Original Contribution

Gains in Body Fat and Vasomotor Symptom Reporting Over the Menopausal Transition

The Study of Women’s Health Across the Nation


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Although most women report vasomotor symptoms (hot flashes, night sweats) during midlife, their etiology and risk factors are incompletely understood. Body fat is positively associated with vasomotor symptoms cross-sectionally, but the longitudinal relation between changes in body fat and vasomotor symptoms is uncharacterized. The study aim was to examine whether gains in body fat were related to vasomotor symptom reporting over time. Measures of bioelectrical impedance for body fat, reproductive hormones, and reported vasomotor symptoms were assessed annually over 4 years from 2002 to 2006 among 1,659 women aged 47–59 years participating in the Study of Women’s Health Across the Nation. Body fat change was examined in relation to vasomotor symptoms by using generalized estimating equations. Body fat gains were associated with greater odds of reporting hot flashes in models adjusted for age, site, race/ethnicity, education, smoking, parity, anxiety, and menopausal status (relative to stable body fat, gain: odds ratio = 1.23, 95% confidence interval: 1.02, 1.48; P = 0.03; loss: odds ratio = 1.07, 95% confidence interval: 0.89, 1.29; P = 0.45). Findings persisted controlling for estradiol, the free estradiol index, or follicle-stimulating hormone concentrations. The relations between body fat changes and night sweats were not statistically significant. Body fat gains are associated with greater hot flash reporting during the menopausal transition.

adipose tissue; adiposity; body composition; body fat distribution; climacteric; hot flashes; menopause

Abbreviations: CI, confidence interval; NIA, National Institute on Aging; NIH, National Institutes of Health; OR, odds ratio; SHBG, sex hormone-binding globulin; SWAN, Study of Women’s Health Across the Nation.
The existing research linking body fat to vasomotor symptoms is cross-sectional, and the directionality or longitudinal nature of these associations is unclear. Of particular importance is whether fat gains are related to greater vasomotor symptom reporting over time. Women typically show progressive gains in body fat over midlife (15, 16), but the influence of these gains on vasomotor symptoms is unknown. Longitudinal research links higher body mass index to more reported vasomotor symptoms (1) and increases in reported weight across 2 time points (17) to higher vasomotor symptom reporting. However, body mass index, a ratio of weight to the square of height, is a rough proxy for body fat; reported weight is typically underestimated among women (18); and neither measure distinguishes between lean and fat mass. Given the importance of body fat to vasomotor symptoms, research with more precise estimates of body fat is important. No investigations have evaluated whether fat gains are related to vasomotor symptom reporting over time.

We hypothesized that gains in body fat would be associated with an increased annual prevalence of reported hot flashes and night sweats. We also examined the role of reproductive hormones in these associations, particularly estradiol; follicle-stimulating hormone, a gonadotropin associated with both gains in body fat and vasomotor symptoms (15, 19); and the free estradiol index, an estimate of the portion of estradiol circulating unbound to sex hormone-binding globulin (SHBG) and thereby biologically available. Given the variations in body composition and vasomotor symptom reporting by race/ethnicity and menopausal stage (1, 15), interactions by race/ethnicity and menopausal stage were examined.

**MATERIALS AND METHODS**

**Study population**

The Study of Women’s Health Across the Nation (SWAN) is a multiethnic cohort study designed to characterize biologic health and psychosocial changes over the menopausal transition. Details of the SWAN design and recruitment procedures are reported elsewhere (20). Briefly, each SWAN site recruited non-Hispanic Caucasian women and women belonging to a predetermined racial/ethnic minority group: African-American women in Pittsburgh, Pennsylvania; Boston, Massachusetts; Michigan; and Chicago, Illinois; Japanese women in Los Angeles, California; Hispanic women in New Jersey; and Chinese in the Oakland area of California. To obtain adequate numbers of women of diverse backgrounds, we used random-digit-dialed sampling from banks of telephone numbers at the Los Angeles, Pittsburgh, and New Jersey sites. The Boston, Chicago, Michigan, and Oakland sites selected randomly from lists of names or household addresses. Select sites supplemented primary sampling frames to obtain adequate numbers of racial/ethnic minority women. SWAN was approved by the institutional review boards at each site, and each participant provided written, informed consent.

