Psychological stress, body shape and cardiovascular events: Results from the Whitehall II study

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ABSTRACT

Background and aim: It is known that persistent psychological stress predicts changes in body shape in two different ways: some stressed people lose weight, others gain weight. It is also known that persistent psychological stress predicts adverse health events. But it is unknown what role the body shape plays in this particular network of relationships. We therefore analyzed the Whitehall II dataset to relate body shape to stress and health risk.

Methods: Data of 4969 men and 2138 women from the Whitehall II cohort were analyzed. Psychological stress (General Health Questionnaire) was measured three times in the years 1991 till 2001. Body shape (BMI, waist and hip circumferences) was measured in the years 1991 till 1994. Childhood adversities were retrospectively assessed by questionnaire. Outcomes included the incidence of non-fatal or fatal CHD events (coronary heart disease) collected up to the years 2012 and 2013 and all-cause mortality collected up to July 2015. Cox proportional hazard models were conducted to estimate the relation between psychological stress and CHD events or all-cause mortality.

Results: There was an increase in the expected hazard to develop CHD with high psychological stress (men: Exp (B) = 1.25 (1.06–1.47); P = 0.008; women: Exp (B) = 1.34 (1.05–1.70); P = 0.017). We found a clear dose-response relationship for the association between psychological stress and CHD events in both genders. That is, subjects with consistently high psychological stress in all assessments had a 2.4-fold (men) or 2.3-fold (women) higher risk for later CHD events compared to never-stressed subjects. Moreover, subjects with a high sum score of all 13 childhood experiences had a 10% increased hazard to develop fatal or non-fatal CHD events in adulthood. Although we could not find stress or BMI linked to all-cause mortality, the waist-to-hip ratio contributed to the risk of all-cause mortality in both genders (Exp (B) = 34.66 (6.43–186.92); P < 0.001 for men; Exp (B) = 60.65 (9.33–394.22); P < 0.001 for women).

Conclusion: This analysis supports the notion that psychological stress and childhood adversities are associated with the risk of fatal or non-fatal CHD events. When this relationship is analyzed in more detail, the Whitehall II dataset provides further insights into the role of body shape. That is, stress is also related to changes in body shape, with waist size in particular predicting higher all-cause mortality.

1. Introduction

Psychological stress occurs in individuals who are uncertain how to safeguard their future physical, mental and social well-being [1]. If uncertainty cannot be resolved, prolonged psychological stress can lead to an allostatic load that contributes to adverse biological effects on the body and brain [2]. Indeed, psychological stress has been shown to predict changes in body shape [3–5] and adverse health outcomes [6–17].

It is known that prolonged psychological stress predicts changes in body shape in two divergent ways [3–5,18,19]. More specifically, persistent psychological stress was associated with the risk of body mass loss in some people and the risk of body mass gain in others [3,5]. Whether and how individuals show changes in their body shape when exposed to stress depends, among other things, on their ability to show habituation, i.e. repetition-induced attenuation of response

(neuroendocrine, cardiovascular, neuroenergetic and emotional) [1]. In accordance with the aforementioned findings on stress and body shape, we previously reported that psychological stress was associated with an increased risk of developing the 'wide-waisted phenotype', while psychological stress combined with low autonomic variability (as a possible sign of habituation) was associated with an increased risk of developing the 'corpulent phenotype' [4].

It is also known that prolonged psychological stress results in adverse health outcomes. Several heterotypic stressors from different stressful environments such as work, partnership and neighborhood expose people to the risk of adverse outcomes. Moreover, exposure to adverse experiences during childhood is known to increase the lifelong risk for coronary heart disease (CHD) [20,21] and mortality [22,23]. Exposure to occupational psychosocial stress defined as job strain or low control or chronic work stress increased the risk for CHD in several studies [7,16]. Using not just one single stress factor, the Women's Health Initiative Observational Study showed that higher stressful life events were associated with higher incident CVD (cardiovascular disease) over an 18.0 years follow-up [9]. Likewise, participants in the Whitehall study who found stress to be severe or extremely damaging to health had an increased risk of cardiovascular disease [11]. The general health questionnaire as a measure of psychological stress was found associated with an increased CHD incidence [12,13,15] or even mortality [10,24]. The latter association of psychological stress and mortality was also confirmed by other studies [8,14,17,25,26], whereas one study did not find any association between psychological stress and mortality [27].

