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The association between psychosocial stress and mortality is mediated by lifestyle and chronic diseases: The Hoorn Study

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ABSTRACT

Psychosocial stress is associated with chronic disease. We evaluated whether in the general population the number of stressful life events is associated with risk of mortality and whether this association is mediated by behavioral factors and morbidities. We conducted this study in the Hoorn cohort; a population-based cohort study among older men and women. Our main variable of interest was the number of stressful life events experienced during the previous 5 years, which were assessed by questionnaire. We calculated Cox proportional hazard ratios (HRs) for all-cause and cause-specific mortality during follow-up for those who experienced stressful life events compared to those who did not.

We included 2385 participants (46% male; 62 ± 7 years). During 20 years of follow-up 834 (35%) participants died, of whom 239 (28.6%) died of cardiovascular disease. Compared to the group with no stressful life events, the age, sex and socioeconomic status adjusted HRs (with 95% confidence intervals) for all-cause mortality, for the groups who had 1 event, 2 events, 3 events and ≥4 events were 0.89 (0.72–1.09), 1.01 (0.81–1.24), 1.29 (1.00–1.66) and 1.44 (1.08–1.92), respectively. Similar results were observed for cardiovascular mortality. Mediation analysis showed that smoking, prevalent type 2 diabetes and cardiovascular disease were statistically significant mediators of the association between the number of stressful life events and mortality. Having 3 or more stressful life events is associated with a significantly increased risk for mortality in an elderly population-based cohort. This association is mediated by smoking, type 2 diabetes and cardiovascular disease.

1. Introduction

It is common knowledge that psychosocial stress has negative consequences on physical health (Yusuf et al., 2004). Psychological stress has the capacity to elicit adverse physiological reactions, including increased heart rate and cortisol levels. When stress is chronic, these adverse reactions could result in increased morbidity and mortality (Heraclides et al., 2009). The literature up until now has shown a robust association between stress, all-cause mortality and cardiovascular mortality (Arnold et al., 2012; Kriegbaum et al., 2008; Martikainen and Valkonen, 1998; Phillips et al., 2008; Rosengren et al., 1993; Russ et al., 2012). Psychosocial stress can be assessed by subjective and objective methods. Subjective methods measure stress as the individuals' perception of how stressful they regard their general life (Arnold et al., 2012; Holi et al., 2003; Phillips et al., 2008; Russ et al., 2012). Objective methods measure (the number of) stressful life events that have been encountered, such as death of a child or financial problems (Arnold et al., 2012; Hollis et al., 1990; Kriegbaum et al., 2008; Martikainen and Valkonen, 1998; Phillips et al., 2008; Rosengren et al., 1993).

Until recently, research on the relationship between stressful life events and mortality has investigated small cohorts ($n < 1000$), included only men or patients and investigated only one particular type of stressful life events (death of a spouse, in particular). Most studies investigated health related stress events, in which the events might be confounding, e.g. it could be that the disease

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increases mortality risk and not the psychological stress caused by the disease (Arnold et al., 2012; Hollis et al., 1990; Kriegbaum et al., 2008; Martikainen and Valkonen, 1998; Phillips et al., 2008; Rosengren et al., 1993). Therefore, the *first* aim of our current study is to evaluate whether in the general population, the number of non-health related stressful life events is associated with mortality (all-cause and cardiovascular mortality).

In the literature, several mediators have been suggested that might explain the association between stressful life events and mortality. Experimental studies report that behavioral and endocrine changes occur after an acute psychological stress test, including cigarette craving (Buchmann et al., 2010), decreased physical activity (Hamer, 2012; Rutters et al., 2009), increased alcohol intake (Pohorecky, 2010), HPA axis activation (Born et al., 2010; Strahler et al., 2010) and inflammatory responses (Carpenter et al., 2010). Furthermore, population-based and patient studies have shown associations between psychosocial stress, chronic HPA axis activation (Karb et al., 2012), disruption of the circadian rhythm (Dedert et al., 2012), sleep deprivation (Mezick et al., 2009), depression (Musselman et al., 1998), type 2 diabetes (Puustinen et al., 2011) and cardiovascular disease (Neylon et al., 2013). Up until now, none of the previous studies on stressful life events have studied mediating factors, therefore, the *second* aim of our study is to evaluate whether the suspected relationship between the number of stressful life events and mortality is mediated by behavioral factors and morbidities.

