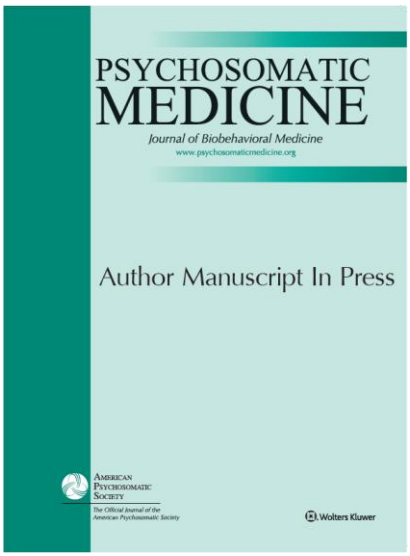

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Authors: Laura Deen, Nadya Dich, Jenny Head, and Alice Jessie Clark Lyth

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Changes in emotional vitality as a predictor of levels and change in allostatic load – longitudinal results from the Whitehall II cohort study

Laura Deen, MSc[1,2], Nadya Dich, PhD[1], Prof Jenny Head, MSc[3], Alice Jessie Clark Lyth, PhD[1]

[1]Section of Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[2]Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg Hospitals, Denmark

[3]Department of Epidemiology and Public Health, University College London, London, UK

Corresponding author: Laura Deen, Department of Occupational and Environmental Medicine, Bispebjerg and Frederiksberg Hospitals, Bispebjerg bakke 23, 2400 Copenhagen NV, Denmark. Email: Laura.deen@regionh.dk; Mobile: +45 27514559

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ABSTRACT

Objective: Increasing evidence has shown an association between reduced psychological well-being and long-term morbidity. However, longitudinal studies addressing potential biobehavioral mechanisms, such as physiological function, are lacking. The aim of this study is to examine the association between changes in emotional vitality on levels and changes in allostatic load (AL), a measure of multisystem physiological dysregulation, as well as its composite risk markers.

Methods: Participants comprised 5,919 British civil servants from phases 3, 5 and 7 of the Whitehall II study. Psychological well-being was operationalized as emotional vitality. AL was measured using 9 biomarkers of the cardiovascular, metabolic, and immune system. Linear mixed-effect models were used to determine the association between changes in emotional vitality between phases 3 and 5 and subsequent levels and change in AL from phases 5 to 7. Generalized linear models were used to address the association between changes in emotional vitality and individual risk markers.

Results: Increase in emotional vitality was associated with a lower mean level of AL, while the AL slope was not markedly affected. Among the included risk markers, only IL-6 was weakly associated with changes in emotional vitality, with a 7% reduced risk of high levels of IL-6 pr. one-unit increase in emotional vitality.

Conclusion: This study found that an increase in emotional vitality was associated with subsequent lower levels, but not rate of change, of AL over time. Further research is needed to address the relationship between trajectories of psychological well-being and physiological dysregulation.

Keywords: Psychological well-being; emotional vitality; Allostatic load; physiological dysregulation.

Abbreviations:

AL= Allostatic load

BP= Blood pressure

BMI= body mass index

HDL= high-density lipoprotein cholesterol

LDL= low-density lipoprotein cholesterol

CRP= C-reactive protein

IL-6= interleukin-6

LME= Linear Mixed Effect

GLM= generalized linear model

RR= risk ratios

CI= confidence intervals

N= number of participants

SD= standard deviation

Introduction

The importance of psychological factors for physical health has long been recognized. However, until recently, research has mainly focused on how negative psychological states are associated with physical health (1–3). Psychological well-being is not the direct opposite of ill-being (4), but reflects the positive components of psychological health and encompasses positive emotions and constructs like life satisfaction, optimism and emotional vitality (5,6). Evidence for an association between psychological ill-being and poor physical health does not necessarily imply that psychological well-being is associated with good physical health. Hence, a growing interest in studying the association between psychological well-being and physical health has emerged, and increasing evidence has linked psychological well-being with better health and longevity (5,7–10).

