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Fat, Fit or Famished? No clear answers from the WHI about diet and dieting for long-standing hot flashes

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We've learned a lot in the last decade about hot flashes thanks to a number of national and international longitudinal studies across the perimenopause transition. Specifically, results from SWAN, the study of women across the nation (SWAN;1), the Melbourne studies (2), the PENN Aging study (3) and the Seattle Midlife Women's Health study (4) have all contributed to a better understanding of the etiology, risk factors, onset and duration of these bothersome but normal changes that accompany the final menstrual period around age 51 and the natural transition to post-reproductive life. In the US, women who smoke, are obese, stressed, have less than college education and difficulty paying the bills, or African-American are at highest risk for debilitating vasomotor symptoms (VMS: hot flashes and night sweats). The continuing analysis of these longitudinal data by members of the committee for Staging Reproductive Phases in Women (STRAW+10) has revealed that VMS peak in frequency relatively late in the transition during the two years after menses has ceased (approximately age 53), now referred to as the early postmenopause phase. (5)

At the same time that this picture was emerging of those individuals most likely to suffer through the transition, we were also confronted with the findings from the iconic Women's Health Initiative (WHI), which targeted a much older and different postmenopausal woman, on average 10–13 yrs removed from the last menstrual period, and willing to be randomized for up to 10 years to hormone and non-drug interventions to prevent cancer, heart disease and osteoporosis. Stopped early in 2002 for the surprising higher-than-expected rates of heart disease in the estrogen/progestogen study group, the subsequent decade's worth of findings continue to intrigue, inform, and occasionally intensify the controversy about the presumed risks and benefits of drug treatments and lifestyle choices for improved postmenopausal health. (6) Case in point is the report by Kroenke et al in this issue of *Menopause* (7) on the latest round of results from the WHI dietary modification (DM) arm, describing associated weight changes and vasomotor symptoms (VMS).

As background, the WHI included a full-scale, randomized controlled trial of a dietary modification (DM) intervention with the goals of reduced fat intake (20% of energy from fat) and increased intake of vegetables and fruit (5 servings/day) and grains (6 servings/day). A total of 48,835 postmenopausal women aged 50–79 years were enrolled, of whom 19,541 (40%) were randomly assigned to the low-fat "dietary pattern" (intervention group) and 29,294 (60%) were assigned as a comparison group to continue their usual diet over the 8 year trial. Women in the intervention group were given intensive behavior modification to support these dietary changes. Moreover, they were advised to maintain their body weight (although how such a strategy was operationalized was not explained). In the first year, the intervention group was exposed to 18 group sessions with nutritionists trained in motivation

and self-management techniques for dietary change, while “control” participants received written health education materials without group exposure to the diet counselors. Neither group was asked to make changes in exercise or other health-related behaviors, although both groups received health-related materials including exercise tips. Dietary intake was monitored by using the WHI food-frequency questionnaire, administered to all participants at baseline and year 1 and thereafter to a rotating sample of one-third of participants every 3 y (8).

As reported previously (9), significant differences in dietary intake were achieved by the intervention group whereas the comparison group’s diet remained relatively stable. By year one, the dietary change group had reduced their total dietary fat from 35% to 24.3% of calories (10.7 percentage points lower than the comparison group, but still not reaching the 20% goal), increased vegetable and fruit intake from 3.6 to 5.1 daily servings (1.2 servings higher than the comparison group), and increased their grain intake from 4.8 to 5.1 servings daily (0.9 servings higher than the comparison group). The dietary change group throughout the study (which ran for 8.1 years) maintained much of the desired modifications, but some subjects returned to previous habits. At study end, no clear dietary effects were observed for the main study outcomes, but the rate of ovarian cancer was significantly reduced (10). A number of other dietary parameters and CVD biomarkers were evaluated and described for the full DM study group, including a modest weight loss of approximately 5 lbs (e.g., 9, 11).

In the work reported here (7), Kroenke and colleagues have teased apart the subset of approximately 17,000 DM participants from the larger cohort who were not also enrolled in either the estrogen or estrogen-progestogen treatments (in the WHI, it was possible to participate in more than one trial arm), or were using menopause hormones at baseline, to examine VMS effects according to weight changes after the 1st year of intervention. Based on evidence from perimenopausal women and breast cancer survivors, the key question was whether weight change affected hot flash frequency in the hypothesized way: improvement with weight loss; exacerbation with weight gain.

Given the average age of the WHI participant was 63, well past the perimenopausal peak time for hot flash complaints, some might ask why it was important to examine this question in the WHI data, and in this particular trial. As expected, earlier results from the estrogen plus progestogen trial had already shown that menopause therapy had a clear benefit over placebo for reducing hot flashes and night sweats, especially in the youngest age group (50–59 yrs) where risk and severity were highest (12, 13). But unfortunately, in follow-up studies, VMS were shown to return after stopping of the hormone trials regardless of age (14). Moreover, both the WHI and HERS trials (HERS participants were 67 years of age on average and 18 years postmenopause (15) found the greatest risk of myocardial infarction among women randomized to the hormone therapy arm who reported vasomotor symptoms at study baseline. At the same time, a further analysis from SWAN investigators revealed hot flashes were associated with greater aortic calcification and other risk parameters of subclinical CVD (16). Taken together, these results suggest that long-standing vasomotor symptoms persist in a sub-group of women well into their 70’s, are not adequately extinguished even with menopause hormone therapy for more than 5 years and more importantly, may serve as early signals of underlying disease. As the DM trial had already produced evidence of an intervention effect on diet and weight loss, the same investigators took the next step to see if dietary modification might offer an alternative solution for VMS.

