not getting better and an actual decline, which was observed in a later analysis (see below).

It appears intuitive that symptoms associated with the MT, specifically VMS, depressive symptoms, anxiety, and sleep disturbance symptoms, would contribute to the cognitive difficulties observed during perimenopause,[54-56] but a subsequent, 6-year, longitudinal analysis from SWAN evaluating a direct relation between these four MT symptoms and cognitive performance did not uphold this thesis.[52] There was no association between cognitive performance and either VMS or poor sleep, but women with depressive symptoms did score lower in the domain of cognitive processing speed and those with more anxiety symptoms had worse verbal episodic memory. When all four symptoms were added to the models of MT stage and cognition, the negative effect of late perimenopause on cognitive performance was *unaltered*, suggesting that the presence of these symptoms does not account for the perimenopause learning decrement.[52]

As the SWAN cohort aged and continued to undergo serial waves of cognitive tests, age-related cognitive decline (also known as cognitive aging) studies have been undertaken. Age-related cognitive decline is a decline in cognitive performance that can be a normal part of aging.[57] There is debate about whether age-related cognitive decline starts in midlife.[58]

To circumvent the practice effects related to the initial two testing occasions, age-related cognitive decline evaluation started at the third cognitive assessment; starting after practice effects have abated, one can observe an actual *decline* in cognitive performance (if present).[58]

At analysis outset, the median age was 54 and 60% had reached menopause. Cognitive processing speed and verbal episodic memory declined with time, adjusted for MT stage, MT symptoms, diabetes, race/ethnicity, education, and attrition, consistent with age-related cognitive decline. To consider whether the menopause, apart from chronological aging, influenced cognitive decline, an alternate analysis strategy was used, gauging cognitive performance as a function of

time before and after the FMP. The decline in cognitive processing speed and verbal memory per year of chronological age was almost identical to the average, between-women difference in cognitive processing speed by age at time of FMP, supporting the thesis that the declines in cognitive performance are not related to menopause, but rather, are a function of chronological aging (Box 2).

Genitourinary and Sexual Health

Vulvovaginal symptoms

In longitudinal analyses, vaginal dryness increased across the MT, from about 19% in pre- and early perimenopause to 34% in postmenopause years. Furthermore, vaginal dryness contributed to pain during sexual intercourse.[59] Advancing menopausal stage was more strongly associated with vaginal dryness than E2 decline, confirming a more complex etiology of this symptom than low E2 levels alone. Naturally postmenopausal women were less likely to develop vaginal dryness than surgically menopausal women.[59] Contrary to popular belief that reduced intercourse frequency leads to poorer vaginal function, reduced intercourse frequency did not precede the development of vaginal dryness or pain with intercourse.[59] Importantly, sexual lubricant use was associated with better sexual functioning scores around the FMP and reduced the likelihood of developing sexual pain (Box 2).[59,60]

Urinary incontinence

About 68% of SWAN women reported monthly or more frequent urinary incontinence (UI; assessed as number of times a participant had leaked urine, even a small amount during the month before each annual visit) symptoms at least once over the first 9 years of follow-up.[61] Although SWAN women who were continent at baseline had higher odds of reporting new onset monthly or less frequent UI in early and late perimenopause, women who were incontinent at baseline actually reported greater improvement in their UI symptoms during this same time frame, that is, mild UI symptoms were just as likely to resolve as develop. Importantly, women in early and late perimenopause were not more likely to develop weekly or more frequent UI or experience worsening UI symptoms than before or after the MT.[62,63] Neither UI development nor worsening was associated with E2 level or change in E2 levels over time.[64] Instead, aging, being overweight, weight gain, and incident diabetes increased the risk of developing UI and having weekly or more frequent UI symptoms.[62-64]

Less than 40% of incontinent women sought treatment for UI from a healthcare provider. Treatment seeking was most strongly related to longer duration and greater frequency of UI symptoms and was not associated with race/ethnicity, education level, or socioeconomic status.[61] Women with frequent UI who did not seek treatment were more likely to report inaccurate beliefs about UI (eg, UI is normal consequence of aging) or motivational barriers (eg, provider never asked about UI) as reasons for not seeking treatment (Box 2).[65]