While previous research has mainly focused on the relationship between psychological well-being and long-term morbidity and mortality, the direction of a possible causal relationship between psychological well-being and health is still not clear and studies addressing potential mechanisms are lacking. It has been suggested that psychological well-being may be linked with better health through multiple biological mechanisms (5), by influencing both the cardiovascular, metabolic and immune system (5,11). Previous studies focusing on individual aspects of physiology have found psychological well-being to be associated with lower levels of inflammatory markers, decreased blood pressure and a healthier lipid profile (12–15). However, it has been argued that the co-occurrence of dysregulation across different body systems, which has been termed allostatic load (AL) (16), better reflects cumulative biological risk and is thus a better predictor of health than the individual risk markers (16,17). AL has previously been linked to poor health (16,18,19), making it an important concept for

understanding predictors of morbidity and mortality. AL has been extensively studied with respect to psychosocial factors (16), but findings have been mixed. While a greater sense of coherence and meaningfulness in life was found to be associated with lower AL after 6 years among Swedish women (20), a recent review, found mixed evidence for an association between psychosocial resources, such as mastery and social support, and AL, with most studies being cross-sectional and with small effect sizes (21). While previous studies have focused on psychosocial factors, studies investigating the relation between psychological well-being and AL are sparse. A recent cross-sectional study found that positive affect was associated with a more favourable AL profile (22). Only one study has previously addressed the prospective association between life purpose, an aspect of psychological well-being, and AL level over a 10-year period (23). This study found that a greater purpose in life predicted lower levels of allostatic load after 10 years follow-up (23).

Given the inability to directly estimate the effect of well-being in a randomized trial, which would be the gold standard, we must rely on observational data. Due to the likely circular relationship between psychological well-being and physiological functioning, assessment of the longitudinal association between *changes* in psychological well-being and subsequent changes in AL may be more instrumental when investigating a potential effect of psychological well-being on AL. As such longitudinal assessment of *changes* rather than a single baseline level of well-being may be considered more appropriate due to the risk of feedback between psychological and physiological functioning. This approach with assessment of changes in exposure rather than a single baseline measure in observational studies has previously been employed to better detangle longitudinal relations (24–26). The longitudinal relation between changes in well-being and AL has not previously been addressed.

Therefore, the aim of our study is to examine the longitudinal association between changes in psychological well-being, measured as emotional vitality, on both AL levels and longitudinal changes in AL, as well as its composite risk markers. Specifically, we hypothesize that an increase in emotional vitality will lead to lower levels of physiological dysregulation and a shallower rate of increase over time."

Methods

Study population

The study was based on data from the Whitehall II cohort study. The original sample, recruited in 1985-1988, included 10,308 British Civil service workers in London aged 35-55 years (27). Follow-up phases have been carried out at two to five-year intervals, including a questionnaire administered at each phase and a clinical examination conducted at odd numbered phases. Further details on the Whitehall II cohort are provided elsewhere (27). The Whitehall II study was approved by the Joint University College London and University College London Hospitals Committees on the Ethics of Human Research and all participants gave informed consent.

Information on psychological well-being measured as emotional vitality was included for the first time in phase 3, and the current study builds on repeated information from phases 3 (1991-1994), 5 (1997-1999) and 7 (2002-2004). A total of 8,815 (85,5% of the original sample) men and women participated in phase 3 of whom, 87% (n=7,666) remained in the study for phase 5. We excluded 998 participants with missing information on emotional vitality at phase 3 and/or 5, and 749 with missing information on one or more covariates at phase 3. This left a total of 5,919 participants eligible for analyses (Figure 1). Participants were between 39 and 63 years old with a mean age of 50 years. The majority were men (71%), reflecting the sex

distribution in the Whitehall II cohort. In the analysis of AL, participants without a full set of risk markers at both phase 5 and 7 were excluded (n=491).

Study design

Information from three successive phases was used to ensure that changes in emotional vitality preceded a change in AL and the individual risk markers. Hence, changes in emotional vitality between phases 3 and 5 were assessed and the AL index were measured at phases 5 and 7. Similarly, in the analysis of individual risk markers, changes in the individual risk markers were assessed between phases 5 and 7. The analyses of individual markers were restricted to individuals without a high-risk level of the individual risk marker at phases 3 and 5 to reduce feed-back mechanisms. The measurement time-points are illustrated in Figure 2.