Baseline eligibility criteria for SWAN included being aged 42–52 years, having an intact uterus and at least 1 ovary, not being pregnant, not using reproductive hormones, and having 1 or more menstrual cycles in the 3 months prior to the interview. Seventy-three percent of the women selected were contacted and provided information to determine eligibility: 51% (N = 3,302) of eligible women enrolled. Annual clinic assessments began in 1996–1997. Determination of body fat based on bioelectrical impedance analysis was initiated in the sixth annual SWAN visit (2002–2004), with continued annual assessments through visit 9. This investigation was a longitudinal analysis of associations between body fat and vasomotor symptoms from study visits 6 through 9.

This analysis was limited to the 1,946 women who had assessment by bioelectrical impedance analysis at 2 or more consecutive study visits. Because no women from the New Jersey site had 2 bioelectrical impedance analysis assessments, they were not included here. Of the 1,946 women, 119 women who had a hysterectomy with bilateral oophorectomy and 27 women with missing data on a covariate or the dependent variable across visits (hot flashes: n = 11; education: n = 10; parity: n = 2; anxiety: n = 4) were excluded from these analyses. In addition, because of the impact of hormone use on vasomotor symptoms and body composition, visits in which women reported taking hormones (hormone therapy, oral contraceptives) within the previous month were excluded, eliminating an additional 141 women. Thus, 1,659 women were included in primary analyses (787 women across 4 visits, 283 across 3 visits, and 589 women across 2 visits). Women missing reproductive hormone data (n = 42) were excluded from models incorporating these variables. Women excluded because of missing data were more likely to be African American (P < 0.0001), to have less than a college education (P < 0.0001), to currently smoke (P = 0.01), and to have higher anxiety (P = 0.02) than women without missing data.

**Design and procedures**

**Vasomotor symptoms.** Hot flashes and night sweats were assessed via questionnaire at each SWAN visit. Women responded to 2 questions that separately asked how often hot flashes and night sweats were experienced in the 2 weeks prior to the interview (not at all, 1–5 days, 6–8 days, 9–13 days, every day). Hot flashes and night sweats were considered separately in all analyses because of the differential pattern of associations of hot flashes versus night sweats with body fat change observed here. Categorization of results for any (from 1–5 days to every day) versus none (not at all) is presented, because a 3-level categorization (none, 1–5, ≥6 days) resulted in small cell sizes in the ≥6-day group.

**Body composition.** Body fat percentage was estimated from bioelectrical impedance analysis (BIA-103 analyzer; RJL Systems, Clinton Township, Michigan). Bioelectrical impedance analysis is based upon measurement of the transmission speed of an electrical pulse between electrodes attached at the feet and the knuckles of the hand. Electrical conductivity is greater in fat-free mass than in fat mass (21); therefore, resistance and reactance (impedance to this electrical current) can be used to estimate fat and lean mass (22).
The present investigation used the sex-specific validation equations of Chumlea et al. (16), with percent body fat estimated as total fat mass/weight. Given prior evidence that the amount of fat gain varies as a function of baseline body fat (23), the change in body fat from visit 6 to visit 9 was considered as relative change (within-woman percentage change in total percent body fat). Women were classified as gaining, losing, or having stable (within ±1%) body fat. Absolute change in body fat (change in absolute total percent body fat) was examined in secondary models.

