From Work Stress to Disease: A Computational Model

Remco Benthem de Grave

Radboud University

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Student nr. 4785126

First Supervisor: Dr. E.H. Bijleveld

Second Supervisor: Dr. F.W. Hasselman

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Abstract

With an estimated annual cost of $400–$500 billion in the U.S. and €67 billion in the EU, current levels of work stress related health problems are unlikely to be sustainable. Although much research has been performed on the topic, computational models of the relationship of work stress and disease do not yet exist. A computational model can benefit science in various ways, for example by facilitating falsifiability, supporting a better understanding of involved processes or generating new predictions. In this study we propose such a computational model, building on allostatic load theory. The plausibility of the model is tested by (a) comparing results from model simulations with empirical findings published in scientific literature and (b) assessing the robustness of the predictions against parameter variation. The model is then used to make several novel predictions about the nature of work stress and disease. Perhaps most notably, results suggest that spreading the same number of working hours over more days (e.g., 6 instead of 5), reduces the risk of developing disease from work stress, whereas compressing the working hours over fewer days increases this risk.

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Work stress has been estimated to cost $300 billion to U.S. industry (Nguyen, 2016) and between $125 and $190 billion to U.S. healthcare (Blanding, 2015). In Europe, total costs were estimated at €67 billion, with €29,2 billion in Germany, between £1.26 and £10 billion in the U.K. and around €4 billion in the Netherlands (Hassard et al., 2014). With these costs, work stress is unlikely to be sustainable and research that can help mitigate the problem may prove to be of high value.

Although a vast body of literature exists on the topic of work stress,[1] a computational model on the topic appears not to exist. A computational model may advance scientific knowledge in various ways, like contributing to the transparency of the theory, generating new predictions (Epstein, 2008) and supporting a better understanding of the underlying mechanisms (Yarkoni, & Westfall, 2017). We will discuss these points in more detail below.

A brief introduction to computational models

This section is intended for readers who are new to computational modelling. Readers who are familiar with computational modelling may want to skip this section.

We will start explaining what computational models are about, by comparing them to what we call "verbal theories" (with theory synonymous for model). By verbal theories, we refer to any theory not described through mathematical equations (or any other structure of formal logic). In this sense, most theories in social sciences are verbal theories. On the other hand, in the realm of physics and chemistry, most, if not all, theories are computational. An example of a theory that is computational is Newton's theory of universal gravitation. The theory describes the force that works between two masses (and why objects close to the earth to fall towards the earth) is captured in the equation $F = G \cdot \frac{m_1 \cdot m_2}{r^2}$ in which m_1 and m_2 are

[1] A Pubmed search using the search terms "work" AND "stress" in publication title or abstract on July 2, 2018 provided nearly 40'000 hits. hits. The topic also has its own dedicated journal Work & Stress (https://www.tandfonline.com/loi/twst20)

the two masses, r the distance between them, G the universal gravitation constant and F the resulting force. Each combination of values that are inserted for the parameters in the right side of the equation result in a single, exact, resulting force. In contrast, in case of a verbal theory, the relationship between parameters is not strictly defined, leaving room for flexibility in interpretation of the theory. For a quantitative test (e.g. statistical analysis) of a verbal theory against empirical data, such an interpretation is required. The result that follows from the quantitative test now depends on the interpretation of the relationship that exists between the parameters (linear or non-linear), how the behavior depends on some previous state of the outcome and any covariates that are considered relevant.

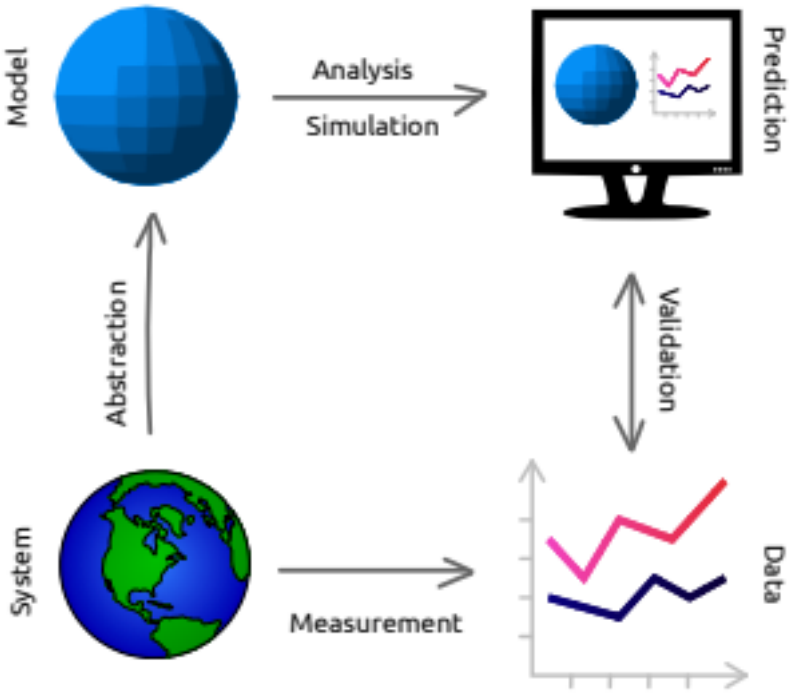

Figure 1. The research cycle of computational modelling. Reprinted from *Modeling and Simulation in Python* by A. B. Downey, 2017, Needham, Massachusetts: Green Tea Press. Copyright 2017 by Allen B. Downey. Reprint permitted a Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License: http://modsimpy.com/license.

The cycle of developing a computational model is depicted in Figure 1. To study a specific behavior, we make a model, an abstraction of the system, that describes the system in the parameters that are considered most relevant for the studied behavior. Also, the interactions between these parameters is defined. In order to test the model, predictions that follow from simulations of this model are compared with empirical data. For example, to study the relationship between the population density and becoming diseased, a model of the human in a local environment can be made. The model may describe the dynamic relationship between the number of immune cells in a human, the outside temperature and the population density. To test this model, the model predictions about the number of people becoming diseased – based on a specific number of immune cells, temperature and population density – is compared against the observed number of diseased people. As may be clear from this explanation, the cycle is in principle no different from any research cycle that aims to empirically verify a verbal theory. In both cases, confirmation or rejection of a theory is done by determining the fit of predictions from the theory against measured data. With regard to this cycle, the main difference between the two approaches is that in the case of a verbal theory an interpretation of the theory is required in order to make predictions from the theory, whereas a computational model allows prediction without the need for additional interpretation.

Benefits of computational modelling. The first value of computational models that we list is that, more so than verbal theories, they facilitate falsifiability. As mentioned before, the limited specificity of a verbal theory allows various ways to define relationships between parameters. This flexibility makes falsifiability difficult, thus limiting what can be learned from a study that attempts to empirically validate that verbal theory. In contrast, computational models are fully specific. The model provides full transparency about the

included parameters and the assumed relationships between the factors, thus limiting interpretational freedom and facilitating falsifiability (Frankenhuis & Tiokhin, 2018; Smaldino, 2017).

Second, computational models can help improve the understanding of underlying causal mechanisms of the relationship that is being studied. Rather than attempting to create a model that exactly mimics reality, the goal of modeling is to provide a model that can satisfyingly approximate empirical observations, while maintaining simplicity as much as possible (Kokko, 2007; Epstein, 2008). As such, modelling can give insight in the key dynamics that govern the process under investigation. Also, through analogies, computational models can increase understanding. In particular, processes that seem unrelated can have models that are computationally the same (e.g., the same model may explain the behavior of both arteries and rubber tubes). This way, strong theories from other fields can help to advance less developed theories and accelerate the rate by which understanding of the processes are gained (Epstein, 2008).

A third value of computational models lies in the possibility to perform simulations and the possibilities that this brings. Through simulations, we can test the parameter ranges under which the model conforms with empirical data, thus testing the robustness of the model (Epstein, 2008). Simulations can also prove valuable to test the logic of intuitive reasoning behind a theory which is sometimes flawed (Farrell, & Lewandowsky, 2010). Simulations of computational models can also generate novel predictions of the behavior that may be observed in real populations (Epstein, 2008). In some cases, intuitive interpretation of a theory does not lead to a clear prediction of the effect of a situational change. Whether, and how, taking days away from work on a Wednesday and a Sunday, instead of a Saturday and a Sunday will influence the risk of developing disease may not follow intuitively from a theory.

Formulating an expectation is difficult in such scenarios and simulating can provide a solution.

This study

Within this study we aim to meet three goals. The first goal of this study is to develop a first computational model of the work stress and disease relationship. Rather than providing a detailed model, including many possible parameters involved in the process of becoming diseased, we aim to create a simple and compact model that concentrates on the main mechanisms involved. We do this as we believe that it will benefit comprehension of the model and limit the number of arbitrary assumptions that have to be made. Also, rather than formulating a whole new theory of the process, we will be using knowledge from existing verbal theory to develop the model.

The second goal of this study is to perform simulations with the model to investigate the model on its ability to reproduce results that have been reported in literature. For these simulations we will not be using data from empirical measurements, but instead simulate individuals for whom we will verify that their collective behavior is comparable to the behavior that is described in scientific literature. This investigation will provide us with feedback about the credibility of the model that has been developed.

As a third goal, we want to perform simulations with our model to formulate new predictions. Specifically, we want to formulate predictions about the impact of changing how working hours are distributed over the working week. For example, whether there is expected benefit from distributing the days that we spend away from work, rather than concentrating those days into a weekend. That could mean taking a Wednesday and a Sunday off, rather than a Saturday and Sunday. Verifying these predictions in future research provides a practical means to verify of falsify – and improve – the model.

In the following sections we will explain how the computational model is formed, examined and applied to derive new expectations. We will do this by first relating to existing theory. Next, we will define the equations for the computational model and examine predictions that follow from these equations in two steps; the first step describing the relationship between stressors and cortisol levels, the second describing the relationship between cortisol levels and disease. Finally, the model will be applied to make predictions about the effects of changing the distribution of working hours.

A computational model of work stress and disease

We will base our computational model from McEwen's (1998) influential[2] allostatic load theory. This theory considers a physiological route to developing disease, which seems to receive better empirical support than theories that have a dominant psychological character (Das & O'Keefe, 2008; Cohen, Gianaros, & Manuck, 2016).