Changes in emotional vitality

Emotional vitality, one dimension of well-being, was assessed by self-administered questionnaires at phases 3 and 5. Emotional vitality was measured using three items from the Short Form-36: "How much of the time during the past 4 weeks: "did you feel full of life", "have a lot of energy", and "have you been a happy person", with six response categories ranging from 1 = "none of the time" to 6 = "all of the time". At each phase the mean across items was computed resulting in a score from 1-6, with higher values indicating higher levels of emotional vitality. The scale showed good internal consistency at both phases 3 and 5 (Chronbach α=0.84 and α=0.86, respectively). The difference in emotional vitality from phases 3 to phase 5 was calculated and used as a measure of changes in emotional vitality (theoretical range -6 to 6).

Allostatic load

AL was assessed at phases 5 and 7 based on nine biological parameters of the cardiovascular, metabolic, and immune body system: Blood pressure (BP), body mass index (BMI), fasting insulin, fasting glucose, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides, C-reactive protein (CRP), and interleukin-6 (IL-6). Following previous work (28), AL was computed as the number of risk markers exceeding predetermined high-risk thresholds (values below the threshold for HDL). Clinically relevant cut-off points were used where such cut-offs have been established: CRP; 3 mg/L (29), HDL; 1.03 mmol/L (30), LDL; 4.9 mmol/L (30), glucose; 5.5 mmol/L (31), triglycerides; 1.7 mmol/L (30), BP; 140/90 mmHg (32) and BMI; 25 or 30 kg/m^2 (33). Where no established cut-off values exist, distribution-based cut-offs (75th percentile based on baseline values), which is another common practice (16), were used: IL-6; 1.98 pg/ml and insulin; 8.3 uiU/ ml. The same cut-off values were used for both phases. The laboratory procedure used to obtain and analyse the biomarkers are described in details elsewhere (34). Table S1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A611) provides pairwise correlations between the individual risk markers at each phase.

Covariates

Prior knowledge and the methods of directed acyclic graphs were used to identify potential confounders (35). These included age (continuous), sex, occupational level (administrative, professionals and executives, clerical and office support), cohabitation (yes/no), self-reported longstanding illness at baseline (Do you have any longstanding illness, disability or infirmity? (no/yes)), baseline level of alcohol consumption (<1, 1-7, 8-14, 15-21, ≥22 units/week), current

smoking (no/yes), physical activity (above the WHO recommended weekly minimum of 150 minutes of moderate physical activity, 75 minutes of vigorous activity, or an equivalent combination; yes/no). Stress was assessed by one item about the perceived amount of stress within the past four weeks (none, a little, a fair amount, quite a lot or a great deal).

Statistical analyses

To optimize the use of the repeated measures of AL, Linear Mixed Effect (LME) models with a random level and slope for each participant were applied (36). There are some advantages in using a LME model over a linear regression analysis. First, participants with missing information on some of the AL measures do not need to be excluded, thereby increasing the statistical power. Further, the LME allows assessment of the between-subject effect of changes in emotional vitality on average *AL levels* as well as the *rate of AL change* (slope) over time throughout the follow-up period.

First, the main effect of changes in emotional vitality on AL levels was assessed, with time from phase 5 to 7 as the underlying time-scale (models 1a-1c). Subsequently, to determine if changes in emotional vitality affected the rate of AL change, an interaction term between changes in emotional vitality on the one hand and time from phase 5 to 7 on the other was included in the model (models 2a-2c). Initially, models were adjusted for age and sex (models 1a and 2a). Then multiple-adjusted models were fitted to adjust for potential confounding from age, sex, occupational level, marital status, longstanding illness, and baseline level of alcohol consumption, smoking and physical activity (models 1b and 2b). Finally, because of the intertwined nature of well-being and stress, the latter was included in the model in a separate step

of the analyses (models 1c and 2c). A summary of these models is provided in supplemental material (Table S2, Supplemental Digital Content, http://links.lww.com/PSYMED/A611).

In order to examine the contribution of individual risk markers to the overall index of AL, the association between changes in emotional vitality and subsequent increases in individual risk markers from normal to high-risk levels between phases 5 and 7 among individuals with normal levels at both phase 3 and 5 was assessed. Individual generalized linear models (GLM) with a Poisson distribution and log link were applied, so the estimates can be directly interpreted as relative risk ratios (RR) (37). Robust 95 % Confidence intervals (CIs) were generated using the Huber/White modified sandwich estimator of variance. First, models were adjusted for age and sex, then multiple-adjusted models were fitted to adjust for potential baseline confounding from age, sex, occupational class, marital status, longstanding illness, alcohol consumption, smoking and physical activity. Finally, stress was added in an additional step. All analyses were further adjusted for length of follow-up between potential changes in emotional vitality at phase 5 and changes in the risk marker in question at phase 7.