The above data provide important insights into the association between psychological stress, body shape changes and adverse health outcomes. However, an integrative approach is still missing. To the best of our knowledge, no attempt was made so far to construct an overall picture of psychological stress as a fundamental cause for both, body shape changes and health risk. Using the Whitehall II data, we therefore investigated the multivariate relationships between psychological stress (both during childhood and adulthood), coronary heart disease and all-cause mortality, focussing specifically on the role of body shape in these associations. In addition, we aimed to gain a more comprehensive understanding of psychological stress and its consequences by searching the literature for evidence from randomized controlled trials, which may allow causal inference regarding the relationships between stress, body shape and health risk.

2. Methods

2.1. Study population

The Whitehall II study is a large ongoing study that investigates determinants of health in British civil servants since 1985. Since this first phase of data collection in 10,308 participants, data have been assessed every two to five years. First measures of psychological stress were assessed in phase 3 (years 1991 till 1994). In phase 3, a total number of 8815 civil servants participated (6057 men and 2758 women). Of all participants in phase 3, complete data regarding psychological stress, outcome measures (fatal or non-fatal CHD events as well as all-cause mortality) and body shape were available from 4969 men and 2138 women; these subjects were thus included in our study. There was a slight participation bias, in that men included in our analysis were younger compared to men excluded from our analysis (49.58 ± 5.96 vs. 51.44 ± 6.08 years; P < 0.001). The same applied to women. Women included in our analysis were younger compared to women excluded from our analysis (50.54 ± 6.09 vs. 52.84 ± 6.17 years; P < 0.001). Participants gave fully informed consent to participate in the study and ethical approval was obtained from the University College London committee on the Ethics of Human Research.

2.2. Assessment of psychological stress

As described previously [4], psychological stress in phase 3 (years 1991 till 1994), phase 5 (1997–1999) and phase 6 (2001) was assessed using the General-Health-Questionnaire (GHQ-30). The GHQ-30 is used to detect subjects likely to have or be at risk of developing psychiatric disorders [28]. The GHQ-30 was validated against clinical interview in the Whitehall II Study. As described previously, standard scoring was utilized, assigning a value of 0 to a response of 'same as usual/no more than usual'. GHQ-30 caseness was defined as a score of ≥5 [6]. To investigate whether the association between psychological stress and outcomes follows a dose-response relationship, we generated groups according to the frequency of elevated psychological stress levels in three assessments: no psychological stress in all assessments, psychological stress in one assessment, psychological stress in two assessments and psychological stress in all three assessments.

2.3. Assessment of childhood adversities as factors of stressful challenges during childhood

In total, 13 adverse childhood experiences were assessed. Nine childhood adversities were assessed retrospectively in phase 5 (years 1997–1999) with the question "Did any of the following things happen during your childhood?". Childhood adversities included 1. hospitalization for four or more weeks, 2. parental divorce, 3. unintentional parental unemployment, 4. financial problems during childhood, 5. parental mental illness or problematic alcohol consumption, 6. physical abuse by someone close, 7. exposure to frequent parental arguments or fights, 8. being in an orphanage/children's home and 9. maternal separation for one year or more. Moreover, subjects were asked about the time and attention their mother and father gave to them (adverse childhood experiences 10 and 11). For that purpose, the subjects had to rate maternal and paternal time and attention by the use of a 4-level scale ranging from "a great deal" to "not at all". In order to achieve a dichotomous classification for these two variables as well, the response options "very much" and "quite a lot" were pooled in our analysis, as well as "a little" and "not at all". In addition, the subjects were asked about their age, when their mothers or fathers died. A childhood adversity due to parental death was assumed when parental death occurred under childrens' age of 18 (adverse childhood experiences 12 and 13). We further calculated a sum score of all 13 childhood adversities to be able to map the entire childhood adversity.

2.4. Assessment of body shape

Anthropometric measures were assessed in phase 3. Body mass was measured in light clothes by an electronic scale; height was measured using a stadiometer. BMI was calculated as body mass (kg) divided by height (m) squared. Waist circumference was measured as the smallest circumference at or below the costal margin. Hip circumference was measured at the level of symphysis. Waist-to-hip ratio was calculated. Cut-off values of the World Health Organisation were used. Elevated values in BMI were set at ≥25 kg/m² and for waist-to-hip-ratio (whr) at ≥0.9 (men) or ≥0.85 (women).

