Psychological states and physical fates

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Chapter 1

General introduction

GENERAL INTRODUCTION

From psychosocial stress to cardiovascular disease

Psychosocial stress is a well-established risk factor for cardiovascular disease (CVD) [1–3]. For instance, a recent individual participant meta-analysis of 10 large prospective cohort studies demonstrated a dose-response relationship between psychological distress and cardiovascular mortality [4]. Likewise, meta-analyses found perceived stress [5] and job strain [6] to be associated with a higher risk of incident coronary heart disease. Explanatory models of how psychosocial stress increases the risk of CVD often suggest the physiological stress response as an important mediator [7,8]. The dominant theory in our field that explains the relationship between psychosocial stress, the physiological stress response, and somatic disease is the theory of allostatic load. This theory has two major hypotheses. The first hypothesis is that repeated exposure to environmental challenges, and the consequent adaptive responses of the stress responsive systems, causes cumulative damage and leads to physiological dysregulation, i.e. allostatic load. As damage accumulates over time it might lead to hyper- or hypoactivation of the stress responsive systems under resting conditions, failure to habituate to a recurrent stressor, or slower recovery back to baseline values after exposure to a challenge [9]. The second hypothesis of the theory of allostatic load is that allostatic load is a mediator between psychosocial stress and adverse health outcomes [10,11]. The three stress responsive systems thought to be involved in mediating the relationship between psychosocial stress and CVD are the hypothalamic-pituitary-adrenal axis (HPA-axis), the autonomic nervous system (ANS), and the immune system [7,8]. Moreover, telomere shortening can be seen as a potential final common pathway from stress responsive system activation to somatic disease [12].

Current evidence for the theory of allostatic load

The first hypothesis

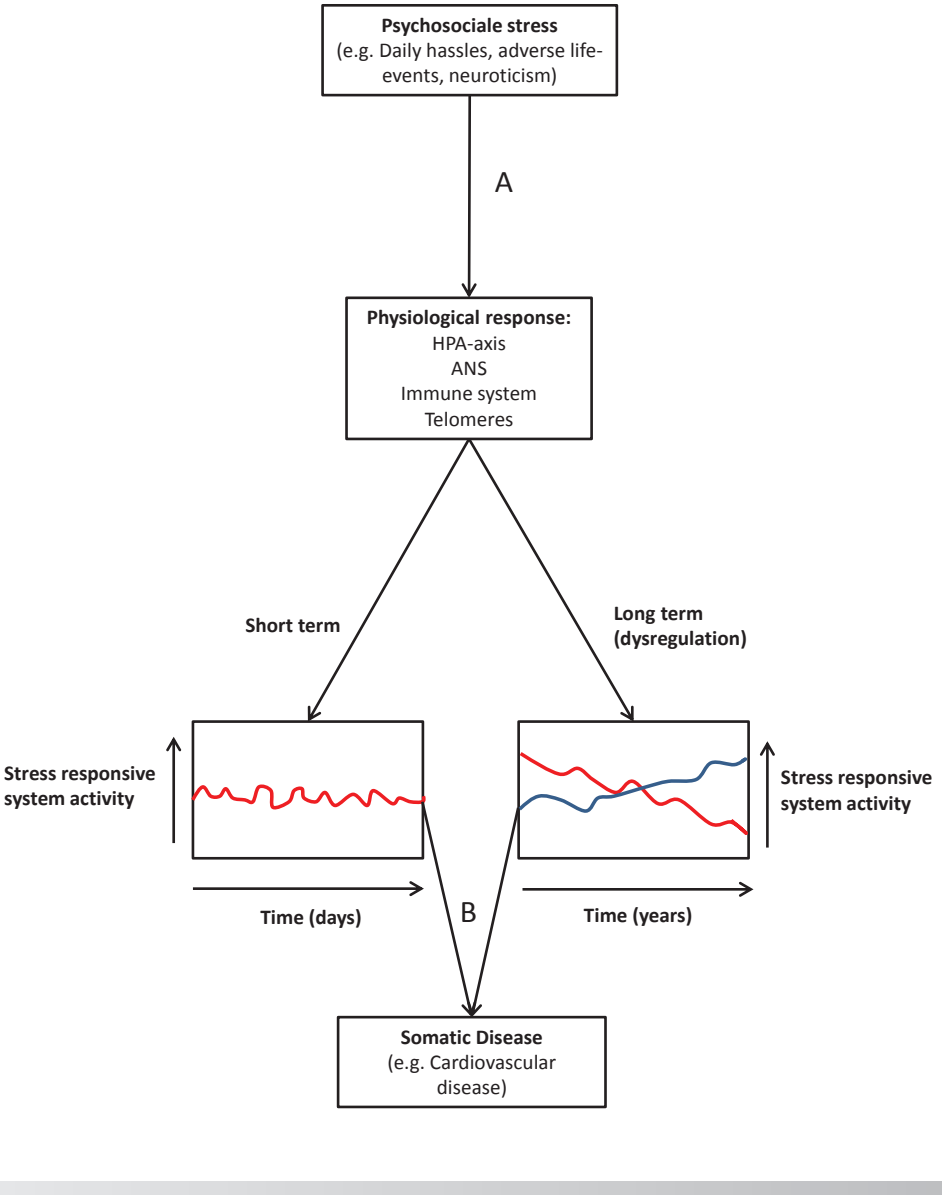
As mentioned above, the first hypothesis of allostatic load states that the effects of psychosocial stress accumulate over life and lead to a dysregulation of the stress responsive systems over time (figure 1, pathway A). The results of studies focusing on the effects of stressors on the function of the stress responsive systems are, however, equivocal. Regarding the HPA axis, there are several studies reporting an association between psychosocial stress and HPA-axis activity [13–16], and others that have found no such relationship [17,18]. Similarly, there are studies showing that psychosocial stress is associated with altered activity of the ANS [19,20], but there are also studies reporting negative results [21,22] or an effect in an unexpected direction [23]. Likewise, some report a link between psychosocial stress and increased levels of inflammation or pro-inflammatory cytokines [24–26], while some do not find an association with levels of inflammation [26,27].