The results reported here are intriguing, although not completely clear. Not surprisingly, given the eligibility criteria of the larger DM trial, only a small proportion (35%) of the 17,473 participants who were approaching age 65 on average reported any VMS at baseline, with most ranking them as mild (those that did not interfere with usual activities); just 2%

reported severe (debilitating) symptoms. Risk factors for VMS were similar to those in perimenopausal cohorts (e.g., age, obesity, ethnicity, smoking). Using a series of statistical modeling procedures and controls for the number of potential confounds, investigators determined that women randomized to the intervention group who self-reported mild hot flashes or night sweats at baseline were more likely to experience elimination of symptoms at year 1 vs control women. Changing to a healthy diet was not effective for those with moderate to severe symptoms. Alternatively, in the overall group of hot flashing women (not categorized by study group), those who lost a lot of weight (10% of weight at baseline) were more likely to eliminate VMS than those who maintained their weight.

But when examined for study group and weight change interaction, things got a bit murky. The impact of weight loss on VMS symptoms was only seen in the intervention group; it was not seen in women with a large weight loss (10 pounds) in the control group (but this may have been due to the small numbers here). Perhaps the most surprising finding, even to the investigators, was that those in the DM group who *gained* excessive weight were also more likely to have symptoms resolve! After detecting no differences in the changes in dietary components in the DM subjects who gained or maintained weight, the authors attribute this latter observation to chance. Despite this, and the acknowledgement that secondary psychosocial benefits of the group interaction itself may have accounted for hot flash relief, the investigators conclude that over and above the effect of weight loss, an intensive intervention to promote a low-fat, healthy diet high in fruits, vegetables and grains helps to reduce vasomotor symptoms. Alternatively, the conclusion in the abstract seems to say the reverse: weight loss as part of a healthy diet regime is the key for hot flash relief. In any case, the report ends by recommending both measures as alternatives to hormone therapy for reducing VMS.

Although few would argue with the advice, the conclusion that the coupling of weight loss with a healthy diet alleviates hot flashes is not as clear cut as the authors suggest. To my mind, the investigators have not supported their argument with confirmative biomarkers of dietary changes frequently used in other studies of diet interventions (e.g., lipid profiles, carotenoids, vitamin K, estrogen concentrations). Perhaps more importantly, the research team fails to adequately investigate the alternative explanation that exposure to intensive regular group sessions led by highly-motivated health counselors was responsible for symptom changes. While recognizing that a sham intervention group to control for the intense social interactions (e.g., self-management of personal finances) would have been cost-prohibitive in this already mammoth research enterprise, a more reflective analysis of the intervention's therapeutic origins seems warranted. Indeed, after re-familiarizing myself with all the details of the WHI design and interventions*, it's clear that a richer description of the sophisticated (for the time) tools and approaches would have sharpened the insights about how such intensive behavior modification strategies might have operated here or be harnessed for real-world benefit. It turns out that the dietary change interventions included nutrition classes every 1–2 weeks, individualized dietary goals, culture-based cooking classes, professional-facilitated group sessions for sustaining lifestyle change, a regular newsletter, follow-up telephone calls and the use of a host of self-monitoring diaries, pictograms and other tools rolled out during the 5 year start-up phase when adherence rates began falling (16). No wonder the intervention group lost three times as much weight and reported fewer mild hot flashes vs controls with such focused attention and support.

Given these caveats, I'm not sure we're that much farther ahead after a decade of scrutiny in understanding how to better manage debilitating hot flashes. Weight loss as part of a healthy

*The information gleaned from earlier reports of WHI data as well as the details of the intervention, and the DM participant newsletter can be found at <http://www.whi.org/findings/dm/cancer.php>

dietary modification may indeed help to eliminate VMS. The problem is we have yet to clearly define a self-management intervention that works without an army of highly-trained lifestyle coaches and battery of research questionnaires, yet motivates women most at risk of adherence failures due to psychosocial and cultural barriers (described in detail in references 17–21), and can be realistically maintained to achieve a large enough weight change for disabling hot flashes.

Although these results are unlikely to create a “tsunami of uncertainty” in the wake of their publication as was seen after the WHI trials were stopped in 2002 (6), they have produced more questions than answers. In a JAMA report from 2006 of the larger DM study findings, that described only modest effects on cardiovascular risk factors and no reduction in CVD outcomes, the authors concluded that “more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk” (9). Although encouraging as a “proof of principle”, this latest slice of the DM salami seems to suggest the same is true for quenching long-standing hot flashes. Perhaps the biggest social benefit of this mother-of-all trials beyond the findings related to the intervention outcomes and risks for older women’s morbidities, will be the insights gained from learning better ways to design studies, test interventions, and interpret the data from the diverse, multi-ethnic WHI participants, based on what mattered to them.

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