Sexual functioning

Sexual functioning is an important component of women's lives with 75% of SWAN women at baseline reporting sex as moderately to extremely important.[66] Pain during sexual intercourse increased and sexual desire decreased over the MT, independent of sociodemographic characteristics, or changes in health and psychological functioning.[67] However, menopausal stage was not associated with frequency of sexual intercourse, emotional satisfaction with partner, or physical pleasure, although vaginal dryness was an important factor for all in adjusted analyses. Longitudinal data showed that concurrent E2 level was not related to any measured sexual function domain, but concurrent testosterone level was positively associated with sexual desire, arousal, and masturbation.[68]

SWAN has also conducted analysis of sexual function relative to the FMP.[60] Using a composite measure of sexual functioning among naturally menopausal women who remained sexually active throughout the MT, a decline in sexual functioning became apparent 20 months before the FMP and slowed 1 year after the FMP through 5 years afterwards. This decline was not explained by factors such as poorer health, VMS, vaginal dryness, depression, or partner status.

Sexual functioning in midlife varied by race/ethnicity. Compared to White women, Chinese and Japanese women reported lower importance of sex, desire, masturbation, arousal, and more sexual pain, whereas Black women reported greater importance of sex, higher sexual intercourse frequency, but more sexual pain, less arousal, less emotional satisfaction, and less physical pleasure.[67,69] Sexually active Black women also had a smaller decline, whereas Japanese women had a larger decline in sexual functioning across the MT (Box 2).[60]

Physiological systems and functions
Cardiovascular and cardiometabolic health

Over the past 25 years, our understanding of whether and how the MT could influence women's cardiovascular disease (CVD) risk has significantly evolved. Menopause is now listed as a female-specific CVD risk factor per the American Heart Association,[70] and has been recognized as a risk-enhancing factor favoring statin therapy initiation in the 2018 updated guidelines of blood cholesterol management (Box 3).[71]

Traditional and novel CVD risk factors

By following women over the MT, SWAN documented sharp increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein (Apo)B levels within a 1-year interval surrounding the FMP.[72] Importantly, the menopause-related acceleration in LDL-C was associated with greater risk of carotid plaque later in life in a follow-up analysis.[73] Conversely, high-density lipoprotein cholesterol (HDL-C) and ApoA did not decline over the MT.[72] In fact, a SWAN analysis by menopausal stage showed HDL-C

Box 3 Take-home messages: physiological systems and functions

Cardiovascular and cardiometabolic health

- Women experience adverse changes in their lipids, body fat distribution, metabolic syndrome risk, and vascular health over the menopause transition.
- Increases in LDL-C around the final menstrual period are associated with greater risk of plaque presence after menopause, but higher levels of HDL-C may not consistently be protective.
- Menopause transition-related fat redistribution extended to other critical locations that are relevant to cardiovascular health.
- Sex hormones and greater vasomotor symptoms appear to be related to adverse changes in cardiovascular health with risk varying by patterns of E2 and vasomotor symptoms over the menopause transition.

Bone health

- Bone mineral density loss starts a few years before the final menstrual period, that is, during the menopause transition, not after menopause.
- Due to confounding by body size, Japanese and Chinese women have lower bone mineral density than do White women, despite having lower fracture rates, but composite strength indices (estimated bone strength relative to demand) are better in Japanese and Chinese than in White women.
- Non-White women in SWAN experience less decline in composite strength indices in the 5 years before through the 5 years after the final menstrual period.

Physical functioning

- Although physical functioning limitations are prevalent among midlife women they are not necessarily a persistent problem.
- The menopause transition is associated with poor self-reported physical function that is related to declines in E2 and T levels over the menopause transition.
- Symptomatic changes experienced by menopausal women including vasomotor symptoms, poor sleep, and perceived stress may negatively affect physical functioning status.
- Physiologic changes across several body systems (eg, inflammation, hemostasis, adipokines) during the menopause transition may underlie the observed changes in physical functioning during this time.