Stress responsive system activation might lead to telomere shortening [12]. Telomere length might thus reflect cumulative damage due to exposure to psychosocial stress particularly

well. Indeed, since Epel and colleagues reported for the first time that psychosocial stress is associated with shorter telomere length in 2004 [28], many studies have focussed on telomere shortening as a potential downstream consequence of exposure to psychosocial stress. Telomeres are TTAGGG nucleotide tandem repeats at the ends of chromosomes in eukaryotic cells. As DNA polymerases cannot copy the end of the DNA strand, telomeres progressively shorten with each cell division. When telomeres become critically short this causes chromosomal instability[29] and cellular senescence [30]. Consequently telomere length is considered a biological marker of aging [31]. A recent review concluded that most studies demonstrated a significant negative relationship between psychosocial stress and telomere length, although some studies failed to show any effect [32]. To date, there is only one prospective longitudinal study that investigated the effects of psychosocial stress on telomere length [33].

The interpretation of previous cohort studies that investigate the relationship between psychosocial stress and stress responsive systems or telomere length is limited for four reasons. First, they generally have a small sample size and were often performed in specific subgroups (e.g. white-collar workers [20] or students [34]). Although, there are two large cohort studies that did use an integrated measure of psychosocial stress and tested its effect on multiple stress responsive systems, these studies were performed in elderly Taiwanese and Costa Rican populations [18,35], making it hard to generalize the findings to the general population. Second, previous studies used heterogeneous measures of stress, for example including one specific type of stressor (e.g. childhood maltreatment [36] or caregivers stress [37], or stress exposure over a short time span [34]). Consequently, these studies do not provide insight into the cumulative effects of lifetime stress exposure, in other words if psychosocial stress causes “wear and tear” of the stress responsive systems as postulated by the theory of allostatic load. Third, previous studies have often failed to adjust for relevant confounders or mediators, such as smoking [38,39], alcohol consumption [40–42], depressive disorder [39,43,44], frequency of exercise [45], body mass index (BMI) [46], and medication [47,48]. Forth, most studies investigated the relationship between psychosocial stress and changes in stress responsive system function cross-sectionally by aggregating data at the group level. As there exists substantial within-individual variation in stress responsive system activity levels on the short-term [49–51], this might obscure the long-term changes that exist, and reduce the power to find a between-individual effect (figure 1). In conclusion, it is not yet clear whether psychosocial stress is associated with altered stress responsive system function or accelerated aging in the general population. In this thesis we will use a large population representative cohort to test this hypothesis.

