

the Baltimore Longitudinal Study of Aging demonstrate heterogeneity that might account for a lack of benefit in studies of treatment for subclinical hypothyroidism in older adults. At the same time, new data suggest the need for a more aggressive threshold for vitamin D in older adults, with a lower threshold associated with a drop in physical function compared to younger adults. Complexity in the regulation of hormonal pathways and the downstream effects on target tissues means multiple individuals with similar hormone levels may have different underlying physiology, with divergent clinical needs. Changes in activity and diet common during aging, and exacerbated by the pandemic, lead to physical and mood changes associated with hormonal dysfunction in popular culture and patient requests for evaluation. The ultimate goal should be personalized treatment decisions based on comprehensive evaluation and pathophysiology.

#### THE MANY FACES OF ELEVATED TSH: WHEN TO AVOID THYROID HORMONE THERAPY IN OLDER ADULTS

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We have previously demonstrated that hypothalamic-pituitary-thyroid axis aging is characterized by several distinct patterns. An elevated thyrotropin (TSH) level (mean 5.6mIU/L) with normal free thyroxine (FT4) was present in 75 BLSA participants with at least 3 visits. Twenty-one percent had an historical pattern consistent with primary gland failure, while 13% had a pattern consistent with an HPT response to stressors (aging-adaptation). The remainder had intermediate patterns of change. FT4 >0.92pg/ml identified those in whom TSH elevations occurred with aging-adaptation with a 90.0% sensitivity and 93.8% specificity, indicating no need for therapy. In addition, among 597 participants with stable TSH levels in the reference range, being on thyroid hormone therapy increased mortality risk (IRR=1.8; 95% CI 0.9-2.1). Thus, including FT4 in the diagnostic criteria for hypothyroidism in older adults could target therapy to avoid the potential harm of reversing the aging adaptations in those who do not have true early hypothyroidism.

#### SEX-SPECIFIC 25-HYDROXYVITAMIN D THRESHOLD CONCENTRATIONS FOR FUNCTIONAL OUTCOMES IN OLDER ADULTS

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25-Hydroxyvitamin D [25(OH)D] has extra-skeletal effects, but it is not known whether the minimum sufficient

serum levels for such targets, like muscle, differ from those for bone health (typically recommended at 20 or 30 ng/dL). Therefore, we derived and validated sex-specific thresholds for serum 25(OH)D predictive of poor physical function using 5 cohorts comprising 16,388 community-dwelling older adults (60.9% women). Using a cohort-stratified random two-thirds sample, we found incident slow gait was best discriminated by 25(OH)D<24.0 versus 25(OH)D≥24.0 ng/mL among women (Relative Risk=1.29; 95% CI 1.10-1.50) and 25(OH)D<21.0 versus 25(OH)D≥21.0 ng/mL among men (RR=1.43; 95% CI 1.01-2.02). Estimates from the remaining one-third validation sample were similar. Empirically identified and validated sex-specific 25(OH)D thresholds from multiple well-characterized cohorts of older adults may yield more biologically meaningful definitions in important sub-populations. Such thresholds may serve as candidate reference concentrations or inform design of vitamin D intervention trials in older adults.

#### TESTOSTERONE THERAPY FOR MEN WITH AGE-RELATED LOW TESTOSTERONE: TEMPEST IN A TEACUP

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Serum testosterone concentrations decrease in men with age, but benefits and risks of raising testosterone levels in older men remain controversial. In the T-Trials, a total of 790 men, age 65 and older, with a serum testosterone concentration of < 275 ng/dL and symptoms of sexual dysfunction, fatigue or physical dysfunction were randomized to either testosterone gel or placebo gel for 1 year. Treatment in the testosterone arm increased serum testosterone levels to the mid-normal range for young men. Testosterone replacement was associated with a significant increase in sexual activity ( $p < 0.001$ ), libido and erectile function. In contrast, there was no improvement in vitality or physical function. Adverse findings included increases in non-calcified plaque formation and a higher rate of prostate events. In sum, testosterone treatment in older men was associated with modest benefits, while the risk on prostate and cardiovascular health remain unclear.

#### ASSOCIATIONS BETWEEN ENDOGENOUS ESTROGEN, POSTMENOPAUSAL HORMONE THERAPY, AND COGNITIVE CHANGES IN OLDER WOMEN

Mark Espeland, and Christina Hugenschmidt, *Wake Forest School of Medicine, Winston-Salem, North Carolina, United States*

How markers of brain health are associated with endogenous estrogen and use of postmenopausal hormone therapy (HT) varies depending on women's years from menopause and metabolic health status, ranging from potential benefit to harm. The Women's Health Initiative (WHI) included 7,233 women age 65-80 who underwent a randomized clinical trial of various HT preparations for an average of 5.9 years. Over up to 18 years of post-trial follow-up, diabetes (DM2) increased the risk of dementia (hazard ratio [HR] 1.54 [95% CI 1.16-2.06]). Having DM2 and also treatment with unopposed conjugated equine estrogens increased the risk to HR=2.12 [1.47-3.06]. We hypothesize

that the metabolic effects of estrogen in the brain drives this interaction. In support of this, the metabolic transition following menopause may alter the impact of other treatments on cognition, for example behavioral weight loss therapy to treat obesity in women with type 2 diabetes (interaction  $p=0.02$  for executive function).

