Research Report

Unilever

Unilever R&D Colworth

Corporate Research **CW 02 0319**

Report Title

A Psycho-social intervention in the workplace: Endocrine and Cardiovascular effects.

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Publication Date: December, 2002

Additional Search Terms

Stress, cardiovascular health, CHD, CVD, cortisol, DHEA, biofeedback.

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Acknowledgements

The study involved a great deal of interaction between different team members. The experimental work across two sites (UK and the Netherlands) was conducted by Vani Naik, Lorraine Butlin, Karen Thethi, Anna Fair, Mark Cobain and Cyrena Tomlin. Analysis of the cortisol and dhea samples was carried out by Duncan Talbot and Lorraine Butlin. Data organisation and analysis was completed by Guy Warner, Peter Murray and Jo Avery.

Assistance with the financing of the study was kindly provided by Dr John Cooper (Chief Medical Officer for Unilever) in Blackfriars.

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Published	**M. Cobain**	**Dec. 2002**

Summary

The links between psychosocial factors and heart disease have been studied for many years, without resolution of the central hypothesis: Does "stress" elevate risk for cardiovascular or coronary heart disease? There are a multitude of reasons for a lack of clarity on this topic ranging from methodological issues (e.g. length of follow up, differing endpoint assessments) and measurement technologies (subjective versus objective measurement of stressors) to a reliance on cross-sectional studies which fail to address issues of causality. The fact that it is a difficult problem does not mean that we should ignore the problem which may contribute significantly to health status. Most research in this area has been conducted within the context of the work environment (e.g. Whitehall studies, the development of the job demand-control model). With this in mind, the Healthy Ageing project collaborated with the Unilever Occupational Health division, and specifically with Dr John Cooper (CMO). One of the Healthy Ageing goals is to discover lifestyle factors and specific interventions that lead to stress reduction and benefits for age-related conditions (e.g. CHD, CVD). Interventions are the most powerful demonstration of causality, yet are the least utilised approach in this area. Similarly, the occupational health division are interested in the efficacy of interventions designed to be employed in the workplace which have health and performance benefits. The collaborative study reported here is a good example of synergy within Unilever – a study designed to deliver benefits both to research and the operating company. The study reported employs a technique known as "biofeedback", in which individuals are trained to master their own cardiovascular physiology "online". Training was provided by Dr Alan Watkins and heart rate monitoring software was loaded onto personal computers. This enabled participants to continue the training over the course of 6 months. Prior and subsequent to training the participants provided a series of measurements (anthropometric, endocrine and subjective measures) against which to assess the impact of the intervention. A control group received no intervention and provided the same measurements at the same time points. Statistical analyses demonstrate within the report a significant increase in DHEA over 3 and 6 months and a significant reduction in blood pressure after 6 months in the intervention group. The control group experienced no beneficial changes over this period. The report also details

the methodological limitations placed on the study and points to improvements that can be made in future studies. These preliminary findings suggest that psychosocial interventions such as these can impact significantly on physiology and should be explored further both in work, clinical and community settings.

Contents

Report

1.0 Introduction

For many years linkages have been made between psychosocial factors and the progression of coronary heart disease (CHD). For example, it has been reported that a combination of high "job demand" and low "job control" is associated with and predictive of future CHD incidence (Sacker et al.,2001), although the nature of the relationship remains controversial. One school of thought is that the association is entirely spurious. Recent studies have raised serious doubts about the validity of the relationship between general psychological "stress" (in particular negative affectivity) and CHD incidence (Macleod et al, 2002). Nevertheless, research remains directed towards understanding the potential mechanisms underlying the relationship between psychosocial factors and heart disease. Several studies demonstrate that psychosocial factors are related to risk of CHD incidence through a mechanism unrelated to traditional risk factors, e.g. blood pressure, cholesterol (Sacker et al.2001). Certainly, there is still considerable variance in CHD incidence that is not explained by the traditional risk factors. Finally, another possibility is that psychosocial stressors act through traditional CHD risk factors when measured appropriately. For example, various job stress measurements have been reported to predict systolic blood pressure increases in cross-sectional and prospective studies (Steptoe and Cropley, 2000; Schnall et al., 1998) when ambulatory blood pressure recordings are taken. A more detailed exploration of these issues can be found in the discussion of this report.

In order to demonstrate that stress is causally related to CHD incidence, through whatever means, there needs to be a clear demonstration that "stress" risk factors are reversible and that these reverses also consequently reduce risk of CHD. Schnall and colleagues (1998) have demonstrated that reductions in job stress are associated with subsequent reductions in systolic blood pressure. Since these reductions in stress were part of an observational study rather than an intervention study they only run in parallel, rather than explain reductions in blood pressure. Clearly the only possible way to resolve these issues is to carry out "stress-reduction" interventions.