Figure 1. Pathways from stress to disease



Towards a new approach

As mentioned in the previous section, stress responsive systems show large within-individual variation. It was mentioned that the ability to find a between-individual effect is reduced if the within-individual variation is not accounted for, something which is not possible in a cross-sectional study. There is, however, a more substantive reason to focus on within-individual variation, namely, that our research questions are often of a within-individual nature (e.g. does exposure to psychosocial stress lead to a change in cortisol levels in that same individual that was exposed). Between-individual variation can rarely convey information on within-individual change. In this section we will discuss and provide a rationale for an alternative approach that is based on within-individual change.

Studies that focus solely on within-individual variation are called idiographic studies. In idiographic research, repeated measurements of an individual form a key-element. Together, such serial measurements create so-called time series. In idiographic research, data is pooled over time by means of time series analyses techniques. This is in contrast to traditional group-based studies (nomothetic studies) where data is pooled over individuals. This is further exemplified in figure 2. The data cube as proposed by Cattell [52] is shown in figure 2.A. The variables of interest (e.g. cortisol or stress) can be found on the x axis, the individuals on the y axis, and each measurement occasion on the z axis (e.g. hours or days). Figure 2.B shows traditional group based research (i.e. nomothetic research). A vertical slice of the data box was taken, and what is subsequently studied is the between-individual variation by pooling the data over individuals. Figure 2.C illustrates idiographic research. A horizontal slice of the data box is taken, which leads each individual to be studied separately by modelling the intra-individual (co)variation of the variables of interest over time.

Many researchers assume, often implicitly, that inferences made at the group level reflect within-individual change (i.e. within-individual variation). This is, however, only correct under very stringent conditions which often cannot be met in the psychological and biological sciences [53]. The conditions under which generalisations from analysis of between-individual variation to within-individual variation is permitted are specified in the classical ergodic theorems. Heuristically described these conditions are twofold [54]. The first condition is homogeneity of the population for the process under study. To give an example, this means that all subjects should respond to the same kind of stressor in exactly the same way. But we know that this is unlikely to be true, as differences in previous experiences, genetics, and in current environment will lead to differences in the appraisal of a stressor. This kind of heterogeneity might get obscured in group-based analysis, while it may form an important role in theory formation. The second condition is that a process needs to have relatively stable statistical properties over time, called stationarity. This means that if we were to measure the same person for a prolonged period of time, that the mean levels of his time series, and the variance within his time series should not change from one period to another (e.g. no sudden shifts or cyclical trends). Moreover, the autocovariance of the time series should be stable over time. Autocovariance is a measure for how well the value of today's levels (of for instance cortisol) can be predicted by values on the previous day(s). Only if both conditions are fulfilled can we generalize findings from group-based studies to the level of the individual and vice versa. If one of these conditions is violated, however, no a priori relationship exists between group level findings and within-individual findings.

This mathematical law holds even if the size of the studied group (n) or amount of time points (t) on the time series of an individual approaches infinity. In this thesis we will explore the feasibility and the necessity of an idiographic approach for the study stress responsive system function.

