

## **Cognitive ability across the life course and cortisol levels in older age**

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## **Abstract**

Elevated cortisol levels have been hypothesised to contribute to cognitive ageing, but study findings are inconsistent. In the present study, we examined the association between salivary cortisol in older age and cognitive ability across the life course. We used data from 370 members of the 36-Day Sample of the Scottish Mental Survey 1947, who underwent cognitive testing at age 11, and were then followed up at around age 78, completing further cognitive tests and providing diurnal salivary cortisol samples. We hypothesised that higher cortisol levels would be associated with lower cognitive ability in older age and greater cognitive decline from childhood to older age, but also lower childhood cognitive ability. Few of the tested associations were significant, and of those that were, most suggested a positive relationship between cortisol and cognitive ability. Only one cognitive measure showed any sign of cortisol-related impairment. However, after correcting for multiple comparisons, no results remained significant. These findings suggest that cortisol may not play an important role in cognitive ageing across the life course.

*Key words:* cortisol; cognitive ability; cognitive ageing; longitudinal study; 36-Day Sample

## 1. Introduction<sup>1</sup>

The glucocorticoid hormone cortisol is important in coordinating adaptive responses to stressful events, but prolonged elevated levels may also be harmful (Sapolsky, 1996; Landfield et al., 2007). Administration of high doses of glucocorticoids has been shown to produce transient cognitive deficits (Newcomer et al., 1994; Kirschbaum et al., 1996), and patients with diseases characterised by elevated cortisol levels, such as Cushing's syndrome, also show impairments in cognition (Mauri et al., 1993; Forget et al., 2000; Belanoff et al., 2001), as well as brain atrophy, particularly in the hippocampus (Toffanin et al., 2011). A number of studies have reported relationships between higher daytime salivary cortisol levels and lower cognitive ability in non-pathological samples (Stawski et al., 2011; Geoffroy et al., 2012; Gaysina et al., 2014). More chronic associations between cortisol and cognition may be due to the adverse effects of sustained high levels of glucocorticoids on neurons (Sapolsky, 1996; Abraham, 2001), including those involved in regulation of the hypothalamic-pituitary-adrenal (HPA) axis. According to Sapolsky et al.'s (1986) glucocorticoid cascade hypothesis, excess glucocorticoids can ultimately impair the ability of the HPA axis to downregulate cortisol after a stress response, thus further increasing cortisol levels and leading to accumulating adverse effects. This may explain, in part, the cognitive deficits associated with mental disorders whose aetiology may involve stress, such as depression (Rubinow et al., 1984; Hinkelmann et al., 2009). Huang et al. (2009) also observed modest correlations (around  $r = .2$ ) between elevated basal plasma cortisol levels, hippocampal atrophy and cognitive decline in 172 Alzheimer's patients, consistent with the glucocorticoid cascade hypothesis.

Chronic exposure to elevated cortisol levels may also play an important role in cognitive ageing (Belanoff et al., 2001; Landfield et al., 2007), whereby neurodegeneration and hypersecretion of glucocorticoids might continuously exacerbate one another, producing cognitive decline even in normal ageing (Sapolsky et al., 1986). Several studies have provided evidence to support this. For example, Lee et al. (2007) observed that higher overall (mean and area under the curve) salivary cortisol was associated with poorer performance in a range of cognitive domains among 967 participants aged 50-70 years. Similarly, Comijs et al. (2010) observed that higher daytime serum concentrations of cortisol related to impairments in memory and processing speed among 1,154 older participants, aged 65-88 years. Others have found similar results in smaller samples (Lupien

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<sup>1</sup> Abbreviations: BMI = body mass index; CAR = cortisol awakening response; FDR = false discovery rate; g = general intelligence; HADS = Hospital Anxiety and Depression Scale; HPA = hypothalamic-pituitary-adrenal; MHT = Moray House Test; MMSE = Mini Mental State Examination; NART = National Adult Reading Test; RAVLT = Rey Auditory Verbal Learning Test; RSPM = Raven's Standard Progressive Matrices; SCRE = Scottish Council for Research in Education; SDMT = Symbol Digit Modalities Test; SMS1947 = Scottish Mental Survey 1947.