Allostatic load theory introduces two physiological concepts that play a central role in the theorized process of stress causing disease: *allostasis* and *allostatic load*. Allostasis is defined as the physiological adaptation to the stressful situation. Increased activity of the Hypothalamus-Pituitary-Adrenal-Axis (HPAA) in face of an appraised stressor (further referred to as stressor) prepares the organism to deal will the stressor. An increase in heart rate, a release of stored nutrients to the bloodstream and suppression of digestion are responses that are generally observed (for a relatively simple, but detailed explanation of the processes involved, see Sapolsky, 2004). Although the process of allostasis is described as a healthy adaptation, the process may produce harmful side-effects under certain circumstances. This is referred to as allostatic load, also described as wear and tear to the physiological system. Allostatic load may develop when allostasis occurs too frequently (Type I), when the

[2] Citations on ISI Web of Knowledge count 1'541 on July 2, 2018. The theory has also been used as a basis for other theories about the stress and health relationship (e.g. Geurts & Sonnentag, 2006).

allostasis is maintained too long (Type II) or when physiological adaptation is inadequate (Type III). As allostatic load accumulates, disease may follow.

To define a computational model, various assumptions will need to be made. Two assumption that are made concern simplification of allostatic load theory. First, we will be considering only Type I, i.e., allostasis occurring too frequently. Second, we will assume that the circulating concentration of the hormone cortisol – frequently used as a measure of stress response (Dickerson, & Kemeny, 2004; Hellhammer, Wüst, & Kudielka, 2009) – provides a measure of the extent to which allostasis is happening.

Part 1: from stress to cortisol

Figure 2 shows a schematic of the computational model that was developed in this study. In the following sections, we describe how the part 1 of this model, from work stressors to cortisol levels was defined and tested. We do this by first reviewing literature that describes various parameters involved in this process. Subsequently, we apply this knowledge to formulate a computational model of this process. The model is then tested on its appropriateness by comparing model simulations to empirical data from published literature.

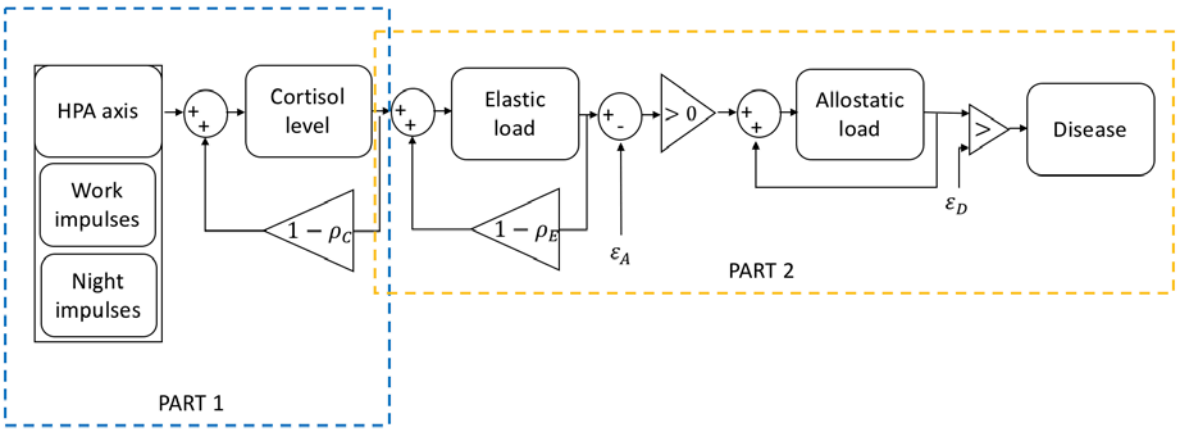

Figure 2. Schematic of the developed computational model, with PART 1 and PART 2 referring to the sections where these parts will be discussed in the text.

Knowledge from literature. When a stressor is appraised a sequence of organs work together to change the blood cortisol levels. Production of cortisol is regulated by the HPAA (Sapolsky, 2004). The HPAA consists of three hormonal glands: the hypothalamus and the pituitary gland in the brain and the adrenal gland located on top of the kidneys. These glands produce the hormones CTH, ACTH and cortisol respectively, by which they influence each other's activity. The cortisol that is produced is eventually decomposed by the liver. Although the hormonal glands are sequentially aligned, with the hypothalamus starting a cascade of activity in response to a neural impulse (Sapolsky, 2004), all 3 hormonal glands have receptors for their own and each other's hormonal output, thus constituting an intricate dynamic system, which also involves the liver function (Hosseinichimeh, Rahmandadb & Wittenborn, 2015).

We can find descriptions of various aspects of the dynamics of circulating cortisol levels in scientific literature. Bloodstream cortisol has a characteristic circadian pattern with a steep rise in the last few hours of the night to a peak at half an hour after awakening (which we will further refer to as 'morning peak') and a gradual decrease during the day (see Wilhelm, Born, Kudielka, Schlotz, & Wüst, 2007 for a review). Apart from this characteristic pattern, individual cortisol levels vary (see e.g. the individual cortisol patterns collected by Carroll et al., 2007 shown in figure 8a). One source of variation is the response to acute stressors (for an extensive review, see Dickenson and Kemeny, 2004). Variation in the rate of decomposition of cortisol is another source of variance. Reported ranges of cortisol half-life vary between 60 and 90 minutes (Carroll et al. 2007; Kovacs & Ojeda, 2011).

Literature that describes the response to acute stressors provides us with information about the dynamics of the cortisol response to a stressor. As a stressor takes place, the cortisol level gradually rises until it reaches its peak after about 30 minutes after which cortisol levels

decrease again (Dickenson & Kemeny, 2004; Goodman, Janson, & Wolf, 2017; Sapolsky, 2004).

In their review, Fries, Dettenborn, and Kirschbaum (2009) suggest that a distinct relationship exists between the acute stressors, happening during the day, and the morning peak. Specifically, Fries et al. suggest that this is an anticipatory relationship, with this peak reflecting the expectation of physiological and psychological demands for that day. Reports of a higher morning peak during the working weak than during the weekend (Schlotz, Hellhammer, Schulz, & Stone, 2004; Thorn, Hucklebridge, Evans, & Clow, 2006) and a study showing an elevated morning peak on performance days in competitive dancers (Rohleder, Beulen, Chen, Wolf, & Kirschbaum, 2007) are examples of studies that support this suggested relationship. In simulations of our model we will consider both scenarios where this relationship is either assumed or is not assumed.

In a computational model. In this part of the model we describe the relationship between neural impulses to the HPAA, I_t, and the change in cortisol concentration $\frac{dC}{dt}$. We assume that all activity of the HPAA is the result of neural impulses to the HPAA, which may either be the result of an internal mechanism taking place during the night, leading to the characteristic time course of cortisol in the night (we will further refer to these impulses as 'night impulses'), or the result of work stressors (for consistency reasons further referred to as 'work impulses'). We assume that each impulse has a fixed duration and a binary intensity (i.e., it is either happening or not happening). Due to this assumption, impulses to the HPAA, at any specific time point, can be described as countable number, $\sum I_t$.

We simplify the dynamics of the HPAA by assuming a linear relationship, κ_{HPA}, between neural impulses, I_t, and a rise in the cortisol concentration, minus a decay of cortisol that is described by a linear relation between the current cortisol concentration, C_t, and a decay constant, ρ_C. The resulting differential equation is:

$$\frac{dC}{dt} = -\rho_C\, C_t + \kappa_{HPA} \sum I_t \quad (1)$$

Simulations. To examine the ability of the model to reproduce the cortisol patterns as reported in literature (specifically Born, Hansen, Marshall, Molle, & Fehm, 1999; Hosseinichimeh, Rahmandadb & Wittenborn, 2015; Miller et al., 2016) we performed simulations with the model, with parameters defined in Table 1. As input to the model, a population of 10'000 people was simulated. These simulated persons were each characterized by an individual cortisol half-life value. Also, each simulated person was given a unique average number of daily work and night impulses (i.e., the impulses related to work stressors and HPAA night activity) was unique for each individual. To mirror the time course of a cortisol response to an acute stressor as described in literature (Dickenson & Kemeny, 2004; Goodman, et al. 2017; Sapolsky, 2004), impulses in our model always lasted 30 minutes. For each individual, a random draw from a normal distribution of cortisol half-life values determined their individual cortisol half-life, with a mean and standard deviation chosen such to reflect the variation of half-life values reported in literature (Carroll et al. 2007; Kovacs & Ojeda, 2011).

With regard to the impulses, we made a distinction between the night impulses and the work impulses. In our model simulation, work impulses could occur at any moment within the working hours. We implemented this through random draws from a uniform distribution ranging from work start to work end. The probability of a night impulse occurring we assumed to increase exponentially during the night, with the maximum probability at awakening. We implemented this through random draws from negative exponential distribution (see Appendix A for a graphical representation of this exponential distribution).

We randomly assigned an individual average of night impulses by a random draw from a Gamma distribution (i.e. a continuous probability distribution for values that can only be positive, such as frequency values; Hazewinkel, 2002), as displayed in Appendix B.

Following this, the number of night impulses that a person received on a particular day we determined from a Poisson distribution (i.e., the discrete frequency distribution) with as expected frequency, λ, the average number of night impulses for that person. This same procedure was followed for work impulses. For illustrative purposes, Figure 3 shows how the Poisson distribution defined, for four random individuals, the amount of days that they had a specific number of night and work impulses. Figure 4 illustrates for four random individuals, the distribution of impulses over a day.

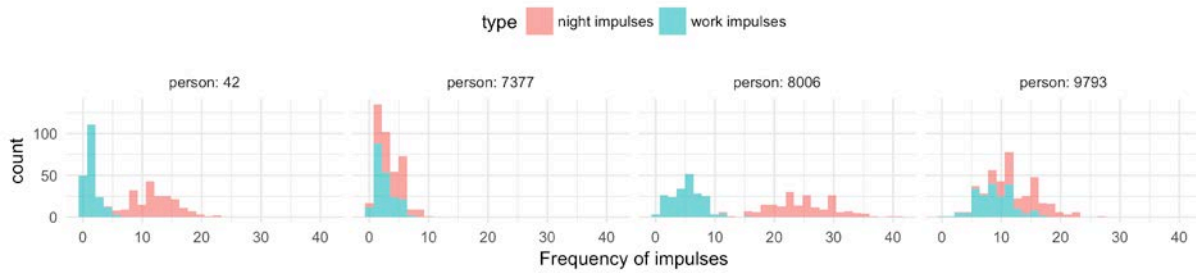

Figure 3. Count of days that an individual has a specific number of impulses. Four random simulated people shown.

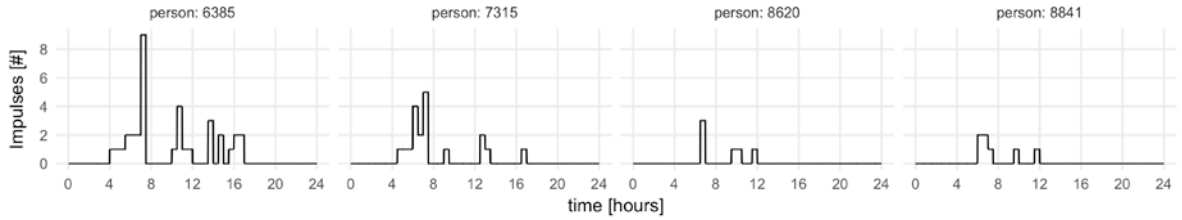

Figure 4. Distribution of impulses over a single day. Four random simulated people shown.