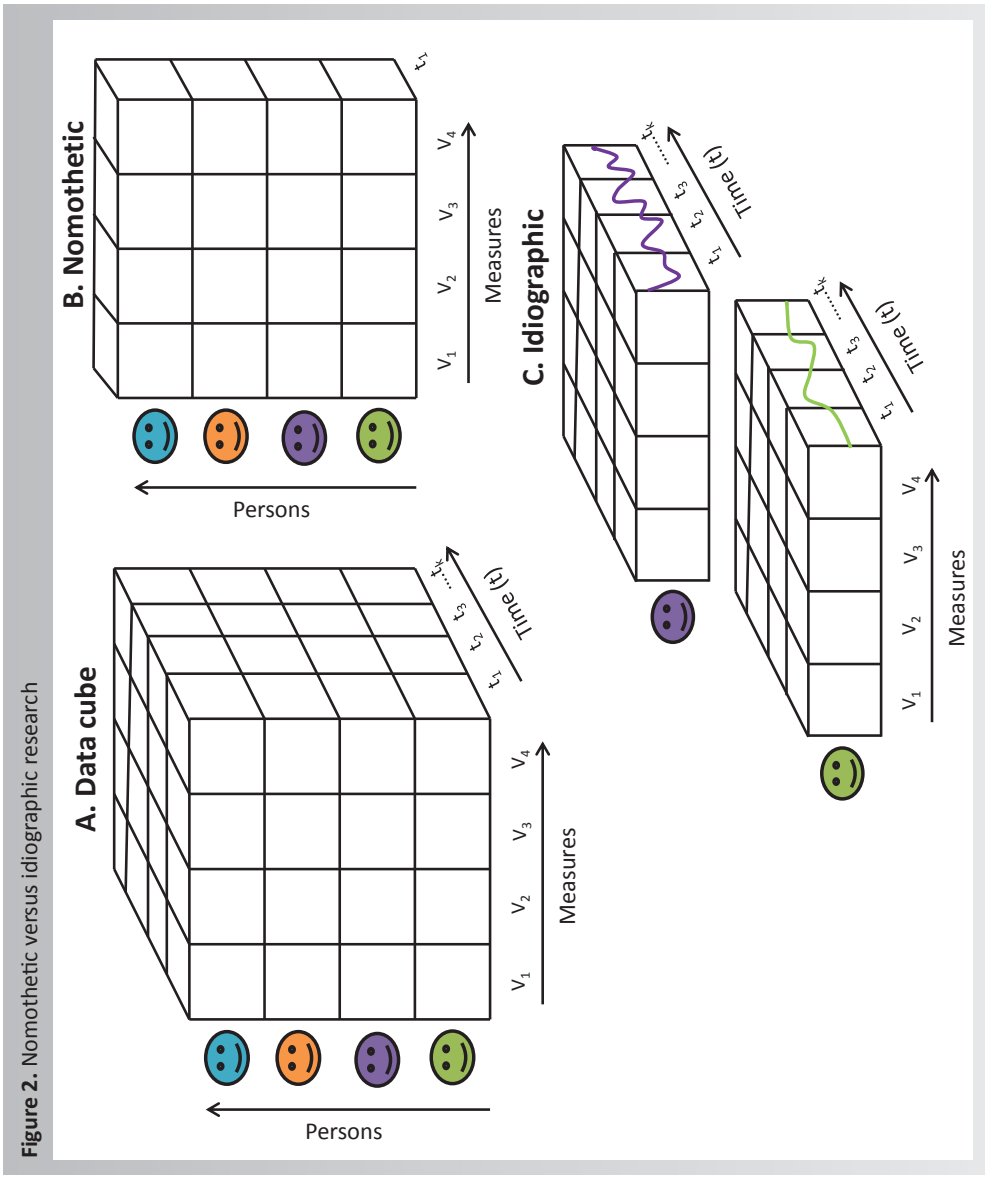


Figure 2. Nomothetic versus idiographic research

The second hypothesis

The second hypothesis of the theory of allostatic load is that dysregulation of the stress responsive systems is associated with adverse health outcomes (Figure 1, pathway B). Over the years quite some evidence has accumulated in favour of this hypothesis, albeit that some stress responsive systems (the ANS, and the immune system) have received considerably more attention than others. Regarding the HPA axis, increased levels of cortisol are associated with increased blood pressure [55], higher BMI [56], higher waist circumference [56], higher fasting glucose levels [56], and decreased HDL levels [56]. Fewer studies have investigated if the HPA-axis activity is associated with hard outcomes such as cardiovascular morbidity and mortality. Two recent prospective studies showed that elevated levels of cortisol predicted cardiovascular death amongst the elderly both with [57] and without preexisting cardiovascular disease [57,58]. Research regarding the ANS has focussed mainly on cardiovascular outcomes. For instance, lower heart rate variability in the high frequency range (HRV-HF), signifying vagal withdrawal, has been shown to be an independent predictor of cardiac events in both healthy individuals and patients with a history of myocardial infarction [59,60]. Moreover, resting heart rate (RHR) has been in the picture in the recent two decades as a potentially modifiable risk factor for CVD. In populations without known cardiovascular disease RHR was found to be a risk factor for both cardiovascular death [61–63] and morbidity [62,63]. Although there are also studies which did not find any relationship between RHR and non-fatal cardiovascular events [64–66]. The immune system plays a role both in the formation of atherosclerotic plagues [67], and worsening of insulin resistance [68] in case of obesity. A meta-analysis by Kaptoge et al showed minor elevations of C-reactive protein, also called high sensitive C reactive protein (hsCRP), to be prospectively associated with cardiovascular disease [69]. HsCRP is, however, most likely only a marker of an inflammatory state and not a causal factor in cardiovascular disease [70]. As mentioned previously, telomere shortening can be seen as a potential final common pathway from stress responsive system activation to somatic disease [12]. Critically short telomeres lead to chromosomal instability [29] and cellular senescence [30]. This could potentially increase the risk for many diseases of aging. Indeed, shorter telomeres are associated with dementia [71], and an increased risk for the development of malignancies [72], diabetes mellitus [73], and CVD [74]. Although the theory of allostatic load is much broader we will limit the scope of this thesis to CVD. The main limitations of previous studies investigating the relationship between stress responsive system dysregulation and CVD are that they have been conducted in elderly populations, and that the focus has mainly been on cardiovascular mortality. Thus the question remains whether similar effects can be found in a younger cohort. Moreover, it is currently unclear if stress responsive system dysregulation is also associated with an increased incidence of nonfatal cardiovascular events, as it is with cardiovascular mortality. In this thesis we will use a large population representative cohort to test the hypothesis that stress responsive system dysregulation is associated with fatal and nonfatal cardiovascular events.