2. Research design and methods

2.1. Study population

The Hoorn Study is a population-based cohort, which is representative for the general, elderly Dutch population. From 1989 to 1992, a population-based survey of glucose tolerance was carried out in the Dutch city of Hoorn, which is a medium-size town of about 57,000 residents with a mixed rural and urban population. The eligible population of the Hoorn Study consisted of 3553 men and women aged 50–75 years randomly selected form the municipal registry. Of the eligible participants, 71.5% agreed to participate, resulting in the Hoorn Study cohort of 2484 participants. From 93% of the non-participants, we obtained relevant information indication on age, sex, height, weight, history of diabetes, treatment of hypertension and cardiovascular complaints was obtained by interview. These characteristics did not differ between participants and non-participants, indicating no substantial bias (Mooy et al., 1995).

For 99 participants, data was missing on one or more stressful life events and these subjects were excluded from the analysis. No differences were observed in gender, age, BMI, waist-to-hip ratio, fasting plasma glucose, 2 h postload glucose, HbA1c, cholesterol, HDL-C, triglycerides, blood pressure, smoking, physical activity, alcohol intake, education level and mortality rates between participant with missing data on stressful life events and participants who did and who did not answer the questionnaire on stressful life events (data not shown).

2.2. Study design

At baseline, the number of stressful life events, several covariants and confounders, potential mediating factors and morbidities were determined. Cause-specific mortality was determined by follow-up until January 2009.

2.2.1. Stressful life events

At baseline, we determined the number of major stressful life events experienced during the past 5 years. We used a simplified version of the questionnaire “Serious Life Events” (Mooy et al., 2000). All questions concerned events that are known to be major stressors and included the following questions, which were answered by yes or no:

- In the past 5 years, have any of your children been sick (long-term and/or serious)?
- Did any of your children die in the past 5 years?
- In the past 5 years did any of your children have long-term and/or serious problems?
- In the past 5 years did you have long-term and/or serious problems with your partner?
- Did your partner die in the past 5 years?
- Have any of your relatives (parents, brothers, sisters, in-laws) died in the past 5 years?
- In the past 5 years, did you have long-term and/or serious financial problems?
- In the past 5 years, did you have to move house?
- Have any of your friends died in the past 5 years?
- In the past 5 years, did you have to end a serious relationship or friendship?

The participants completed the ‘Serious Life Events’ questionnaire at home. During a personal interview, the researcher made sure that the participant had completed the questionnaire at home; if the questionnaire was not complete, the participant had to complete it at the spot, during the visit at the research center.

2.2.2. Mortality

Data on the participants' vital status was collected from the population register of the city of Hoorn up to January 1st 2009. Information on the cause of death was extracted from the medical records of general practitioners, local hospitals and local nursing homes. Cause of death was coded according to the International Classification of Diseases, Injuries and Causes of Death, ninth revision. Fatal cardiovascular disease was defined as ICD codes 390–459 (diseases of the circulatory system).

2.2.3. Co-variants and confounders

Baseline age, sex and socioeconomic status were also determined. Socioeconomic status was defined by education level, which was measured using a questionnaire. We measured education level in 7 categories, which we divided in 3 levels: categories 1, 2 as low level education (primary education), categories 3–5 as middle level (secondary education) and categories 6, 7 as high level education (tertiary education).

Additionally, weight and height were measured at baseline, with participants wearing light clothes only and the body mass index (BMI) was calculated as weight/height squared (kg/m^2). Waist circumference and hip circumference were measured according to a standardized procedure (Seidell et al., 1988) and the waist-to-hip ratio was defined as waist circumference divided by hip circumference. Finally, we determined triglycerides and high-density lipoprotein cholesterol (HDL-C) levels at baseline in the fasting blood sample, using enzymatic techniques (Boehringer Mannheim, Mannheim, Germany). Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer (Hawksley–Gelman, Lancing, UK) and the average was used for analyses. Hypertension was defined as systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure 90 mmHg and/or the use of antihypertensive drugs.

2.2.4. Mediating factors

In our current study, we have collected information on the following possible mediating factors: smoking, alcohol intake, physical activity, diabetes status and cardiovascular disease status.