et al., 1994; MacLulich et al., 2005; Beluche et al., 2010; Lara et al., 2013;  $N = 19-197$ ). Importantly, O'Brien et al. (1994) demonstrated that ageing-related cognitive deficits were associated with impaired cortisol suppression, following administration of dexamethasone, providing clearer evidence in support of the glucocorticoid cascade hypothesis of cognitive ageing. A number of studies have focused on the hippocampus, which participates in regulation of the HPA axis, and is also involved in memory. Several have associated higher cortisol levels with greater hippocampal atrophy and reduced hippocampal activation (Lupien et al., 1998; McAuley et al., 2009), as well as poorer performance on hippocampus-dependent memory tests (Lupien et al., 1998; Segerstrom et al., 2016). More recently, in another sample, Cox et al. (2015) formally tested the role of neurodegeneration in the association between cortisol and cognitive decline across the life course, observing that white matter microstructural measures mediated the relationship – at least for reactive cortisol measures – also supporting the hypothesis. However, looking at ageing-related changes in hippocampal morphology and microstructure, Cox et al. (2017) were unable to conclude that cortisol is an important mediator.

It is unclear if cortisol levels are sufficiently high in non-pathological ageing to have a detectable deleterious effect, and results do not always support an association between excess cortisol and cognitive decline. For example, in a large study of 3,229 middle-age to old-age participants, Singh-Manoux et al. (2014) found no evidence of an association between diurnal salivary cortisol levels and cognitive decline over around five years. Other studies have even shown that cortisol facilitates memory consolidation (McGaugh & Rozendaal, 2002) and can be neuroprotective (Abraham et al., 2001), thereby ameliorating brain ageing (Patel & Finch, 2002). In a study of 1,226 older people, Potvin et al. (2013) observed an association between higher morning salivary cortisol levels and cognitive impairment among participants with a history of anxiety or depression, but the opposite relationship in those with no such history. In another recent study of 4,244 older people, Geerlings et al. (2015) found that, while higher evening cortisol levels were associated with smaller total brain volume and poorer cognitive functioning, higher morning levels were associated with greater white matter volume, faster processing speed and executive functioning. Other recent studies suggest that dysregulation of diurnal cortisol secretion (Johar et al., 2015), reduced variability in levels (Dijckmans et al., 2017) or blunted cortisol responses to stress (Almela et al., 2014) may be more important than overall elevation of levels in mediating cognitive ageing. Additionally, Franz et al. (2011) observed that lower early-adulthood cognitive ability predicted higher later-adulthood cortisol levels (in salivary samples taken over three days), rather than the other way around, which may indicate a different mechanistic relationship between cortisol and cognition

across the life course. As these mixed findings suggest, the relationships between various cortisol characteristics and cognitive ability in older age are complex, and not yet fully understood.

With the present study, we aimed to shed further light on the association between cortisol and cognitive ageing. We made use of data from 396 members of the 36-Day Sample, a group of Scottish people born in 1936, who were assessed on intelligence at around age 11 years, and provided salivary cortisol samples and contemporaneous cognitive scores at around age 78 years. These data allowed us to make several important contributions to the field: i) all participants were the same age, removing the important potential confounding effect of age, ii) we were able to examine the relationship between cognitive ability in youth, and cortisol levels ~67 years later, and iii) we were able to examine associations between cortisol levels in older age and relative change in cognitive ability across most of the life course. In accordance with the hypothesis that higher cortisol levels contribute to neurocognitive decline in ageing, we expected to observe associations between higher older-age cortisol levels – whether at specific times of day or overall – and lower contemporaneous cognitive ability at age 78, as well as greater cognitive decline from age 11 to age 78 years.