2.5. Outcomes

Outcomes included the incidence of non-fatal or fatal CHD events collected up to phase 11 (years 2012 and 2013) as well as all-cause mortality collected up to July 2015.

Non-fatal CHD included first non-fatal myocardial infarction (MI) or first definite angina. Using MONICA criteria, non-fatal MI was defined based on study electrocardiograms, hospital acute ECGs, and cardiac enzymes, whereas incident angina was defined on the basis of clinical records and nitrate medication use [11].

Mortality data were provided by the British National Health Service

(NHS) Central Registry, who notified the Whitehall study group of the date and cause of all deaths of Whitehall study participants. Deaths were classified as coronary if ICD-9 (International Classification of Diseases, 9th edn) codes 410–414 or ICD-10 (International Classification of Diseases, 10th edn) codes I20–I25 were present on the death certificate.

In total, 1217 cases of fatal or non-fatal CHD and 880 all-cause deaths occurred during the follow-up period.

2.6. Covariates

We considered a wide range of covariates (Supplemental Table 1): ethnicity, blood pressure, blood lipid and blood glucose concentrations, any longstanding illness, exercise, alcohol and nicotine abuse, use of medication, menopause (women) and family history of cardiovascular disease.

2.7. Statistical analysis

Data analysis was performed using SPSS software (SPSS 26.0, Inc., Chicago, USA). Descriptive statistics were given as mean ± SD (standard deviation). To examine outcome risk (fatal or non-fatal CHD events and all-cause mortality), Cox regression analyses were performed adjusted for age. Thereby, survival time was defined as the time (in years) between the follow-up date (date of participation/loss to follow-up) and the date of the clinical/mortality event. Hazard ratios and 95% confidence intervals were estimated. In a few cases in supplemental analyses, where heavily skewed distributions of predictor variables resulted in unreasonable estimates of standard errors, bootstrap resampling (1000 bootstrap samples) was used to calculate P-values and 95% confidence intervals. Partial correlation (adjusted for age) was used to calculate the association between the sum score of childhood adversities and psychological stress in adulthood. A P-value (two-sided) of 0.05 was considered statistically significant.

3. Results

Participant characteristics at baseline are presented in Table 1. Compared to women, men were younger, had a higher waist circumference, and a higher waist-to-hip ratio. Moreover, women experienced higher levels of psychological stress than men. Because of these gender differences, we analyzed men and women separately.

3.1. Psychological stress was related to the risk of fatal or non-fatal CHD events in men and women

We found that subjects with high psychological stress in phase 3 had an increased hazard to develop fatal or non-fatal CHD events ~20 years later. More specifically, there was a 25% increase in the expected hazard to develop CHD with high psychological stress in men *(Exp (B)= 1.25 (1.06-1.47); P=0.008; Cox regression analysis adjusted for age)*. Likewise, there was a 34% increase in the expected hazard to develop CHD with high psychological stress in women *(Exp (B)=1.34 (1.05-1.70);*

Table 1
Participant characteristics at baseline assessment in phase 3; mean ± SD.

	Men (n = 4969)	Women (n = 2138)
Age (y)	49.58 ± 5.96	50.54 ± 6.09***
Body mass (kg)	78.08 ± 11.01	66.93 ± 12.33***
Body height (cm)	176.47 ± 6.66	162.04 ± 6.42***
BMI (kg/m^2)	25.05 ± 3.13	25.50 ± 4.56***
Waist circumference (cm)	87.20 ± 9.18	75.10 ± 11.48***
Hip circumference (cm)	96.65 ± 6.01	96.95 ± 9.31
Waist-to-hip ratio	0.90 ± 0.06	0.77 ± 0.07***
Psychological stress[a]	2.76 ± 4.83	3.29 ± 5.37***

***P < 0.001.
[a] Assessed by GHQ-30 questionnaire.

P=0.017; Cox regression analysis adjusted for age) (Supplemental Fig. 1). To address potential confounding factors, we considered a wide range of covariates in Cox regression analyses to examine the association between psychological stress (in phase 3) and fatal or non-fatal CHD events (~20 years later) in more detail. The increased hazard to develop fatal or non-fatal CHD events with high psychological stress was very robust after adjusting for the wide range of covariates (Supplemental Table 1).