In sensitivity analysis, the analyses of AL were restricted to a healthy sub-population without longstanding illness at baseline, in order to minimize the risk of reverse causation. Further, when studying AL medication use may be a concern, since this may alter biomarker level and therefore analysis adjusting for self-reported baseline use of prescribed medicine was performed. Following another common method of operationalization of AL, a sub analysis with cut-offs based on the 75^{th} percentiles (IL6; 1.98 pg/ml, CRP; 1.74 mg/L, HDL; 1.67 mmol/L, LDL; 5.02 mmol/L, glucose; 5.5 mmol/L, insulin; 8.3 uiU/ ml, triglycerides; 1.74 mmol/L, BP; 129/86 mmHg and BMI; 26.96 kg/m^2) was undertaken for the measure of AL. Further, in order to examine whether a change in emotional vitality affected a concurrent change

in AL, an analysis of the effect of changes in emotional vitality on concurrent changes in AL from phase 3 to 5 was conducted. Finally, analyses stratified by baseline AL level was conducted to account for potential differences in baseline level of AL.

Results

Changes in emotional vitality were normally distributed with a range from -4 to 4, a mean of 0.04 and a standard deviation of 0.90. Baseline characteristics of the study population according to changes in emotional vitality are shown in table 1.

Relative to those with a positive change in emotional vitality, participants with a negative change in emotional vitality were slightly younger, more likely to be female, less likely to be living alone and to be at an administrative occupational level. Additionally, fewer participants with a negative change reported a high-risk alcohol consumption, were physical inactive, had perceived stress and they had a higher mean emotional vitality level relative to those with a positive change.

Changes in emotional vitality and allostatic load

Fifty eight percent of the sample had AL measures (with full biomarker information) for phase 5 and 7 and 92% had AL measures for at least one of the two phases. The AL scores ranged from 0-8 at phase 5 with a mean (SD) of 2.30 (1.78), meaning that each participant had on average 2.30 risk markers above the high-risk cut-offs. At phase 7 the range was 0-9 with a mean (SD) of 2.57 (1.82).

Table 2 presents the estimates of fixed effects for the LME model. The results showed that an increase in emotional vitality between phases 3 and 5 was inversely associated with mean AL levels throughout phases 5 and 7. As seen in table 2, a one-unit increase in emotional vitality was associated with a 0.11 lower mean level of AL (95% CI=-0.16 to -0.06) in the multiple adjusted model. This estimate is comparable in size with the effect of being two years older in our data.

To assess if changes in emotional vitality not only affected AL levels, but also the slope of AL, we further tested an interaction of changes in emotional vitality with time from phase 5 to phase 7. In both the unadjusted and the multiple adjusted model, changes in emotional vitality did not markedly affect the slope of AL. Thus, the rate at which AL increased between phases 5 and 7 did not depend on preceding changes in emotional vitality. Additional adjustment for stress did not markedly alter the estimates of either AL level or slope.

Restricting the analyses to participant without a longstanding illness at baseline did not change the estimates markedly, nor did the analysis adjusting for baseline prescribed medication use. Sub-analyses using high-risk cut-offs based on the 75th percentiles yielded results similar to the main analyses. Further, analysis of the effect of a change in emotional vitality on concurrent changes in AL from phase 3 to 5 did not affect the conclusions of the main analysis noticeably. Lastly, the analysis stratifying by baseline AL level suggested that the association between a change in emotional vitality and AL levels was strongest among the subset with higher baseline AL levels, thus implying that those starting out with a more adverse physiological function are most sensitive to changes in emotional vitality (Table S3, Supplemental Digital Content, http://links.lww.com/PSYMED/A611).

Changes in emotional vitality and individual risk markers

The proportion of individuals who experienced an increase in individual risk markers from normal to high-risk levels between phases 5 and 7 ranged from 1.6% for HDL to 34% for IL-6. Table 3 presents the estimates from the GLM model. Among the included risk markers, changes in emotional vitality was only associated with IL-6, with a one unit increase in emotional vitality from phase 3 to 5 being associated with a 7% lower risk of exceeding the high-risk cut-off of IL-6 between phase 5 and 7 (RR=0.93, 95% CI:0.87-1.00). Again, additional adjustment for stress had only minor effect on the estimates.

