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Title: Improvement of menopausal symptoms and the impact on work ability: a retrospective cohort pilot study

Authors: Marije Geukes, Johannes R. Anema, Mariëlle P. van Aalst, Renee X. de Menezes, Henk Oosterhof



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Title page

Title: Improvement of menopausal symptoms and the impact on work ability: a retrospective cohort pilot study

Author names and affiliations:

Marije Geukes^{a,1}, Johannes R. Anema^b, Mariëlle P. van Aalst^c, Renee X. de Menezes^d, Henk Oosterhof^a

^a Department of Obstetrics and Gynaecology, Nij Smellinghe Hospital, Post box 20200, 9200 DA Drachten, The Netherlands

^b Department of Public and Occupational Health, Amsterdam Public Health research institute, VU University Medical Center, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands

^c Van Aalst Arbo Advies, Lange Singel 24, 9243 KJ Bakkeveen, The Netherlands

^d Department of Epidemiology and Biostatistics, VU University Medical Center, van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands

Corresponding author: Henk Oosterhof

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E-mail addresses:

Marije Geukes: m.geukes@vumc.nl

Johannes R. Anema: h.anema@vumc.nl

Mariëlle P. van Aalst: info@vanaalstarboadvies.nl

Renee X. de Menezes: r.menezes@vumc.nl

Henk Oosterhof: h.oosterhof@nijsmellinghe.nl

Highlights

- Both menopausal symptoms and work ability improved following treatment
- Depressive symptoms are mainly responsible for improvement in work ability

¹ Present address: Department of Obstetrics and Gynaecology, VU University Medical Center, Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

- Improvement in work ability similar with HRT and non-hormonal treatment

Abstract

Objective

In this study we aimed to pilot test the hypothesis that in women who are severely bothered by their menopausal complaints, improvement of menopausal symptoms is associated with an improvement in self-perceived work ability.

Study design

This retrospective cohort study assessed the work ability of first-time attendees ($n = 31$) of a menopause clinic at baseline (T0) and 3 to 9 months follow-up (T1). All patients received care as usual according to local protocol, no interventions were applied by the researchers. Self-reported questionnaire data assessing work ability (Work Ability Index; WAI) and menopausal symptoms (Greene Climacteric Scale; GCS) were used.

Main outcome measures

Multiple linear regression was used in an exploratory analysis to examine the relationship between change in WAI score (Δ WAI) and change in menopausal symptoms (Δ GCS), after adjustment for potential confounders. Additional exploratory univariate linear regression analyses were performed to assess the associations of change in WAI score with change in the different GCS domains and with type of treatment.

Results

Twenty-seven out of 31 women reported improvement in work ability at follow-up (T1) ($M = 30.73$, $SD = 6.42$ respectively, $M = 34.86$, $SD = 5.98$). All women reported to be less bothered by their menopausal symptoms at T1 ($M = 26.57$, $SD = 8.69$ respectively, $M = 14.73$, $SD = 6.36$). Multivariate linear regression demonstrated a significant association between the WAI and GCS change scores after correction for confounders (beta Δ GCS = 0.283, $p = 0.014$). After additional adjustment for WAI at baseline, this association was no

longer significant (beta Δ GCS = 0.172, $p = 0.164$). Change in GCS depression domain (Δ GCS depression) was significantly associated with Δ WAI, although after correction for WAI at baseline the effect of Δ GCS depression was no longer significant (beta = 0.855, $p = 0.113$). The WAI and GCS change scores were highly correlated, as a result their coefficients were not statistically significant separately.

Conclusions

Treatment aimed at alleviating menopausal symptoms in symptomatic women could lead to improvement of menopausal symptoms along with improvement in work ability. Improvement of depressive symptoms seem particularly important for this outcome.