E2, estradiol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SWAN, Study of Women's Health Across the Nation; T, testosterone.

to be the highest during the late peri- and early postmenopause stages.[74] Analysis from the SWAN Heart ancillary study suggested potential changes in HDL quality over the MT, with increases in HDL-C associated with less carotid intima medial thickness (IMT) before, but with greater carotid IMT after the FMP.[75] Recent preliminary work showed that the ability of HDL particles to promote cholesterol efflux capacity, the main function by which HDL removes cholesterol from peripheral cells, was reduced over the MT.[76] Unlike lipids, changes in blood pressure, insulin, glucose, and BMI during midlife were not associated with the MT, independent of chronological aging.[72,77,78] However, the odds of developing metabolic syndrome were the highest during the perimenopause independent of age.[79] Moreover, SWAN found a relation between body composition, fat distribution, and the MT.[80-82] Using dual energy x-ray absorptiometry, SWAN examined change in body composition, beginning 9 years before and concluding 9 years after the FMP.[80] About 2 years before the FMP, the rate of fat gain doubled and lean mass started to decline. Fat gains and lean losses continued until 2 years after the FMP and then flattened. Weight increased

linearly during the MT, but also plateaued 2 years after the FMP.[80] Black and White women had similar patterns of change in body composition and weight in relation to the FMP. Japanese women lost some lean mass during the MT but, unlike White and Black women, did not gain fat mass. Uniquely, Chinese women gained lean mass and lost fat mass after menopause.[80]

Menopause-related fat distribution extended to other critical locations that are relevant to cardiovascular health. In SWAN Cardiovascular Fat ancillary study, postmenopausal women had greater volumes of heart fat within and outside the pericardial sac,[81] with the latter fat, known as paracardial fat, associated with greater risk of coronary artery calcification in postmenopausal than premenopausal women.[82] The proximity of heart fat to the myocardium and the vasculature may result in a higher pro-atherogenic contribution for this fat compared to other fat depots.[83] Heart fat has been associated with worse CVD risk factors and a greater risk of CVD events.[84]

VMS, the hallmark of menopause, were associated with a more adverse CVD risk factor profile, independent of age or sex hormones. Reporting of VMS over the course of the MT was associated with higher LDL-C, Apo B, triglycerides,[85] and insulin-resistance,[86] and with a greater risk for incident hypertension (Box 3).[87]

Subclinical vascular health

SWAN reported detrimental changes to vascular health over the MT. In SWAN Heart ancillary study, yearly increases in carotid IMT and interadventitial diameters, markers of carotid atherosclerosis and remodeling, accelerated during the late perimenopause stage independent of age.[88] Additional work from SWAN Heart ancillary study showed that metrics of vascular function also were compromised over the MT. Women who transitioned over a mean of 2.4 years of follow-up experienced greater progression in aortic pulse wave velocity, a marker of arterial stiffness, than women who remained premenopausal or those who were postmenopausal at baseline.[89]

Further work showed that changes in E2 and FSH might contribute to vascular remodeling over the MT. Lower levels of E2 and higher levels of FSH were associated with a wider adventitial diameter or a thicker IMT over time independent of age.[90] When considering patterns of E2 and FSH changes over the MT[91]; women who experienced a rise in E2 5 years pre-FMP with an early decline at 1 year pre-FMP had lower risk of carotid plaque after menopause than women with a flat E2 decline trajectory. Furthermore, women with a lower FSH rise over the MT had thinner IMT postmenopause.[91]

Similar to being adversely associated with traditional CVD risk factors (described above), VMS might be a marker of adverse underlying vascular changes. Women with hot flashes had a lower flow-mediated dilation and a greater aortic calcification independent of CVD risk factors and E2.[92] Moreover, reporting more frequent VMS was associated with thicker IMT.[93] The timing of VMS across the MT might be relevant for midlife vascular health according to a recent work

from SWAN.[94] Women with early-onset VMS had thicker IMT after menopause, independent of demographics and CVD risk factors (Box 3).[94]

Bone mineral density, bone strength indices, and fractures

Although bone loss has long been considered a hallmark of menopause, before SWAN, longitudinal examinations of how bone mineral density (BMD) changed in relation to the MT were scarce. In 1992, a landmark study of 75 US White women illustrated that the term ''post-menopausal bone loss'' was misleading: BMD loss started a few years before the FMP, that is, during the MT, not after menopause.[95] SWAN solidified and generalized this finding by quantifying changes in spine and femoral neck BMD in relation to time before and after the FMP in more than 2,000 Black, Chinese, Japanese, and White women; in each group, BMD loss began 1 year *before* the FMP and decelerated, but did not cease, ~2 years after it.[96]