To investigate whether the association between psychological stress and fatal or non-fatal CHD events follows a dose-response relationship, we generated groups according to the frequency of elevated psychological stress levels in three assessments (~10 years of follow-up). We found a clear dose-response relationship in both genders (Fig. 1). Compared to men with no psychological stress, men with psychological stress in one phase had a 1.4 fold higher risk for fatal or non-fatal CHD events, whereas men with consistently high psychological stress in all phases had a 2.4 fold higher CHD risk. Likewise, women with psychological stress in one phase had a 1.4 fold higher risk, whereas women with recurrent high psychological stress levels had a 2.3 fold higher risk for fatal or non-fatal CHD events compared to never-stressed women.

Next, we examined whether childhood adversities were associated with fatal or non-fatal CHD events. To this end, we conducted a stepwise Cox regression analysis with forward selection of predictors. All 13 factors of childhood adversities along with age were included as candidate predictor variables. We found that four childhood adversities, namely "parental divorce", "maternal separation for more than one year", "parental unemployment" and "hospitalization for more than four weeks" were associated with fatal or non-fatal CHD events in men. In women, "parental divorce" and "maternal separation for more than one year" were related to fatal and non-fatal CHD events (Table 2).

We further found that subjects with a high sum score of all 13 childhood experiences had a 10% increased hazard to develop fatal or non-fatal CHD events in adulthood *(men: Exp (B)= 1.10 (1.05-1.15); P < 0.001* and women: *(Exp (B)= 1.10 (1.02-1.19); P=0.011; Cox regression analysis adjusted for age)*. The sum score of all 13 childhood experiences was also related to psychological stress in adulthood (r = 0.098; P < 0.001 in men and r = 0.101; P < 0.001 in women; partial correlation adjusted for age).

3.2. While stress contributed to the risk of CHD events in both sexes, body shape only contributed in men

As we previously reported in the Whitehall II study cohort, analysis of variance for repeated measures showed men with high psychological stress to be at risk for developing the 'wide-waisted phenotype' *(F=3.4, P=0.038)* [4]. In contrast, men with high psychological distress and low autonomic variability (HRV) were prone to develop an increased body mass, hip-to-height ratio and thus a 'corpulent phenotype' (psychological distress: F = 4.3, P = 0.016; HRV: F = 5.0, P = 0.008) [4].

We here investigated whether the body shape in turn contributed to stress-related fatal or non-fatal CHD events. Using a multivariate approach, we found that in addition to stress only men showed an extra contribution of waist-to-hip ratio and BMI to the risk of fatal or non-fatal CHD events (Table 3).