However, we also assessed relations between these cognitive measures and other derived measures of the diurnal cortisol profile, testing the hypothesis that dysregulation and blunted responses play a more important role. Furthermore, given previous findings that intelligence predicts later cortisol levels, we explored the hypothesis that cortisol levels are influenced by cognitive ability (rather than the other way around), by testing associations between childhood IQ and cortisol measures. Higher childhood intelligence could be associated with the use of better coping mechanisms in response to stress throughout life, the cumulative benefits of which could lead to lower cortisol levels in older age, in line with Franz et al.'s (2011) findings. Finally, considering that cortisol levels and cognitive ability may each influence the other, and that there may be a complex relationship between them throughout life, we explored whether the degree of cortisol's impact on older-age cognitive ability is determined by prior cognitive ability, by testing for interactions between childhood IQ and cortisol measures.

## **2. Material and methods**

### *2.1. Participants*

On 4<sup>th</sup> June 1947, almost all children born in 1936 and attending school in Scotland ( $N = 70,805$ ) completed the second Scottish Mental Survey (SMS1947; Scottish Council for Research in Education; SCRE, 1949). Shortly afterwards, a representative sample of the cohort (including those absent from school on the day of the SMS1947;  $N = 7,380$ ) completed a short sociological schedule (MacPherson, 1958). As participants were

selected according to their dates of birth being on one of the first three days of the month (i.e. 36 days throughout the year), they were known as the ‘36-Day Sample’. Within this sample, the ‘6-Day Sample’ (born on the first day of the six even-numbered months;  $N = 1,208$ ), were also studied in greater depth over the following 16 years (Maxwell, 1969).

In 2012, the 6-Day Sample and, in 2013, the remainder of the 36-Day Sample (or ‘30-Day Sample’) were traced through the United Kingdom National Health Service Central Register (Brett & Deary, 2014). Those who were still alive, and resident in Scotland, England or Wales ( $N = 2,977$ ) were invited to participate in a follow-up study. Those who agreed to participate completed a detailed questionnaire booklet ( $N = 722$ ), physical testing ( $N = 423$ ) and a telephone interview ( $N = 365$ ; Deary & Brett, 2015). Physical testing included providing three (waking, waking+45min and evening) salivary cortisol samples, and a range of cognitive tests were administered during the telephone interview (several weeks later, avoiding any potential effects of test anxiety on sampled cortisol levels). For the present study, we selected participants who provided viable cortisol samples – 157 (81 female) from the 6-Day Sample and 239 (95 female) from the 30-Day Sample. Participants who reported a diagnosis of dementia ( $N = 2$ ), scored below 21 on an adapted Mini Mental State Examination (MMSE;  $N = 7$ ) or were currently using steroid-based medications ( $N = 17$ ) were then excluded from all analyses. Descriptive statistics for the 370 remaining 36-Day Sample follow-up participants included in this study are reported in *Table 1*.

## 2.2. Cortisol samples

36-Day Sample follow-up participants were provided with three Salivette (Sarstedt, Rommelsdorf, Germany) sample tubes, and asked to provide saliva samples immediately after waking, 45min later and in the evening of the same day. When samples were returned to us by post, they were centrifuged for 5min at 3000rpm and then frozen at  $-80^{\circ}\text{C}$ . Cortisol levels were then measured using a commercial immunoassay kit with chemiluminescence detection (IBL-Hamburg, Hamburg, Germany) at the University of Dresden. Three samples – selected as examples of low, intermediate and high cortisol concentrations – were quality control assessed; all inter-assay coefficients of variability were below 8%. Values above 70nmol/L were deemed to be outliers (consistent with information provided by Clemens Kirschbaum, personal communication) and removed from subsequent analyses. The concentrations of the three samples represented waking, waking+45min and evening cortisol levels. As shown in *Table 1*, and as would be expected, cortisol levels were lower in the evening than upon waking, and highest 45min after waking. The second measurement is therefore subsequently referred to as ‘peak’ cortisol level, although cortisol levels could have been higher earlier or later in the day. The measures’

distributions were close to normal, but negatively skewed, so raw values were square-root transformed before performing further analyses. We also calculated three further measures of cortisol activity in older age: cortisol awakening response (CAR; the difference between peak and waking cortisol levels), diurnal cortisol slope (the difference between evening and waking levels) and mean cortisol level (the mean of waking, peak and evening levels). CAR and diurnal slope represented measures of change in cortisol levels throughout the day, rather than overall levels, which allowed us to assess aspects of cortisol dysregulation other than excessive levels. All six measures were corrected for age at time of sampling by linear regression.