Other results offered insight into the biology underlying this temporal pattern of MT-related bone loss: 2 years before the FMP, a sharp decline in serum E2 was accompanied by a marked increase in urinary N-telopeptide (a bone turnover marker), suggesting that a drop in E2 is one of the triggers of the greater-bone-turnover-greater-bone-loss cascade.[97,98] Approximately 1.5 years after the FMP, urinary N-telopeptide levels stabilized and serum E2 reached its nadir level, presaging the lesser rate of BMD loss that commences at about 2 years post-FMP.

In predominantly cortical bone, bone loss is characterized by endosteal (inner surface) resorption and compensatory periosteal (outer surface) formation, which increases the bone diameter.[99] SWAN showed that this cortical bone remodeling also began 1 year before the FMP.[100] However, gain in bone diameter did not counterbalance the BMD loss, resulting in a 0.7% average annual decline in femoral neck strength (estimated using composite strength indices, which quantify bone strength relative to loading demand).[100,101]

Racial/ethnic variation in osteoporotic fracture risk is recognized—for example, fracture rates among US Black and Asian women are approximately half those of White women —but our comprehension of the biology underlying the fracture differential remains limited.[102] Moreover, in some instances, between-group differences in BMD do not parallel between-group fracture risks; for example, average BMDs of Japanese and Chinese women are lower than White women's. SWAN baseline, cross-sectional analyses documented the paradoxical differences in BMD between its Asian and White participants.[103] But BMD alone is insufficient to capture fracture risk.[104] Composite indices of femoral neck strength, which forecast fracture risk in older adults, combine BMD, femoral neck width, body height, and weight to estimate bone strength relative to the demand experienced during a fall from standing height. These indices help remove the confounding of BMD by body size and bone size, which is a particular problem in crossracial/ethnic BMD comparisons.[101] On average, baseline composite strength indices were *greater* in Chinese and Japanese compared to White women, concordant with ethnic/racial differences in fracture risk.[105] Baseline values of composite strength indices predicted incident fracture during 9 years of follow-up. Race/ethnicity predicted incident fracture independent of BMD, but did not predict fracture independent of composite strength estimates.[106]

Longitudinal analysis of change in composite indices in relation to FMP-time disclosed a possible etiology of lesser fracture risk in Asian and Black women compared to White women.[100] On average, at the end of the 10-year interval bracketing the FMP (5 years prior through 5 years after it), values of the composite strength indices were less in White women than those of each of the three non-White subgroups (Box 3).[100]

Physical functioning

Limitations in physical functioning have been widely studied among older adults, but data from SWAN has been instrumental in characterizing the midlife as a critical window for the onset of poor physical functioning. In a cross-sectional analysis of SWAN screening data, almost one-fifth of the participants reported either moderate or substantial limitations using the SF-36 physical functioning questionnaire.[107] When considering the federal gait speed standard requirement for safely crossing a pedestrian intersection (<1.22 m/s) as a benchmark for physical functioning mobility concerns, an analysis among SWAN women from the Michigan site showed that a surprisingly high percent of women, 31% (mean age 47 years), had mobility issues that may affect their pedestrian safety.[108]

Although physical functioning limitations are prevalent among midlife women, findings from SWAN demonstrated that they are not necessarily a persistent issue across time. In a prospective analysis of five biennial measures of physical functioning, only one-third of women never reported physical functioning limitations, whereas 42% and 26% of women reported ever experiencing some and substantial limitations, respectively.[109] On average, the probability of improving in functioning was greater than the probability of worsening and older age and high levels of economic strain were found to be predictive of greater worsening.[109]

Changes in endogenous sex hormones during the MT, including greater reductions in E2 and testosterone were predictive of poorer physical functioning in SWAN women.[110] The burden of physical functioning limitations differs by menopausal stage. Late perimenopause, postmenopause, or surgical menopause women reported poorer levels of physical functioning[111,112] as compared to premenopausal women, adjusted for age. With respect to the impact of symptoms on physical functioning, women experiencing greater burden of VMS, urine leakage, poor sleep, and perceived stress had poorer physical functioning.[112] Thus, the physiologic and symptomatic changes experienced by menopausal women may negatively affect physical functioning status.