Discussion

The present study used data from a large longitudinal cohort study to investigate the effect of changes in emotional vitality on levels and slope of AL, a cumulative measure of physiological dysregulation. We found that an increase in emotional vitality predicted lower levels of AL but did not affect the subsequent rate of change in AL over time. No previous study has examined the effect of changes in emotional vitality on AL, but a cross-sectional study found that positive affect was associated with lower AL levels (22). This cross-sectional finding is in line with the results of a previous study where purpose in life measured at one time-point was seen to predict lower levels of AL at a 10 year follow-up (23). By looking at changes in emotional vitality, this study adds to this by providing evidence on the effect of changes in emotional vitality on AL levels. While evidence on the relationship between positive psychological measures and AL is scarce, the relationship between negative emotions and AL have been studied to a wide extend, and previous studies in the Whitehall II cohort have suggested that factors like work stress and negative emotional response to major life events are

associated with higher levels of AL over time, but not the rate of AL change (28,38). However, since psychological well-being represents something more than merely the opposite or absence of ill-being, an association between negative emotions and AL does not indicate that psychological well-being is associated with physiological functioning and the current study thereby supplements this by showing an association between changes in emotional vitality and subsequent level of AL.

Further, we found that an increase in emotional vitality was associated with a lower risk of increases in IL-6, but not associated with exceeding the high-risk thresholds of cardiovascular and metabolic risk markers. This is supporting the findings of previous cross-sectional studies, which have uniformly reported a negative association between different aspects of well-being and IL-6 (39–41), and one longitudinal study of 340 elderly men, which found higher overall optimism to be associated with lower levels of, but not changes in, IL-6 over 11 years follow-up (12). However, unlike the current study, these previous studies did not assess the potential effect of changes in well-being and is thus not directly comparably.

A number of previous studies have found an association between aspects of psychological well-being and risk markers of the cardiovascular (14,42–44) and metabolic (15,39,43,45) body systems. We could not support these findings in longitudinal analyses of changes in emotional vitality and later changes in risk markers. Failure to replicate previous results in a longitudinal design might suggest that a previously found cross-sectional associations are not causal.

The relationship between well-being and physiological functioning is likely to be bi-directional. Our design, whereby we assessed the changes in emotional vitality and their

association with subsequent AL levels and changes in AL, aimed to contribute to disentangling the temporal relation between changes in well-being and physiological functioning. The current study did not find strong support for an effect of changes in well-being, in particularly on changes in AL. In other words, people who experienced increases in emotional vitality accumulated the physiological wear and tear, as indexed by AL, at the same rate as those whose emotional vitality remained stable or declined. One of the reasons why we did not see an effect of changes in emotional vitality on changes in AL could be due to short-term reversible effects of emotional states on physiological functioning. In other words, the changes in emotional vitality might have affected risk marker levels simultaneously, but this did not translate into any long-term changes that the present study was designed to capture. Future studies with more fine-grained time resolution may be helpful in exploring this further.

Strengths and limitations

Some limitations of the current study merit attention. First, well-being is a multifaceted construct, which alongside with emotional vitality includes such factors as life satisfaction, positive affect and purpose in life. Since the current study assessed changes in well-being, items measuring aspects of well-being needed to be available for two consecutive phases, and therefore only one facet of well-being, emotional vitality, was included in the current study. Emotional vitality has, however, been found to have good face validity and strong correlations with other aspects of well-being (10). Further, emotional vitality was based on a crude measure consisting of only three items from the short form-36. Previous studies in the Whitehall II cohort used two additional items (10,42), however due to the focus on changes in the current study, items had to

be available at two consecutive phases, resulting in only three available items. Use of more comprehensive scales of emotional vitality could have yielded different results.

Second, emotional vitality was self-reported in the current study, which might have resulted in some misclassification. However, since the focus was on changes in emotional vitality instead of emotional vitality level at a single time-point, reporting bias may be of less concern. If we assume that the reporting bias remains stable across phases participants would remain in the same category of emotional vitality if no real change in emotional vitality had occurred. As such, a reported change in emotional vitality is less likely to be the result of reporting bias, and more likely to reflect a real change in emotional vitality.