Keywords: menopause; work; menopausal symptoms; work ability; Greene Climacteric Scale; Work Ability Index

1. Introduction

The menopausal transition, i.e. perimenopause, begins on average four years before the last menstrual period, which occurs between the ages of 50 to 51 years in normal women. Most women will experience symptoms associated with menopause. Symptoms typically last about 5 to 7 years after the last menstrual period, although in some women they continue for up to 10 years [1]. Quality of life may be severely affected, although the extent to which women are bothered by these symptoms in both their personal and working lives is variable [2,3]. Work and paid employment are important factors contributing beneficially in physical and mental health and overall well-being [4].

As a consequence of the rise in retirement age and the increase in employment rate for women throughout whole Europe, many women will be active members of the workforce during their menopausal transition and beyond. Unfortunately, however, women in this age class have the

highest annual decline in work ability [5]. There is growing evidence that menopausal symptoms may have negative impact on women's self-perceived work ability, productivity, capacity to work and work experience [6,7,8,9,10]. Recent studies have explored employment conditions and workplace interventions that could help women cope with menopause at work [3,10,11,12]. In addition, the European Menopause and Andropause Society has published recommendations for working conditions for menopausal women [13]. To our knowledge there are however no intervention studies in the workplace to test the effectiveness of such recommendations. Also there is a paucity on research about improvement of menopausal symptoms and the effect on the ability to work. There is global consensus regarding the effectiveness of hormone replacement therapy (HRT) in the treatment of vasomotor symptoms associated with menopause. Quality of life, sexual function and other menopause-related complaints, such as joint and muscle pains, mood changes and sleep disturbances, also improve by HRT [14]. For women who cannot or do not wish to take estrogens, several non-hormonal management strategies are available for treatment of menopausal vasomotor symptoms. While some non-hormonal medications (i.e. gabapentin, pregabalin, clonidine, verapride and beta-blockers) and application of cognitive behavior therapy seem effective, the evidence for lifestyle modifications, diet and food supplements and alternative medicine is inconclusive [15,16]. In this retrospective cohort study, we aimed to pilot test the hypothesis that in women who are severely bothered by their menopausal complaints, improvement of menopausal symptoms is associated with an improvement in work ability.

2. Methods

2.1 Participants and recruitment

We performed a retrospective cohort study, in which we analyzed questionnaire data from patients of our outpatient menopause clinic. All new patients to our clinic fill out a screening

questionnaire about menopausal symptoms (i.e. the Greene Climacteric Scale, GCS) as standard procedure. In the context of a previous study [7] first-time attendees were asked to complete a second questionnaire concerning self-perceived work ability (i.e. the Work Ability Index, WAI) and sociodemographic questions regarding age, level of education, body mass index, smoking status and participation in sports during leisure time. Subsequently, women were asked to fill out the two questionnaires (i.e. GCS and WAI) again at their follow-up appointment 3 to 9 months after their first visit. Women were notified through the invitation letter that filling out the questionnaires was considered as informed consent. We retrospectively assembled the cohort with those patients that completed both questionnaires at baseline (T0) and follow-up (T1). Inclusion criteria for this study were, not having received any medical treatment for their menopausal symptoms at baseline and being employed. This study was approved by the Medical Ethics Committee of the Nij Smellinghe Hospital, Drachten, The Netherlands.

2.2 Care as usual

All patients received care as usual according to local protocol at our outpatient menopause clinic. This is an observational cohort study, hence there were no interventions applied by the researchers. Hereafter, the usual care as provided in our clinic is described. All new patients to our clinic consult a specialist nurse during 60 minutes at their first appointment. This nurse provides the patients with patient education focused on menopause and associated symptoms. In addition the nurse points out desirable changes in lifestyle (e.g. smoking cessation, healthy diet, daily exercise) and explains several strategies to reduce the extent to which women are bothered by their menopausal complaints. At the end of the consultation, the responsible gynecologist is briefly informed about the patient's symptoms and wishes regarding medical treatment. After considering the short-term and longer-term benefits and risks of the several

types of therapy, patients make an informed choice to start with treatment. These therapies include hormone replacement therapy (HRT), non-hormonal treatment, including non-hormonal medication and non-pharmaceutical therapy, e.g. phytoestrogen supplements, or no additional treatment besides the nurse's advice already received. Six weeks thereafter the patients have a 15 minute appointment with the gynecologist to evaluate or actually start medical treatment. Three to 9 months after their first appointment, they meet the specialist nurse again for a 30 minute follow-up.