The rapid physiologic changes occurring across several body systems during the MT may underlie the observed changes in physical functioning during this time. In site-specific analyses, the systemic inflammatory biomarker, C-reactive protein, was associated with poor self-reported physical functioning[113] and high levels of leptin, a proinflammatory adipokine, predicted poor performance on mobility-related tasks.[114] Inflammation was associated with poor physical functioning in SWAN study-wide analyses as well; adverse levels of C-reactive protein and hemostatic markers including plasminogen-activator inhibitor 1, tissue plasminogen activator antigen, and factor VIIc predicted poor performance-based outcomes of physical functioning.[115]

Physical functioning is hypothesized to be not only an outcome of adverse health factors during the midlife, but as a marker of poor health. Women with poor self-reported physical functioning were at greater risk for metabolic syndrome[116] and those with low grip strength had greater risk for diabetes.[117] Poor physical functioning may also be a marker of early cardiovascular risk; walking speed was inversely associated with carotid adventitial diameter among SWAN women, a finding that was independent of traditional cardiovascular risk factors.[118] It is likely that the relationships between health behaviors, health outcomes, and physical functioning are bidirectional, and so longitudinal studies such as SWAN are critical to our understanding of the complexities of these processes (Box 3).

CLINICAL IMPLICATIONS AND NEXT STEPS

Since its beginning in 1996, SWAN has made wide-ranging contributions to women's health and well-being at midlife. SWAN has elaborated on the biological, symptomatic, and psychosocial changes that accompany the MT, and characterized the health sequelae of the MT. SWAN findings emphasize the diversity of the MT experiences among women, especially those of different racial/ethnic backgrounds, and underscore the multifactorial nature of the MT as a landmark event in women's lives. In addition, the findings point to midlife as a critical stage for adopting healthy behavior and preventive strategies.

SWAN's characterization of the MT was instrumental to the development of the criterion standard staging system, STRAW+10, which characterizes the stages of reproductive aging. Use of such a standardized reproductive aging staging system is critical to improving comparability across studies of midlife and menopause and providing uniform clinical terminology. SWAN findings underscore the heterogeneity of the endocrinologic and symptomatic experience of the MT as defined by patterns and timing of changes in sex hormones, VMS, and sleep complaints. The heterogeneous patterns of changes in E2 and VMS over the MT in SWAN were associated with differences in cardiovascular health outcomes after menopause, supporting the role of these factors in cardiovascular risk stratification. The between-women heterogeneity documented by SWAN underscores the appropriateness of implementing a personalized approach in both research and clinical practice when evaluating MT health sequelae or designing MT-related therapeutic or behavioral interventions.

SWAN's strong design and the breadth of information collected over approximately two decades of follow-up time enabled SWAN to unravel the contribution of the MT versus midlife aging in several physiological systems and health domains (Fig. 1; *Central Illustration Figure: blue bars depicting changes that were more driven by midlife aging while light orange bars depicting changes that were more driven by the MT*). The adverse changes observed in markers of cardiovascular (eg, lipids, vascular remodeling, body fat deposition) and musculoskeletal (eg, bone density and physical function) health during midlife were more influenced by the MT, whereas increases in blood pressure and BMI were more influenced by midlife aging. Transient rise in cognitive difficulties occurring during perimenopause, decline in sexual functioning due to increased pain and decreased sexual desire, and increases in sleep complaints and vaginal dryness were more driven by the MT. Although women reported greater depressive and anxiety symptoms during the MT, those symptoms were transient and more impacted by stressful life events, sleep problems, and low physical activity than the MT.

The reported findings from SWAN along with those of other studies focusing on midlife[1-5] point strongly to midlife as a window of opportunity for maintaining or establishing positive health behaviors to delay or prevent poor health outcomes or disability later in life (Fig. 1). For example, smoking cessation, healthy diet, and regular physical activity are three important modifiable factors that can significantly reduce cardiovascular risk.[119] SWAN documented extremely low prevalence of each of these modifiable factors with only 1.7% of the women evidencing positive healthy behaviors over time.[120] These findings call for more effort to educate women about MT-related acceleration in their cardiovascular risk and the importance of implementing a heart-healthy lifestyle to reduce risk of CVD in later life.

