# Cardiovascular and Immune Responses to Acute Psychological Stress in Young and Old Women: A Meta-Analysis

ROBERT J. BENSCHOP, PHD, RINIE GEENEN, PHD, PAUL J. MILLS, PHD, BRUCE D. NALIBOFF, PHD, JANICE K. KIECOLT-GLASER, PHD, TRACY B. HERBERT, PHD, GIETA VAN DER POMPE, PHD, GREGORY E. MILLER, PHD, KAREN A. MATTHEWS, PHD, GUIDO L. R. GODAERT, PHD, STEPHANIE L. GILMORE, PHD, RONALD GLASER, PHD, COBI J. HEIJNEN, PHD, JOEL M. DOPP, PHD, JOHANNES W. J. BIJLSMA, PHD, GEORGE F. SOLOMON, MD, AND JOHN T. CACIOPPO, PHD

*Objective:* To describe the relationships between cardiovascular and natural killer (NK) cell number changes on acute psychological stress in women. *Method:* Data from eight different studies were analyzed. A total of 128 healthy female subjects, 85 younger (18–45 years) and 43 older (49–87 years), had been subjected to a speech stressor ($N = 80$) or a mental effort stressor ($N = 48$), mental arithmetic, or the Stroop test. Correlations between changes in NK cell numbers, systolic (SBP) and diastolic (DBP) blood pressure, and heart rate (HR) were computed. Meta-analysis programs were used to study correlations across studies and to examine whether correlations differed with stressors or age. *Results:* In all studies, significant increases over baseline were observed for each variable. Across studies, the mean weighted $r$ between changes in HR, DBP, and SBP was medium ($r_w = .25$) to large ($r_w = .64$). A medium to large average correlation between HR and NK changes ($r_w = .37$) was observed, whereas average correlations of changes in NK cell numbers with blood pressure changes were small to medium ($r_w \leq .23$). Correlations between changes in NK cell numbers and cardiovascular variables were homogeneous across studies, whereas mutual correlations between cardiovascular variables were heterogeneous. One moderator variable showed itself: correlations between HR and DBP reactions were larger in studies with older than younger subjects. *Conclusion:* NK cell changes and HR responses induced by acute stress in women are regulated, to some extent, by the same mechanisms. Neither the type of stressor nor age seem to be very important when considering correlations between NK cell and cardiovascular changes. This study integrates information about NK cell and cardiovascular responses in women that can be used as reference material in future studies. **Key words:** psychological stress, cardiovascular, immune system, natural killer cells, women.

HR = heart rate; NK = natural killer; SBP = systolic blood pressure; DBP = diastolic blood pressure.

## INTRODUCTION

Acute psychological stress in humans alters both cardiovascular and immune variables. Within the cardiovascular system, increases of HR and blood pressure (BP) on stress have invariably been reported. As for immune variables, the increase in the number of circulating NK cells is the most consistent finding in acute stress studies, irrespective of the stress model used (1–8). These stress-induced changes in cardiovascular variables and NK cell numbers, at least in part, reflect the activation of the sympathetic nervous system (5, 9–12).

A typical design using cardiovascular and immunological responses to acute stressors will reveal individual differences that may be crucial to the growth of knowledge in several areas, such as stress and coping, emotions, pathophysiological processes, and health outcomes. Recently, a positive relationship between cardiovascular reactivity and changes in NK cell numbers has been reported in men (13–15). No such analyses are available for women, perhaps because, traditionally, psychoneuroimmunological research includes more men (young) than women (middle-aged). Availability of subjects (students) and the existence of possible confounding variables (eg, menstrual cycle, menopause, use of oral contraceptives) may guide these choices. Nevertheless, many diseases with involvement of the immune system (eg, multiple sclerosis and some types of rheumatic diseases and cancer) predominantly strike women (16). Cardiovascular and immune responses to acute stress may be regulated differently in men and women. Several studies have shown that cardiovascular responses to acute stress can be different between men and women (17–19): Men tend to be vascular reactors (characterized by changes in BP and total peripheral resistance), whereas women tend to be cardiac reactors (responding predominantly via changes in cardiac output and HR). These data indicate that acute stress may trigger different response mechanisms in men and women and, therefore, findings in men may not necessarily apply to women.