An important consideration in measuring "stress" is to have an operational definition so that studies can be conducted. This is a tricky proposition, since numerous attempts to discover "objective" indicators of stress have met with mixed success. One method, used frequently over the last few years is to assess neuroendocrine markers that are reflective of the "stress response", mediated by the Hypothalamic-Pituitary-Adrenal axis. The impact of acute stress on cortisol has been well documented (e.g. Kirschbaum, Pirke and Hellhammer, 1993). Furthermore, parameters of neuroendocrine status have also been utilised in epidemiological studies to good effect. Cortisol levels predict brain atrophy in the elderly (Lupien et al., 1999) cognitive decline in the elderly (Greendale et al., 2000), and are associated with intima media thickness, a marker of atherosclerosis (Eller et al., 2001). In addition, the role of DHEA has also been investigated in epidemiological studies in the context of a range of psychiatric and age related conditions. For example, low levels have been associated with coronary heart disease (Barrett-Connor et al., 1986) and depression (Schmidt et al., 2002). Interestingly, the conjunctive use of cortisol/DHEA ratios are also claimed to be good predictors of age-related and psychological conditions (e.g. Young et al., 2002). Advances in non-invasive measurement techniques now permit measurements to be taken without blood sampling, a factor which has in the past clouded associations with mental state. Therefore evaluations of intervention should include HPA axis hormones as independent variables.

In this paper we report the impact of an "emotional management" program on neuroendocrine measures and blood pressure. The program (*Freeze Framer, Heart Math LLC, USA*) is a commercially available program that has been used in occupational and educational settings, although it typically involves elements of stress reduction used in other studies. Previously, use of this particular technique has been associated with improvements in cortisol, DHEA and blood pressure (McCraty et al., 1998), although this particular study contained no control group and therefore was not a reliable test of stress reduction *per se*. We compared two groups in this pilot intervention, matched for reported stress and age, and assigned to an intervention or control group. These groups were both drawn from members of the Unilever workforce.

2.0 Methods

2.1 Subjects

25 males and females, age range 22-50 were treated as part of the intervention program, whilst 25 individuals were treated as controls. Participants were drawn from the Unilever workforce in the UK and the Netherlands. Participants all gave informed written consent, and the study was reviewed and passed by the Unilever Research Ethics Committee.

2.2 Assessment and Intervention

All participants attended a baseline measurement session, at which they completed psychometric scales, measurements of blood pressure, waist:hip ratio, and weight. They were also given instructions on ambulatory cortisol and DHEA measurements for the following 24 hours. Following the baseline measurement session, participants assigned to the intervention attended a one-day training session as a group whereby they were taught a combination of practical emotional management techniques. These included cardiovascular biofeedback, cognitive re-appraisal methods and relaxation. After the training session each individual was given a piece of software designed to stimulate use of the biofeedback technique. After 5 weeks, the intervention group received a second session, to review the use of the techniques and check on the utility of the software.

Three months after the intervention, participants were asked to attend a repeat measurement session, where they completed identical measures to those taken at the baseline session. Participants assigned to the control condition were asked to attend a baseline measurement session and a second identical measurement session 3 months later, with no active intervention in between test sessions.

2.3 Psychometric scales

Two established psychometric scales were used to establish the impact of training on subjective reported mood changes. The Perceived Stress Scale (PSS;Cohen, 1985) was used pre and post training to assess the effect on “chronic stress”, whilst the Profile of Mood States (POMS) was used to assess a wider qualitative range of moods.

2.4 Neuroendocrine measures

Ambulatory salivary measures of cortisol and DHEA were taken during the 24 hours prior to training, and 24 hours post 3 months of training. Control participants provided the same measurements at the same time. Salivary cortisol was collected by asking participants to chew on cotton salivettes (*Sarstedt*) for a minute, or until saturated. Salivary cortisol measures were taken on awakening and at fixed time intervals. These intervals were 2pm, 6pm, 10pm, and on the following day "awakening", +30 mins, +60mins. Participants were asked to remain in bed at least during the period between awaking and the +30 minute sample. A salivary DHEA measurement was taken at a single time point just before the cortisol "awakening" sample. This sample was taken by means of a "passive drool" sample, collected in a universal tube, and was not collected by use of a salivette to prevent the cotton from interfering with the DHEA assay.

2.5 Cardiovascular/Metabolic measurements

On the baseline day of measurement, blood pressure, waist-hip ratio, and weight measures were taken. Seated systolic and diastolic blood pressure readings were taken 3 times with a 2 minute rest interval between each reading. Waist:Hip ratios were calculated using waist and hip circumference measurements. Body Mass Indices were also calculated for each participant after taking weight and height measurements.