Two separate scenarios were simulated. In Scenario I we assumed that night impulses are uncorrelated with work impulses (see Figure 5a). In Scenario II, reflecting an assumed anticipation of workday stressors, night impulses were assumed to correlate with work impulses (see Figure 5b). In the case of Scenario II, the average number of night impulses for

a person were defined by summing the work impulses of that day with a random value from a gamma distribution with shape parameter $k = 1$ and scale parameter $\theta = 8$[3].

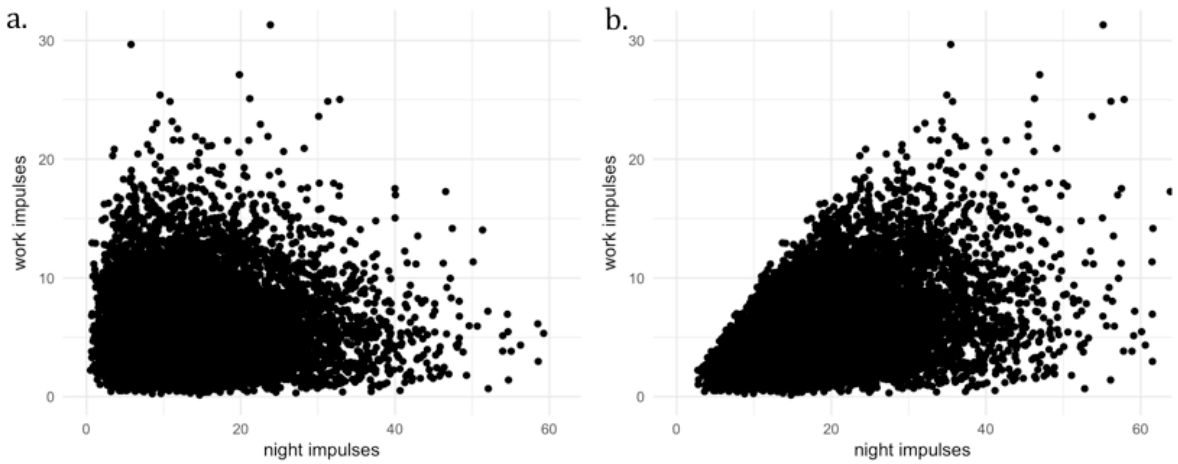

Figure 5. Correlations between work impulses and night impulses in Scenario I, uncorrelated (a) and Scenario II, correlated (b).

[3] This resulted in a distribution of average night impulses for scenario II (correlated) that is visually equal to the distribution of average night impulses for the scenario I (uncorrelated), which is described by the gamma distribution $\Gamma(k = 3, \theta = 14)$, see Table 1 and Appendix B.

Table 1

Parameter settings for simulating cortisol time courses in Part 1

Parameter	Value
Sampling frequency	2
People simulated	10’000
Days simulated per person	200
Night impulses, quantity	$\Gamma(k = 3, \theta = 14)$[a,b]
Night impulses, moment	$T_{wake} - \mathrm{EXP}(\lambda = 1)$[a,b]
Work impulses, quantity	$\Gamma(k = 3, \theta = 6)$[a,b]
Work impulses, moment	$\mathcal{U}(a = T_{ws}, b = T_{we})$[a]
Cortisol decay constant (ρ_C)	$\mathcal{N}(\mu = .52, \sigma^2 = .05^2)$[a]
HPAA scaling constant (κ_{HPA})	2.20
Impulse duration	30 min
Wake time, T_{wake}	7AM
Work start, T_{ws}	8:30AM
Work end, T_{we}	4:30PM
Working days	Mon-Fri

[a]Random draw(s) from this distribution.

[b]Values are determined through visual calibration on cortisol time courses published in Miller et al. (2016; see Figure 6a)

Simulation results. Figures 6 to 8 show comparisons of cortisol time courses from the simulations with cortisol time courses from literature sources. For each person, only the first day of the simulation was used to create these plots. In two of the comparisons (Figure 6 and 7) only the results from Scenario I (no correlation between work and night impulses, see Figure 5a) are displayed, as results from Scenario II (correlation between work and night impulses assumed, see Figure 5b) are optically highly similar (a comparison of the profiles from Scenario I and II can be found in appendix C). Units of the simulated cortisol time course, however, are arbitrary. Comparison of the simulated cortisol time courses since awakening with those from about 19’000 people from Miller et al. 2016 is shown in Figure 6. Comparisons of simulated cortisol time courses through the night with those from 15 people from Born, Hansen, Marshall, Molle, and Fehm (1999) are displayed in Figure 7. Figure 8 shows the comparison of a random sample of individual 24-hour cortisol time courses from simulation Scenarios I and II with those from Carroll et al. (2007).

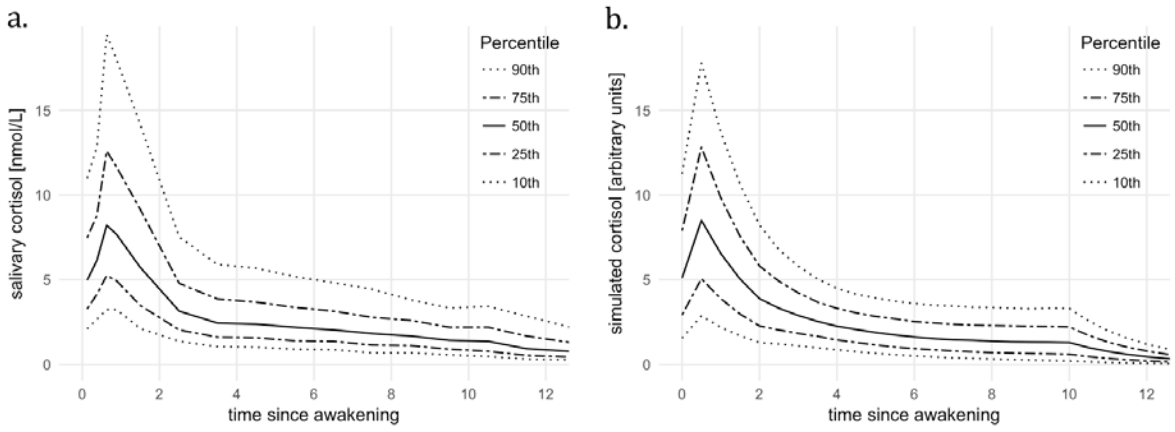

Figure 6. Empirical cortisol time courses from 18'698 individuals as published in Miller et al. 2016 and replotted with permission from the authors (a) and simulated cortisol time courses from 10'000 fictive individuals, based on the described model (b).

Note: in both cases, data is shown until 13 hours after awakening, which corresponds with corresponds with midnight in the simulation.

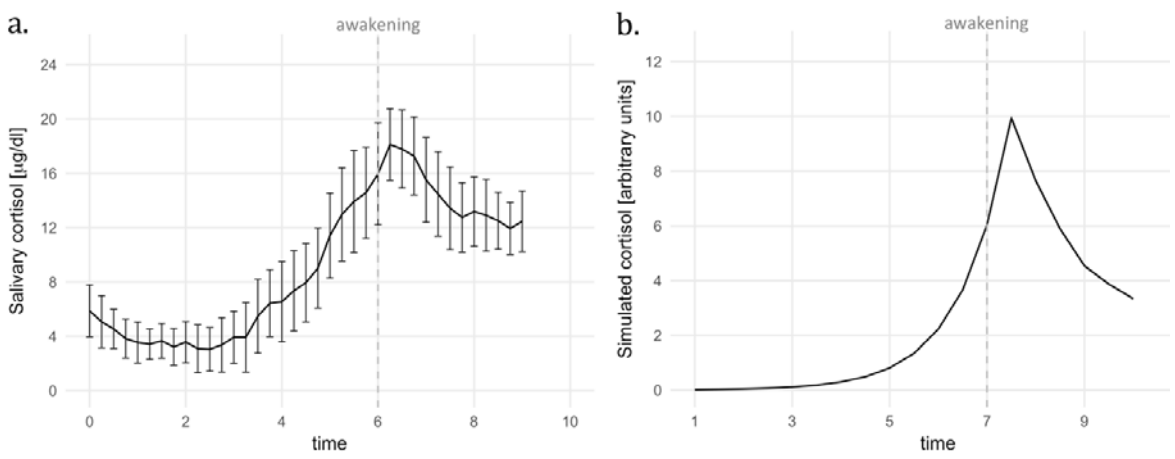

Figure 7. Empirical cortisol time courses during the night of 15 persons (mean and 95% confidence interval) replotted from Born et al. (1999; data presented in Clow et al., 2009; permission from the authors pending) (a) and cortisol time courses for the comparable time range as simulated from the computational model (b). Note that, in (b) the 95% confidence interval around the average is too small to be distinguishable.