Similar to cardiovascular health, the midlife is a critical stage for musculoskeletal health. The decline in dual energy x-ray absorptiometry-assessed BMD starts several years before the FMP. This finding again points to the potential for early intervention, including lifestyle modification along with possibly prophylactic therapeutics that may delay and/or reduce the burden of osteoporosis and fracture risk later in life. Being physically active was associated with greater peak femoral neck strength relative to load in pre- and early perimenopausal women.[121] SWAN also showed serum 25-hydroxyvitamin D level below 20 ng/mL, which is partially determined by diet, was associated with 85% hazard for nontraumatic fracture development.[122]

The burden of physical functioning limitations among SWAN women also call for identifying ways in which women can improve midlife physical functioning. Health behaviors and the prevention of certain health conditions may be key targets for potential interventions given their association with midlife physical functioning. SWAN women who had a better
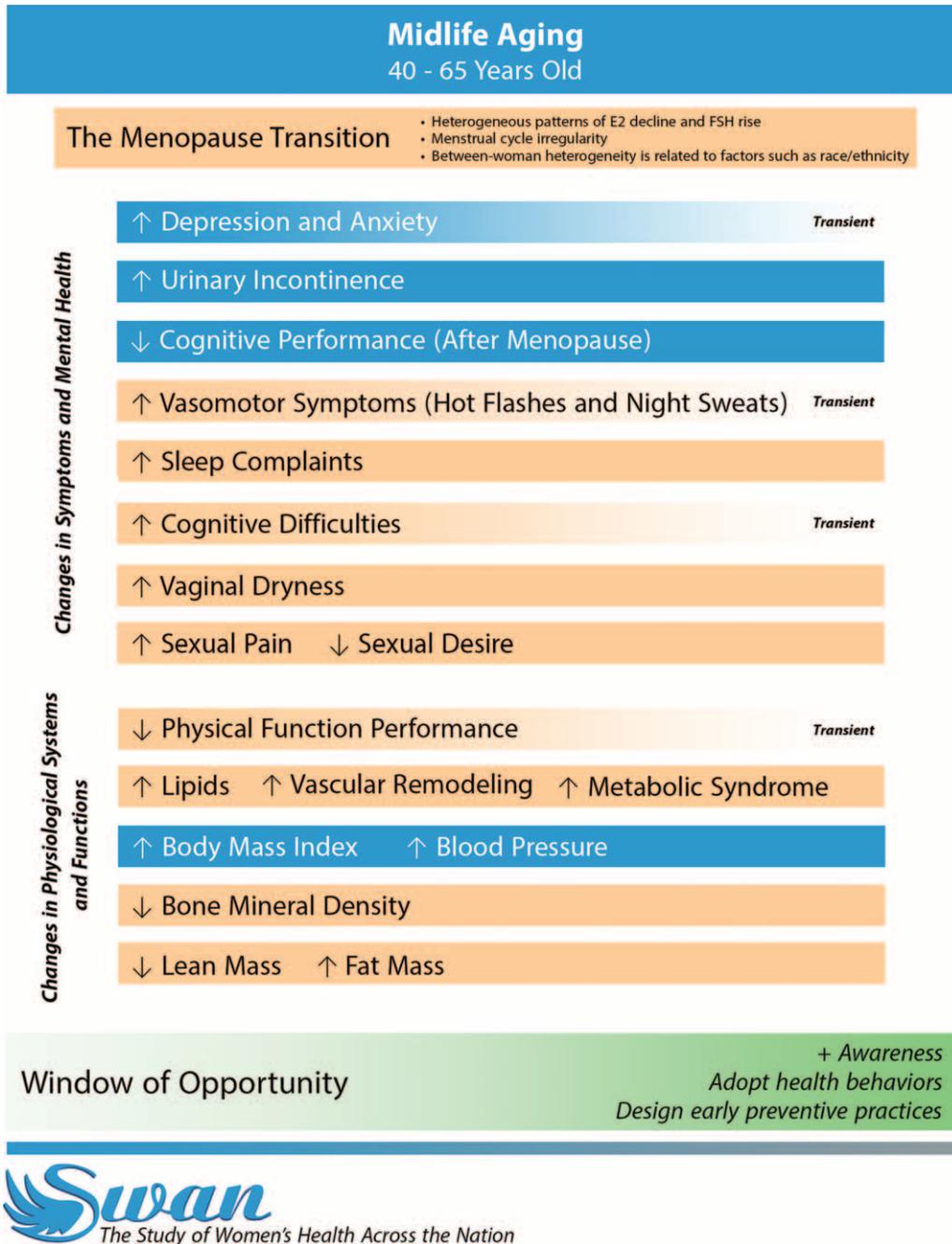
FIG. 1. Central Illustration Figure. The Contribution of the Menopause Transition and Midlife Aging to Women's Health and Well-being: What Have We Learned from the Study of Women's Health Across the Nation (SWAN)?; SWAN contributed to our understanding of the impacts of the menopause transition versus midlife aging on women's health and well-being in different domains. The figure lists changes *occurring during the menopause transition* that were reviewed in this paper, and differentiates whether these changes were more driven by the menopause transition or midlife aging using different color schemes. *Light orange* bars depict changes that were mostly driven by *the menopause transition*, whereas *blue* bars depict changes that were mostly driven by *midlife aging*. *Transient* changes are identified when applicable by fading color bars and listing the word ''*Transient*'' at the end of relevant bars. SWAN has identified midlife as a critical stage for adopting healthy behavior and preventive strategies.