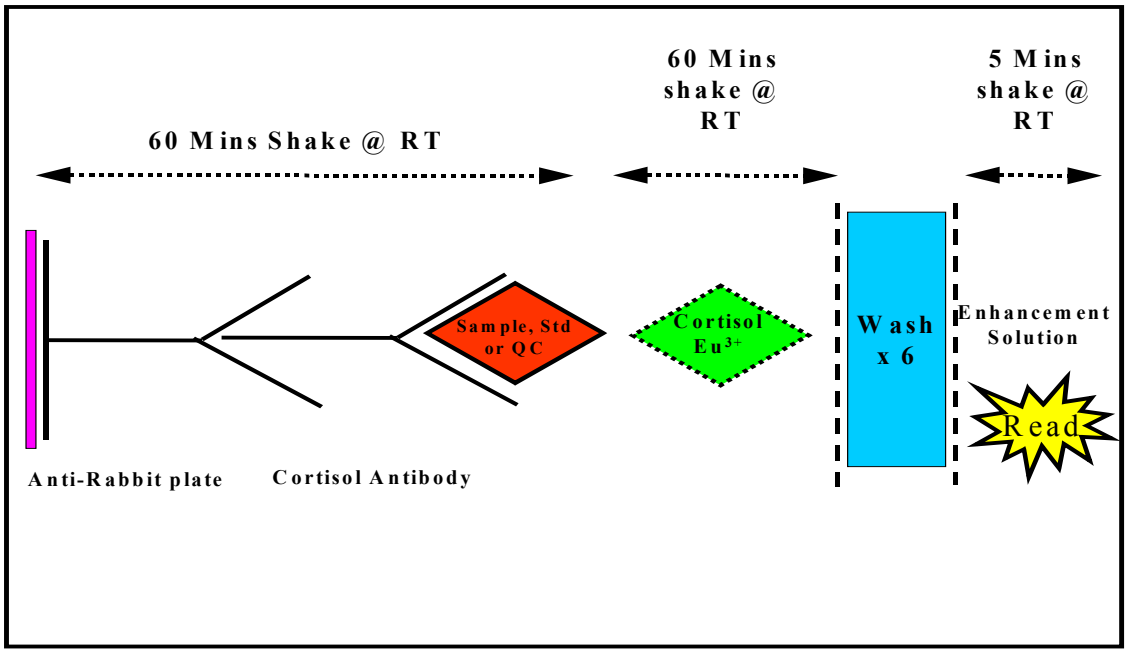
3 months after training identical measurements were taken in both control and intervention groups.

2.6 Neuroendocrine Analysis

2.6.1 Cortisol Assay

Cortisol was assayed by automated fluorescence immunoassay, validated and reported by our group previously (CW02 0290). A schematic diagram is provided for the assay below.

Salivary cortisol AutoDelfia assay format



2.6.2 DHEA (dihydroepiandosterone) Assay

DHEA was assayed using the Salimetrics DHEA Elisa kit cat no. 1201 Break-Apart plate (Salimetrics LLC, State College, PA, USA). All samples were analysed in duplicate alongside provided standards.

2.7 Statistical analysis

In assessing the impact of intervention on all measurements, analysis of covariance (ANCOVA) models were used, with the increase between the phase 1 and phase 2 scores as the response (i.e. phase 2 minus phase 1) and the phase 1 score as the (baseline) covariate. When evaluating the neuroendocrine data, cortisol and DHEA values were log transformed, since this created greater conformity with the statistical assumptions underlying ANCOVA. Cortisol analysis required the determination of area under the curve values, awakening increases (30 mins minus awakening), first morning cortisol, and evening cortisol values. Cortisol/DHEA ratios were constructed from the first morning cortisol sample and the morning DHEA sample. All analyses were carried out using SAS by members of the Colworth Data Sciences group.

3.0 Results

3.1 Psychometric data

There were no significant differences observed between the participant group and the control group in reported mood changes, either through the analyses of the Perceived Stress Scale or the Profile of Mood States questionnaire. Only one sub-scale of the POMS showed a reduction due to treatment ("confusion-bewilderment" scores) which was approaching significance ($F_{1,31}$=3.53, p=0.06).

3.2 Neuro-endocrine data

Analyses revealed that the increase in cortisol post-waking response from phase 1 to phase 2 was significantly different between control and intervention groups ($F_{1,31}$=5.43, p<0.05), however this was due to an increase in the control group (p<0.01), as opposed to a specific lowering response in the intervention group (p=0.45). Analysis of all other cortisol measurements (total AUC, awakening AUC, morning and evening cortisols) revealed no significant difference in between phase 1 and phase 2. Analysis of the DHEA measurements on the other hand did reveal significant differences between the intervention and control group ($F_{1,34}$=7.49, p<0.01). The differences in this case, were specifically due to a significant increase in DHEA between phase 1 and phase 2 (p<0.01; see figure 1). Finally, cortisol/DHEA levels differed between the two groups, at a level which was approaching significance ($F_{1,34}$=2.74, p=0.1).