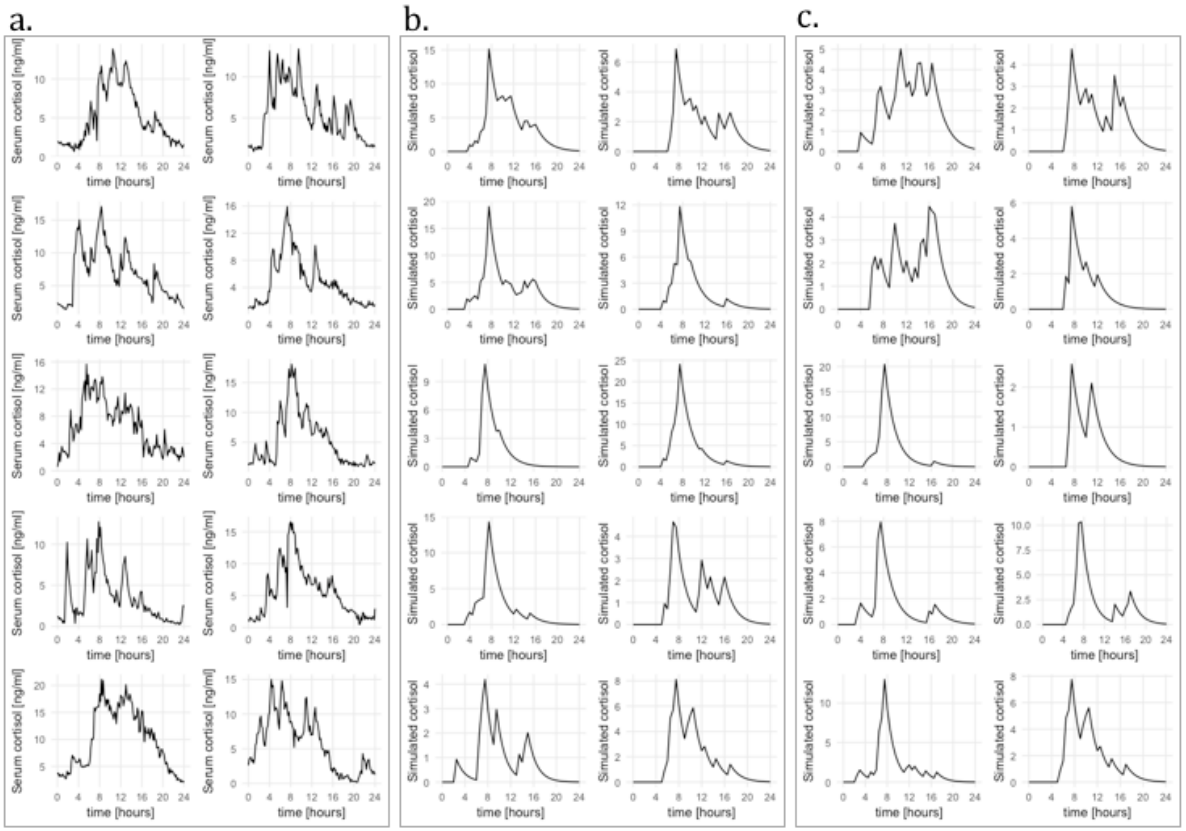

Figure 8. 24-Hour cortisol time courses of 10 healthy individuals from Carroll et al. (2007; data presented and shared for public use by Hosseinichimeh, Rahmandad, & Wittenborn, 2015; a) and simulated 24-hour cortisol time courses of 10 random individuals using the computational model for Scenario I (b) and Scenario II (c).

Discussion. The comparisons of the results from the model simulations with the empirical data suggest that our model is able to reproduce empirical findings. The shapes of the time courses seem comparable in all three comparisons. Therefore, we conclude that, by applying our model, we could successfully reproduce night and day cortisol time courses, both on the group and the individual level.

However, we also note differences between the simulation outcomes and the empirical results, which we will discuss here. First, whereas empirical cortisol levels never approach zero, this does happen in the simulated cases. Furthermore, when comparing the time courses

since awakening, we can note a difference from 10 hours after awakening. This difference may have various explanations: (a) In the simulation, no impulses after work were included and work was modelled to always end 9.5 hours after awakening. In the data by Miller et al. (2016), some people appeared to be active long after this time point and well into midnight (original data published by Miller et al. includes measurements up to 20h after awakening for some participants); (b) Whereas true cortisol levels never approach zero, this was possible in our model. Including minimal cortisol levels that vary between people, may account for a considerable portion of the difference.

As a second difference, is that the simulated time courses (Figure 7b) appear to have a somewhat steeper rise and fall than the time courses from Born et al. (1999; Figure 7a). The simulated time course may however be expected to fall within the 95% confidence interval of the data from Born et al. On a macroscopic level, the two graphs are found to be similar.

Although these differences suggest out that simulations with the model do not explain all the variation that is found in the empirical data, the results show that the model allowed us to reproduce the observed variation of several key data to a large extend. We conclude that these results therefore suite well with our goal for the model and allow us to continue to model the relationship between cortisol levels and disease.

Part 2: from cortisol to disease

In the following sections, we describe how Part 2 of the model, from cortisol levels to disease (see Figure 2) was defined and tested. Based on research on the process of becoming diseased from stress, we formulate an analogy that simplifies these processes. The model is then tested on its appropriateness by (a) comparing model simulations to empirical data from published literature, and (b) by testing the robustness of the predictions for variation in parameter values.

Knowledge from literature. The process of increases in cortisol concentrations leading to disease varies strongly between the organ systems affected (e.g. the cardiovascular, immune and metabolic systems) and the biological mechanisms involved are complex (see Sapolsky, 2004 for an overview of the processes). Considering these processes in detail is beyond the scope of this article. Nevertheless, we believe we can distinguish some key mechanisms that allow us to simplify these processes, so that we can describe the cortisol–health relationship in a simple model.

If we consider the cardiovascular system, *allostasis* is reflected in an increase of the heart rate. Oxygen and nutrients arrive to the organs at a higher rate. As a consequence of the increased of heart rate, blood pressure also increases, and thus, the force by which blood cells collide with the artery walls increases. Although unproblematic until a certain extent, this process may eventually lead to wear and tear of the arteries. Specific circulating components—such as LDL-cholesterol and platelets—may now stick to sites of injury, causing arterial plaques. As a plaque gets loose, which may occur as the result of yet another moment of high blood pressure, it can get stuck in a smaller artery and deprive surrounding tissue of vital nutrients, causing malfunctioning or even necrosis of the tissue. A heart attack is an example of this (Sapolsky, 2004).

With regard to the metabolic system, allostasis results from releasing nutrients from storage sites into the bloodstream and suppressing further storage of nutrients (insulin suppression is one way in which the system achieves this). High levels of nutrients may however do damage at some point; a situation more likely to result if the stressor is not met with a response of physical activity (e.g. running away), which is a likely scenario in our current environment of psychological stressors. The ulcers observed in diabetic patients are extreme examples of what may happen in case of high circulating levels of nutrients (Sapolsky, 2004).

Considering the immune system, allostasis seems to exist in suppression the immune system that might otherwise become over-active in response to a physical injury (that, in case of a psychological stressor, may be suffered from a bite from a predator). An over-active immune system may express itself in auto-immune disease. Too much suppression of the immune system, which can happen in case of extensive exposure to stressors, may actually weaken the immune system, rather than keeping it in heathy range. With a compromised defense against pathogens and the risk of becoming infected increases (Sapolsky, 2004).

In an attempt to capture the essence of the dynamics of cortisol concentrations causing disease, we make use of an analogy. We think of the stretch of a blood vessel under blood pressure and make an analogy to a rubber tube (an analogy that isn't new, see e.g. Taylor & Gerrard, 1977a). As the tube is expanded under pressure, the elasticity of the tube will cause an opposing force to return it to the original shape. If the tube is however stretched beyond the range in which it is elastic, plastic deformation (i.e., lasting deformation) starts to occur and, at some point, the tube will tear. The plastic deformation represents the damage (i.e., allostatic load) and tearing of the tube represents the point at which the person becomes diseased.

With regard to the empirical relationship between work stressors and disease, the highest level of evidence is available for the relationship between *job strain* (the combination of a high job demand and low control) and cardiovascular disease is found (Kivimäki & Kawachi, 2015; Nyberg et al., 2013; Sapolsky, 2004; Steptoe & Kivimäki, 2013; Theorell et al., 2016). A large meta-analysis by Kivimäki and Kawachi, studying this relationship between work stress and cardiovascular disease, included over 600'000 participants from 27, both published and unpublished, cohort studies. They found a positive relationship between work strain and cardiovascular disease with a cumulative effect size of 1.33 (95% confidence interval 1.19 to 1.49). Noting that job strain concerns perceived work stress and that our

model input reflects perceived work stressors, we take this observed positive relationship as benchmark for our model predictions.

In a computational model. Returning to the analogy of the rubber tube representing the process of cortisol to disease, we will now use this analogy to formulate the equations that describe Part 2 of our computational model (see Figure 2). Stretching the tube within the elastic range will result in the tube returning to its original shape when the pressure is released. With E_t the stretch of the tube at a given time point, ρ_E, the elasticity constant and C_t the force on the tube induced by the pressure (represented by the cortisol level in our model), we can write this behavior in a difference equation:

$$\frac{dE}{dt} = -\rho_E \, E_t + C_t \tag{2}$$

In comparison to the allostatic load theory, this equation introduces a new variable, E, which we will refer to as 'elastic load'. In terms of the elastic load, equation 2 describes the change in elastic load as a load resulting from the current cortisol level, minus a 'recovery from load', described by the current amount of elastic load and the elasticity constant.

Stretching the tube beyond a certain point, ε_A, results in plastic deformation (i.e., lasting deformation). In a rubber tube this may be visible as a change in shape or color that remains after the pressure is removed. In case of the artery, this represents the point where the plaques start to form. This plastic deformation represents allostatic load, A, in our model. The allostatic threshold, ε_A, is the point where allostatic load starts to form. We can write:

$$\frac{dA}{dt} = \begin{cases} 0, & E_t < \varepsilon_A \\ E_t - \varepsilon_A, & E_t > \varepsilon_A \end{cases} \tag{3}$$

This equation states that allostatic load does not change if the current elastic load is below the allostatic threshold, ε_A. When the elastic load, E_t, is larger than the allostatic threshold, ε_A, allostatic load increases by the amount by which the elastic load is above the allostatic threshold, $E_t - \varepsilon_A$.

Stretching the tube even further will cause plastic deformation—allostatic load—to accumulate and the tube will eventually tear. In case of the artery, this reflects the point where the plaques start to cause functional impairments and the person becomes diseased (e.g., suffers from a cardiovascular accident). This point we will define by the disease threshold, ε_D and we can write:

$$D_t = \begin{cases} False, & A_t < \varepsilon_D \\ True, & A_t > \varepsilon_D \end{cases} \quad (4)$$

The equation states that the diseased state, D, is 'false' (i.e. the person is not diseased) if allostatic load, A_t, is below the disease threshold, ε_D, and 'true' if A_t is above this threshold.

Together, equations 2, 3 and 4 describe the process from cortisol level to disease in the computational model. To illustrate what variation of elastic load, allostatic load and disease may occur, Figure 9 provides an example from 5 randomly selected people over 7 days.

