Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study

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Summary Alterations in the patterning of diurnal cortisol secretion are associated with poor health in clinical populations with ‘flat’ patterns a particular risk. Flatter patterns in cortisol secretion may reflect impaired negative feedback in the hypothalamic-pituitary-adrenal axis. The correlates of discrete clusters of patterns in the diurnal secretion of cortisol have not been well described in large community dwelling populations. We describe discrete clusters of patterns of cortisol secretion and examine the correlates of these patterns using a latent variable mixture modelling approach. Analyses use data from 2802 participants with complete information on cortisol secretion, age, walking/gait speed, stress, waking up time and sleep duration. Cortisol was assessed from six saliva samples collected at waking, waking plus 30 min, 2.5 h, 8 h, 12 h and bedtime. We find two patterns (“curves”) of diurnal cortisol secretion. These curves are described as ‘normative’ [prevalence 73%] and a ‘raised’ [27%] curve differentiated by a lower cortisol awakening response in the normative group, a higher diurnal cortisol and ‘flatter’ pattern of release in the raised group. Older age, being male, a smoker, stress on the day of sampling, slower walking speed and shorter sleep duration increased the odds of being in the raised curve, relative to the normative curve. In conclusion, two patterns of cortisol secretion occur in middle aged men and women. Raised pattern of secretion, which occurs in 27% of our participants is associated with demographic variables, adverse health behaviours, psychosocial environment and impaired physical functioning.

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1. Introduction

The use of salivary sampling as a noninvasive tool for the assessment of free cortisol and therefore as a marker for activity of the hypothalamic-pituitary-adrenal (HPA) axis is
well established in human stress research (Kirschbaum and Hellhammer, 1989). This sampling method captures the diurnal variations in cortisol secretion with the large rise associated with the awakening response and the subsequent decline in levels across the day and has provided the opportunity to examine predictors of variation in these patterns in a naturalistic setting.

A number of ‘patterns’ in cortisol release have been described. For instance, studies of serum cortisol variations in patients with severe long lasting psychiatric depression have shown that these patients have raised evening levels of cortisol which correspond to an inability to lower appropriately serum cortisol during the dexamethasone test (Rubin et al., 1987). Conversely, those with pronounced symptoms of exhaustion such as the chronic fatigue syndrome are unable to raise their cortisol level in challenging situations and they also show very small diurnal variation (‘low flat curves’) (Demitrack et al., 1991). Cortisol hyposecretion is associated with post traumatic stress disorder (Yehuda et al., 1991) and a ‘flat pattern’ is associated with fatigue in cancer patients (Abercrombie et al., 2004) and in mal-treatment in childhood (Tarullo and Gunnar, 2006). These patterns in cortisol secretion may reflect disturbances of the capacity to regulate cortisol secretion. Flatter patterns in cortisol secretion, in which evening levels of cortisol secretion are raised, may occur due to impaired feedback in the hypothalamic-pituitary-adrenal (HPA) axis or to hypersensitivity to cortisol stimulation later in the day with evidence suggesting a role for the former rather than latter mechanism (Spiegel et al., 2006).

Patterns in the diurnal release of cortisol secretion are usually described from visual inspection of means or population specific arbitrary cut points in slope of cortisol levels (Smyth et al., 1997; Ice et al., 2004; Ranjit et al., 2005; Cohen et al., 2006). A recent study used growth curve modelling and described three curves in cortisol secretion in children aged 3 years (van Rysin et al., 2009). Previous analyses have not formally described how the different patterns of diurnal cortisol secretion group or cluster together in older groups because few studies have assessed diurnal cortisol secretion in populations sufficiently large enough, that is, with many hundreds of participants, to examine clustering of these patterns.