Figure 1

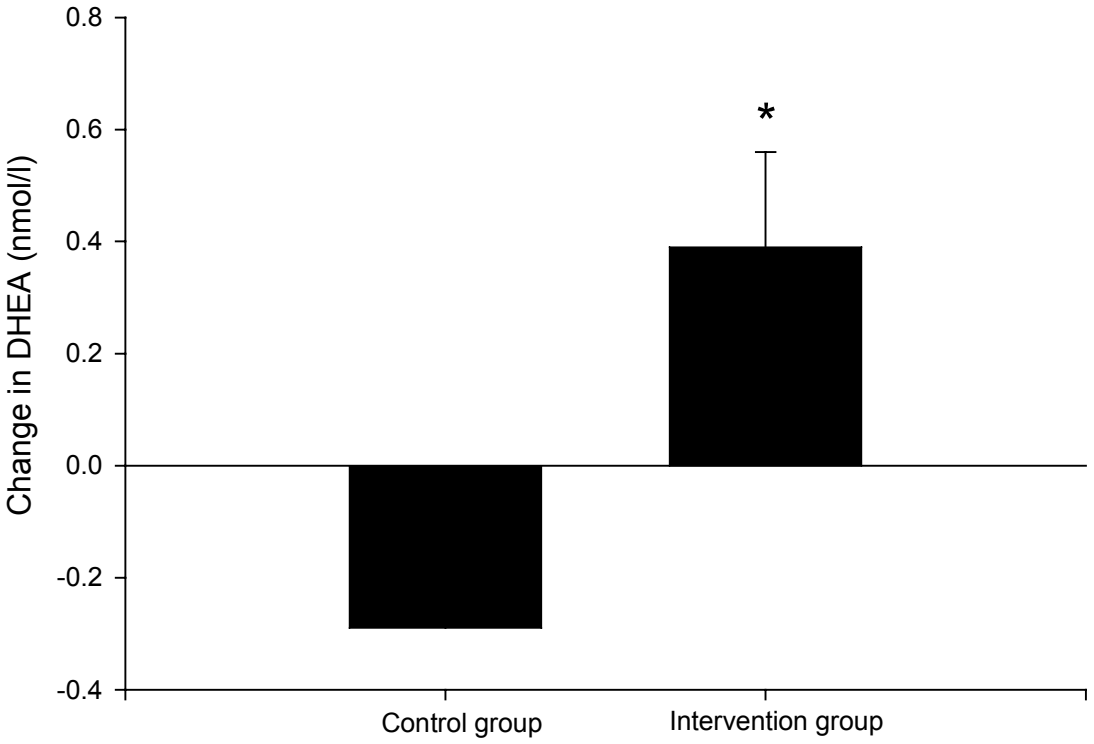


Figure 1: Changes in salivary DHEA (post intervention – baseline) controlled for baseline DHEA levels. * = significantly different at $p<0.05$ level compared to control group.

3.3 Cardiovascular/Metabolic indices

There were no significant differences observed between the treatment and control group in terms of systolic or diastolic blood pressure ($p>0.05$). In addition, there were no significant differences observed between groups in terms of waist:hip ratios. Significant differences were observed however between the groups in terms of weight ($F_{1,36}=4.14$, $p<0.05$, see figure 2) and body mass index ($F_{1,36}=13.27$, $p<0.001$). The differences in BMI observed, were however due to an increase in the control group ($p<0.001$) and not due to a specific decrease in the intervention group ($p=0.61$).

3.4 Six month follow up

Three months after the post-training measurements were taken, participants in the intervention group were contacted again in order to assess the stability of any observed changes witnessed at 3 months. Unfortunately it was not possible to recall the control group, and therefore any effects observed at 6 months post training, could not be compared to control status. However, it was considered worthwhile to collect preliminary data in order to test the stability of within group changes in cardiovascular and neuroendocrine status.

The same measurements were collected on all participants who could be recalled from phase 2 testing. As no control condition was used in phase 3, the only analyses possible were comparisons within the intervention group at the 3 different phases and no inference can be drawn about absolute measurement differences. All analyses were carried out using SAS.

3.4.1 Psychometric data

Similar to findings at phase 2 there were no significant differences between phases 1,2 and 3 in POMS scores or PSS scores. There were, however, non-significant trends to reduced scores across the three time points.