### *2.3. Cognitive measures*

*Childhood IQ:* Almost all Scottish children born in 1936 and present at school on the day of the SMS1947 completed the Moray House Test No. 12 (SCRE, 1933, 1949). This included the majority of 36-Day Sample members: 372 of the 396 follow-up participants included in this study. We regressed the total score on this test over age on the day of the SMS1947, and standardised the residuals with a mean of 100 and SD of 15. This produced an IQ-type score (MHT IQ), which we used as a measure of childhood intelligence.

*Older-age cognitive tests:* The final stage of the 6-Day Sample follow-up study was a telephone interview, conducted in late 2013. The 30-Day Sample completed the same interview in early 2015. During the interview, participants completed a number of cognitive tests, including Raven's Standard Progressive Matrices (RSPM; Raven, 1938), a 60-item assessment of non-verbal reasoning; the Symbol Digit Modalities Test (SDMT; Smith, 1968), a series of 110 symbols to translate into digits, testing processing speed; the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), assessing verbal memory; a simple test of semantic fluency, involving naming as many animals as possible in one minute; and the National Adult Reading Test (NART; Nelson & Willison, 1991), a 50-item vocabulary test. Test materials, such as the RSPM question booklet and NART word list, were sent to participants in advance by post, contained in a sealed envelope that they were instructed not to open until the time of the interview. Total scores on each test were regressed over age at testing before further analysis.

*Derived measures:* We ran a factor analysis on the five residualised older-age cognitive test scores, extracting a single factor with loadings of .66, .76, .52, .40 and .57, for RSPM, SDMT, RAVLT, semantic fluency and NART, respectively. Scores on this underlying factor were used as a measure of general intelligence (g). We also regressed this measure of older-age g over childhood IQ, and the standardised residuals served as a measure of relative cognitive change from childhood to older age. Participants with positive cognitive change

scores therefore showed higher older-age cognitive ability than their childhood IQ would predict, relative to the rest of the sample, whereas negative cognitive change represented relatively greater cognitive decline.

#### *2.4. Control variables*

The questionnaire participants completed included questions on education, previous occupations, current health, currently prescribed medications and current smoking habits. From participants' responses to these questions, we derived the measures years of education, social class (scored on a five-point scale according to the UK Classification of Occupations; Office of Population Censuses and Surveys, 1980), diagnosis of dementia, use of steroid-based medications and current smoking (measured in or converted to cigarettes per day). As part of the physical testing, participants provided measures of height and weight, from which we derived body mass index (BMI) according to the standard formula (Keys et al., 1972). During the telephone interview, participants also completed an adapted Mini Mental State Examination (MMSE; Folstein et al., 1975; Roccaforte et al., 1992; Newkirk et al., 2004), as a measure of cognitive impairment, and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), comprising 14 items, half measuring anxiety symptoms and half measuring depressive symptoms. In addition to age and sex, years of education, social class, current smoking, BMI, HADS anxiety and HADS depression were controlled for in final analyses. Dementia, use of steroid medications and a low score (less than 21 of a possible 26) on the MMSE were used as exclusion criteria, as above.

#### *2.5. Analysis*

Data were analysed in Matlab R2013a (The Mathworks, Natick, MA). Following the compilation and preprocessing of cognitive and cortisol variables, as above, we tested for sex differences in these variables (cortisol levels having previously been found to vary by sex; Van Cauter et al., 1996) using a series of unpaired t-tests. Standardised  $\beta$  coefficients and 95% confidence intervals were derived by generalised linear modelling (estimated using the 'glmfit' Matlab function, with the default identity link function, assuming normal distributions) for associations between all cognitive measures and all cortisol measures, controlling for sex. Age was already controlled by residualising each measure of cortisol and cognitive ability, as above. Analyses were then repeated twice, each time also including the additional controls years of education, social class, smoking, and BMI, but dealing with HADS anxiety and depression in two different ways; firstly, also including subscale scores as covariates, and secondly, excluding participants who scored eight or above on either subscale. We then tested for interactive effects between childhood IQ and older-age cortisol on older-age cognitive ability by rerunning the models (for all cognitive measures other than MHT IQ and cognitive change) while additionally



incorporating MHT IQ and an interaction term. All  $p$  values were corrected for multiple comparisons using false discovery rate (FDR; Benjamini & Hochberg, 1995).