Cortisol secretion is hypothesized to be etiological in the development of a number of conditions including heart disease (Rosmond et al., 2003), osteoporosis (Raff et al., 1999), cognitive decline (Karlamangla et al., 2005) and recently with frailty (Varadhan et al., 2008). These are conditions that are manifest in older age groups, and understanding how the patterns of diurnal cortisol secretion group together in an older population and also the predictors of these groups could help us identify normative and “abnormal” patterns of diurnal cortisol secretion and hence help identify the role of changes in cortisol secretion in the development of these morbidities and disease. Correlates of cortisol secretion in older age groups are mixed for basic descriptive correlates such as age in community dwelling populations. For example, previous reported associations of cortisol secretion with age and gender have been equivocal. Thus, associations with age are reported to be positive (Deuschle et al., 1997; Powell et al., 2002) or null (Van Cauter et al., 1996). Others have suggested that an association is apparent for those with depression only (Kudielka et al., 2000). Ice et al., describe a flatter slope in cortisol secretion associated with increasing age in 48 community dwelling volunteers aged 65 years and older. In this study, 2% of participants were described as having flat slopes in cortisol secretion, while Smyth et al. (1997) describe ‘flat’ patterns in 17% of younger participants.

Here we examine patterns of cortisol secretion in a large community dwelling population using a latent variable mixture modelling (LVMM) approach. The primary objective of LVMM is to uncover groups of individuals who share similar characteristics on a set of observed variables (in this paper cortisol). The unobserved patterns of cortisol release are described by a mixture of components, identified by categorical latent variables (latent classes): the object of the analysis is to find the smallest number of latent classes that can describe the associations among the set of observed continuous cortisol values observed across the day. The analysis adds classes stepwise until the model fits the data well.

We use the LVMM to examine whether different patterns in the diurnal variation of salivary cortisol can be identified in the population. Specifically,

1. What are the patterns (clusters) of diurnal cortisol secretion?
2. With which variables are the LVMM patterns associated? The predictors examined are those which have been demonstrated to modulate cortisol secretion in nonclinical studies and include biological (age and sex), behavioural factors (current smoking (Badrick et al., 2007), waking up time (Williams et al., 2005) and sleep duration (Spiegel et al., 1999), psychosocial (perceptions of stress) and a physical measure of functioning relevant to older age groups, gait/walking speed (Melzer et al., 2003).

2. Materials and methods

2.1. Study population

Data reported here are from phase 7 (2002–2004) of the Whitehall II study. The cohort was initially recruited between 1985 and 1988 (phase 1) from 20 London-based civil service departments, 10,308 people participated. Eight phases of the study have been completed, details of the study have been reported elsewhere (Marmot and Brunner, 2005). The number participating at phase 7 was 6968, of these 6484 had a clinical assessment. The collection of saliva samples was instigated part way through phase 7 and 4967 were asked to provide a cortisol sample out of whom 90.1% (n = 4609) returned samples. This group had fewer participants in the lowest civil service employment grades compared to phase 1 of the study, however this difference was small. Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research. Informed consent was gained from every participant.

2.2. Cortisol collection and analysis

The protocol has been described previously (Badrick et al., 2007). Briefly, participants were requested to provide six

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saliva samples in salivettes over the course of a normal weekday at waking, +30 min, +2.5 h, +8 h, +12 h and bedtime. Participants were instructed to avoid caffeine and acidic drinks, not brush teeth, eat or drink anything for 15 min prior to a sample collection. Participants used an instruction booklet to record information on the day of sampling including wake time (participants were instructed that this should be time of waking and not the time at which they got out of bed) and time each sample was taken. The salivettes and booklet were returned via post. Salivettes were centrifuged at 3000 rpm for 5 min resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Hamburg, Germany). The lower concentration limit of this assay is 0.44 nmol/l; intra and interassay coefficients of variance were below 8%. Any sample over 50 nmol/l was repeated. During analysis a total of 1002 individual samples were not assayed due to loss of sample in transport between London and Germany or insufficient saliva.