2.3 Study measures

The Work Ability Index (WAI) was used to evaluate work ability and the Greene Climacteric Scale (GCS) to measure menopausal symptoms. The women also answered sociodemographic questions regarding age, level of education, body mass index, smoking status and participation in sports during leisure time.

2.3.1. Work Ability Index (WAI)

The Work Ability Index is a validated questionnaire developed by the Finnish Institute of Occupational Health [17]. It assesses how well a worker is able to perform his or her work regarding the physical and mental work demands. The WAI covers 7 dimensions: current work ability compared with best of lifetime; work ability in relation to job demands; number of current diseases diagnosed by a physician; estimated work impairment due to disease; illness related absenteeism during the past 12 months; own prognosis of work ability 2 years from now; mental resources (refers to the worker's life in general, both at work and during leisure-time). The WAI total score is the sum of the scores obtained from each dimension (7-49 points). Scores below 37 points are referred to as low work ability.

Change in WAI score between baseline (T0) and follow-up (T1) was our primary outcome.

2.3.2. Greene Climacteric Scale (GCS)

The Green Climacteric Scale is a 21-item validated instrument [18] to measure menopausal symptoms. Scoring generates a total score and 4 domain scores (psychological (subdivided into anxiety and depression), somatic, vasomotor and sexual functioning). Responses are scored as follows: 0, not existing; 1, sometimes (symptom exists but is not bothersome); 2, often (bothersome during daily activities); and 3, very often (interfering with daily activities). The GCS total score is the sum of the scores obtained for each domain and ranges from 0 to 63 points; higher scores on all scales indicate experiencing more bothersome symptoms.

2.4 Statistical analysis

Normality of continuous variables was determined using Shapiro-Wilk's test and Kolmogorov–Smirnov test. Categorical variables are presented as numbers with percentages, and continuous variables are presented as means with SDs (normally distributed) or medians with lower and upper quartile (Q1, Q3) (not normally distributed). Delta scores were calculated for change in GCS score (Δ GCS) and change in WAI score (Δ WAI) from baseline to follow-up (follow-up minus baseline).

The relationship between the primary outcome (Δ WAI T1-T0) and change in menopausal symptoms (Δ GCS T1-T0) was analyzed with multiple linear regression in an exploratory analysis. To control for potential confounding effects, age, level of education, body mass index, smoking status, participation in sports during leisure time were included as covariates. These variables were selected as covariates as per previous literature [19]. Additional adjustment for baseline WAI-score was undertaken in a second model. A potential confounder was included in the analyses when a >10% change occurred in the regression coefficient of the variable of interest (Δ GCS) in an univariate analysis. Assumptions of the analysis were

verified by hypothesis tests and inspection of graphs of residuals. Respondents with missing data were excluded from analysis.

To assess the association of the change (Δ) in the different GCS domains (anxiety, depression, somatic, vasomotor and sexual functioning) and Δ WAI, separate univariate linear regression models were run with Δ WAI as dependent variable and Δ GCS anxiety, Δ GCS depression, Δ GCS somatic, Δ GCS vasomotor and Δ GCS sexual functioning entered as independent variables.

Furthermore, we investigated if type of treatment was associated with change in WAI score. For this we created two groups based on the outcome of the usual care provided in the clinic. One group that had been administered HRT as additional treatment, and a second compound group who either had received no additional treatment or was treated with non-hormonal medication and/or non-pharmaceutical therapy, referred to as the non-hormonal treatment group. The created groups were checked for baseline differences in outcome variables or potential confounders using Student's t test or Mann-Whitney U test for continuous measures and Pearson's chi-squared test for categorical data, as appropriate.

Analyses were performed using SPSS (Statistical Package for the Social Sciences, Armonk, NY: IBM Corp) Version 24.0 and p-values < 0.05 were considered statistically significant.