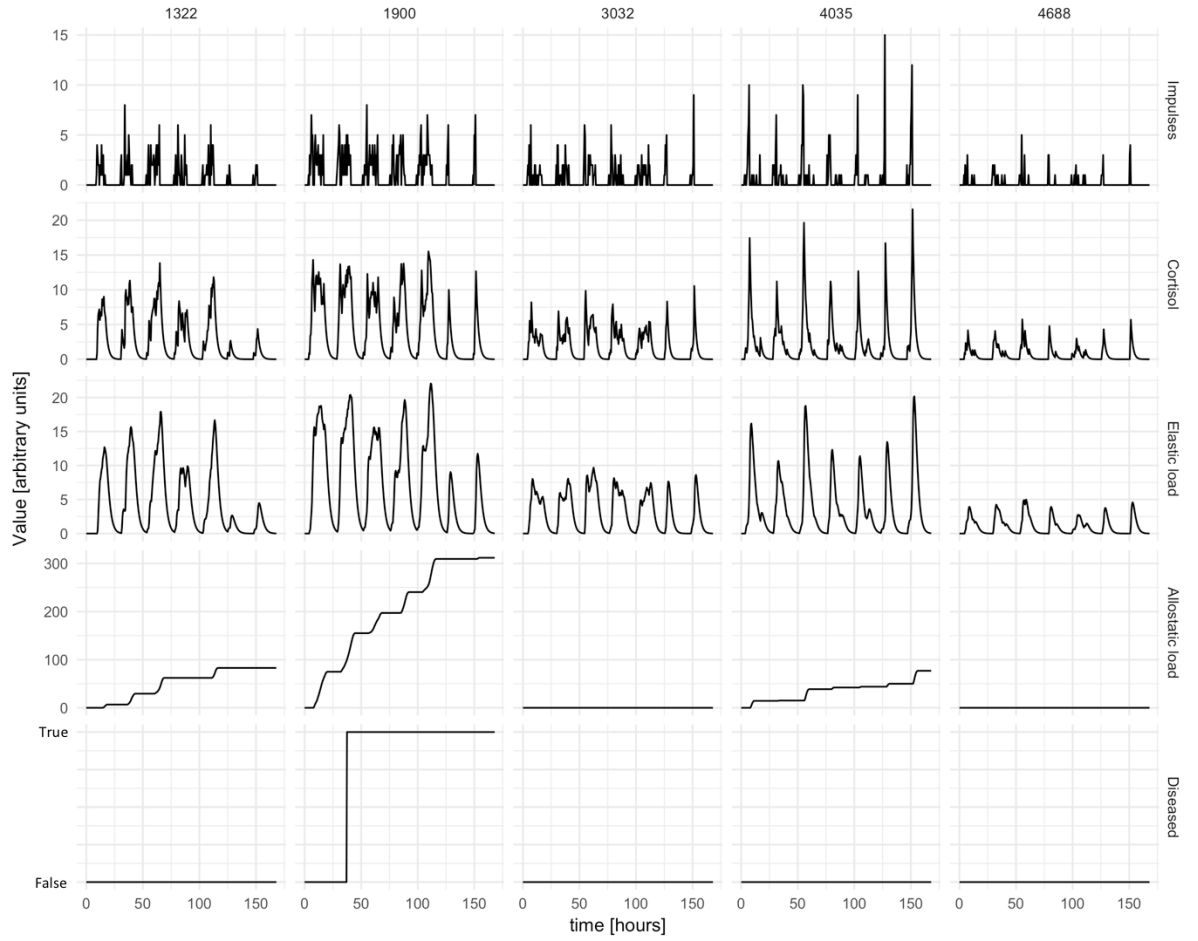

Figure 8. Sample of seven days showing variation on all model variables from 5 random simulated people

Simulations. We simulated this model using a range of values for the parameters ρ_E, ε_A and ε_D (3 values for each parameter and all 27 possible combinations between). As the model is an abstraction of reality (e.g., we assumed that the biological process works *akin to* a rubber tube), the choices for the parameter values were rather arbitrary. By performing the simulations for a range of these arbitrary values, we could examine the impact of choosing specific values. We chose range of parameters such that in each simulation at least some people would become sick and at least some people would stay healthy. Apart from this restriction, we aimed to choose values over the full range.

As input, cortisol time courses were created as described in Part I, apart from two minor variations. The reason for the first variation was to increase the precision of detecting

differences that exist in the fictive population, without needing to increase the number of simulated people. Instead of simulating a population with a variation in work impulses that is described by a Gamma distribution as in Part 1, we simulated individual variation in work impulses from a uniform distribution over the same range of work impulses. In other words, instead of creating a population with a variation in work impulses that is assumed to be a representation of the true population variation, as done in Part 1, we simulated a population with work impulses that are evenly distributed over the whole range of work impulses. Note that apart from increasing the precision of detecting effects, this variation would not otherwise influence the outcome of the simulations. The model itself is not changed by changing the input. To save computational time, another difference was that only 5000 instead of 10'000 people were simulated per simulation. As in Part 1, we simulated both the scenario where night impulses and work impulses were uncorrelated (Scenario I), as well as the scenario where they were correlated (Scenario II).

Simulation results. Figure 10 and 11 show the results of the simulations. Figure 10 shows the simulated allostatic load against the individual average of work impulses at the last day of the simulation. Different subplots show the results for the various parameter combinations and the two scenarios (Scenario I, no correlation between work and night impulses in Figure 9a and correlation between the impulses, Scenario II, in Figure 9b). Figure 10 shows, for different numbers of days into the simulation, the simulated relative risk (odds ratios) of people becoming sick when they differ on the number of work impulses.

The results indicate that, in case of Scenario II, where work and night impulses are correlated, the model is robust to variation of the parameters ρ_E, ε_A and ε_D. Irrespective of the variation in the parameters values, we find a positive relationship between the frequency of work impulses and the simulated risk of becoming diseased and little variation in the

predicted effect sizes is observed. These results are in line with the findings by Kivimäki and Kawachi (2015), which we aimed to reproduce.

This same robustness is not observed in the case of Scenario I. Although we observe a positive relationship between work impulses and the simulated risk of disease for a number of parameters, this is not the case for all parameters. Investigation of the data behind the graphs shows that the cases where a positive relationship was observed for Scenario I, an unrealistic high proportion of simulated people had become sick (appendix D).

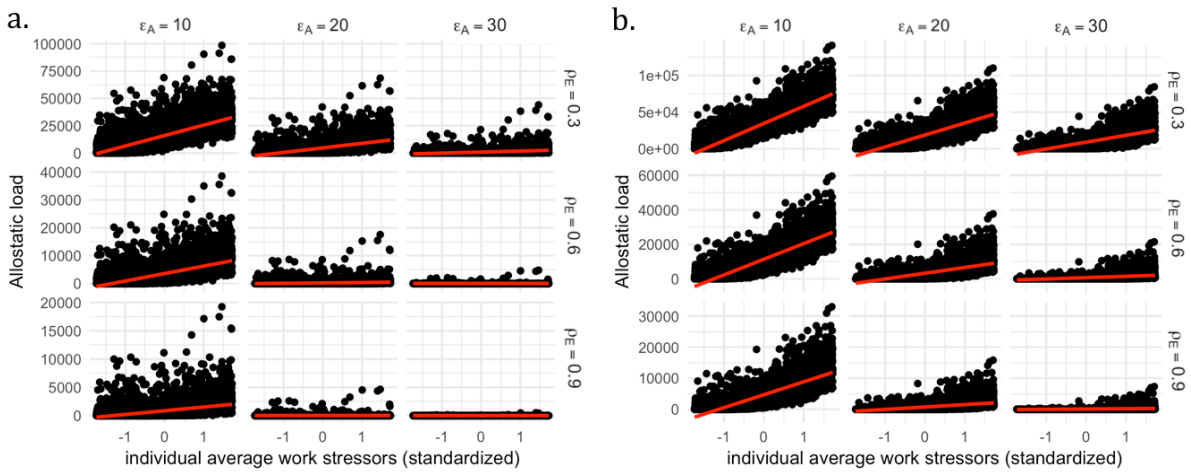

Figure 10. Simulated allostatic load against the average frequency of work impulses (standardized) for Scenario I (a; no correlation between work and night impulses) and Scenario II (b; correlation between work and night impulses). Different subplots represent the various tested parameter combinations.

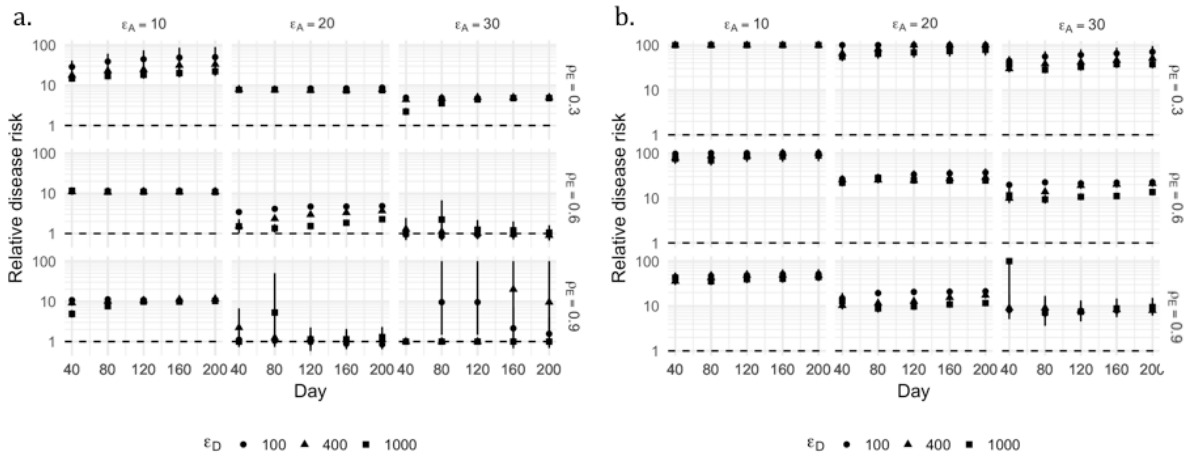

Figure 11. Simulation results of relative risk of becoming diseased at various time points in the simulation for Scenario I (a; no correlation between work and night impulses) Scenario II (b; correlation between work and night impulses). The odds ratios are calculated from the standardized averages of work impulses (i.e., the effect sizes represent one SD difference in the average number work impulses). Effect sizes above 100 are presented as 100.

Discussion. Simulation results show that, for a population that exhibits correlation between work and night impulses (Scenario II)—which we would expect to observe in case of workday anticipation—the model was successful in reproducing a positive correlation between work impulses and disease. This relationship, in line with the relationship between work stress and disease as observed in empirical literature, holds for a wide range of values of the parameters ρ_E, ε_A and ε_D, indicating the robustness of the model. However, we did not find a robust relationship between work impulses and disease if work and night impulses were uncorrelated (Scenario I).

This finding suggests that acute responses to work stressors play only a limited role. Rather, it appears that, in comparison to the response to acute work stressors (the work impulses in our model), the contribution of the night impulses is so high, that the cortisol spikes from the acute stressors during the working day have relatively little effect on allostatic

load that is developed. In line with this observation, investigation of individual time courses of allostatic load, as displayed in Figure 9, show that the increase in allostatic load is mainly seen at the time point of the cortisol peak just after awakening.

Model predictions for variations in working time

To recap, so far, we developed a computational model of work stress and disease. We compared the predictions from model simulations will empirical data and found that, if correlation between work impulses (i.e., appraised work stressors) and night impulses (i.e., activity of the HPAA during the night) is assumed, the model can reproduce results from empirical research. Based on these results we concluded appropriateness of the model under the examined conditions.