2.3. Covariates

Age and sex were assessed by questionnaire. Smoking status was assessed as previously described (Badrick et al., 2007). Current smokers, at phase 7, were defined as those that reported smoking cigarettes, cigars or a pipe, social or occasional smoking or taking nicotine replacement products. Waking up time was assessed by asking participants to record the time of waking on the day of the collection of saliva. That is the time at which the participants were aware of being awake for the day and were not going to go back to sleep. Participants were also asked to record the time of falling asleep the night before and sleep duration the night before sample collection was calculated from these responses. In addition, participants were asked to rate the most stressful event on the day of sample collection using the categories ‘not at all stressed’, ‘somewhat stressed’, ‘moderately stressed’, ‘very stressed’ or ‘the most stressed I have ever felt’. Participants classified as having a stressful experience if they responded that they were ‘very stressed’ or ‘the most stressed I have ever felt’. Walking/Gait speed, a measure of physical functioning was assessed by a nurse over a clearly marked 8 ft walking course using a standardised protocol (Guralnik et al., 1994).

2.4. Statistical methods

Missing data: A delay in taking sample 1 results in a reduced cortisol awakening response (CAR) (Kudielka et al., 2003). Therefore, data from 726 participants who reported taking samples later than 10 min after waking and 123 who reported that they ate, drank, exercised or brushed their teeth before the first sample were removed from the analyses. Additionally, those taking steroid medication (n = 260), with incomplete data on all six cortisol samples (n = 329) and outliers (3 standard deviations or greater from the mean, n = 220) were excluded. This left 3133 participants with valid and complete cortisol data (including time of sampling). Additional missing values for covariates (in particular, reported stress and walking speed) reduced this to 2802 participants.

2.5. Latent variable mixture modelling (LVMM)

The aim of the LVMM is to use the inherent variability in the data to find groups (latent classes) of individuals who are similar to each other, which is then represented by an unobserved (latent) categorical variable (Lazarfeld and Henry, 1968; McLachlan and Peel, 2000). For the analyses in this paper, as the six cortisol measurements are collected from the same person on the same day, we adopt the least restrictive assumption for a multivariate Gaussian mixture model so that the six cortisol measurements may covary in different ways in each latent class.

There are a number of considerations used to decide on the number of latent classes. The analysis adds classes stepwise until the model fits the data well starting with the simplest (a one class) solution. The number of classes to include is assessed first by an examination of the model evaluation statistics (see Appendix A for more detail). The second consideration is summarized using an entropy measure based on the class membership probabilities. Entropy measures how well the model is able to predict class membership given the observed cortisol values for each individual. The third consideration is the usefulness of the latent classes in practice. This can be determined by examining the trajectory shapes for similarity, the number of individuals in each class, and whether the classes are associated with observed characteristics in an expected manner (Muthén and Muthén, 2006; Nylund et al., 2007; Lo et al., 2001).

Once a class solution has been found, background variables which predict membership into the categorical latent classes by multinomial logistic regression are simultaneously modelled in the LVMM. These background variables are hypothesized predictors of diurnal cortisol release (biological and behavioural factors that alter HPA axis activity).

Full details of the latent variable mixture model (with MPlus command syntax) are specified in Appendix A. Analysis steps:

1. Use latent variable mixture modelling (LVMM) to decide on the number of patterns (latent classes) in diurnal cortisol secretion.
2. Add in covariates as background variables and see if the patterns remain similar.

3. Results

Compared to all those who were asked to complete sample collection at phase 7, the subsample of 2802 participants that were analyzed were very similar (Table 1).