3. Results

Forty-four women completed both questionnaires at baseline (T0) and follow-up (T1). Out of these 44 included women, 13 women returned incomplete questionnaires, leaving 31 women for analysis. Sample characteristics are presented in Table 1. The median age was 52 years, approximately half were perimenopausal, the others postmenopausal. The majority of women were employed in education, health care and administration and were working part-time. At

the time of their first visit, 5 women were on long-term sickness absenteeism. Median time to complete the follow-up questionnaires was 112 days (Q1,Q3 = 61 – 163 days).

3.1 Work ability and menopausal symptoms at baseline and follow up

The majority of women (84%) reported low work ability (WAI < 37 points) at baseline (T0) (M = 30.73, SD = 6.42). Twenty-seven out of 31 women reported higher work ability at follow-up (T1), although 61% of all women still had a WAI-score < 37 points (M = 34.86, SD = 5.98). This is illustrated in Figure 1. One of the 5 women that were on long-term sickness absenteeism at baseline, had resumed her work at follow-up. Of the remaining 4, three reported an improvement in work ability.

All women reported to be less bothered by their menopausal symptoms at T1 (M = 14.73, SD = 6.36) compared to baseline (M = 26.57, SD = 8.69), indicated by a lower GCS total score, as well as lower scores for the different GCS domains (Figure 2).

3.2 Association between change in menopausal symptom reporting (Δ GCS) and change in WAI score between baseline and follow-up (Δ WAI)

Table 2 shows the results of the multivariate linear regression analyses. Change in total GCS score (Δ GCS) was significantly associated with change in WAI score (Δ WAI), also after correction for potential confounders. After additional adjustment for WAI score at baseline, the effect of Δ GCS was no longer significant.

In additional separate exploratory univariate analyses for the outcome variable Δ WAI and change in the different GCS subscales, we found a significant association between Δ WAI and change in the GCS depression domain (Δ GCS depression). The other subscales demonstrated

no significant associations. In multivariate linear regression, this association between Δ GCS depression and Δ WAI remained significant after adjusting for potential confounders, but became non-significant after correction for WAI at baseline. The results indicate that if one of the 5 GCS depression items improved from, for example, '*symptom bothersome during daily activities*' to '*symptom exists but is not bothersome*', the WAI score increased by 0.855 points.

The finding that once WAI at baseline was added, the effect of both Δ GCS and Δ GCS depression was no longer significant is not unexpected. As Δ WAI theoretically depends on not only Δ GCS, but also on the baseline WAI score. In univariate analysis Δ WAI was indeed also associated with WAI at baseline (beta = -0.353, 95% CI -0.597 – -0.109, p = 0.006).

In addition, WAI score at baseline had significant negative correlations with Δ GCS ($r = -0.516$, p = 0.002), as well as with Δ GCS depression ($r = -0.667$, p < 0.001). As a result the final multivariate models did fit the data better than expected by chance, but the individual variables Δ GCS, Δ GCS depression and WAI at baseline, were not statistically significant due to their underlying correlations.

3.3 Change in WAI score and type of care

Women in the HRT group were more bothered by their menopausal symptoms at baseline (M = 28.76, SD = 8.39) than women in the non-hormonal treatment group (M = 21.00, SD = 7.18), indicated by a higher GCS total score. Other baseline characteristics did not differ between the subgroups (Supplemental table).

Women in both groups reported a similar significant change in WAI score from baseline (T0) to follow-up (T1), but no significant association between type of treatment and Δ WAI was found.

4. Discussion

4.1 Main findings

This study demonstrates that in symptomatic menopausal women both menopausal symptoms and work ability improve after treatment directed to alleviate menopausal symptoms, within a short period of time, i.e. three to 9 months. Of the GCS subscales, change in GCS depression was significantly related with change in WAI, although this association was non-significant after correction for WAI at baseline. These variables were highly correlated, as a result their coefficients were not statistically significant separately. However the value of the Δ GCS depression beta coefficient reflects the importance of this variable in explaining Δ WAI.