Third, a change in emotional vitality may depend on other circumstances, such as major life events, which might also cause a change in AL risk markers. Since no information on major life events was available in the included phases of the Whitehall II cohort it was not possible to account for this, and thus it cannot be ruled out that this may confound the relationship between emotional vitality and AL.

Fourth, there is no universally accepted method of quantifying AL in empirical studies (46), and a different operationalization of AL might have altered the results. The sum of pre-determined high-risk cut-offs for the individual biomarkers based on existing literature was used to measure AL in the current study. This approach enables implementation of the results in clinical practice and strengthens the comparability across studies. Another common approach is the use of distribution-based cut-offs with values above the 75th percentile considered to be high-risk. This approach ensures a certain degree of power but limits the comparability across studies. Sensitivity analyses based on cut-offs with values above the 75th percentile considered to be

high-risk yielded similar results as the clinically based cut-offs used in the main analyses. Further, previous studies comparing these approaches have yielded similar results (38). Additionally, inclusion of risk markers in the AL index varies and some previous studies have also included endocrine measures, such as cortisol. However, no measure of cortisol was available in the included phases of Whitehall II. Studies have found associations between higher levels of well-being and lower cortisol levels (47), and the inability to include cortisol might have attenuated the effect of emotional vitality on AL.

Lastly, participation rates in Whitehall II varied between 87% and 72% of those invited in the included phases, with non-responders generally being more likely to be women and from low socioeconomic groups. Whether they differed in terms of well-being and physiological function is not known. Further, due to the focus on changes in emotional vitality, only continuous participants of phases 3 and 5 were included. The differences in baseline characteristics between the analytic sample and excluded participants indicate that the continuing participants in general were younger, healthier and with a higher socioeconomic status. Further, they were more likely to have an increase in emotional vitality and lower AL level over time than non-eligible participants. Thus, due to the restriction to continuous participants, selection bias may have affected the result and might have resulted in underestimation of the longitudinal relationship between changes in well-being and subsequent changes in physiological functioning.

However, our study also has several strengths, including the use of longitudinal data with frequent repeated measures, which provide unique information on the relationship between changes in emotional vitality and subsequent level and changes in AL. The collection of objective measures of several risk markers allowed for assessment of changes in AL, thus contributing to the sparse evidence on the association between well-being and systemic

dysregulation. Combining multiple biological measures into one cumulative index of physiological dysregulation has been widely accepted, and the AL index is considered a more comprehensive measure of physiological changes than considering any individual biomarker in isolation (18,19,48). Finally, the Whitehall II study includes information on several important demographics, socioeconomic, biological and lifestyle factors, which enabled a thorough adjustment of potential confounders.

Considering the established role of AL as a predictor of disease and mortality, the present study contributes with further knowledge on psychosocial factors, which may have an effect on the rate of accumulation of physiological wear and tear. We did not find that prior changes in emotional vitality increase or decrease that rate. Further research is needed to address the possibility that trajectories of well-being and physiological dysregulation have a concurrent effect on one another.

Conflict of interest statement

The authors have no conflict of interest to report.

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FIGURE CAPTIONS

Figure 1. Flowchart illustrating the baseline study population

Figure 2. Measurement time-points for the effect of changes in emotional vitality on subsequent level and changes of AL and individual risk markers.