### 3. Results

Before assessing relations between cognitive and cortisol measures, we assessed sex differences in all key variables among the 36-Day Sample. Men performed significantly worse on the RAVLT in older age ( $t_{321} = 4.44, p < .001, g = .50$ ), but significantly better on RSPM ( $t_{322} = 2.33, p = .02, g = .26$ ) and semantic fluency ( $t_{325} = 2.85, p < .01, g = .32$ ). Peak cortisol levels were also significantly higher ( $t_{350} = 3.49, p < .001, g = .37$ ) and CAR was significantly greater ( $t_{339} = 3.57, p < .001, g = .39$ ) in women, while evening levels were higher in men ( $t_{353} = 2.16, p = .03, g = .23$ ). These differences could have been related to effects of sex that would influence cortisol-cognition associations, so all subsequent analyses were performed while controlling for sex.

We next assessed associations between six cortisol measures – waking, peak, evening and mean levels, CAR and diurnal slope – and eight cognitive measures – childhood MHT IQ, older-age RSPM, SDMT, RAVLT, semantic fluency and NART scores,  $g$ , and lifelong cognitive change. After an initial run, controlling only age and sex (*Table S1*), we repeated analyses, additionally including all of the following covariates: years of education, social class, current smoking, BMI, HADS anxiety and HADS depression. As shown in *Table 2*, all associations between cortisol and cognitive measures were small, but nine of the 48 tested associations were significant. Higher waking ( $\beta = .11 [.00, .23], p = .04$ ) and peak ( $\beta = .13 [.01, .24], p = .03$ ) cortisol levels were both associated with better SDMT performance. Higher peak cortisol also predicted poorer semantic fluency ( $\beta = -.12 [-.23, -.01], p = .04$ ) and better NART performance ( $\beta = .11 [.01, .22], p = .04$ ). A greater CAR was associated with a higher childhood MHT IQ ( $\beta = .12 [.00, .24], p = .05$ ) and a higher NART score ( $\beta = .12 [.01, .23], p = .04$ ). A flatter diurnal slope predicted both poorer SDMT performance ( $\beta = -.15 [-.26, -.04], p = .01$ ) and relatively greater cognitive decline ( $\beta = -.13 [-.24, -.01], p = .03$ ). Lastly, higher mean cortisol levels were associated with poorer semantic fluency ( $\beta = -.16 [-.27, -.05], p < .01$ ). However, after correcting for multiple comparisons, none of these associations remained significant.

Due to the more specific effects of anxiety and depression on associations between cortisol and intelligence previously observed (Potvin et al., 2013), we also repeated analyses excluding participants who scored eight or above on either of the HADS subscales ( $N = 25$ ). This made little difference to the results, but did affect which achieved nominal significance before correcting for multiple comparisons. Four of the nine associations observed when including these participants remained, the strongest being between a flatter diurnal slope and poorer SDMT performance ( $\beta = -.16 [-.28, -.04], p = .01$ ). Four additional results were also

significant, the strongest being between evening cortisol levels and poorer NART performance ( $\beta = -.15 [-.26, -.04]$ ,  $p = .01$ ). Again, no results remained significant after correcting for multiple comparisons. Results are reported in full in *Table S2*. Too few participants scored high on the HADS subscales to also test associations within this group.