We found no evidence of association between type of treatment received and change in work ability.

4.2 Comparison with other studies

There is little research into improving menopausal symptoms and the effect on the ability to work. Most of the studies that do exist have another primary outcome than work and are limited by the use of a single question to identify work-specific effects. Our findings are congruent with a recent randomised controlled trial (RCT) performed by Hardy et al [20]. This study showed a positive effect of self-help behavior therapy (SH-CBT) compared to no treatment in women with problematic vasomotor symptoms (VMS) on VMS frequency and problem rating as well as on presenteeism (working while sick) due to menopause. The effect on other work related outcomes was however less evident. Women in the SH-CGT group reported no differences at the end of the study with regard to absenteeism, self-reported job

performance in relation to others or the intention of the employee to leave the organization. As the authors suggest, this could be explained by the short follow-up period (i.e. 16 weeks posttreatment), hence there was insufficient time for changes to occur. Another explanation could be that the majority of women already rated their work performance as very good or excellent at baseline, leaving little room for improvement.

Although vasomotor symptoms are perceived as bothersome and difficult to cope with at work, they do not necessarily result in lower work ability. Symptoms resulting from VMS are more commonly reported as problematic for work performance, i.e. menopausal associated sleep disturbances, resulting tiredness and symptoms like poor concentration, poor memory, feeling low/depressed and lowered confidence [8,21,22]. In the present study the participants reported improvement on all GCS domains. In separate exploratory univariate analyses, the only significant association with change in work ability was found for depressive symptoms, not for VMS. This is in line with above-mentioned studies, since the GCS depression domain covers those items identified as problematic for work performance. This also corresponds to our previous research where the GCS psychological subscale, that includes the depression domain, was the main predictor for variance in work ability in a group of healthy working women [6].

Work ability has a multifactorial nature. According to the biopsychosocial model, a widely accepted model used to better understand the predictors of work ability, work ability is influenced by individual-level psychosocial factors and workplace or organizational factors in addition to the presence of symptoms of a disease or condition [23]. Individual-level psychosocial factors can be divided in attitudes and beliefs (e.g. unhelpful expectations about recovery), behavior (e.g. coping problems), emotional responses (e.g. low mood and aversion to activity) and social support (e.g. a woman's perception that the environment is not supportive) [24]. Workplace or organizational factors cover issues as physical job demands,

job stress and control, ability to modify work and safety and wellness culture of employer organizations. Studies aimed at reducing sickness absence show that workplace interventions are particularly effective to improve work ability. The evidence for interventions aimed at improving individual-level psychosocial factors is in general less strong [25]. Our findings are therefore promising, as in the case of menopause the improvement of emotional responses, i.e. depressive symptoms, does seem to be accompanied by an improvement in work ability.

Recent research on menopause and work is mainly focused on employment conditions and workplace interventions [3,10,11,12,13,14]. Studies addressing individual-level psychosocial factors are lacking. In addition, the main goal of many healthcare professionals treating women with menopausal symptoms is above all to improve VSM. Depression risk is known to increase in the perimenopausal and early postmenopausal period. It is thought that the changing hormonal environment of the menopause transition contributes to the increased risk for perimenopausal depression. A recent study found that administration of transdermal HRT can prevent this transition-related increase in risk for depressive mood [26]. This knowledge, together with the findings of the present study indicate that healthcare professionals should be alert to depressive symptoms in menopausal women. In addition to treatment of VSM, attention should be focused on treating or even preventing these depressive symptoms, in order to improve the quality of (working) life.

4.3 Strengths and limitations

This is the first cohort study that explored the relationship between improvement of menopausal symptoms and improvement in work ability. As a retrospective cohort study, we could not control for which patients were asked to complete the questionnaires, which meant that the enrollment of patients might have been biased by the physicians' estimate if a patient

was willing to make the effort to complete the questionnaires, which is a limitation. Furthermore, the duration to follow-up was variable, which affected the correctitude of this cohort. Women reported better work ability at their follow up visit, independent of what kind of treatment they had received. Hence, we did not find an association between the type of treatment received and change in work ability. This could be a result of this study's small sample size. In addition, given the multifactorial nature of work ability, we cannot be certain that some unknown factors are partly responsible for our findings. Therefore our results need to be interpreted with caution.