In the past few years, small samples of women have participated in research of cardiovascular and immune responses to acute stressors. However, the relationships between these changes have not been compared directly, as has been done in the studies using male subjects (13–15). Therefore, raw data from different research groups were collected and reanalyzed to compute correlations between cardiovascular and NK cell number reactivity scores. A meta-analytic approach was then used to compare correlations across the different studies, enabling us to consider the homogeneity of results and the effect of potential moderator variables (viz., age, type of stressor) in an explorative manner. Our objective is to document the relationship between cardiovascular and NK cell number responses to acute psychological stress in women. The results of these analyses serve to increase our knowledge regarding underlying mechanisms of stress-induced changes in women and to provide reference material for future studies that examine how stress affects immunity and health in specific groups of women with, eg, chronic illness.

The National Jewish Medical and Research Center (R.J.B.), Denver, Colorado, Utrecht University (R.G., G.L.R.G.), Utrecht, the Netherlands, University of California (P.J.M.), San Diego, California, University of California (B.D.N., G.E.M., S.L.G., J.M.D., G.F.S.) Los Angeles, California, Ohio State University (J.K.K.-G., R.G., J.T.C.), Columbus, Ohio, Carnegie Mellon University (T.B.H.), Pittsburgh, Pennsylvania, University Hospital for Children and Youth "Wilhelmina Kinderziekenhuis" (G.v.d.P., C.J.H.), Utrecht, the Netherlands, University of Pittsburgh (K.A.M.), Pittsburgh, Pennsylvania, and University Hospital Utrecht(J.W.J.B.), Utrecht, the Netherlands.

Address reprint requests to: Rinie Geenen, PhD, Department of Clinical and Health Psychology, Utrecht University, PO Box 80140, 3508 TC Utrecht, the Netherlands. E:mail: R.GEENEN@FSW.RUU.NL.

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## METHODS

### Subjects and Experimental Design

Data were obtained from eight independent studies. Details of materials and methods are listed in the original papers (1, 4–7, 20–22). All subjects were healthy. Some of the characteristics regarding the subjects and the stressors of each study are listed in Table 1. Inasmuch as not all of the studies provide data on the menstrual cycle phase, or indicate whether the older women were on estrogen replacement, we did not account for these effects. One study showed that there is no effect of menstrual cycle phase on lymphocyte subset reactivity (23). All studies used a design yielding cardiovascular recordings during, and NK cell numbers immediately after, a prestressor baseline and a stressor condition.

### Cardiovascular Methods

In all studies, HR was determined via the electrocardiogram. Six studies used a BP monitor providing the average BP value during several heart beats (studies 23, 1, 4, 6, 22, and 7; Table 1), whereas two studies used a BP monitor providing beat-to-beat BP values (studies 20 and 21; Table 1).

### Immunological Methods

In all studies, the number of NK cells was determined by flow cytometry. NK cells were characterized by $CD16^+$ (studies 23 and 1), by $CD56^+$ (study 7), or by the combination of $CD16^+CD56^+$ cell surface markers (studies 20, 4, 6, and 21; Table 1).

### Statistical Analyses

Cases with one or more of the four variables of interest missing were removed. Within each study, data were inspected for outliers. A total of 10 cases having baseline values, stressor values, or difference scores that deviated more than 2.5 SD from the respective subsample mean were removed, leaving a total sample of 128 subjects (Table 1). Cardiovascular variables were distributed normally, but the distribution of NK cell numbers (both rest and stressor values) was positively skewed. Because correlations are sensitive to outliers, the NK cell data were log-transformed before performing statistical analyses. Reactivity for cardiovascular variables and NK cells were defined as change scores (stressor minus baseline values). Inasmuch as a test of correlated variances showed no dependency between physiological responses and initial levels (24), raw difference scores were used instead of residualized gain scores. Following the recommendations of Cohen (25, 26), correlations will be referred to as "small" (.10), "medium" (.30) or "large" (.50).