## Session 4165 (Symposium)

### WELL-BEING AMONG AGING WOMEN: OBSERVATIONS FROM THE WOMEN'S HEALTH INITIATIVE STUDY (WHI)

Chair: Barbara Cochrane

Discussant: Barbara Cochrane

Previous efforts to assess well-being in relation to health have relied on descriptive analyses of hedonic or eudaemonic well-being indicators. Factor scores from principal components analysis offer a summary measure of well-being, but limited interpretability in epidemiologic analyses, e.g. estimated risk ratios. Use of latent class analysis to identify groups differing by levels of both hedonic and eudaemonic indicators preserves information about both dimensions while supporting interpretation of well-being effects on health indicators important for studying older women's health. For this symposium, we report on analyses to: (1) Develop a multi-dimensional profile of well-being that would preserve the individual dimensions of well-being (hedonic, eudaemonic) using latent class analysis; and (2) Support epidemiologic analyses of well-being as both an outcome and a predictor of health outcomes, enhancing interpretability of levels of well-being across various dimensions. Data on well-being in over 80,000 older women in the Women's Health Initiative Study were obtained in 2011-2012, along with their baseline demographic characteristics in 1993-1998. All-cause mortality included death from any cause occurring from 2012-2020. Four classes of well-being were identified: (1) lowest hedonic and eudaemonic well-being scores; (2) higher hedonic/lower eudaemonic scores; (3) lower hedonic/higher eudaemonic scores; and (4) highest hedonic and eudaemonic scores. Results will be presented in three papers addressing the development of the well-being profile; relationships of the profile with predictors of well-being; and the relationship of the profile to all-cause mortality. The discussion will focus on future research questions, such as likely factors mediating well-being and health outcomes.

### ASSESSING WELL-BEING AMONG AGING WOMEN: OBSERVATIONS FROM THE WOMEN'S HEALTH INITIATIVE

Kenneth Pike,<sup>1</sup> Eileen Rillamas-Sun,<sup>2</sup> Barbara Cochrane,<sup>1</sup> and Nancy Woods,<sup>1</sup> 1. *University of Washington, Seattle, Washington, United States*, 2. *Fred Hutchinson Cancer Research Center, Seattle, Washington, United States*

Our aim was to develop a profile of well-being preserving the ability to estimate differential effects of both hedonic and eudaemonic dimensions of well-being on health outcomes. Numerous indicators of well-being from over 80,000 aging women included hedonic (enjoyment of life, happiness, satisfaction with life, quality of life) and eudaemonic (personal growth, purpose in life, environmental mastery, control, self

mastery) dimensions. Using latent class analysis, we identified groups of women with distinct profiles of well-being. A four-class solution had both good statistical fit and made conceptual sense. Class 1 ( $n=9,146$ , 11%) had the lowest scores on hedonic and eudaemonic indicators, while Class 4 ( $n=38,246$  47%) had the highest levels of all well-being indicators. Class 2 ( $n=7,106$ , 9%) had higher hedonic and lower eudaemonic scores and Class 3 ( $n=26,650$ , 33%) had lower hedonic and higher eudaemonic scores. These classes form a well-being profile useful for estimating differential effects on health outcomes.

### PREDICTORS OF CLASSES OF WELL-BEING AMONG AGING WOMEN

Nancy Woods,<sup>1</sup> Eileen Rillamas-Sun,<sup>2</sup> Barbara Cochrane,<sup>1</sup> and Kenneth Pike,<sup>1</sup> 1. *University of Washington, Seattle, Washington, United States*, 2. *Fred Hutchinson Cancer Research Center, Seattle, Washington, United States*

Our aim was to examine the relationship of predictors of well-being from prior studies to the well-being profile developed from data from aging WHI participants. Class 1 included women with both low hedonic and eudaemonic well-being scores, class 4 with the highest scores. Classes 2 and 3 had moderate scores, with class 2 having higher hedonic and lower eudaemonic scores and class 3 having lower hedonic and higher eudaemonic scores. We examined associations between predictors and well-being classes. Youngest women were in Class 4 (mean=60.2 years) and oldest in Class 3 (mean=63.2). African American women had higher proportions in in Classes 2 and 3, Latinas in Classes 1 and 3, and Asian/Pacific Islanders in Class 3. College graduates, married women and those with household incomes >\$50,000 were most likely in Class 4. Associations with age, race/ethnicity, education, marital status and income were consistent with prior analyses incorporating individual well-being indicators.

### WELL-BEING AND ALL-CAUSE MORTALITY IN AGING WOMEN IN THE WOMEN'S HEALTH INITIATIVE (WHI)

Eileen Rillamas-Sun,<sup>1</sup> Kenneth Pike,<sup>2</sup> Barbara Cochrane,<sup>2</sup> and Nancy Woods,<sup>2</sup> 1. *Fred Hutchinson Cancer Research Center, Seattle, Washington, United States*, 2. *University of Washington, Seattle, Washington, United States*

To study the relationship between well-being and all-cause mortality, we estimated mortality among women in four classes of well-being using the well-being profile from the Women's Health Initiative Study (WHI). Demographic characteristics were self-reported at enrollment (1993-98). All-cause mortality included death from any cause between 2012-2020. We used logistic regression to examine all-cause mortality risk across the classes, using Class 4 (highest hedonic and eudaemonic well-being scores) as the referent, adjusting for age and race. Compared to Class 4, all other classes had higher age- and race-adjusted odds of death. Highest risks were in Class 1 women (OR=2.61; 95% CI: 2.46-2.76) and Class 3 women (OR=1.62; 95% CI: 1.55-1.68). Women in Class 4 had the lowest risk of all-cause mortality over an 18-year follow-up. These results confirm the utility of a profile of well-being for predicting all-cause mortality while preserving ability to identify the differences among well-being indicators across classes.