For the six older-age cognitive measures we assessed interactions between childhood IQ and each of the six cortisol measures. All of the above covariates were included in each model, along with MHT IQ and an interaction term. As for the analyses reported in *Table 2*, participants scoring high on HADS subscales were included, but both subscales were included as covariates. These interactive effects were also all small, and only one was nominally significant. An interactive effect between higher childhood MHT IQ and higher peak cortisol levels predicted better RSPM performance ( $\beta = .12 [.02, .21]$ ,  $p = .02$ ). As for bivariate associations, this result did not remain significant after correcting for multiple comparisons. Results for all interactions are included in *Table S3*.

#### **4. Discussion**

In this study, we assessed associations between cortisol measures in older age, and cognitive ability at the same age, in childhood and across the life course. Across all analyses, there were only a small number of nominally significant associations. Higher cortisol levels showed several significant associations with poorer semantic fluency, but also with higher SDMT and NART scores in older age, as well as higher MHT IQ in childhood. Only a flatter diurnal slope was associated with negative lifelong relative cognitive change (i.e. greater cognitive decline). The few significant interactions between childhood IQ and cortisol levels predicted better RSPM performance and semantic fluency, but poorer SDMT performance. However, none of these associations remained significant after correcting for multiple comparisons. Excluding participants who scored relatively high on anxiety or depression affected which few associations were nominally significant, but still none remained significant after multiple-comparison correction.

Although we cannot definitively infer anything from results that did not survive FDR correction, most of those that were significant before FDR correction were not in the expected direction. In older age, SDMT and NART scores were associated with higher cortisol levels (and, accordingly, a greater CAR and steeper diurnal slope), where Sapolsky's (1986) glucocorticoid cascade hypothesis would predict that higher cortisol levels should actually be associated with lower cognitive performance. Lifelong cognitive decline was only associated with a flatter diurnal slope, generally considered to be a healthier cortisol profile, driven by lower peak levels. These results appear more consistent with previous work supporting the opposite relationship, between higher

cortisol levels and higher cognitive ability, or reduced cognitive decline (Patel & Finch, 2002; Geerlings et al., 2005), or those relating cognitive decline to blunted diurnal cortisol responses (Johar et al., 2015). The few significant associations between childhood IQ and higher older-age cortisol were also contrary to our expectation, based on previous evidence of a longitudinal association between higher earlier cognitive ability and lower later cortisol levels (Franz et al., 2011), and instead also suggest a positive relationship between cortisol and cognition. Conversely, the several significant associations between cortisol and semantic fluency were negative, as hypothesised and as would be expected if glucocorticoids do indeed play a role in cognitive ageing. Together with the results for other cognitive measures, this raises the possibility that higher cortisol levels are detrimental only to some cognitive abilities, which may explain the lack of consensus among previous studies.

However, none of the significant associations between cortisol and cognitive measures that we observed remained significant after correcting for multiple comparisons, while the majority of tested associations were not strong enough to achieve even nominal significance. Although these results do not represent conclusive evidence that diurnal salivary cortisol and cognitive ability are unrelated, they are consistent with such an explanation, and with Singh-Manoux et al.'s (2014) findings in a larger sample. However, within the context of this account, the numerous prior studies showing evidence of a relationship between cortisol and cognitive ability are difficult to explain. Some studies observed effects as small, or smaller, than some of those we observed, but found them to be significant in a larger sample (Geoffroy et al., 2012; Gaysina et al., 2014), while others also observed larger effects (Huang et al., 2009; Franz et al., 2011). Perhaps, by the age of 78 years, other factors have much greater influence over cognitive decline, leading to a weaker association with cortisol levels. However, previous studies have observed significant associations in samples of around the same age (Beluche et al., 2010; Comijs et al., 2010). Another possibility is that the association between cortisol and cognitive ability in older age is mediated by other variables that were not taken into account. For example, Potvin et al. (2013) observed an association between higher cortisol levels and cognitive impairment only in participants with a history of anxiety and depression. Our participants may have been less likely to have a history of anxiety or depression than the general population, as members of the original samples with such mood disorders would have been less likely to participate in the follow-ups.