To study the moderating effect of age, correlations observed in subsamples with younger (≤45 years; studies 1, 2, 3, 4, 7, 8 from Table 1; $N = 85$) and older (≥49 years; studies 2, 3, 5, 6 from Table 1; $N = 43$) subjects were compared. To evaluate the moderating effect of stressors, subjects were categorized into studies that did (studies 1, 5, 6, 7, 8 from Table 1; $N = 80$) and did not (studies 2, 3, 4 from Table 1; $N = 48$) use a speech stressor. Meta-analysis programs were used (27, 28), a) to compute weighted-N averages of pre- and poststressor change effect sizes, b) to compute weighted-N averages of (Fisher z transformed) correlations between cardiovascular responses and NK cell changes, and c) to examine whether correlations depended on age or type of stressor. In meta-analysis, the weighted statistic that is computed by using the results of separate studies is determined by the sign and size of correlations or effect size as well as the size of subsamples. The resulting average statistic does not show the original homo- or heterogeneity of scores. Therefore, as descriptive and inferential measures of homogeneity, the percentage of error variance to observed variance and a $\chi^2$ statistic were computed. The meta-analysis program used (28) is based primarily on two handbooks (29, 30).

## RESULTS

### Effect Sizes

All studies reported stress-induced increases in cardiovascular measures and NK cell numbers (Figure 1). Within the subsamples all $p$ values of pre- to poststressor changes in HR, DBP, SBP, and NK were significant ($p < .05$ or better). Effect size estimates across studies were homogeneous (Table 2). These homogeneous effect sizes actually refute the need to search for moderator variables. Nevertheless, we explored mean effect sizes of the younger and older ages and the samples that were and were not subjected to a speech stressor (lower part of Table 2). Mean effect sizes did not differ significantly for these conditions ($t$ and $p$ values not shown), confirming that the magnitude of NK cell and cardiovascular reactivity is independent of age and stressor in these studies.

### Correlations

Pearson correlations between the reactivity scores of the four variables are shown in Table 3. Across studies, the mean weighted $r$ between changes in HR, DBP, and SBP was medium ($r_w = .25$) to large ($r_w = .64$). A medium to large correlation between HR and NK changes ($r_w = .37$) was observed, whereas correlations of changes in NK cell numbers with BP changes were small to medium ($r_w \leq .23$). Correlations between changes in NK cell numbers and cardiovascular variables were homogeneous across studies (Table 3). According to the descriptive criterion (75% error variance) mutual correlations between cardiovascular variables were heterogeneous across studies (Table 3). The $\chi^2$ values of the test of heterogeneity of HR-SBP and DBP-SBP correlations were highly significant ($p < .01$), but did not reach significance in

**TABLE 1. Characteristics of Samples**

| Study | Stressor | Duration (min) | $N$ | Age Distribution, Mean (Range) |
|---|---|---|---|---|
| Mills et al. (23) | Speech | 6 | 26 | 31 (20–41) |
| Naliboff et al. (1) | Mental arithmetic | 12 | | |
| Young | | | 8 | 30 (22–40) |
| Old | | | 11 | 71 (65–87) |
| Geenen et al. (20) | Stroop | 3 | | |
| Young | | | 7 | 32 (23–45) |
| Old | | | 11 | 58 (49–67) |
| Herbert et al. (4) | Stroop | 21 | 11 | 22 (18–29) |
| Cacioppo et al. (6) | Speech + mental arithmetic | 2 × 6 | 11 | 66 (56–73) |
| van der Pompe et al. (21) | Speech | 8 | 10 | 54 (50–59) |
| Miller et al. (22) | Interpersonal conflict resolution | 15 | 17 | 31 (23–44) |
| Matthews et al. (7) | Speech + mirror tracing + Stroop | 11 | 16 | 27 (20–35) |