3.3. No detectable association between psychological stress and the risk of all-cause mortality

We could not detect any relation between psychological stress in phase 3 and all-cause mortality risk ~23 years later for neither men *(Exp (B)=0.97 (0.78-1.20); P=0.755; Cox regression analysis adjusted for age)* nor women *(Exp(B)=0.84 (0.62-1.13); P=0.251; Cox regression analysis adjusted for age)*. Similarly, we found no association between childhood adversities and all-cause mortality in either sex *(all P > 0.05; Cox regression analysis adjusted for age; data not shown)*. We also could not find a dose-response relationship between psychological stress and mortality. Subjects with elevated psychological stress in one assessment
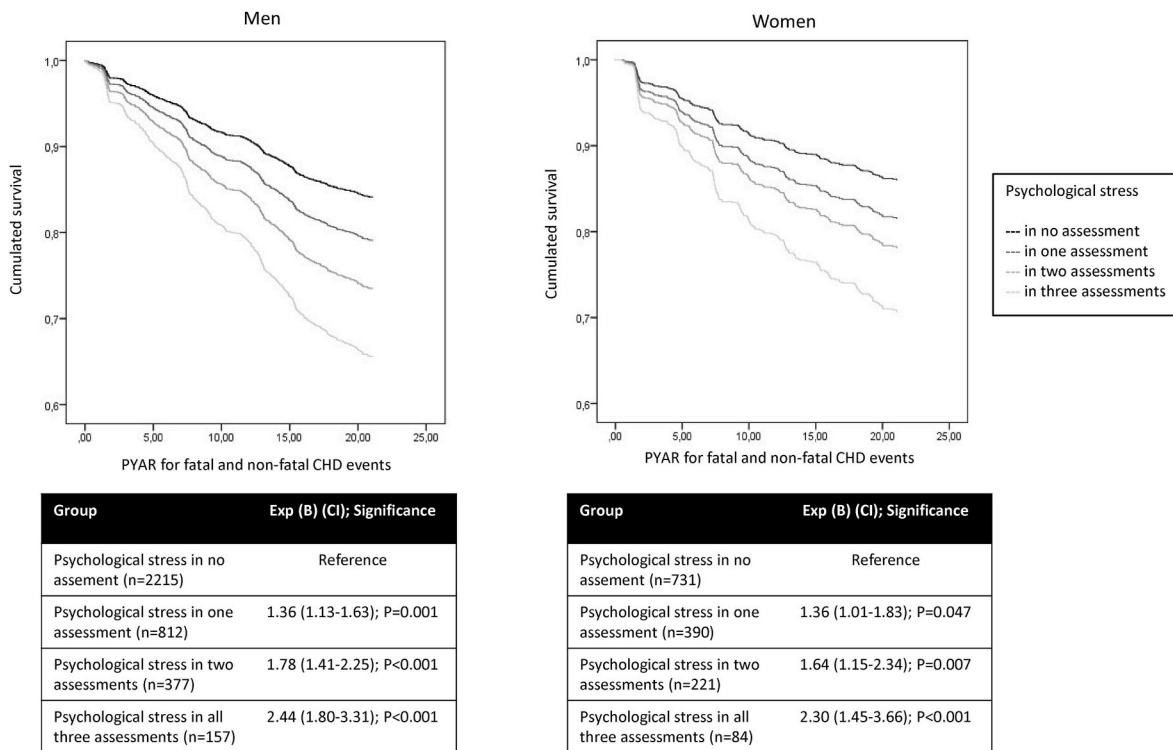
Fig. 1. Dose-response relationship for the association between psychological stress and fatal or non-fatal CHD events. Note that due to some missing answers in the questionnaire we had to use a slightly smaller sample size. PYAR, person years of risk.

Table 2
Childhood adversities that contributed to fatal or non-fatal CHD events in adulthood (stepwise Cox regression analysis with forward selection of predictors; all 13 childhood experiences along with age were included as candidate predictor variables; Exp(B) (95% CI). Note, due to some missing values regarding questionnaire completion, we had to use a slightly smaller sample.

Childhood adversities	Men (n = 3676)	Women (n = 1397)
Parents divorced	1.52 (1.00–2.30); P = 0.049	2.50 (1.45–4.31); P = 0.001
Maternal separation for one year or more	1.28 (1.02–1.60); P = 0.035	1.43 (1.01–2.01); P = 0.041
Parents unemployed	1.57 (1.27–1.95); P < 0.001	–
Hospitalization for more than 4 weeks	1.24 (1.00–1.53); P = 0.050	–

had no detectable higher mortality risk compared to non-stressed subjects (Exp (B) for men 1.14 (0.88–1.49); P = 0.326 and Exp (B) for women 1.17 (0.82–1.67); P = 0.397). Likewise, subjects with consistently high psychological stress levels had no detectable higher mortality risk compared to non-stressed subjects (Exp (B) for men 1.0 (0.54–1.83); P = 0.995 and Exp (B) for women 0.70 (0.28–1.74); P = 0.444). When we considered CHD as a covariate, we also did not find a dose related association between psychological stress and mortality (all P > 0.05), but CHD as a covariate reached significance in this association (Men: Exp (B) = 1.46 (1.15–1.85); P = 0.002 and women: Exp (B) = 1.86

(1.32–2.64; P < 0.001).

3.4. Waist-to-hip ratio - but not BMI - contributed to the risk of all-cause mortality

To untangle our finding that there was no detectable association between psychological stress and all-cause mortality risk we next focused on body shape. We used a multivariate Cox regression model and found that only age and waist-to-hip ratio contributed to all-cause mortality, but not stress or BMI (Table 3).