Figure 1

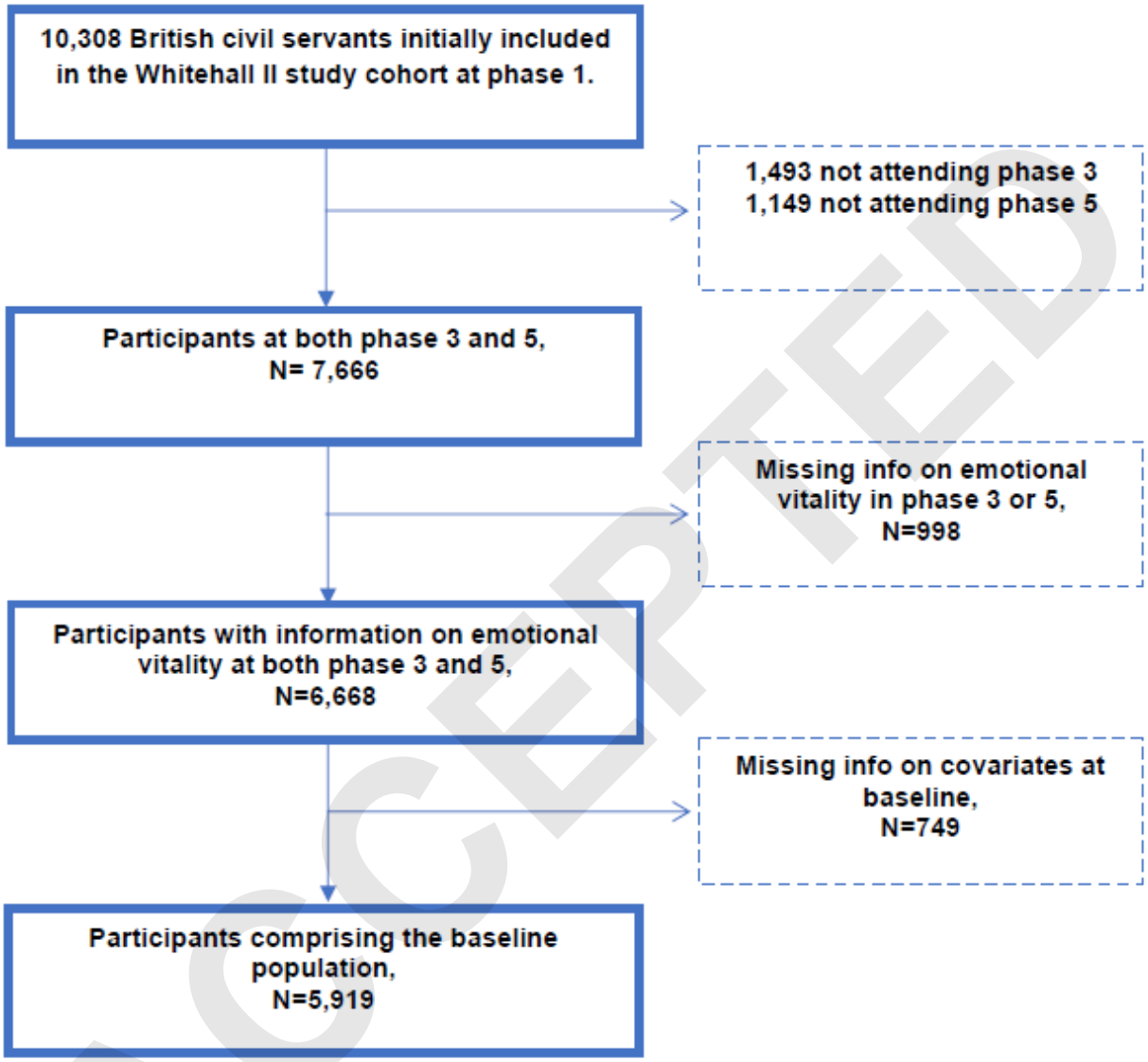

Figure 2

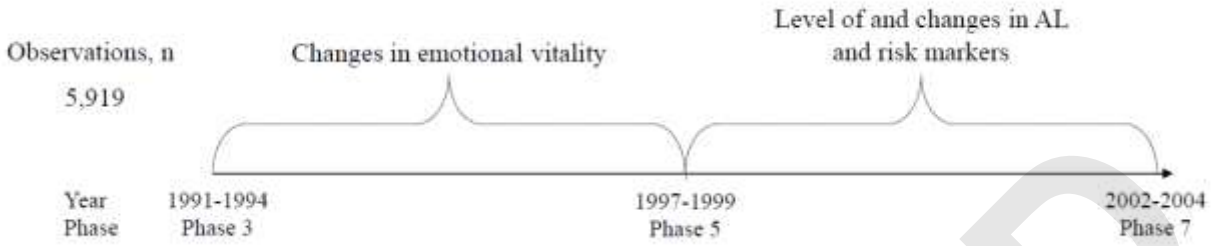

Table 1. Baseline characteristics of the 5,919 participants from the Whitehall II study according to changes in emotional vitality.