**Reproductive hormones.** Concentrations of follicle-stimulating hormone, estradiol, and SHBG were obtained annually from a single morning fasting blood sample. Values from visits 6–9 are used here. Samples were taken on days 2–5 of a spontaneous menstrual cycle (timed sample); if a timed sample could not be obtained, a random fasting sample was taken (untimed sample). Estradiol assays were conducted in duplicate and follicle-stimulating hormone and SHBG in singulate. Assays were performed by using an ACS-180 automated analyzer (Bayer Diagnostics, Tarrytown, New York). Estradiol was measured with a modified ACS-180 (E2-6) immunoassay, with inter- and intraassay coefficients of variation of 10.6% and 6.4%, respectively, and a lower limit of detection of 1.0 pg/mL (24). Follicle-stimulating hormone assays were performed by using a 2-site chemiluminometric immunoassay, with inter- and intraassay coefficients of variation of 11.4% and 3.8%, respectively, and the lower limit of detection = 1.1 mIU/mL. The 2-site chemiluminescent SHBG assay was developed on site by using rabbit anti-SHBG antibodies, with the lower limit of detection = 1.95 nmol and inter- and intraassay coefficients of variation of 9.9% and 6.1%, respectively (25). The free estradiol index was calculated as $100 \times$ estradiol (pg/mL)/272.11 × SHBG (nmol) (26).

**Covariates.** Race/ethnicity, parity (number of livebirths; any vs. none), and educational attainment (years of completed education categorized as “less than” vs. a “college degree or higher”) were derived from the SWAN screening interview. The time-varying variables age, smoking status (current vs. past/never), anxiety, and menopausal status were derived from questionnaires administered during visits 6–9. Race/ethnicity was determined in response to the question, “How would you describe your primary racial or ethnic group?” Anxious symptoms were a sum score of the number of days in the past 2 weeks (from 0 = no days to 4 = every day) reporting irritability or grouchiness, feeling tense or nervous, heart pounding or racing, or feeling fearful for no reason. Menopausal status was obtained at each visit from self-reported bleeding patterns over the year preceding the visit, categorized as premenopausal (bleeding in the previous 3 months with no change in cycle predictability in the past year), early perimenopausal (bleeding in the previous 3 months with a decrease in cycle predictability in the past year), late perimenopausal (<12 and ≥3 months of amenorrhea), or postmenopausal (≥12 months of amenorrhea). Women previously classified as pre- or perimenopausal and reporting hormone use since the last study visit but not in the past month were considered to be of indeterminate status because of the impact of hormone use, even if discontinued, on bleeding.

**Data analyses**

Group differences in and associations between demographic, psychosocial, and medical characteristics and hot flashes or body fat change were estimated using t tests, chi-square tests, and correlation coefficients. Follicle-stimulating hormone, estradiol, and the free estradiol index were log transformed to normalize their distributions. To account for the nonindependence of longitudinal observations derived from the same woman and data in which the number of observations may differ across women, associations between body fat change and hot flashes or night sweats were estimated in a generalized estimating equation model (27), with a first-order autoregressive covariance matrix, a logit link, and a binary outcome distribution. Models were first adjusted for age and site and next additionally for race/ethnicity, educational attainment, menopausal status, smoking status, and anxiety. Finally, follicle-stimulating hormone, estradiol, and the free estradiol index were each added separately to covariate-adjusted models with additional consideration of cycle day of blood draw. Because the cycle day of blood draw and menopausal status were collinear (only early peri- and premenopausal women had menstrual cycles to provide a timed sample), they were considered as a composite variable (premenopausal timed sample, premenopausal untimed sample, early perimenopausal timed sample, early perimenopausal untimed sample, late perimenopausal, postmenopausal). Covariates were selected on the basis of previously documented associations with vasomotor symptoms and obesity (1, 28) and present associations with hot flashes/night sweats at $P < 0.20$. For time-varying covariates, values at visits concurrent with the symptom report were used. Interactions between body fat change and both race/ethnicity and menopausal status in relation to hot flashes/night sweats were examined. Analyses were performed with SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). Models were 2 sided, with alpha = 0.05.