This dissertation

The first part of this dissertation sets out to test the two hypotheses of allostatic load. To this end we used a population representative sample of the PREVEND cohort. In chapters 2-4 we tried to test the first hypothesis of the theory of allostatic load by answering the question

if psychosocial stress is associated with stress responsive system dysfunction and with accelerated aging in the general population. More specifically, in chapter 2 we investigate whether cumulative exposure to adverse life events leads to dysregulation of three stress responsive systems: the HPA-axis, the ANS, and the immune system (SALUT cohort). We take a life-course approach in that we both investigate the effects of cumulative exposure over the life-span and investigate whether a childhood is a 'critical period' in which stress can do more damage than in other periods of life. In chapter 3, we investigate cross-sectionally whether exposure to adverse life-events in childhood or cumulatively over the life-span is associated with shorter telomeres. Moreover, we investigate longitudinally whether cumulative exposure to adverse life-events in the previous year leads to accelerated telomere shortening (SALUT cohort). In chapter 4, we investigate whether neuroticism, a stress sensitive personality trait, is associated with accelerated aging as indexed by telomere shortening (PREVEND random sample). In chapter 5, we investigated the second hypothesis of the theory of allostatic load that a dysregulation of the stress responsive systems is associated with adverse health outcomes. We do this by assessing whether higher levels of urinary free cortisol and higher resting heart rate increase the risk of fatal and non-fatal major adverse cardiovascular events (PREVEND random sample).

The second part of this thesis is concerned with idiographic research (chapters 6-7). For this part, we use data from the 'cortisol dynamics in healthy individuals' cohort. In chapter 6 we discuss the practical issues related to measuring neuroendocrine parameters in idiographic studies. To this end, we review the literature on several biological matrices in which neuroendocrine parameters can be measured (e.g. saliva, urine, hair, and nails) and judge their suitability for utilization in idiographic studies. In chapter 7, we investigate the time series of urinary and salivary cortisol levels of 10 healthy individuals that have been measured for 63 consecutive days. We assess the stability of within-individual levels of cortisol over time, and test the within-individual effect of various life-style factors on fluctuations in urinary and salivary cortisol by means of multivariate time series analyses. The thesis is finalized by a summary and general discussion of the findings with recommendations for future research. This introduction ends with a short description of the cohorts that were analysed in this thesis.