Table 3
Multivariate Cox regression analysis for stress on fatal or non-fatal CHD events and all-cause mortality with consideration of body shape and age.

|	Men (n = 4969) Fatal or non fatal CHD Exp (B) (95%CI); Significance	Women (n = 2138) Fatal or non fatal CHD Exp (B) (95%CI); Significance	Men (n = 4969) All-cause mortality Exp (B) (95%CI); Significance	Women (n = 2138) All-cause mortality Exp (B) (95%CI); Significance
Stress	1.24 (1.05–1.45) P = 0.011	1.35 (1.06–1.71) P = 0.015	0.96 (0.77–1.19) P = 0.695	0.85 (0.63–1.14) P = 0.279
Waist-to-hip ratio	12.20 (3.0–49.66) P < 0.001	5.94 (0.99–53.62) P = 0.051	34.66 (6.43–186.92) P < 0.001	60.65 (9.33–394.22) P < 0.001
BMI	1.05 (1.02–1.08) P < 0.001	1.02 (0.99–1.05) P = 0.153	1.01 (0.98–1.04) P = 0.583	1.00 (0.97–1.03) P = 0.983
Age	1.06 (1.05–1.07) P < 0.001	1.05 (1.03–1.07) P < 0.001	1.11 (1.10–1.13) P < 0.001	1.09 (1.07–1.12) P < 0.001
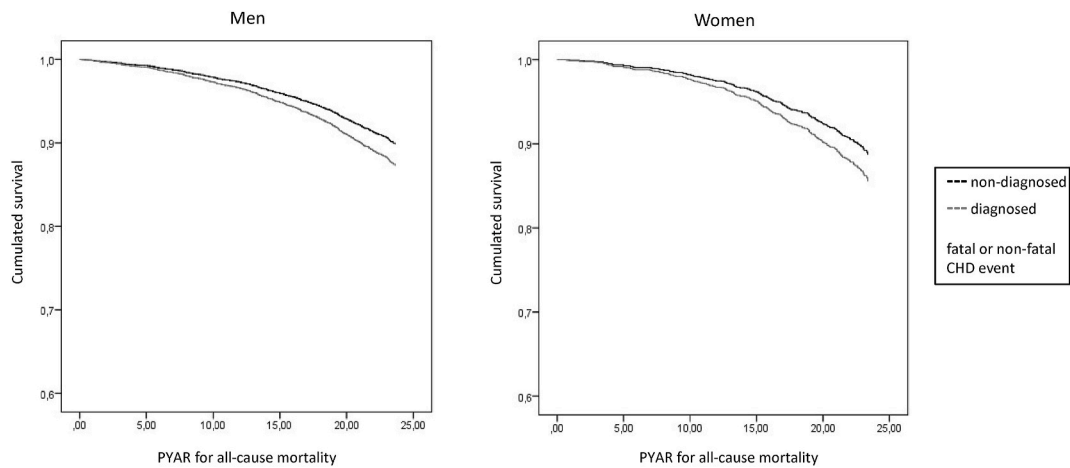
Fig. 2. Fatal or non-fatal CHD events were related to all-cause mortality in men. PYAR, person years of risk.

3.5. CHD events contributed to all-cause mortality

We also investigated whether a diagnosed fatal or non-fatal CHD event was related to all-cause mortality (Fig. 2). In total, 1217 (883 men, 334 women) cases of fatal or non-fatal CHD and 880 (600 men, 280 women) all-cause deaths occurred during the follow-up period. From among all dead subjects, 153 men (25.5%) and 61 women (21.8%) had a fatal or non-fatal CHD event. We found that men with a fatal or non-fatal CHD event had a 1.27 higher all-cause mortality risk *(Exp (B) = 1.27 (1.06-1.53); P=0.011; Cox regression analysis adjusted for age)*. We also found statistical trends that women showed the same pattern *(Exp (B) = 1.30 (0.98-1.73); P=0.070; Cox regression analysis adjusted for age)*.

We next investigated the role of fatal or non-fatal CHD events in the relation between psychological stress and mortality. We extended the multivariate approach shown in Table 3 by adding fatal or non-fatal CHD events to the Cox regression analysis. We found that fatal or non-fatal CHD events contributed to the multivariate model of psychological stress on all-cause mortality in men (Exp (B) = 1.22 (1.01–1.47); P = 0.036). We also found statistical trends that women showed the same pattern (Exp (B) = 1.25 (0.94–1.67); P = 0.124).

4. Discussion

Using the Whitehall II data set, we constructed an overall picture of psychological stress and its hazardous outcomes. This construct describes the strong association between psychological stress and risk of fatal or non-fatal CHD events seen by others, and additionally includes body shape and how it fits into the network of associations between psychological stress, CHD, and all-cause mortality. Fig. 3 gives an overview of our results.