**RESULTS**

Women reporting hot flashes at visit 6 were more likely to be African American, older, parous, currently smoking, later in the menopausal transition, more anxious, to have less than a college education, and to have higher follicle-stimulating hormone and lower estradiol and free estradiol index concentrations than women without hot flashes (Table 1). In the 2 weeks prior to the visit 6 interview, 33% of participants ($n = 555$) reported both hot flashes and night sweats, 8% ($n = 130$) reported night sweats only, 18% ($n = 300$) reported hot flashes only, and 41% ($n = 674$) reported neither hot flashes nor night sweats.

Participants as a whole gained fat over the 3 years, with average yearly gains of 1.74% (standard deviation = 6.77) of percent body fat (relative within-woman change) and 0.46 (standard deviation = 1.97) percent body fat (absolute change). On average, 23% of women had stable body fat, 53% increased, and 24% lost body fat. Significant ethnic differences were evident ($P = 0.002$), with the majority of Chinese (66.5%) and Caucasian (52.2%) women gaining body fat compared with 49.7% of African-American and 50.0% of...
Japanese women. Women who gained over the 3 years had lower body fat at visit 6 (36.1%) than those who had stable (40.5%) or declining (39.6%) body fat ($P < 0.0001$).

Women who gained fat were more likely to report hot flashes than women with stable body fat (Table 2). Associations persisted including covariates and, additionally,
estradiol, follicle-stimulating hormone, or free estradiol index concentrations (Table 3). Associations between body fat changes and night sweats were not statistically significant: minimally adjusted models, gain (odds ratio (OR) = 0.95, 95% confidence interval (CI): 0.79, 1.13; \(\text{P} = 0.54\)); loss (OR = 0.99, 95% CI: 0.82, 1.19; \(\text{P} = 0.91\)), relative to stable fat.

The interaction between body fat change and menopausal stage in relation to hot flashes was not significant (\(\text{P} = 0.22\)). However, a significant interaction with ethnicity was observed (\(\text{P} = 0.03\)). The relations between fat gain and hot flashes were most pronounced among Caucasian (OR = 1.41, 95% CI: 1.08, 1.85; \(\text{P} = 0.01\)) and Chinese (OR = 1.94, 95% CI: 0.95, 3.94; \(\text{P} = 0.07\)) women, as opposed to African-American (OR = 0.93, 95% CI: 0.68, 1.28; \(\text{P} = 0.67\)) or Japanese (OR = 0.78, 95% CI: 0.44, 1.40; \(\text{P} = 0.41\)) women. In covariate-adjusted models, relative to stable body fat, fat loss was nonsignificant in all groups.

Several additional analyses were considered. To evaluate any dose-response relation between fat gains and hot flashes, we considered gain as moderate and high gain; no dose response was observed (data not shown). Moreover, rather than considering relative change, models were estimated with absolute change in percentage body fat. Findings were comparable (data not shown). Additionally, instead of change in body fat, we examined the association between total percent body fat (time varying) and hot flashes. The marginal associations in minimally adjusted models (for every 1% body fat: OR = 1.01, 95% CI: 1.00, 1.02; \(\text{P} = 0.05\)) were not significant in covariate-adjusted models. Further, antidepressant use (use of medications for a nervous condition) was considered as an additional covariate, with results unchanged (data not shown). Further, when additionally adjusted for visit 6 percent body fat, findings were consistent with primary results (data not shown). Finally, consistent with cross-sectional findings (12), no associations were observed between changes in lean mass and hot flashes (per 1% increase in lean mass: OR = 1.00, 95% CI: 0.99, 1.02; \(\text{P} = 0.60\), minimally adjusted; OR = 1.00, 95% CI: 0.99, 1.01; \(\text{P} = 0.80\), covariate adjusted).