3.4.2 Neuro-endocrine data

Analyses of within condition changes in cortisol revealed a disappointing lack of evidence for stable neuroendocrine changes. There were no significant reductions in either cortisol awakening values across the time points, nor in any of the other cortisol measurements taken. However, consistent with the previous findings, there was a significant increase in DHEA levels across the three time periods ($F_{2,27}=6.26$, $p<0.01$). Furthermore, comparisons between phase 1 and phase 3 revealed a still highly significant difference in DHEA between the two time points ($p<0.005$; see figure 2). There was, in addition, a trend towards a further increase in DHEA levels between phase 3 and phase 2. Analysis of the cortisol/DHEA levels unsurprisingly also demonstrated a significant reduction over the three phases ($F_{2,23}=3.72$, $p<0.05$), with DHEA levels at phase 3 being significantly higher than phase 1 levels ($p<0.05$).

Figure 2

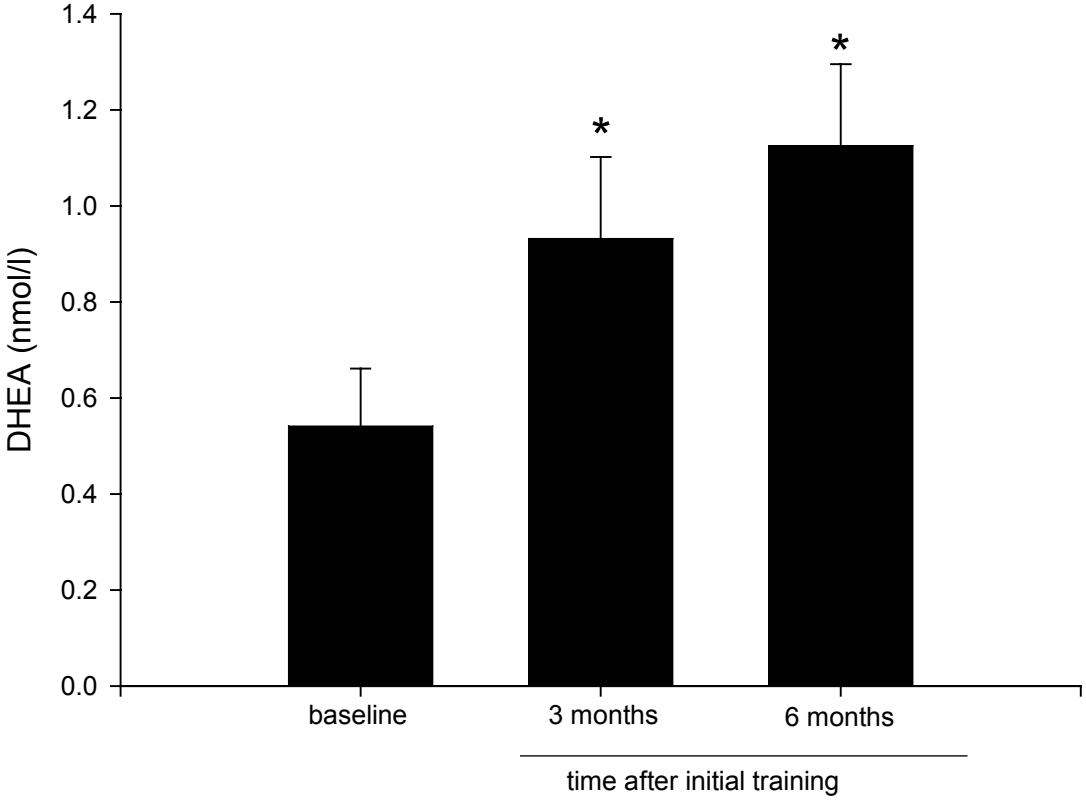


Figure 2: Increases in salivary DHEA in intervention group over time. * = significantly different at $p<0.01$ level.

3.4.3 Cardiovascular/Metabolic indices

In marked contrast to the lack of effect at phase 2, analyses revealed a significant effect of training on systolic blood pressure ($F_{2,31}=3.59$, $p<0.05$). Although contrasts between phase 1 and phase 2 were non-significant ($p=0.37$) there was a significant reduction in systolic blood pressure between phase 1 and phase 3 ($p<0.05$) and phase 2 and phase 3 ($p<0.05$) (see figure 3). No significant reductions were witnessed in measurements of diastolic blood pressure across the 3 phases.

With respect to measures of weight and body shape, there were marked differences between the effects of training at phase 2 and phase 3. Significant effects of training were seen on both weight ($F_{2,31}$=6.65, p<0.01) and waist:hip ratio ($F_{2,31}$=4.65, p<0.01). Analysis of the contrasts between phases, however revealed that significant increases in weight had accrued between phase 1 and phase 3 (p<0.005), whilst reductions in waist:hip ratios were observed between both phase 1 and phase 2 (p<0.005), and phase 1 and phase 3 (p=0.053). The overall trend was an increase in body weight over the course of training, but a reduction in waist:hip ratios.