TABLE 2. Effect Size Estimates of Pre- to Poststressor Changes for Eight Studies and Weighted Effect Sizes (D +) for the Total Sample and for Age and Stressor Groups Separately[a]

| | HR | DBP | SBP | NK | *N* |
|---|---|---|---|---|---|
| Mills et al. (23) | 1.18 | 1.85 | 1.65 | .65 | 26 |
| Naliboff et al. (1)[b] | 1.19 | 1.90 | 1.02 | .68 | 19 |
| Young | 1.55 | 2.79 | 1.63 | .81 | 8 |
| Old | .91 | 1.65 | .91 | .57 | 11 |
| Geenen et al. (20)[b] | 1.06 | 1.54 | 1.53 | .87 | 18 |
| Young | 1.62 | 1.30 | 1.02 | 1.00 | 7 |
| Old | .72 | 1.67 | 1.93 | 1.01 | 11 |
| Herbert et al. (4) | 1.31 | 1.04 | 1.94 | .87 | 11 |
| Cacioppo et al. (6) | 1.25 | .55 | .59 | .37 | 11 |
| van der Pompe et al. (21) | 1.80 | 1.32 | 1.43 | 1.02 | 10 |
| Miller et al. (22) | 1.06 | 1.23 | .90 | .91 | 17 |
| Matthews et al. (7) | 1.47 | 1.42 | 1.43 | 1.29 | 16 |
| D + | 1.20** | 1.37** | 1.25** | .79** | |
| homogeneity[c] | 100% | 91% | 97% | 100% | |
| $\chi^2$ ($df$ = 7) | 1.7 | 6.7 | 6.5 | 3.0 | |
| Young D + | 1.25** | 1.46** | 1.36** | 1.25** | |
| Old D + | 1.06** | 1.19** | 1.09** | .69** | |
| Speech D + | 1.25** | 1.30** | 1.20** | .80** | |
| Not speech D + | 1.14** | 1.50** | 1.34** | .77** | |

** $p < 0.01$.

[a] Difference scores were divided by the pooled SD of baseline and stressor scores to yield effect size estimates of each study; D + is the weighted population effect size.

[b] To compute the effect sizes of distinct age groups, the subsamples with young and old subjects of these studies were used.

[c] As a descriptive and inferential measure of homogeneity, the percentage of error variance to observed variance and a $\chi^2$-statistic are shown, respectively; a set may be interpreted to be homogeneous if the percentage is 75% or more, or if the $\chi^2$ value is not significant.

the case of HR-DBP correlations ($\chi^2$ =12.2; $p$ = .09; Table 3). This indicates that differences between studies are important in determining cardiovascular responsiveness. The heterogeneity in the correlations between SBP and DBP is likely due to positive bias (30). The Fischer $z$ transformation expands large correlations relative to small ones. As a consequence, the range of Fischer $z$ correlations (and thus the heterogeneity) expands when correlations are quite large as is the case with the SBP-DBP correlations. Apart from the summarizing statistics, Table 3 shows the correlations that were obtained in each separate study. Many specific procedural details of studies may explain these differences, for instance, the age of subjects and the type of stressor used, but also characteristics of studies that are not shared by distinct studies and that are, therefore, beyond the control of meta-analysis. Table 3 (and Table 2 for effect sizes) can be used to learn how correlations obtained in future studies relate to the correlations of the studies used in this meta-analysis.

Meta-analysis programs were used to search for moderators explaining the inconsistent correlations across studies. To examine whether any of the correlations were dependent on age or type of stressor, the average correlations of studies with younger and older subjects were compared, as well as the correlations of studies using or not using a speech stressor. These average correlations of age and stressor groups are shown in the lower part of Table 3. Because $t$ values of moderator tests had to be quite high with the low number of studies, we will also discuss one marginally significant ($p <$ .10) $t$ value. None of the $t$ values were significant for correlations between NK cell number changes and cardiovascular variables. This finding confirms the previous observation that correlations between these variables were homogeneous across studies. Overall, correlations between changes in cardiovascular variables seemed to be larger in studies with older than younger subjects (Table 3). One $t$ test of this moderating effect of age reached significance: The mean correlation between HR and DBP was larger in older than younger subjects ($t$ = 2.96; $p < .05$). Tests of the moderating effect of stressors were never significant, although HR-SBP correlations tended to be larger in studies using a speech stressor ($t$ = 2.12; $p$ = .08).