### Table 2. Association Between Change in Body Fat and Any Reported Hot Flashes, Study of Women’s Health Across the Nation, United States, 2002–2006

<table>
<thead>
<tr>
<th>Change in body fat</th>
<th>Adjusted for Age and Site</th>
<th>Covariate Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Gain</td>
<td>1.21</td>
<td>1.01, 1.45</td>
</tr>
<tr>
<td>Lose</td>
<td>1.10</td>
<td>0.92, 1.31</td>
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<tr>
<td>Stable(^{b})</td>
<td>Referent</td>
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<tr>
<td>Age, years</td>
<td>1.00</td>
<td>0.97, 1.04</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>1.71</td>
<td>1.35, 2.17</td>
</tr>
<tr>
<td>Chinese</td>
<td>0.66</td>
<td>0.44, 0.98</td>
</tr>
<tr>
<td>Japanese</td>
<td>0.84</td>
<td>0.56, 1.27</td>
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<tr>
<td>Caucasian</td>
<td>Referent</td>
<td></td>
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<tr>
<td>Menopausal stage</td>
<td></td>
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<tr>
<td>Premenopausal</td>
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<tr>
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<td>0.50</td>
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<td>Postmenopausal</td>
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<td>0.91, 1.38</td>
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<tr>
<td>Indeterminate</td>
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<tr>
<td>Anxious symptoms</td>
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<td>1.11, 1.20</td>
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<td></td>
</tr>
<tr>
<td>Current</td>
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<td></td>
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<tr>
<td>Past/never</td>
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<td></td>
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<tr>
<td>Parity (any children)</td>
<td>1.02</td>
<td>0.80, 1.29</td>
</tr>
<tr>
<td>Education</td>
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<td></td>
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<tr>
<td>Less than college</td>
<td>1.36</td>
<td>1.13, 1.64</td>
</tr>
<tr>
<td>College or greater</td>
<td>Referent</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) All models were adjusted for site in addition to the covariates listed.

\(^{b}\) Within \(\pm 1\)% change.
Gains in body fat over 3 years were associated with increased reporting of hot flashes. Associations persisted after controlling for confounding factors, as well as estradiol, follicle-stimulating hormone, or free estradiol index concentrations. This longitudinal analysis extends prior cross-sectional research (12), demonstrating that gain during the menopausal transition is associated with increased reporting of hot flashes.

The role of body fat in hot flashes has been controversial. Because of the conversion of androgens to estrogens by the cytochrome P450 aromatase enzyme in body fat (29) and inverse relations between estrogens and hot flashes (19), fat was long thought to deter hot flashes. However, thermoregulatory models purport that hot flashes are heat dissipation events occurring in the context of a narrowed thermoneural zone among menopausal women (14). Body fat is an insulator (30), and therefore women with more body fat may have more heat dissipation events, or hot flashes, to dissipate a given amount of heat. Our prior investigations showing positive cross-sectional associations between total (12) and subcutaneous (13) fat and hot flashes or vasomotor symptoms provided initial support for this thermoregulatory model. The longitudinal analyses reported herein extend this work to show that fat gains are associated with increased hot flash reporting over time.

Estradiol, follicle-stimulating hormone, and the free estradiol index were related to hot flash reporting. However, adjustment for these hormones had little impact on associations between fat gain and hot flashes, consistent with cross-sectional observations (12, 13). Thus, while these hormones may play a role in hot flashes, they may do so via a mechanism separate from that linking body fat to hot flashes. Further, whether body fat releases estrogens in a fashion as opposed to entering the circulation (29), important as hot flashes likely originate in the brain (14).

No significant associations between fat gains and night sweats were observed. The reasons for differential associations for hot flashes versus night sweats are not entirely clear, although links between adiposity and hot flashes appear to be more consistent than for night sweats (11, 13, 31). There may be several reasons for this difference. First, night sweats may be more difficult to report reliably, given their occurrence during sleep. Some research indicates that reported night sweats are more related to mood and subjective sleep disturbance than to physiologically detected night sweats (33). Second, whether the physiologies of hot flashes and night sweats are interchangeable has not been demonstrated (34). Thus, because reported hot flashes and night sweats may not be identical, they may vary in their determinants.