Figure 3

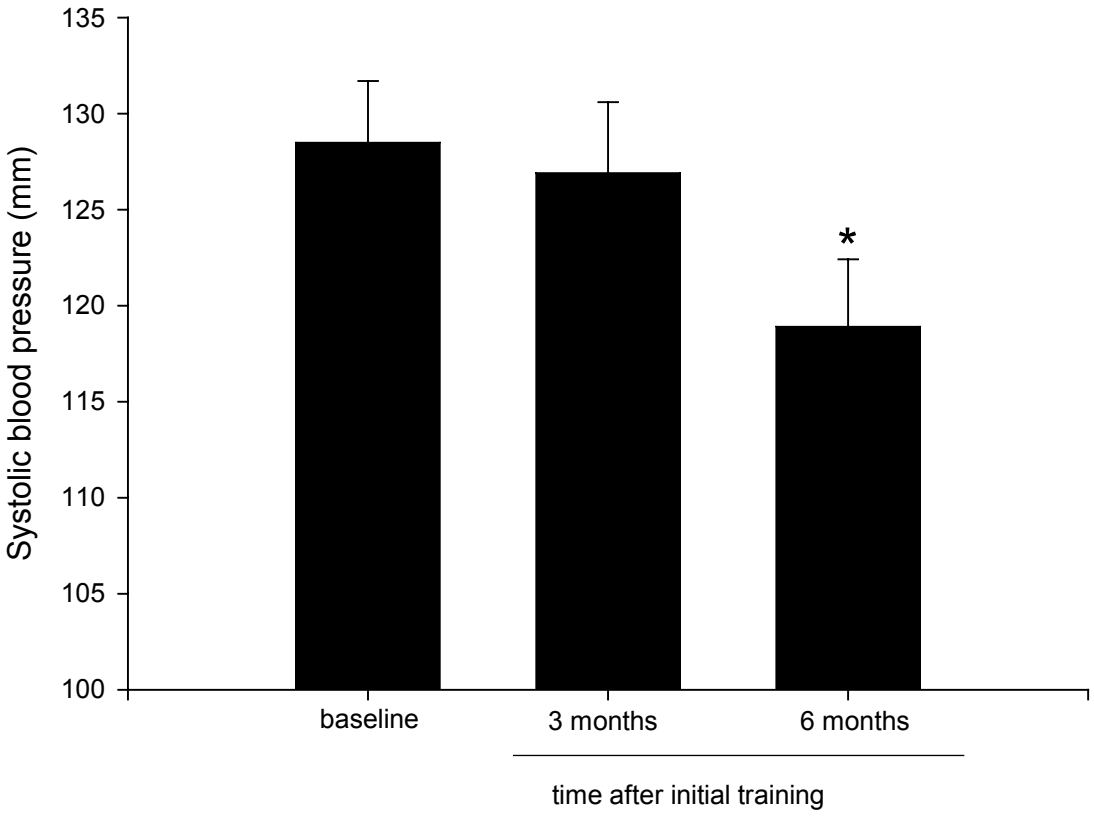


Figure 3: Reductions in systolic blood pressure in intervention group over time. * = significantly different at p<0.01 level.

4.0 Discusssion

The results of this study suggest that providing tools for people to manage emotional control in the workplace can lead to beneficial alterations in stress hormone metabolism and concurrent changes in systolic blood pressure over a 6 month period. DHEA levels were increased by around 70% after 3 months, consistent with, but slightly lower than a previous study (McCraty et al., 1998) where increases of 100% were observed when the same technique was employed. In addition, reductions in systolic blood pressure were also observed after prolonged use of the technique (6 months after training had been initiated). These findings were also supplemented by some suggestive findings that measures of weight and adipose obesity were altered in the intervention group. The remainder of the discussion will address the following points. How important physiologically are the observed changes? Are there any alternative explanations for the data? What are the weaknesses of the study? How can they be improved for future intervention studies?