Now that the model has been defined and examined, we continue with exploring the effect of variations in working time on the relative risk of becoming diseased. Variations in working hours and workdays are explored, while always maintaining a 40-hour working week (by the U.S. Department of Labor [2008] considered as the maximal number of weekly working hours before being considered as overtime and special pay regulations apply).

Simulations. Next to a 'standard working week' (i.e., Monday to Friday, 8 hours daily), as was implemented when developing the model, five variations of a working week have been simulated. Table 2 summarizes the different working week situations that have been explored in different simulations. Table 3 describes the parameter values that were identical between the simulations. Note that these values are the same as the values used in Part II, apart from using only one combination of the parameters ρ_E, ε_A and ε_D (simulations for a number of other parameter combinations is shown in Appendix E). Also, based on our finding that empirical observed relationships of work stress and disease were reproduced in a robust fashion only if correlation between work and night impulses was assumed (Scenario II), we simulated only a scenario in which this correlation was assumed.

Table 2

Explored worktime situations

Situation	Days worked (per week)	Working hours (per workday)	Working days
1	5	8h	Mon-Fri
2	5	8h	Mon, Tue and Thu-Sat
3	4	10h	Mon, Tue and Thu-Fri
4	3	13h20min	Mon, Tue and Thu
5	6	6h40min	Mon-Sat
6	7	5h43min	Mon-Sun

Table 3

Parameter settings that were held constant between the simulations of varying worktime situations as described in Table 2.

Parameter	Value
Sampling frequency	2
People simulated	5'000
Days simulated per person	200
Night impulses, quantity	$\Gamma(k = 3, \theta = 14)$[a]
Night impulses, moment	$T_{wake} - \mathrm{EXP}(\lambda = 1)$[a]
Work impulses, quantity	$\mathcal{U}(a = 1, b = 50)$[a]
Work impulses, moment	$\mathcal{U}(a = T_{ws}, b = T_{we})$[a]
Cortisol decay constant (ρ_C)	$\mathcal{N}(\mu = .52, \sigma^2 = .05^2)$[a]
HPAA scaling constant (κ_{HPA})	2.20
Impulse duration	30 min
Wake time, T_{wake}	7AM
Work start, T_{ws}	8:30AM
Elasticity constant (ρ_E)	0.6
Allostatic threshold (ε_A)	20
Disease threshold (ε_D)	400

[a]Random draw(s) from this distribution.

Simulation results. Figure 12 provides an overview of the simulation results comparing the various worktime situations (Table 2) with the standard work week. The results show an increase in predicted disease risk in situations 3 and 4, which both concern a

compressed working week (concentration of the working hours to a limited number of days) as compared to the standard working week. In contrast, the results show a decrease in disease risk in situations 5 and 6, which concern spreading out the working hours over the week. No effect is found from situation 2, which concerns distributing work-free days over the week, rather than concentrating them into a weekend. Similar results were found for other combinations of parameters ρ_E and ε_A (Appendix E).

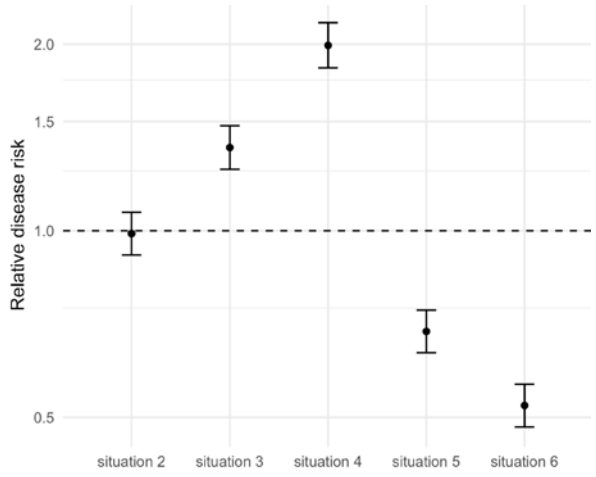

Figure 12. Relative risk of developing disease for varying worktime situations compared to the standard working week (i.e. working Monday to Friday, 8h daily). Situation 2 = working Monday, Tuesday and Thursday to Saturday, 8h daily. Situation 3 = working Monday, Tuesday, Thursday and Friday, 10h daily. Situation 4 = working Monday, Tuesday and Thursday, 13h20 daily. Situation 5 = working Monday to Saturday, 6h40 daily. Situation 6 = working Monday to Sunday, 5h43 daily.

Discussion. The results of these simulations suggest that spreading our working hours over a longer stretch of time, rather than concentrating the worked hours in a few days is beneficial for preventing the development of disease. In these simulations, a higher number in a workday, means more work impulses that day. As night impulses and work impulses are

correlated, a higher number in work impulses, means a higher number in night impulses and a more pronounced morning peak. As such, the simulations suggest that a limited number of a more pronounced morning peaks contributes more to the risk of developing disease, than a higher number of less pronounced morning peaks. This finding suggests again an important role of the morning peak in the risk of developing disease.

General discussion

In this study we developed and examined a first computational model of the work stress and disease relationship. We showed that a model that simplifies the mechanism of the cortisol response as two linear relationships, i.e., a cortisol release that is proportional to the number of stressors and a cortisol decay proportional to the cortisol level (resulting in an exponential decay), is able to reproduce the cortisol time courses as they have been previously reported in literature (Born et al., 1999; Carroll et al. 2007; Miller et al., 2016). We also showed that describing the process of developing allostatic load through the analogy of a rubber tube was able to reproduce the previously reported relationship between work stress and cardiovascular disease (Kivimäki & Kawachi, 2015). This was however only the case if we assumed that night impulses and work impulses were correlated, but not if these were uncorrelated.

Based on the created computational model, we also derived novel predictions relating to the relationship between work stress and disease. Through simulations, we predicted that, compared to compressing the working hours within a few days, spreading the working hours over more days reduces the risk of developing disease. We also predicted however, that there is no difference to be found from work-free days being concentrated together or spread out over the week.

Implications

To discuss the possible implications of the study that we conducted, we will reflect on the benefits of computational modelling as we have listed them in the introduction: contributing to falsifiability, enhancing understanding and making novel predictions.

Contributing to falsifiability. By creating a computational model of the work stress and disease relationship, we have created a theory that can be genuinely falsified. There are no implicit assumptions and the is no flexibility in interpretation of the parameter interactions. We have made the model-based prediction that distributing working hours over the week will reduce the risk of becoming diseased. Finding empirical evidence that is in contrast with this prediction would falsify the model. In that case the model would need to be improved or replaced by a model that is able to cover the range of empirical findings.

Enhancing understanding. Through the creation of the computational model, various new insights about the process under consideration have emerged. We have learned that a simplification of the cortisol dynamics, describing these by a cortisol release that is proportional to impulses to the HPAA and a cortisol decay that is proportional to the cortisol level, can reproduce empirical findings of cortisol variation rather well.

We have also learned that the logic of allostatic load theory can hold when its predictions are scrutinized using a computational model as we did in this study. In relation to this observation, we also learned that a correlation between (expectance of) appraised stressors would probably need to exist for a positive relationship between work stressors and disease to be observed

Making novel predictions. Through simulations of our model we have made new predictions about effects that may be observed real populations. First of all, we predict a preventive effect from distributing working hours more evenly over the week. On the other hand, concentrating the working hours within a few days was predicted to increase the risk of developing disease.

These predictions relate to a concept of the *compressed working week* (CWW). Within the CWW, employees perform their weekly number of working hours in fewer than the conventional five working days (Baltes, Briggs, Huff, Wright, & Neuman, 1999). Multiple studies have empirically investigated the effectiveness of CWW (see e.g. the meta-analysis by Baltes et al. and review papers by Bambra, Whitehead, Sowden, Akers, & Petticrew [2008] and Dall ’ora, Ball, Recio-Saucedo, & Griffiths [2016]). The compressed working week is expected to benefit the well-being of employees by providing them with a longer weekend in which they can pursue leisure activities and invest in their social relationships (Baltes et al.; Bambra et al.; Dall ’ora et al.) and detach and recover more effectively (Geurts, Beckers, & Tucker, 2014). Despite these expectations, empirical results of these benefits are found to be inconclusive, but “cautiously positive” (Bambra et al.), although detrimental effects of working 12 hours daily (Dall ’ora et al.) are also mentioned.

Interestingly, by suggesting a detrimental health effect from compressing the working week, the predictions from our model simulations suggest an opposite health effect as expected from this body of literature. Although empirical findings are said to be inconclusive about any true effects existing and did not reflect a direct link with disease rates, negative health effects were neither concluded. We may attribute the apparent inconsistency of our model predictions and expectations from empirical literature to one specific assumption in our model simulations, namely the assumption that number of daily perceived work stressors is linearly related to the number of working hours. Literature on *work time control* (the autonomy over the timing of ones working hours) suggests a positive effect of autonomy over the timing of the working hours on health outcomes (for an overview, see Beckers, Kompier, Kecklund, & Härmä, 2012) and, as can be found in my psychology textbooks, perceiving control is found to be powerful as a mechanism to cope with stressors. Rather than a longer working days representing a linear increase in the number of perceived work stressors,

employees may have perceived the longer working day as an expression of control of their working hours, mitigating the negative effect from an increase in the perceived (or maybe better, anticipated) work stressors from working more hours.

Researchers continuing on the work presented in this study using a computational model of work stress and disease, may want to consider adding a parameter to account for the effect of a reduction in anticipated stress from perceived control over the work time. Researchers could do this, for example, by determining what the equivalent of working hours of original 'stressfulness' would be for the benefit from perceived control to cancel out the negative effect of a higher morning peak resulting anticipated workday stress in case of CWW.

Note that predictions from our simulations result suggest no special direct health benefit from having a longer, compensating, weekend. Increases in simulated allostatic load happened on the workday itself, rather than happening over the span of the week. Weekend recovery would however be expected to make a difference, if the weekend recovery would influence the expected ability to cope with stressors on the workday, thus reducing the anticipation of workday stress. Implementing such an effect in the model would be possible but would add additional arbitrary parameter choices to the simulation. Researchers should therefore only include effects of weekend recovery if expecting a significant contribution from doing so.

Only empirical research investigating the relationship between compressing or distributing hours over the week and disease outcomes can provide conclusive answers on this issue. The outcome of such a study may carry important consequences for work time regulations if the predictions from our simulations are empirically verified, or a health benefit from CWW is found (which would falsify our model).