## DISCUSSION

The aim of the present study was to document stress reactivity patterns in women with particular focus on the relationship between cardiovascular responses and changes in NK cell numbers. The analyses of data from eight independent studies reveal a medium to large significant correlation between NK cell number changes and HR responses and small to medium correlations between NK cell number changes and BP responses. The positive correlation between changes in HR and NK cell numbers was found consistently across studies, independent of age or type of stressor, and is congruent with studies using male subjects (13–15). The smaller correlations between stress-induced BP responses and changes in NK cell numbers contrasts with the reports using male subjects. In the studies on males, the positive correlations between BP and NK changes are as high as the correlations between changes in NK cell numbers and HR (13–15). Although the published data on male stress reactivity are in agreement, a meta-analysis of more than these three studies is necessary for a proper comparison with stress reactivity in women. Provided that the consistent higher correlations between BP responses and NK cell changes of male subjects are replicated in future studies, this suggests potential differences in the mechanisms underlying stress responsivity between men and women.

Physiological adaptation to acute stress involves changes in many different systems and mediators. Acute stressors as used

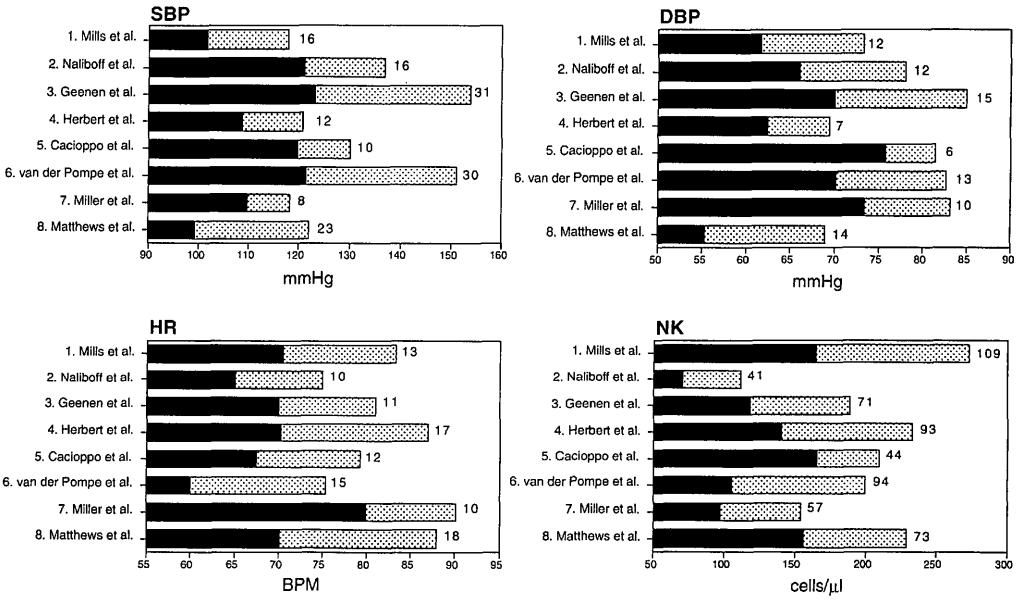


**Figure 1.** Mean rest and stressor levels for cardiovascular variables and NK cell numbers in each separate sample. Mean values of NK cell numbers were computed from log-transformed numbers and transformed back for illustrative purposes. *Solid bars* represent the mean rest value; the *stippled bars* indicate the mean values upon stress; the numbers shown next to the stippled bars indicate the value of the mean reactivity scores (stressor minus rest).

in these studies will induce the release of adrenaline and noradrenaline, although qualitative and quantitative differences may exist (8, 31, 32). Both hormones will bind and activate $\alpha$- and $\beta_1$-adrenoceptors, whereas only adrenaline is a strong stimulator of $\beta_2$-adrenoceptors (33). Cumulative data from the literature suggest that changes in the numbers of NK cells, which are the most responsive of all lymphocyte subsets in acute stress situations, are regulated predominantly via $\beta_2$-adrenoceptors (34). Infusion of noradrenaline induces only a small increase in NK cell numbers, which is certainly negligible compared with the increase observed after infusion of adrenaline (12). Therefore, it is safe to assume that, upon acute stress, an increase in NK cell numbers in peripheral blood is a reflection of an increase in adrenaline. Such an increase will also cause elevation of HR, and several $\beta$-blockade studies have shown a simultaneous inhibition of stress-induced increases in NK cell numbers and in HR (9–11). Thus, the positive correlation between NK changes and HR responses in women indicate that, as observed in men, individual differences in adrenaline release and $\beta$-adrenoceptor activation seem to become manifest during investigations using acute stressors.