4.4 Study implications for research

As with any single group retrospective study, we remain uncertain whether our findings would hold true in a larger, prospective setting. To evaluate whether type of treatment affects these results, an RCT addressing this subject should be performed. Given the pilot nature of this study, the results are sufficiently incentive to conduct such a proof of concept RCT.

5. Conclusion

In conclusion, this study found that treatment aimed at alleviating menopausal symptoms in symptomatic women led to improvement of menopausal symptoms and work ability.

Healthcare professionals should be aware of the impact of menopausal symptoms, and depressive symptoms in particular, on work ability and should not hesitate to offer women appropriate treatment and education about menopause.

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Conflict of interest

Marije Geukes

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Johannes R Anema

Declarations of interest: none.

Mariëlle P van Aalst

Declarations of interest: none.

Renee X de Menezes

Declarations of interest: none.

Henk Oosterhof

Declarations of interest: none.

Ethical statement

This study was approved by the Medical Ethics Committee of the Nij Smellinghe Hospital, Drachten, The Netherlands (REF NH/HdJ/ID 5009).

ACCEPTED MANUSCRIPT

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Tables

Table 1. Demographic characteristics of the participants (n = 31)

Characteristics	n	%	Median	Q1	Q3
Age, years, median – Q1,Q3			52	49	54
BMI, median – Q1,Q3			25.59	21.63	27.99
Highest level of education, n - %					
Low	3	9.7			
Intermediate	18	58.1			
High	10	32.3			
Smoking habits, n - %					
Non-smoker	15	48.4			
Previous smoker	11	35.5			
Current smoker	5	16.1			
Participation in sports, n - %					
(Almost) none	7	22.6			
< 3 times a week	19	61.3			
3-7 times a week	5	16.1			
Time to follow up, days, median – Q1,Q3			112	61	163
Menopausal status, n - %^a					
Perimenopausal	14	45.2			
Postmenopausal	16	51.6			
Employment status, n - %					
Part-time	26	83.9			
Full-time	5	16.1			

Abbreviations: BMI, body mass index; Q1, 25th percentile of the data; Q3, 75th percentile of the data; n, number of women.

^aMissing data n = 1

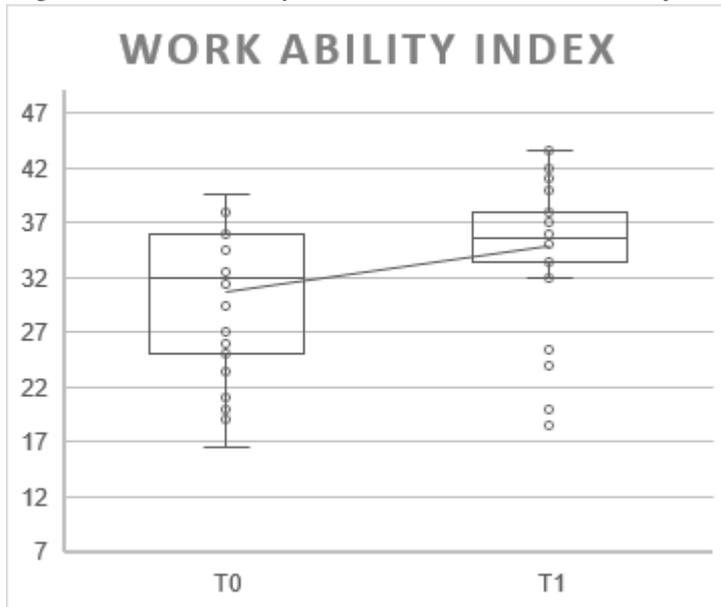
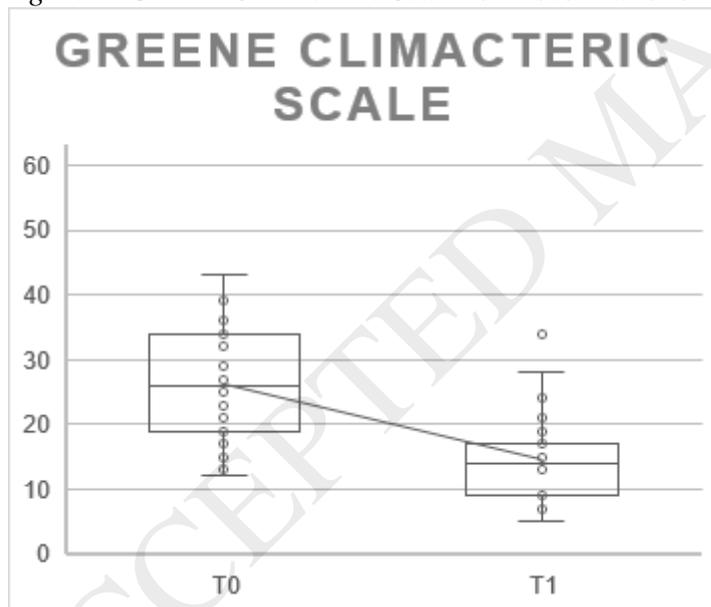
Table 2. Multivariate regression analysis for association between Δ WAI and Δ GCS and Δ GCS depression ($n = 29$)