3.1. Prevalence of discrete patterns of cortisol secretion

The fit statistics of the 1–6-class solutions for the latent variable mixture model (LVMM) are displayed in Table 2. Fig. 1 graphs the Bayesian Information Criteria (BIC) fit statistic and this shows that there was little improvement in model fit after the 4-class solution. This suggests that a 2–4-class solution may be appropriate. We can further assess whether we have chosen the right number of classes using the Vuong—Lo–Mendell Rubin (VLR) test (MPlus tech11, Lo et al., 2001). Please cite this article in press as: Kumari, M., et al., Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study. Psychoneuroendocrinology (2010), doi:10.1016/j.psyneuen.2010.01.010.
This test compares the model with \( K \) classes to a model with \( K/2 \) classes. The VLR test has a \( p \)-value of <0.05 for the 4- and 5-class models, and <0.01 for the 2- and 3-class models. This suggests that two or three classes are sufficient and that more than three classes are not needed. Furthermore, the entropy for the 3-class model (0.71) was considerably worse than for the 2-class model (0.78). Additional tests using parametric bootstrapped likelihood ratio tests (MPlus tech14) were carried out, but these results were likely to be inaccurate as the log likelihood was not replicated in repeated bootstrap draws, indicating local maxima (Nylund et al., 2007).

The mean cortisol values for the 1–3-class LVMM solutions are shown in Fig. 2. Comparing the 2-class solution with the 1-class solution, there appears to be a “normative group” (class 1, \( N = 2042 \)) with a similar profile to the 1-class solution. Furthermore, there is a “raised” cortisol profile group (class 2, \( N = 760 \)) with higher cortisol awakening response and higher mean day and evening time values compared to the normative class. The two groups differed in terms of the slope; the linear decline in cortisol from awakening to bedtime (ignoring the cortisol awakening response).

For the 3-class solution, in addition to the two groups described in the 2-class solution, there is another normative group (class 2, \( N = 1374 \)) with a “cortisol awakening response” and average cortisol over the day in between the raised cortisol profile group (class 3, \( N = 377 \)) and the first normative group (\( N = 1051 \)), which has the “flattest” profile in terms of diurnal cortisol slope.

As a result of inspecting the model fit statistics and the pattern of the cortisol profiles, we chose to investigate a 2-class solution further, using covariates to predict membership of these 2 latent classes. The mean cortisol values of the 2-class solution with covariates are displayed in Fig. 3. The profile is remarkably similar to the 2-class solution without covariates (Fig. 2). There is a normative profile class and a raised profile class with the latter class having a higher cortisol awakening response as well as higher day and evening cortisol secretion. Further in Fig. 3, additional analyses analyzing the 3-class solution with covariates were carried out: the VLR test has a \( p \)-value of <0.05 for the 3-class model, suggesting two classes are sufficient.

### 3.2. Predictors of discrete patterns of cortisol secretion

Table 3 displays the results of the logistic regression relating the binary 2-class pattern of cortisol release with a set of predictor variables, age, sex, smoking status, waking up time and sleep duration entered simultaneously. The normative group was chosen as the reference group. Participants with a raised cortisol profile (who had on average a greater CAR of 1.8 nmol/l and greater total cortisol of 2.7 nmol/l) tended to be older, men, smokers, had shorter sleep duration, reported events as more stressful, woke up earlier and walked more slowly compared to the normative group. We tested for 2-way interactions between all the covariates and did not find any...
Figure 2  Figures (a–c) 1, 2 and 3 class solutions for latent variable mixture models of diurnal cortisol: no covariates.

Figure 3  Two class solution (with covariates predicting latent class membership).
significant associations. We also repeated the analyses, restricting the sample to those people who had taken their second saliva sample between 30 and 45 min after awakening (N = 2755), and found the same pattern as for the whole sample.

4. Discussion

We find two common curves in this large community dwelling population using a latent class analysis approach. These curves represent a ‘normative curve’, and a ‘raised curve’. The raised curve was composed of an increased CAR and higher day time cortisol and flatter slope compared to normative curve.

The epidemiology of the HPA axis is relatively unexplored in large community dwelling populations, here we find in nearly 3000 participants, that those with a raised cortisol profile tend to be older, be men, have shorter sleep duration, wake earlier, report events as more stress and walk more slowly than those with normative curves. Those with a raised profile in cortisol secretion have flatter slopes in secretion than the normative profile in release.