Description of cohorts

PREVEND cohort

For chapters 2-5 of this thesis we used data from subcohorts of the Prevention of REnal and Vascular ENd stage Disease (PREVEND) study. PREVEND is a population based cohort study originally designed to investigate microalbuminuria as a risk factor for renal disease and CVD. The recruitment of participants for PREVEND has been extensively described elsewhere[75]. In brief, 8,592 subjects completed the baseline screening survey in 1997-1998 (T1), rendering the PREVEND study cohort. Insulin dependent diabetes mellitus and pregnancy were exclusion criteria. Because of its purpose, the PREVEND study was enriched for albuminuria which is a risk factor for developing renal disease. We used two subcohorts of PREVEND for our studies, namely the PREVEND random sample and the SALUT cohort (figure 3). Selection

of subjects for the two subcohorts was aimed at recruiting a representative sample of the general population of Groningen, while simultaneously rectifying PREVEND's oversampling for albuminuria. The coming about of the PREVEND random sample and SALUT are described below.

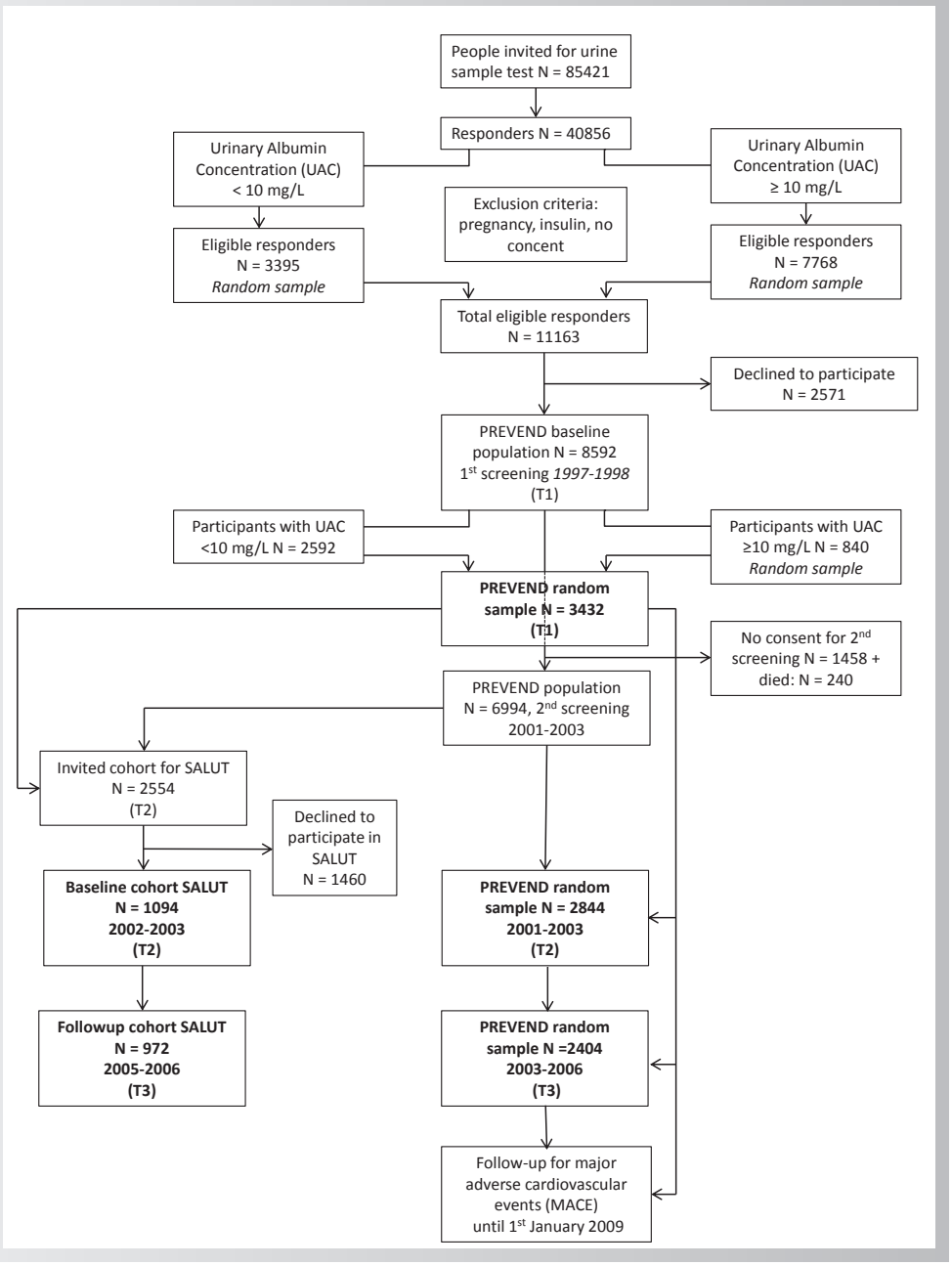
PREVEND random sample

To obtain a large representative random sample of the Groningen general population, all subjects with a urinary albumin concentration (UAC) <10mg/L that had completed the first screening (N=2592) were included, next to a random subset (n=840) from the "overrepresented" subjects with an UAC >10mg/L proportional to the degree of overrepresentation. This resulted in a group of 3432 subjects with a population representative ratio of albuminuria negative and positive subjects. The average age was 49 years; minimum and maximum age were 28–75 years (T1). The second screening took place from 2001-2003 and was completed by a total of 2844 participants (T2). The third screening took place from 2003 until 2006 and was completed by 2404 participants.

SALUT cohort

The SALUT study is a subcohort of PREVEND in which additional psychosocial measurements were taken. To recruit participants for this study, research assistants approached participants in the PREVEND study during their visit to the outpatient clinic during the second screening (2,554 participants). Questionnaires were completed by a total of 1,094 participants (43%), forming the population cohort of the present study. There was no significant difference in gender, age, or scores on a 12-item neuroticism scale between PREVEND participants who were invited to participate in the present study but declined and PREVEND participants who agreed to participate. The sample consisted of 588 females (53.7%) and 506 males (46.3%). The mean age of the participants was 53 years and the minimum and maximum age 33-79. Baseline