Variable	β^a	SE	95% CI	Std. β	p	β^b	SE	95% CI	Std. β	p
Constant	29.205	10.605	7.365 – 51.046		0.011	35.118	10.689	13.057 – 57.179		0.003
Δ GCS	0.283	0.107	0.063 – 0.504	.466	0.014	0.172	0.120	-0.075 – 0.420	.283	0.164
			$R^2 = 0.225, p = 0.024$					$R^2 = 0.390, p = 0.015$		
Constant	21.976	10.068	1.241 – 42.712		0.039	28.446	11.467	4.779 – 52.114		0.021
Δ GCS depression	1.251	0.391	0.446 – 2.056	.551	0.004	0.855	0.519	-0.216 – 1.925	.376	0.113
			$R^2 = 0.296, p = 0.008$					$R^2 = 0.405, p = 0.012$		

Abbreviations: SE, standard error; Std., standardized; CI, confidence interval; Δ , delta = change/difference = T1 – T0; GCS, Greene Climacteric Scale; WAI, Work Ability Index.

^aAdjusted for BMI and age

^bAdjusted for BMI, age and WAI at baseline (T0)

Figures*Figure 1. Work Ability Index score at baseline and follow-up**Figure 2. Greene Climacteric Scale total score at baseline and follow-up*

Author Contributions Statement

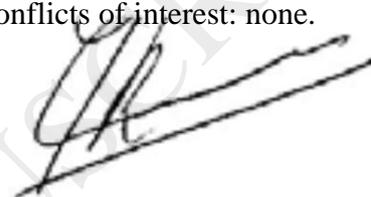
Marije Geukes

I declare that I participated in the development of the study, collection, analysis and interpretation of data and writing of the manuscript. I have seen and approved the final version. I have the following conflicts of interest: none.



Johannes R Anema

I declare that I participated in interpretation of data and editing of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none.



Mariëlle P van Aalst

I declare that I participated in the development of the study, collection of data and editing of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none.



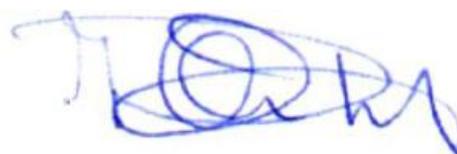
Renée X de Menezes

I declare that I participated in the analysis and interpretation of data manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none.



Henk Oosterhof

I declare that I participated in the development of the study, collection of data and editing of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none.



Data Statement

Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared. Processed data will be made available on request.

ACCEPTED MANUSCRIPT