	Total population	No change in emotional vitality	Positive change in emotional vitality	Negative change in emotional vitality
All participants, N	5,919	1,189	2,516	2,214
Mean allostatic load (SD)[a]	2.3 (1.8)	2.2 (1.8)	2.2 (1.8)	2.3 (1.8)
Mean emotional vitality level (SD)	3.9 (1.0)	4.2 (1.0)	3.5 (1.0)	4.2 (0.9)
Mean age (SD), years	49.5 (6.0)	49.8 (6.2)	49.9 (5.9)	48.8 (6.1)
Women, %	28.9	26.2	28.8	30.5
Living alone, %	23.2	18.8	24.5	21.5
Occupational level, %				
Administrative	42.0	45.3	43.7	38.2
Professional/Executive	45.5	42.8	45.4	47.2
Clerical/Support	12.5	11.9	11.0	14.6
High risk alcohol consumption[b], %	17.7	16.9	19.2	16.5
Smokers %	11.5	10.0	11.8	11.9
Physically inactive[c], %	45.4	43.3	47.7	44.0
Stress, %				
None	6.3	8.2	4.8	7.0
A little	38.5	40.4	35.6	40.7
A fair amount	30.7	29.9	31.5	30.4
Quite a lot	18.4	16.5	20.8	16.8
A great deal	6.0	5.0	7.3	5.2
Longstanding illness, %	34.0	29.8	34.9	35.2

[a]Based on the 4,709 participants with complete information on AL at baseline. [b]≥14 units/week for women and ≥21 units/week for men. [c]Physical activity below the WHO recommended minimum.

Table 2. Effect of changes in emotional vitality from phase 3 to phase 5 on average AL level and the rate of AL change (slope) from phase 5 to phase 7: estimates and 95% confidence intervals (CI) for the fixed effects.

	Adjusted for age and sex[2]	Multiple adjusted[3]	Multiple adjusted[3] + stress
Mean difference in the level of AL	-0.11 (-0.16 to -0.06)	-0.11 (-0.16 to -0.06)	-0.11 (-0.16 to -0.06)
Effect on the rate of AL change[1]	-0.05 (-0.15 to 0.06)	-0.07 (-0.17 to 0.04)	-0.07 (-0.17 to 0.04)

[1] Data present estimates for the interaction term between changes in emotional vitality and time from phase 5 to 7.

[2]Adjusted for age, sex and follow-up.

[3]Adjusted for age, sex, follow-up, occupational class, marital status, longstanding illness, alcohol consumption, smoking, physically activity.

Table 3. Changes in emotional vitality from phase 3 to phase 5 and the risk ratios (RR (95% CI)) of exceeding the high-risk cut-off of individual risk markers between phase 5 and phase 7 among participants without high-risk levels of the risk marker in question at phase 3 and 5.

Risk markers	No. of cases / N	Adjusted for age and sex[1]	Multiple adjusted[2]	Multiple adjusted[2] + stress
Immune system risk markers				
IL-6 (≥1.97 pg/mL)	676 /2,659	0.93 (0.86-0.99)	0.93 (0.87-1.00)	0.93 (0.87-1.00)
CRP (≥3 mg/L)	424 / 3,075	0.99 (0.90-1.08)	1.00 (0.91-1.09)	1.00 (0.91-1.10)
Metabolic risk markers				
HDL (<1.03 mmol/L)	57 / 3,518	1.06 (0.84-1.33)	1.01 (0.82-1.26)	1.01 (0.79-1.30)
LDL (≥4.8 mmol/L)	66 / 2,897	1.01 (0.77-1.32)	1.03 (0.79-1.34)	1.02 (0.78-1.33)
Glucose (≥5.5 mmol/L)	680 / 2,452	1.02 (0.95-1.10)	1.02 (0.95-1.10)	1.02 (0.95-1.10)
Insulin (≥8.3 uiu/ml)	467 / 1,810	0.93 (0.85-1.01)	0.93 (0.85-1.02)	0.94 (0.86-1.03)
Triglycerides (≥1.7mmol/L)	296 / 3,001	0.97 (0.86-1.10)	0.98 (0.87-1.10)	0.97 (0.86-1.09)
Cardiovascular risk markers				
BP (≥140/90 mmHg)	495 / 3,262	0.96 (0.87-1.05)	0.95 (0.87-1.05)	0.97 (0.88-1.06)
Anthropometric risk markers				
BMI (≥25 or ≥ 30 kg/m^2)	577 / 3,872	1.01 (0.93-1.10)	1.02 (0.93-1.11)	1.01 (0.92-1.10)

[1]Adjusted for age, sex and follow-up.

[2]Adjusted for age, sex, follow-up, occupational class, marital status, longstanding illness, alcohol consumption, smoking, physical activity.