diet quality[123] as well as an overall healthier lifestyle,[124] and particularly more physical activity[125] had better midlife physical functioning. Furthermore, women free from health conditions that commonly onset during the midlife, including depressive symptoms, vision impairment, knee osteoarthritis, and peripheral nerve impairment, have better functioning than women afflicted with these conditions.[126-129]

Taken together, adopting healthy lifestyle behaviors is critical to midlife women who face several changes in their physical and psychological well-being, many of which are highly related to the MT. Although this article has reviewed findings by distinct scientific areas, it is essential to point out that these domains are interrelated. For example, changes in sex hormones have been linked to changes in cardiovascular

and physical functioning health.[81,90,91,110] Both cardiovascular health and physical functioning are tightly linked and SWAN demonstrated their interconnection.[116,118] Sleep and VMS symptomatology are interconnected and both have been linked to cardiometabolic health.[39,41,85,94] It is critical to understand the impact of symptomatology changes on physiologic changes as well as how changes within a body system might impact changes in another system. Such knowledge will elucidate mechanistic pathways of how midlife and the MT might impact disease development and the aging process.

The MT experience of midlife women is strongly influenced by their racial/ethnic background. SWAN has documented significant racial/ethnic differences in the rate and magnitude of change in multiple health indictors, including patterns and timing of sex hormones changes and VMS reporting, declines in BMD, body composition, sleep characteristics, depressive symptoms, and sexual health. The reported racial/ethnic differences at midlife may drive the widening of health disparities later in life; a hypothesis that should be tested in future studies. It is critical that clinicians and researchers realize the diversity in endocrinologic, symptomatic, and physiologic changes of the MT among women of different racial/ethnic backgrounds and how might this diversity impact women future risk of disease and disability as well as their therapeutic and prevention options.

Important limitations of the SWAN study included the limited sample size of Hispanic participants which may reduce ability to detect significant differences in MT characteristics and its correlates among this ethnic group; recruiting women aged 42 to 52 years old (mean age 47 years old) at baseline making SWAN unable to study early menopause and its sequels; and limited generalizability to geographical locations not included in the study, for example, southeast.

Next steps

SWAN has advanced our understanding of the impact of the MT on health and well-being in midlife women. Whether the MT-related changes during midlife set the stage for poor health and well-being in early old age or represent a temporary set of physical and mental challenges is not known. Owing to its long duration, SWAN participants have now reached early old age. Therefore, SWAN now has the opportunity to examine the relation between prospectively characterized MT and midlife health measures and later life health and functional outcomes. This previously unavailable link between the MT, midlife, and older age will allow identification of interventions that may optimally preserve health and function as women age.

CONCLUSION

Over the past 23 years, SWAN has advanced our understanding of the impact of the MT and midlife aging on health and well-being in women. SWAN will be instrumental to determine whether MT-related changes during midlife are related to unfavorable health and well-being in early old age.

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