Associations between fat gains and hot flashes were most pronounced among the Caucasian and Chinese women. The reasons for these ethnic differences are not clear and are generally not observed in cross-sectional studies (12, 13). In SWAN, African-American women report the most hot flashes, and Chinese and Japanese the fewest (1), with body fat percentage following a similar pattern (12, 13). Notably, Caucasian and Chinese women were somewhat overrepresented among women who gained in this study. Chinese women were among the leaner women at visit 6, and the leaner women showed the greatest gains. These differential distributions of gain are important to consider in interpreting these findings. Further, there may be as-yet-identified physiologic or psychological reasons driving ethnic differences in associations between fat gain and hot flashes.

Several additional findings deserve mention. Associations were observed for fat gains rather than overall body fat level, suggesting that it is the acquisition of body fat that is important. Although speculative, fat gains may present a particular thermoregulatory challenge, requiring more dramatic thermoregulatory compensatory actions. Moreover, the magnitude of observed associations was modest. Other
factors beyond fat gains are clearly important. Finally, although associations between body fat and hot flashes have been observed to be most pronounced earlier in the transition (35, 36), these findings are generally not observed in studies using detailed measures of body composition (12, 13), in contrast to cruder measures such as body mass index.

This study had several limitations. Vasomotor symptoms were assessed annually via a self-reported measure in which women recalled symptoms over the past 2 weeks. Although widely used in epidemiologic research, these measures are a relatively crude estimation of symptom frequency that may be more prone to reporting biases than more intensive diary or physiologic measures (37). Thus, this study cannot delineate whether fat gains are associated with increased occurrence of versus the perception/reporting of hot flashes. In addition, the only estrogen assessed was estradiol, and serum hormone measures were obtained yearly among women that likely had fluctuating hormone concentrations. Future work with more detailed hormone measurements should evaluate the role of reproductive hormones in these associations. Moreover, body fat measurements were available to examine change over a 3-year period. Accordingly, body fat changes over this relatively short time frame were small. Further, the bioelectrical impedance analysis equations used in this report were validated relative to dual-energy x-ray absorptiometry in the Third National Health and Nutrition Examination Survey (NHANES III). This study sample is representative of US African-American, non-Hispanic Caucasian, and Hispanic, but not Asian, populations (16), limiting the understanding of the validity of bioelectrical impedance analysis measures in the Asian subgroups studied here. Finally, the generalizability of findings to African-American women, less educated women, and smokers may be more limited because of greater missing data among these groups.

This study had several important strengths. It included a large, well-characterized, population-based sample of midlife women. Several racial/ethnic groups were represented, allowing examination of variation among groups. The use of bioelectrical impedance analysis, rather than cruder measures such as body mass index, permitted more detailed investigation of body composition in relation to hot flash reporting. Moreover, this investigation allowed initial examination of follicle-stimulating hormone and estradiol in these associations. Finally, women were tracked over the menopausal transition, allowing a longitudinal investigation of fat gains over time in relation to hot flashes.

The majority of US women are overweight or obese (38), and progressive fat gains throughout adulthood are the norm (15, 16, 39). The present study indicates that women who gained body fat during midlife had an increased likelihood of reporting hot flashes over time. This finding is particularly relevant given the current interest in behavioral methods to manage hot flashes, as few validated and effective behavioral options are available. Whether prevention of these gains during the menopausal transition, such as via dietary, physical activity, or other methods, would help prevent or manage hot flashes is at present unknown. However, during this period of midlife fat gain (15, 16) and increasing cardiovascular risk for women (40, 41), preventing gains in body fat and maintaining positive health behaviors may be beneficial to both physical health and quality of life.

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