This bias in our follow-up samples (Johnson, Brett, Calvin & Deary, 2016), although an inevitable product of selection pressures influencing survival to older age, as well as ability and willingness to participate, is an important study limitation. Had we been able to use a more representative sample, such as the entire

original 36-Day Sample, we may have observed stronger associations between cortisol and cognitive ability. Those more affected by chronically elevated cortisol levels and cognitive decline may have been unable to participate in our follow-up study due to associated physical health conditions, pathological cognitive ageing or even mortality. This is likely to have led to narrower ranges in both cortisol levels and cognitive decline among our sample, making our results a probable underestimate of the effects which may be stronger in less well-educated and healthy individuals. Notwithstanding these limitations, a larger sample would also have afforded us greater statistical power with which to more reliably detect smaller effect sizes.

Our data collection methods also represent limitations of this study. For example, participants were unsupervised when providing salivary samples, which introduces problems of non-compliance, such as invalid diurnal cortisol profiles (Kudielka et al., 2003). Participants were also assessed on older-age cognitive ability by telephone, which meant that they could not be monitored as closely throughout testing, and meant using less widely-validated adaptations of some tests. These methods were not ideal, but methods such as face-to-face cognitive testing were not practical, as follow-up participants were spread across Great Britain. An additional limitation was that cortisol levels were only assessed in older age, at around the same time as cognitive ability. Our analyses were based on the assumption that older-age levels reflected levels earlier in life, but little is known about the lifelong stability of cortisol levels. Cortisol profiles earlier in adulthood or even childhood could possibly be more strongly related to cognitive decline and ability in older age. This should certainly be investigated by future longitudinal studies.

#### *4.1. Conclusions*

This study assessed associations between lifelong cognitive ability and cortisol at around age 78. Few other studies include cognitive data from both childhood and old age, allowing the testing of both contemporaneous and longitudinal associations between cortisol and cognitive ability, but also associations with cognitive change over almost seven decades. However, in this relatively healthy sample of older individuals, we found little evidence of an association between cognitive ability across the life course and cortisol levels in older age. Only very few associations, specifically for one cognitive measure, were significant and in the expected direction, relating higher cortisol levels to lower cognitive ability. Most of the few significant associations were in the opposite direction, while the majority of tested associations were closer to zero and not significant. Furthermore, after correcting for multiple comparisons, there were no significant results. Overall, our findings suggest that glucocorticoids may not play such an important role in cognitive ageing in healthier individuals. The initially significant associations we observed may indicate that the relationship between cortisol and

cognitive ageing is more complex than previously hypothesised, with higher cortisol levels having a negative impact on only some aspects of cognitive ability, while perhaps being of benefit to others. However, stronger evidence of the weak associations we observed and better understanding of the overall relationship between cortisol and cognitive ageing is still dependent on further research.

### **Acknowledgements**

The 36-Day Sample follow-up study (MRC G1001401/1) and the Centre for Cognitive Ageing and Cognitive Epidemiology (MR/K026992/1) are supported by the cross-council Lifelong Health and Wellbeing Initiative. Funding from the Biotechnology and Biological Sciences Research Council (BBSRC) and Medical Research Council (MRC) is gratefully acknowledged. Thanks to Clemens Kirschbaum and his laboratory team for assistance with processing cortisol samples.