The importance of the physiological changes depend, in part, on the importance of the steroid hormone DHEA, since these were the most dramatic and immediate changes observed in the treatment group. DHEA and its sulfated form is a steroid hormone that declines with age (Orentreich et al. 1984) and has often been promoted as an "anti-aging hormone". This is in marked contrast to cortisol concentrations that essentially change very little with age (Carvalhaes-Neto et al.2002). The levels achieved by age 60 are approximately one-third of those observed in young adults. However, the association of low levels of DHEA with increasing age may be little more than a biological "clock" marker unless its physiological role is critical. DHEA has been demonstrated to be inversely related to cardiovascular disease in studies such as the Massachusetts Male Ageing Study (Feldman et al.2001), and the Rancho-Bernardo Study (Barrett-Connor et al., 1986), however findings have not been totally convincing (Barrett-Connor and Goodman-Gruen, 1995; Hak et al.,2002) and current opinion favours caution (e.g. Khaw et al.1996). It appears that DHEA is more consistently associated with differences in mortality than morbidity. Recently, lower DHEA levels of male survivors in the Baltimore Health Longitudinal Study predicted mortality. In addition, the only intervention so far to have provided an increase in longevity, calorie restriction, is accompanied by an increase in DHEA levels (Roth et al., 2002). The importance of DHEA may be related to the degree to which low levels of the hormone clusters with other important age-related changes, such as lipid peroxidation (Khalil et al.2000), and insulin sensitivity

(Roth et al.2002, De Pergola, 2002). Therefore, the status of DHEA is one of promise than a mature risk factor for a disease condition. Therefore our findings that DHEA is elevated through training does not constitute health improvement in itself. Health improvements must still be judged on the basis of improvements in known risk factors for morbidity and/or functional outcomes.

One of the well-established risk factors for cardiovascular disease morbidity and mortality is elevated blood pressure. Furthermore, it has recently been established within the Framingham Heart Study data that "high normal" blood pressure levels (i.e. below the threshold for hypertension (140/90) but above normal (120/80)) increases the risk of cardiovascular events (Vasan et al.,2001). In the words of the authors these findings demonstrate *"the need to determine whether lowering high normal blood pressure can reduce the risk of cardiovascular disease"*. In the normal population, it is highly likely that lifestyle interventions will be the safest and most appropriate choice for attempting to lower "high normal" blood pressure. In this study, we demonstrated a blood pressure reduction of around 8mm, which is a real and substantial reduction, taking the population represented by the treatment sample from an almost "high-normal" category to an "optimal" category (<120 sbp). In addition to the cardiovascular risk benefits, blood pressure levels are also linked to improvements in cognitive function (Amenta et al.2002), even in individuals outside the hypertension range (internal data, not shown). Therefore we consider that these preliminary findings are worthy of further investigation, since they potentially add another intervention strategy to those already known to lower blood pressure in unmedicated individuals (reduced sodium intake, aerobic exercise, increased physical activity and weight loss).

It is tempting to speculate that since DHEA and weight related changes occur prior to blood pressure lowering, the therapeutic mechanism may be due to improvements in glucose/lipid metabolism. DHEA has been closely associated with obesity and insulin resistance (Suzuki et al., 1999), both pre-cursors for diabetes. In addition, treatment of insulin resistance with benfluorex leads to normalisation of insulin profiles and elevations of DHEA (Nestler et al.1995). Insulin resistance and related factors have been associated with higher blood pressure levels, even when comparing optimal blood pressure with normal blood pressure levels in young people (Kazumi et al.,2002). Insulin resistance was not measured in this study directly, but DHEA and waist:hip ratio changes would be consistent with improvements in

insulin sensitivity. Future studies should assess the impact of such training on insulin sensitivity/resistance.

Finally, it is possible, however, that the intervention did not work directly by modification of stress-induced physiological or hormonal changes, but perhaps by other routes. For example, by reducing negative health behaviours (poor dietary habits) and increasing positive health strategies (increased physical activity). These effects can often occur unsolicited in treatment groups, as increased self awareness of health issues can act as an intervention. A weakness of this particular study was a failure to monitor these activities prospectively and therefore it is not possible to rule out these factors. A diagram representing the different causal pathways from stressful events to CVD is presented in Figure 4. It is probable that for maximum practical effect, all of these pathways should be targetted, however it would be of benefit scientifically to understand the relative contributions of all. There were of course other weaknesses in the study that detract from the overall findings. The control group could not be followed at the 6 month time point and therefore it is not known whether a similar drop in blood pressure and waist/weight measurements occurred in this group at this time. It is reasonable however to expect that the control group would have maintained the stability in blood pressure measurements seen between baseline and 3 month follow up at the 6 month time measurement. Nevertheless, future studies should continue to follow up both groups equally. In addition, it is not known whether a similar intervention (meditation, progressive relaxation, yoga etc) could have produced an equal benefit on blood pressure responses (e.g. transcendental meditation lowers blood pressure by 9 mm - Wenneburg et al.,1997), although the benefits of various relaxation techniques appear to be less strong (Schneider et al.1995). Therefore, in order to powerfully demonstrate the impact of psychosocial interventions such as this, it is recommended that at least a “sham” intervention group be included that mimics as many non-critical aspects of the intervention as possible. This would reduce the placebo expectancy effect and allow a true comparison of the magnitude of health benefit.