Besides this prediction, that we explicitly sought to make within this study, we can also infer other predictions from the model structure and simulations. The relationship between the morning peak (the cortisol peak after awakening) and risk of developing disease, as predicted by the model simulations, provides expectations about processes that may occur, or may have occurred, in people suffering from chronic stress. Concerning the size of the morning peak, contrasting results are observed in scientific literature. Some studies reporte an increase in the morning peak, whereas other studies report a decrease in the morning peak (Fries et al, 2009; Oosterholt, Maes, Van der Linden, Verbraak, & Kompier, 2015). Fries et al. suggest that the lower cortisol peak after awakening is the results of longer periods of chronic stress. With burnout being considered as a prolonged effect of chronic stress (Maslach, Schaufeli, & Leiter, 2001), Oosterholt et al. (noting predominantly evidence for a decrease in the morning peak and contributing to this evidence by their own empirical study) provides support for the suggested relationship by Fries et al.

The predicted relationship between the morning peak and disease outcomes from our simulations suggests that this lowered morning peak prevents (further) development of disease. Whether this suggested preventive function is the result of a consequential breakdown of the HPAA from previously elevated cortisol levels (Fries, Hesse, Hellhammer, & Hellhammer, 2005) or a functional mechanism to protect the organism against severe physiological (through a breakdown of the HPAA) is not answered by this prediction.

The mentioned decrease in cortisol levels from prolonged chronic stress may however come with a problematic side effect when cortisol levels of the morning peak return to normal levels. Such a return to normal levels of the morning peak were observed in clinical burnout patients in a follow-up, 1.5 years after the burnout was diagnosed (Oosterholt, Maes, Van der Linden, Verbraak, & Kompier, 2016). As Silverman and Sternberg (2012) suggest, elevated cortisol levels (or *hypercortisolism*), preceding the decreased cortisol levels (or

hypocortisolism), may reduce the sensitivity of immune cells to cortisol. As chronic stress persists and hypocortisolism results, the immune system responds by increasing the sensitivity of the HPAA. This may eventually lead to an overreactive immune system causing inflammation at various sites in the body. As such, the return of the morning peak to original level may contribute to inflammation and, consequentially, disease.

Other predictions that can be inferred from the model and model simulations concern e.g. (a) the assumed central role of the liver in controlling cortisol levels, (b) possible mechanisms behind the assumed exponential growth of HPAA activity during the night and (c) implications from the analogy of the process of developing allostatic load with a rubber tube. Discussion of these predictions we however leave to future research endeavors.

Limitations

Limitations in our study mainly concern the assumptions that were made to derive the computational model. First of all, in our model we consider only variation in the frequency of appraised work stressors, but no variation in the duration of the stress response. Examination of the model simulations in comparison with empirical cortisol time courses did however not indicate that this simplification is an important limitation to the model. Next to the variation in the frequency of stressors, the duration of a stress response may therefore not add much variation to the model outcomes.

A second limitation concerns the fact that only the cortisol level was used as an indicator of allostasis. Besides this hormonal activation, sympathetic activation is another important path by which the HPAA causes allostasis (McEwen, 1998; Rohleder et al. 2007; Sapolsky, 2004). Although both routes are activated in case of a stressor, the relative activation of each is found to differ somewhat depending on the type of stressor (Sapolsky, 2004). However, apart from the situational variations in relative activation or these two paths, it is our understanding that both routes are good indicators of the HPAA activity and we are

unaware of any literature indicating that, to consider in only cortisol levels as an indicator of allostasis, would be problematic. Thus, the simplification to describe allostasis only through one of the two paths, the one of which the documentation is more extensive, seems to fit well with the goal of this study. Eventually scrutinizing of model predictions against empirical data will need to determine whether the simplification was justified.

A third limitation concerns the simplifications compared to the analogy of the rubber tube. In our model we have assumed that the elasticity constant, ρ_E and allostatic load threshold, ε_A, remain the same, irrespective of the amount of allostatic load that may develop over time. We may consider the rubber tube from our analogy and imagine a local swell that has remained after an amount of internal pressure was applied; an amount of pressure beyond the range in which the stretch is purely elastic and plastic deformation starts occurring (the allostatic load threshold in our model). If a high amount of pressure would be applied once more, we would expect this swell to expand first. Based on this analogy, it would be unlikely for ρ_E and ε_A to remain the same after allostatic load was formed. Instead, one would expect these parameters to change such that allostatic load is already developed at lower concentrations of cortisol. However, if we take a closer look at our data (appendix D), we can notice that the majority of simulated people that develops any amount of allostatic load, also becomes sick eventually. In other words, if we simulate a sufficient number of days, all these people will eventually become sick and the relationship between the work stress and disease would stabilize. Our results in Figure 10 indicate that stable results were already observed within the 200 days that we simulated (the risk ration hardly changes over the number of simulated days). Implementing dependence of ρ_E and ε_A on the amount of allostatic load that is formed to reflect an acceleration in allostatic load that is developed would therefore not be expected to cause a major change in the predictions about disease risk. Moreover, implementing such variability of ρ_E and ε_A would require yet more parameters that would be

arbitrary to at least some extend. Taking it all together, we therefore consider implementing this variability as unnecessary and undesirable.[4]

This is not an exhaustive list of limitations. Other limitations for example lie in the fact that people are not expected to change their behavior during the simulation or the fact that other stressors than work stressors have not been considered. For most of these limitations, the justification would be that including this variation would not be expected to have a large influence on the final result of the simulations, but mainly add noise to the predictions. Moreover, adding parameters would most likely require yet other arbitrary assumptions; assumptions of which verification of their appropriateness would be difficult. Until the model has been falsified against empirical data, there seems to be little reason to implement more sources of variation to the model.

Future directions

The most important next step after this study is clearly to collect empirical data that allows critical examination of the model predictions. Upon publication of this study, the simulation code will be made available in the supplementary materials. We encourage all interested researchers to take the developed model, use it and optionally alter it to allow it to make predictions about the scenario's that they wish to study and then test these predictions against empirical data to verify the model predictions.

Conclusion

In this study we developed and examined a first computational model of the work stress and disease relationship. Based on simulations of this model, we suggest that the risk of becoming diseased can be reduced if working hours are more evenly spread over the working week, rather than compressed within a limited number of days. The opposite, a detrimental

[4] The situation is different if one is interested in making a different sort of prediction. If a researcher wants to use the model to make predictions about the time course of disease development, the discussed variability would likely give different results. Appendix F provides additional information.

health effect from compressing the working week is also expected. Moreover, we suggest that the cortisol peak observed after awakening plays a critical role in the health benefits or risks that follow from work stressors. Empirical research is needed to verify whether this prediction holds in real populations.

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Appendix A

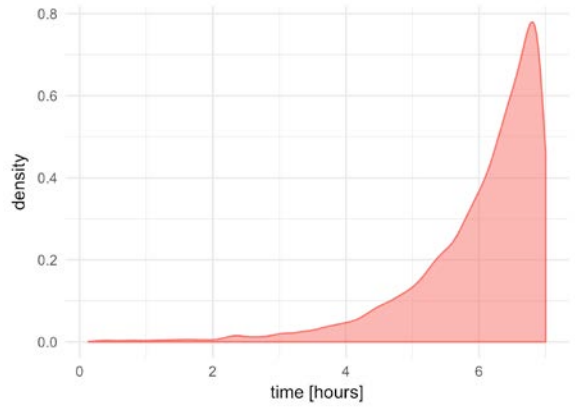

Figure A1, exponential distributions from which the time point of any random night impulse was determined.

Appendix B

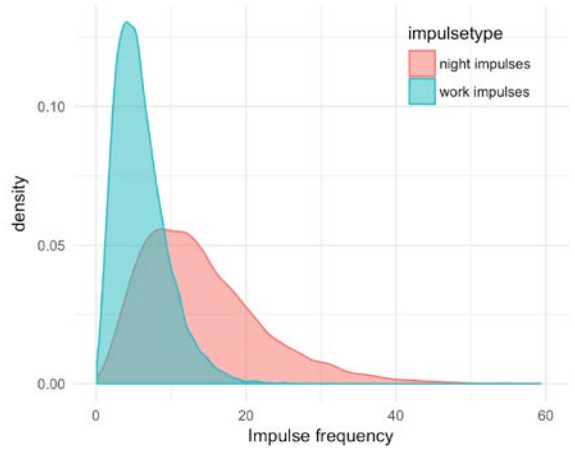

Figure B1, distributions of individual averages of night impulses and work impulses of 10’000 fictive people.

Appendix C

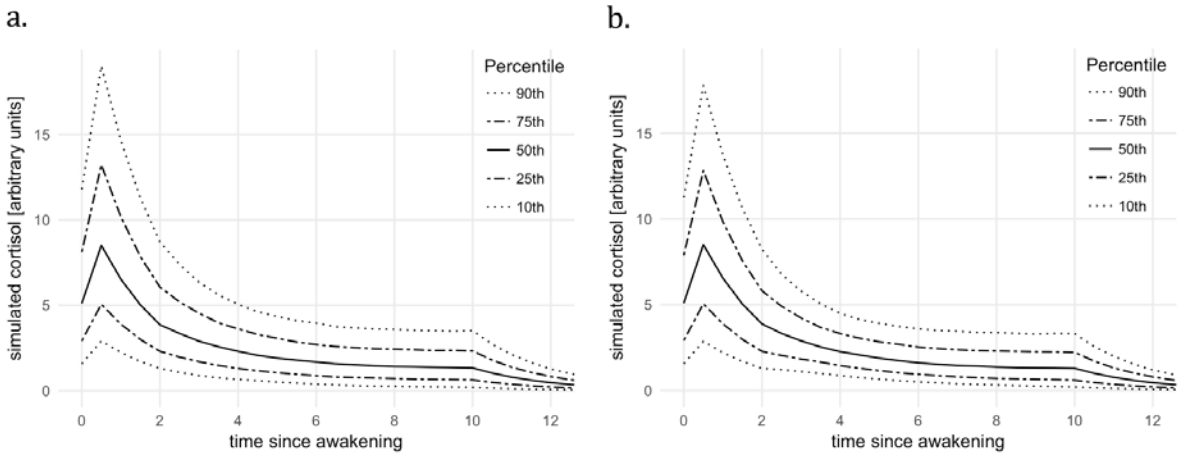

Figure C1. Cortisol time courses since awakening from simulating Scenario I (a; no correlation between work and night impulses) and Scenario II (b; correlation between work and night impulses).