In all studies, BP increased significantly over baseline. Whereas both sympathetic and parasympathetic mechanisms determine changes in HR, the regulation of changes in BP is still more complex (35) and can even occur when $\beta$-adrenoceptors are pharmacologically blocked (see Ref. 36 for a review). An increase in BP can be caused via stimulation of $\alpha$-adrenoceptors, which results in vasoconstriction. $\beta$-Adrenergic mechanisms may also be responsible for a BP increase via increasing cardiac output. In the current analysis, the correlations between BP and changes in NK cell numbers were small to medium across studies. In young (mean 23 years) and middle-aged (mean 41 years) men, changes in NK cell numbers correlate equally well with changes in HR *and* in BP (13, 14). Given that changes in NK cells are elicited by $\beta$-adrenergic stimulation, this suggests that in men differential HR and BP reactivity, to a large extent, reflects differential $\beta$-adrenoceptor stimulation. The present analyses for women show that correlations between NK cell changes and BP responses are smaller than the correlation between NK cell changes and HR. These results suggest that in women, more than in men, systems other than the $\beta$-adrenergic system must be considered to understand the physiological response to acute stress. The $\alpha$-adrenoceptor system and vagal inhibition may play a more important role in the physiological adaptation to stress. In support of this, it has been reported that the excretion of adrenaline during examination stress is higher in men than in women (37, 38), whereas in women vagal inhibition, rather than sympathetic activation, seems to underlie cardiovascular responses during acute psychological stress (19). Targeted blockade studies and detailed assessment of cardiovascular parameters (eg, vagal inhibition, total peripheral resistance (TPR), cardiac output) should be performed to investigate this matter.

Two studies have reported that no gender difference exists for immune changes induced by acute psychological stress (4, 5). In contrast, gender differences have been reported for

TABLE 3. Correlations Between Changes in NK Cell Numbers and Changes in Cardiovascular Variables for Subsamples, and Weighted Average of the Correlations ($r_w$) for the Total Sample and for Age and Stressor Groups Separately

| | HR-DBP | HR-SBP | DBP-SBP | NK-HR | NK-DBP | NK-SBP | *N* |
|---|---|---|---|---|---|---|---|
| Mills et al. (23) | .56** | .66** | .66** | .39* | .12 | .31 | 26 |
| Naliboff et al. (1)[a] | .06 | .37 | .70** | .54 | −.02 | .05 | 19 |
| Young | −.45 | .36 | .40 | .48 | −.59 | −.22 | 8 |
| Old | .48 | .56 | .75** | .58* | .24 | .14 | 11 |
| Gecnen et al. (20)[a] | .21 | −.02 | .74** | .33 | −.10 | −.25 | 18 |
| Young | .20 | .04 | .84** | .42 | −.55 | −.52 | 7 |
| Old | .48 | .29 | .73** | .69* | .09 | −.27 | 11 |
| Herbert et al. (4) | .01 | .10 | .69* | .08 | .63* | .43 | 11 |
| Cacioppo et al. (6) | .62* | .69* | .88** | .25 | .65* | .49 | 11 |
| Van der Pompe et al. (21) | .59 | .93** | .69* | −.14 | .37 | .04 | 10 |
| Miller et al. (22) | −.18 | .13 | .51* | .49* | .22 | .37 | 17 |
| Matthews et al. (7) | .01 | .72** | .01 | .53* | −.04 | .45 | 16 |
| $r_w$[b] | .25** | .51** | .64** | .37** | .19* | .23** | 128 |
| Homogeneity[c] | 64% | 26% | 14% | 100% | 91% | 94% | |
| $\chi^2$ ($df$ = 7) | 12.2† | 26.0** | 30.1** | 6.7 | 8.8 | 8.5 | |
| Young $r_w$ | .13 | .46** | .54** | .41** | .07 | .25* | 85 |
| Old $r_w$ | .54** | .68** | .78** | .40** | .36* | .11 | 43 |
| $t$ ($df$ = 8)[d] | −2.96* | −1.57 | −1.68 | 0.13 | −1.40 | 0.12 | |
| Speech $r_w$ | .34** | .66** | .59** | .37** | .23* | .35** | 80 |
| Not speech $r_w$ | .10 | .37** | .71** | .37** | .12 | .03 | 48 |
| $t$ ($df$ = 6)[d] | 1.08 | 2.12† | −0.58 | −0.06 | 0.08 | 1.41 | |