A number of techniques are used to examine the circadian profile of cortisol when assessed by multiple sampling methods. These include measures that utilize information on the slope of the decline from the peak to trough levels (De Beurs et al., 2001), separate assessments of morning and/or evening cortisol levels (Steptoe et al., 2000) or total cortisol concentration over the day, using a measure such as area-under-the-curve (Pruessner et al., 2003; Dekker et al., 2008). Several studies focus on the rhythm profile of cortisol, as the CAR, as well as the extent of decline to the evening nadir (Smyth et al., 1997; Sephton et al., 2000; Schmidt-Reinwald et al., 1999; Adam et al., 2006).

Alternative approaches seek to describe the cortisol rhythm in all its complexity, and use non-parametric approaches to fit smoothing splines (Wang and Brown, 1996) which provide better fit but, while useful for exploration, do not yield quantitative parameters to allow for group comparison. Multilevel modelling approaches may be used because of the hierarchical structure of the data (Schmidt-Reinwald et al., 1999; Adam et al., 2006). However, only one study has used a method that describes how different patterns of diurnal cortisol secretion in a population cluster together (Van Ryzin et al., 2009). The latent variable mixture modelling method used in this and our paper is different from most methods in terms of letting the patterns of diurnal cortisol secretion be identified from the data themselves, rather than arbitrarily imposing cut off points in terms of slope or area under curve parameters.

4.1. Discrete patterns of cortisol secretion

The analysis showed two discrete patterns of diurnal cortisol release with clear separation between these patterns.

It could be argued that the CAR and decline of cortisol secretion throughout the day should be examined separately as predictors may be different for these aspects of cortisol secretion (Clow et al., 2004). We did this in further analysis to look at the differences between the two curves in terms of the diurnal decline in cortisol. The decline in cortisol was shallower in the raised curve, suggesting a ‘flatter slope’. The raised curve may represent groups in which cortisol is chronically raised due to a failure in negative feedback or hypersensitivity to cortisol stimulation at the end of day. Spiegel et al. (2006) suggested a flat curve in association with a raised CAR represented impaired negative feedback. More ‘extreme’ curves, for example, a pattern of low CAR and a flat curve as found in post traumatic stress disorder (Yehuda et al., 1991) are not apparent in the curves identified using this method suggesting that this population is healthy or that the population is a particularly compliant group. However, in our population, we have a prevalence of 27% of participants who have ‘flatter’ curves than the rest of the population. This prevalence of flatter curves is higher than previously reported levels; for example Ice et al. (2004) reported 2% of flat curves, while Smyth et al. (1997) reported 17%. This discrepancy may relate to the nature of cohort study populations to volunteer populations. It remains to be determined which aspect of cortisol secretion, these curves or more typically described parameters (Adam and Kumari, 2009), the CAR or slope in cortisol secretion are predictive of disease when participants are followed up for health events and other outcomes.

Table 3 Odds ratios (95% confidence interval) of the logistic regression of binary latent class membership regressed on background variables.

<table>
<thead>
<tr>
<th>Odds of being in raised profile class vs. normative profile class</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.01 (0.99, 1.03)</td>
</tr>
<tr>
<td>Sex (1 = men)</td>
<td>1.90 (1.48, 2.45)</td>
</tr>
<tr>
<td>Smoker (1 = smoker)</td>
<td>2.02 (1.45, 1.90)</td>
</tr>
<tr>
<td>Sleep length (hours)</td>
<td>0.76 (0.69, 0.84)</td>
</tr>
<tr>
<td>Wake up time 0:500 h or earlier</td>
<td>1.94 (0.99, 3.79)</td>
</tr>
<tr>
<td>Wake up time 05:00—06:00 h</td>
<td>1.70 (1.11, 2.60)</td>
</tr>
<tr>
<td>Wake up time 06:00—07:00 h</td>
<td>1.34 (0.95, 1.90)</td>
</tr>
<tr>
<td>Wake up time 07:00—08:00 h</td>
<td>1.13 (0.79, 1.60)</td>
</tr>
<tr>
<td>Wake up time 08:00 h or later (ref.)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stress on day of sampling (1 = stressed)</td>
<td>1.37 (1.04, 1.80)</td>
</tr>
<tr>
<td>Walking speed test (seconds)</td>
<td>1.21 (1.05, 1.39)</td>
</tr>
</tbody>
</table>