Our findings confirm and extend prior research. We confirmed the association between psychological stress on fatal and non-fatal CHD events later in life. We were able to show that one-time, recurrent or persistent stress was associated with mild, moderate and severely increased CHD risk. The Swedish INTERGENE cohort also found a dose-response relationship between depressiveness, anxiety and negative life events on the one hand, and increased risk of CVD on the other hand [29]. Likewise, psychological stress was related to all-cause mortality in a dose-response manner in the US National Health Interview Survey [17] and to incident coronary heart disease in the Whitehall Study [6]. Given all these findings, the persistence and the severity of psychological stress as shown in our analysis seem to matter for the hazardous health outcomes.

We also confirmed the decisive role of childhood adversities on later health risks. We were able to show that people with high levels of overall childhood adversities were at higher risk for fatal or non-fatal CHD events. That only 4 factors (men) and 2 factors (women) for childhood adversities were associated with CHD in a stepwise Cox regression
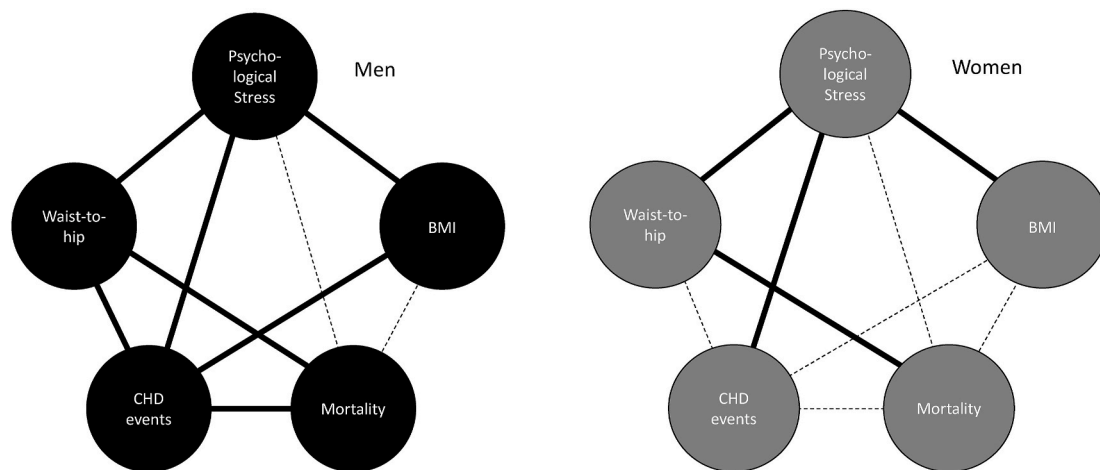

Fig. 3. Summary of our results. In a multivariate Cox regression model, the risk of fatal or nonfatal CHD events is predicted by psychological stress, waist-to-hip ratio, and BMI in men, but is predicted only by psychological stress in women. As shown in our previous work, both the risk for changes in waist-to-hip ratio and the risk for changes in BMI can be predicted by psychological stress [4]. In another multivariate model, risk of all-cause mortality is predicted by waist-to-hip ratio but not by stress or BMI. Solid lines indicate statistically significant relationships.

analysis may be due to the small sample size for women. Further investigation would be needed in this regard. However, childhood adversities have been repeatedly linked to CHD [20,21] and even to the risk of mortality [22,23]. Interestingly, one recent study in France showed the considerable influence of psychological stress during childhood over psychological stress during adulthood on later mortality risk [8]. Especially for women, childhood adversities and a higher number of events predicted mortality even after controlling for recent stressful experiences including illness. Recent stress was not a strong risk factor for mortality [8]. In contrast, one recent study showed that the majority of adverse childhood experiences had no negative associations with the development of coronary heart disease later in life [30].

Our study also extends prior research. To the best of our knowledge, this is the first study giving an overall picture of the relationship networks between psychological stress, body shape and health risk (Fig. 3). We could show that stress increases the risk of both, body shape changes [4] and CHD events, with waist circumference but not BMI increasing the risk of all-cause mortality (current work). The latter association is consistent with many other studies showing that waist circumference indicates a high risk and BMI a low risk of mortality [31–39].