† $p \leq .10$; * $p \leq .05$; ** $p \leq .01$, 2-tailed.

[a] To compute the weighted correlations of distinct age groups, the subsamples with young and old subjects of these studies were used.

[b] Weighted average of the 10 correlations after Fisher z transformation.

[c] As a descriptive and inferential measure of homogeneity, the percentage of error variance to observed variance and a $\chi^2$-statistic are shown, respectively. A set may be interpreted to be homogeneous if the percentage is 75% or more or if the $\chi^2$-value is not significant.

[d] t Values of comparison between mean correlations in young and old and speech and non-speech subsamples, respectively.

cardiovascular reactivity (17–19). These gender differences were apparent with some but not all stressors applied, suggesting that the nature of the stressor plays a role in revealing gender differences in cardiovascular reactivity. Speech stress is considered a more "feminine" stressor (ie, will evoke a specific response in women), whereas stressors such as mental arithmetic or mirror tracing are less discriminative between men and women (17, 39). The results of two independent studies show that both speech and mental effort stress are associated with release of adrenaline, whereas the release of noradrenaline is more pronounced under speech stress (31, 32). This would suggest that women would respond stronger to speech stress using a slightly different pathway, which could be reflected especially in a different relationship between cardiovascular and NK cell changes. In the current analysis, we found that the type of stressor did not explain much of the heterogeneity in the relationship between cardiovascular variables. It must be noted however, that the analyses here are limited in that the categories that we defined do not contain a homogeneous group of stressors. Some stressors, such as the Stroop task, were applied for different times and some of the studies in the speech category consisted of a combination of stressors or contained stressors with speech elements (eg, conflict situations). The current analyses incorporate all of the studies of women that are known to us. An increase in the number of studies of women in the next couple of years might enable us to look more carefully at the potential effect of stressor type on stress reactivity in women and its mechanisms.

The final issue raised in this meta-analysis is the comparison of the reactivity pattern between younger and older women. No difference was observed when comparing the effect size for each individual variable in the two age groups across studies. Age, however, did influence the relationship between cardiovascular changes, with larger correlations in older subjects. This finding could indicate that with progressing age the regulation of cardiovascular responses becomes more uniform (a reflection of one dominant pathway) or that the overall range of reaction possibilities is smaller as a result of physiological limitations (eg, atherosclerosis). Interestingly, noradrenaline output (especially cardiac spillover) under mental stress is higher in older than younger subjects (40), whereas adrenaline changes are more pronounced in younger than older subjects (41). This could be indicative of a more unidimensional stress response with increasing age and is congruent with the current results. More work is needed to substantiate this result of the meta-analysis.

The overall aim of this study was to document the relationship between cardiovascular and immune changes (ie, NK cell numbers) in women, in order to gain knowledge regarding underlying mechanisms of stress-induced changes in women. Medium to large correlations between HR and NK cell changes were interpreted to be indicative of individual differences in adrenaline release and $\beta$-adrenoceptor activation. Differential activation of the $\alpha$- and $\beta$-adrenoceptor systems and perhaps also vagal inhibition seem to underlie small to medium correlations between NK cell increases on stress and BP reactivity. Measuring changes in the levels of catecholamines could potentially solve this issue and substantiate these predictions. In women, differential physiological activation seems, in part, to depend on age. Whether this age-dependency also plays a role in determining stress-responses in men is not known at present. The data of the current investigation may be used as reference material in

examining cardiovascular and immunological responses in women and as a basis for designing future studies in the area of stress responsivity.

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