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4.2. Predictors of discrete patterns in cortisol secretion

Previous reported associations of cortisol secretion with age and gender have been equivocal. Thus, associations with age are reported to be positive (Deuschle et al., 1997; Powell et al., 2002) or null (Van Cauter et al., 1996). Others have suggested that an association is apparent for those with depression only (Kudielka et al., 2000). Our findings fail to clarify this relationship as they suggest that in a relatively healthy community-based sample, participants with increasing age have increased risk of being the elevated group supporting the hypothesis that negative feedback in the hypothalamic-pituitary-adrenal axis may change with aging (Jacobs et al., 1984) but this association failed to reach significance and requires clarification in additional studies. Reported associations of sex with cortisol secretion are mixed. Our data do not accord with studies indicating raised cortisol in women (Wust et al., 2000). We (Badrick et al., 2007) and others (Steptoe and Ussher, 2006) have shown that cigarette smoking is associated with raised total cortisol secretion and these findings are confirmed in the latent class analyses which indicate that smoking is associated with elevated patterns of cortisol secretion. Similarly, we find that in accordance with previous reports (Spiegel et al., 1999), short sleep duration is associated with elevated patterns of cortisol secretion. Short sleep duration is predictive of mortality associated with cardiovascular disease (Ferrie et al., 2007) and our findings accord with the notion that cortisol may play a role in mediating this relationship (Rosmond et al., 2003; Smith et al., 2005). Stress on the day of sampling is associated with increased membership of raised curve militating against a definitive conclusion on whether raised curve represents hypersensitivity to cortisol increase in the day or with impaired negative feedback. Our findings support the notion that cortisol secretion is associated with measures of physical functioning (Varadhan et al., 2008) and suggest that these associations are pertinent to younger, relatively healthy populations and to men. In particular our finding of a cross sectional association of these measures of cortisol with walking/gait speed points to a potential role for cortisol in the development of poor physical function and other outcomes associated with ageing.

The advantages of our study are that we conducted the collection of saliva from a large group of well characterized participants and achieved a high response rate. We see no evidence of participants not understanding the instructions. However, our participants are high functioning, currently or recently in white collar occupations and thus may not represent the population as a whole. Additionally, we assessed compliance by self report, we did not objectively verify reports but our rates of ‘late’ collection are not different to studies in which reporting was assessed objectively (Kudielka et al., 2003). Recent reports suggest that participants are generally accurate in their records of time of data collection (Dockray et al., 2008; Desantis et al., 2009). We measured cortisol in less than half of the original cohort (phase 1), we found that participants were generally healthy in comparison to the rest of the cohort that attended clinic at phase 7. Finally, cortisol was assessed on a single day as it would have been impractical to collect on more than one day in a sample this size and age and this may have resulted in some bias towards situational rather than trait factors as predictors of cluster membership (Hellhammer et al., 2007). Collection of cortisol in a single day also precluded us from comparing our findings to previously reported patterns in secretion which measure consistency of cycles across days of collection such as in Smyth et al. (1997). Cortisol is being reassessed in this cohort, which will allow us to examine the long term stability of group membership.

In summary, we find two common curves in this large community dwelling population using a latent class analysis approach. We find a normative curve and a ‘raised curve’. The raised curve may relate to impaired negative feedback or increased sensitivity to cortisol stimulation later in the day. We find that compared with the normative curve, the risk factors associated with the raised cortisol curve includes older age, male gender, smoking, short sleep duration, increased reporting of a stressful event and slow walking/gait speed. Follow up of this cohort will allow us to determine and compare whether the clusters or more typically collected aspects of cortisol secretion such as the cortisol awakening response or the slope in cortisol secretion predict the development of hypothesized morbidities and diseases.

Role of the funding source

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Conflict of interest

The authors have no conflicts of interests to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.psyneuen.2010.01.010.
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