measurements for SALUT took place from 2002 until 2003 (T2). Follow-up measurements were made approximately two years later, from 2004 until 2006 (T3), and were completed by a total of 976 participants. As part of SALUT, participants underwent an intelligence test and a structured psychiatric interview assessing somatization, anxiety and depression. They also completed a questionnaire covering physical and mental health, stress, personality, lifestyle factors and demographic characteristics.

Figure 3. Flow-chart PREVEND cohort



The 'cortisol dynamics in healthy individuals' cohort

For chapters 6-7 we use data from the 'cortisol dynamics in healthy individuals' study. This is a longitudinal idiographic observational study that generated time series data of 10 healthy participants. The study took place in the city of Groningen, the Netherlands from 9th of July 2012 through 10th of March 2013. Participants were recruited by means of poster adverts that were displayed in university buildings, hospitals, and supermarkets in the city of Groningen. They were paid €5 per day of study participation, thus a total of €315 after completion of the entire study period. Inclusion criteria were being a healthy adult between the ages of 18 and 65 years and being available for 63 consecutive days. Exclusion criteria were any current somatic and/or mental illnesses and medication use other than oral contraceptives or occasional acetaminophen. The aim was to include 10 participants. A total of 11 participants were included in the study. One person discontinued participation in the study due to a major life event after two days. The 10 other participants successfully completed the entire study period.

As part of the daily assessments, participants were asked to fill out an electronic diary in the evening before going to bed and in the morning directly after waking up. The diary was web based (Qualtrics, Provo, UT) and could also be accessed with smartphones. In the morning, participants filled out the Pittsburgh sleep diary (wake time). In the evening, participants were asked how much they had exercised, and how many caffeine containing drinks, alcoholic beverages, and cigarettes they had used that day. Additionally, they filled out questionnaires on affect and the stressfulness of events. As part of the study, participants were also requested to collect biomaterials. They collected all their urine and three saliva samples per day for 63 consecutive days. In these samples cortisol was measured by means of liquid chromatography tandem mass spectrometry (LC-MS/MS). Moreover, fingernails were collected every two weeks, and a hair sample was taken at the beginning and at the end of the study.

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