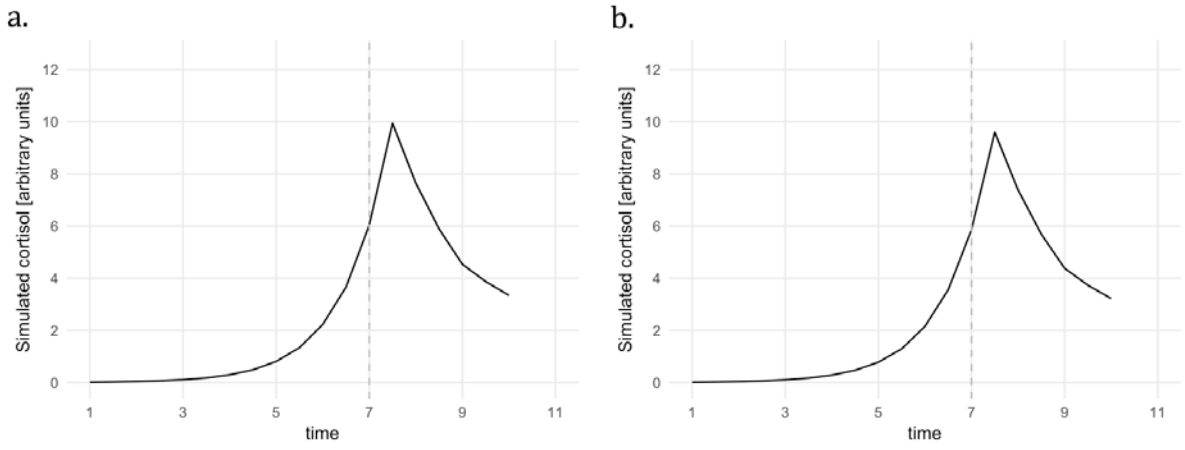

Figure C2. Cortisol time courses through the night from simulating Scenario I (a; no correlation between work and night impulses) and Scenario II (b; correlation between work and night impulses).

Appendix D

Table D1

Disease ratio for each tested parameter combination in Scenario I (work impulses and night impulses uncorrelated)

Simulation	Parameter values			Allostatic load (%)[a]	Diseased (%)	OR>1[b]
	ρ_E	ε_A	ε_D			
1	0.3	10	100	99.3	96.1	yes
2	0.3	10	400	99.3	93.0	yes
3	0.3	10	1000	99.3	89.3	yes
4	0.3	20	100	87.7	73.4	yes
5	0.3	20	400	87.7	64.6	yes
6	0.3	20	1000	87.7	56.2	yes
7	0.3	30	100	61.6	40.0	yes
8	0.3	30	400	61.6	30.0	yes
9	0.3	30	1000	61.6	21.3	yes
10	0.6	10	100	95.2	81.7	yes
11	0.6	10	400	95.2	72.0	yes
12	0.6	10	1000	95.2	61.5	yes
13	0.6	20	100	55.5	23.4	yes
14	0.6	20	400	55.5	11.7	yes
15	0.6	20	1000	55.5	4.8	yes
16	0.6	30	100	8.5	1.1	no
17	0.6	30	400	8.5	0.5	no
18	0.6	30	1000	8.5	0.3	no
19	0.9	10	100	86.3	57.2	yes
20	0.9	10	400	86.3	41.6	yes
21	0.9	10	1000	86.3	27.1	yes
22	0.9	20	100	17.6	2.3	no
23	0.9	20	400	17.6	0.9	no
24	0.9	20	1000	17.6	0.5	no
25	0.9	30	100	1.1	0.1	no
26	0.9	30	400	1.1	0.1	no
27	0.9	30	1000	1.1	0.0	no

[a]Allostatic load refers here to the percentage op people that has developed any amount of allostatic load in the model

[b]We tested the 95% confidence interval of the odds ratio (OR) against the condition of no noticeable difference (an OR of 1).

Appendix E

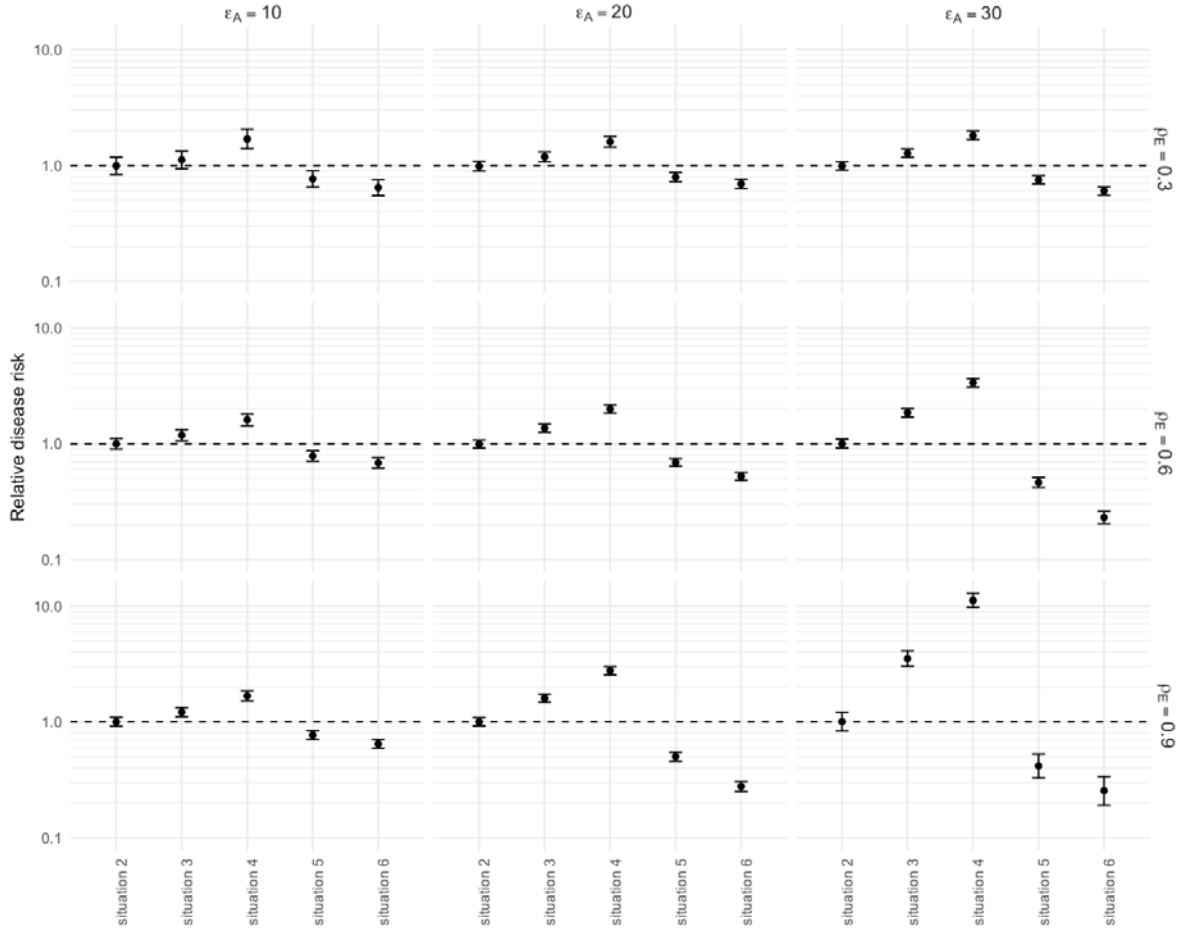

Figure E1. For the various tested parameter combinations, predictions of relative disease risk from varying worktime, compared to the standard week.

Appendix F

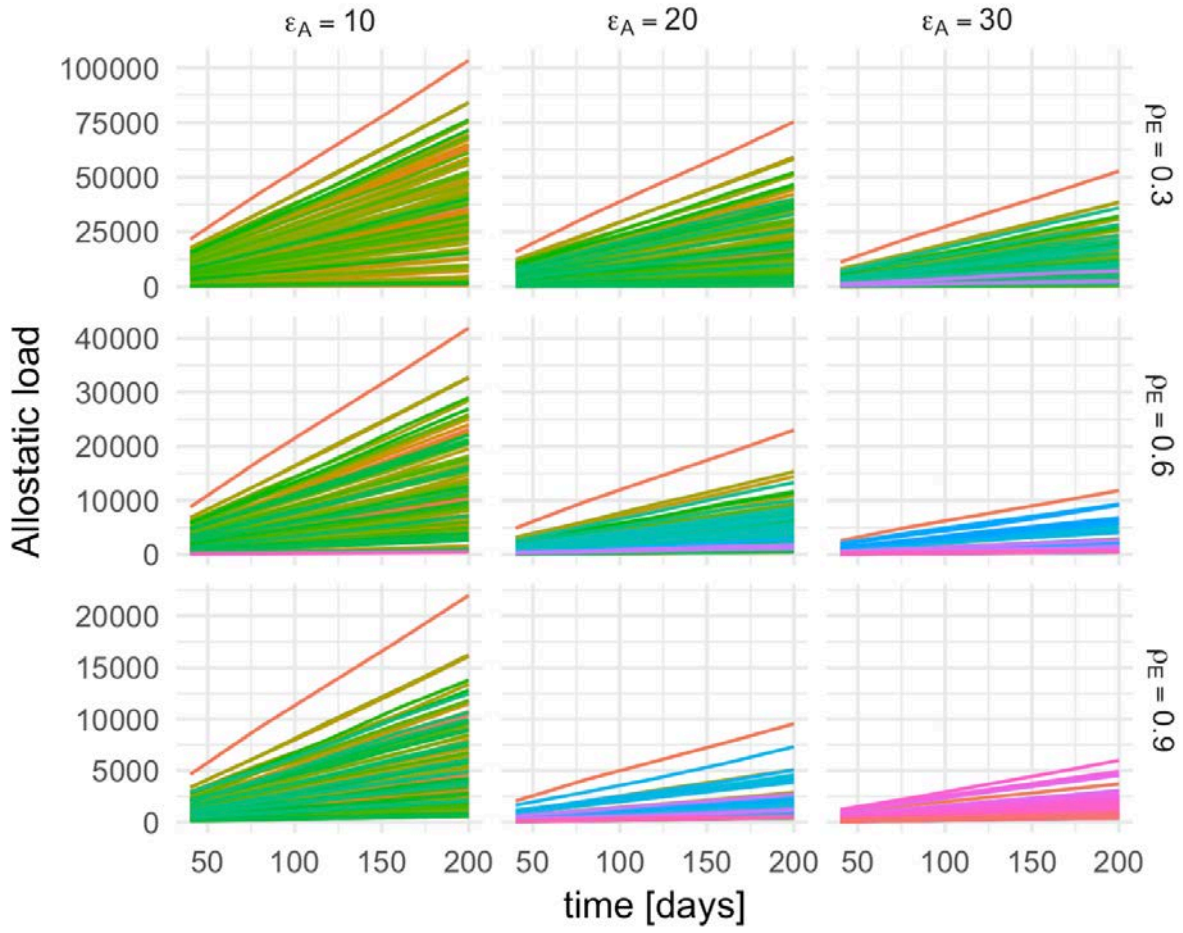

Figure F1. For the various tested parameter combinations, development of allostatic load over time for 100 simulated people that had become diseased at the end of the simulation, after 200 simulated days.