In conclusion, it is evident that there are potential benefits to intervening on a psychosocial level for cardiovascular health. Further validation may come from repeated demonstrations of efficacy in different populations, understanding the mechanism(s) of action, and demonstrating on a larger scale the impact of such interventions in the workplace and beyond.

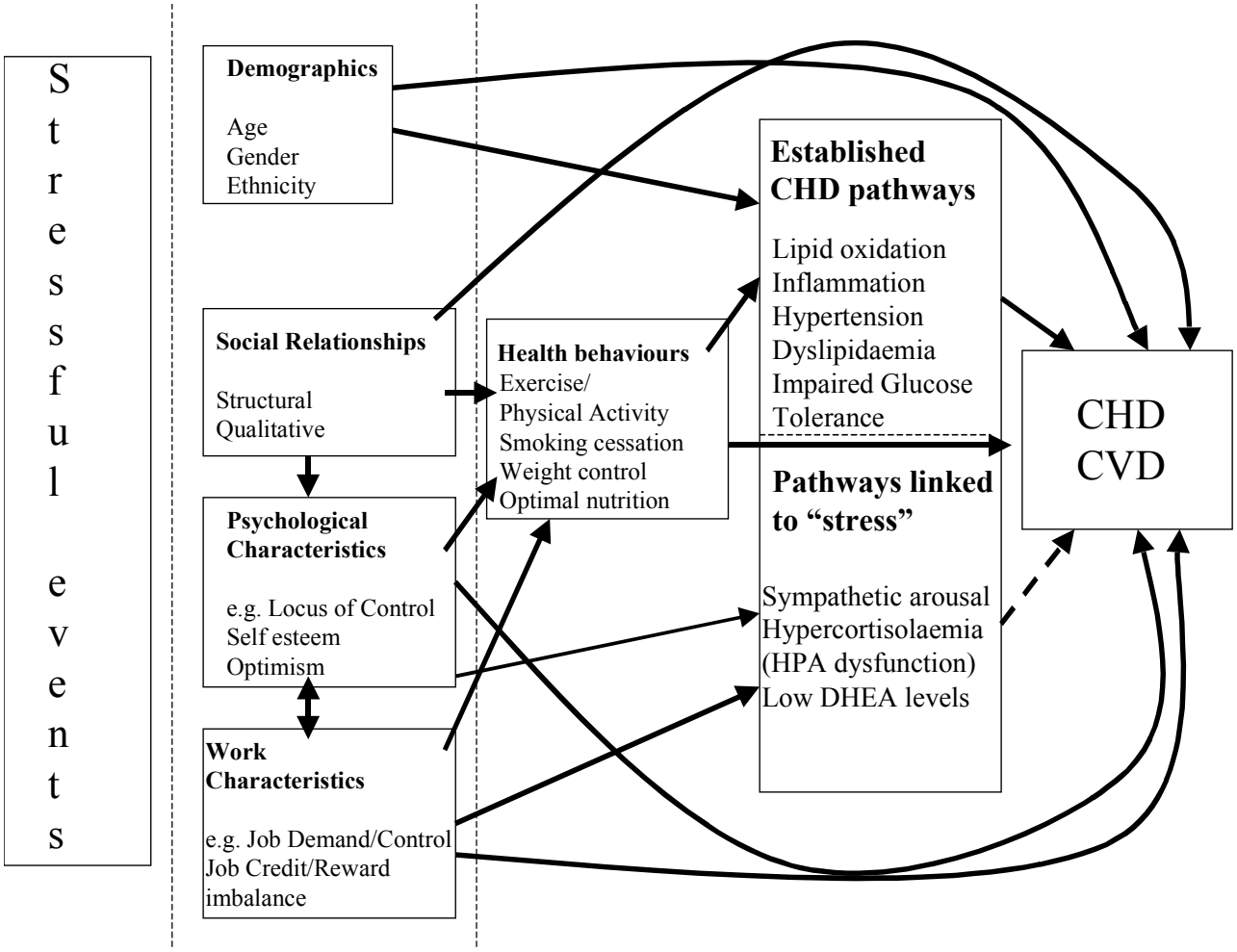


Figure 4: Schematic representation of relationships between "stressful events" and the incidence of heart disease.

→ = established relationship

⇢ = partially established relationship

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J Rycroft
D Talbot
K Thethi
J Thompson
C Tomlin
F van der Ouderaa
G Warner
S Wilson

URPS

W Gibson

URVL

B de Boer
I Gortemaker
C Nijman
P Pauwels
A Thomas
S Wiseman

T Koning
H Zevenbergen

Unilever, Blackfriars

J Cooper

UBF, Crawley

M Drathen

Liptons US

G Meijer

Slim Fast

E de Robertis