Since Whitehall II is an observational study, we could only show associations and were not able to draw conclusions about the causes. Certainly, causal inference requires data from randomized controlled trials. Here we summarize evidence from RCTs on whether or not causal relationships exist between stress, body shape, cardiovascular events and all-cause mortality. There is indeed evidence from RCTs that confirms that stress leads to CHD events and that stress management programs reduce stress responses and improve cardiovascular survival [40–44]. In two Swedish studies, subjects in the intervention group participating in a stress reduction program had a lower rate of second or third myocardial infarction and a lower rate of cardiovascular mortality as compared to the control group [41,43]. Thus, prolonged psychological stress can cause CHD events, and anti-stress programs can counteract this effect.

There is additional evidence from RCTs confirming that stress causes changes in body shape. In a randomized study in non-human primates, early life stress resulted in higher BMI and abdominal circumferences [45]. Furthermore, a randomized study in children found that a stress-relief intervention versus a control program leads to reductions in abdominal fat [46] supporting a causal link between psychological stress and body shape. Likewise, women practicing yoga to reduce psychological stress showed decreases in abdominal fat compared to a control group [47]. Ludwig and coworkers' randomized social experiment shows a relationship between the feeling of uncertainty and the change in body shape. The authors showed that participants in the intervention group who could move from a high-poverty to a lower-poverty neighborhood felt less uncertain, had better long-term (10–15 years) psychological well-being and were less likely to develop extreme obesity than controls [48,49].

There is some weak, yet unconfirmed evidence from an RCT-based meta-analysis that body weight may influence all-cause mortality. Among the 34 RCTs included in this meta-analysis, there was only one large study designed with sufficient statistical power besides numerous small, underpowered studies. Almost half of the included studies lasted only 12 months, a duration that is somewhat problematic when analyzing mortality outcomes. This meta-analysis in obese adults showed a slight protective effect of weight-reducing diets (usually low-fat and saturated fat, with or without exercise recommendations) on all-cause mortality, but not on cardiovascular or cancer mortality [50]. According to that publication, weight loss seemed to be rather protective against non-cardiovascular, non-cancerous causes of death (such as accidental injuries, suicide, lung disease, etc.) – a finding that is unexpected. It is therefore important that the result of this meta-analysis is confirmed by data from several sufficiently large RCTs.

There is, however, solid RCT evidence against body mass or waist circumference causing cardiovascular disease. The LOOK AHEAD study, a large-scale randomized controlled trial with intensive lifestyle intervention in more than 5000 overweight or obese patients with type 2 diabetes, was originally planned with a follow-up period of 13.5 years, but the study was stopped early based on a futility analysis when the mean follow-up period was less than 10 years [51]. Although the intervention resulted in long-term weight and waist reduction, no change in cardiovascular morbidity and mortality could be demonstrated. The LOOK AHEAD study is - to the best of our knowledge - by far the largest RCT on the issue and the only one that had sufficient statistical power to detect an effect of body weight change on cardiovascular morbidity. Thus, the evidence to date already excludes a causal relationship between body weight and CHD events with high probability.

In summary, the evidences from randomized controlled trials show a causal relationship between (i) psychological stress and CHD events, (ii) psychological stress and body shape changes, but (iii) reject a causal relationship between body shape (high BMI or waist size) and CHD events. Psychological stress can thus be regarded as a common fundamental cause of both undesired body shape and cardiovascular morbidity and mortality.

Of course, our analysis is not free from limitations. We were not able to detect any direct relation between psychological distress or childhood adversities on all-cause mortality risk. These results are in agreement with another study also not showing any association between psychological distress and mortality risk [27], but contrast to many other studies [8,14,17,24–26]. It is possible that the observation period of the Whitehall dataset was too short. Furthermore, the methods used might not be accurate enough. Cohort studies have the common problem of non-response and underreporting, which could result in an underestimation of psychological distress. In addition, the GHQ-30 questionnaire cannot measure the real stress burden individuals are exposed to. That is, individuals may display low values in the GHQ-30 questionnaire either because they experience low psychological distress or because they have already become habituated to it. If the latter one is true, habituation may mask the exposure to a threatening environment by its buffering effect on psychological distress.

In conclusion, our analysis supports the notion that psychological stress results in adverse health outcomes, namely fatal or non-fatal CHD events. Based on the knowledge obtained from RCTs, our results support the view that body shape –more specifically waist size– is symptomatic for stress and indicates all-cause mortality. It appears that the body mass index per se does not play the damaging role that is traditionally attributed to it.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2021.100104.

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