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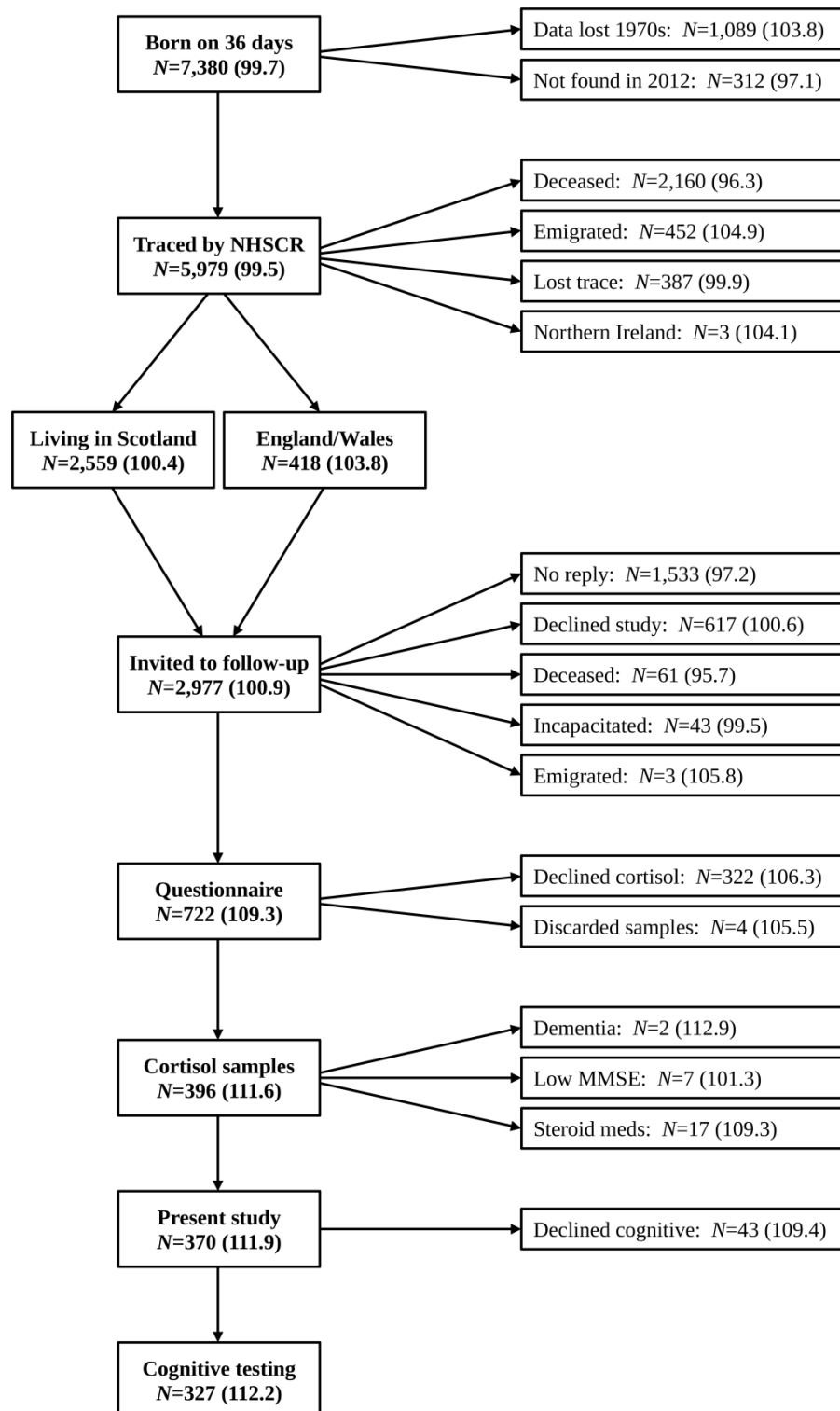
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**Figure 1**

*Process for selection of follow-up study participants from original 36-Day Sample*



*Note.* NHSCR = (United Kingdom) National Health Service Central Register; MMSE = (adapted) Mini-Mental State Examination. Figures in brackets represent mean childhood IQ for each respective subsample.

**Table 1***Descriptive statistics for 36-Day Sample follow-up participants*

	6-Day Sample only	30-Day Sample only	36-Day Sample combined
<i>N</i>	146	224	370
Sex (M/F)	71 / 75	133 / 91	204 / 166
Age at SMS1947 (M, SD)	11.0 (0.3)	11.0 (0.3)	11.0 (0.3)
Age at cortisol sampling (M, SD)	76.7 (0.4)	78.4 (0.3)	77.7 (0.9)
Age at cognitive testing (M, SD)	77.1 (0.4)	78.8 (0.3)	78.2 (0.9)
Years of education (M, SD)	12.5 (3.0)	11.7 (2.7)	12.0 (2.9)
Social class: 1 (N, %)	2 (1.4)	2 (0.9)	4 (1.1)
2 (N, %)	22 (15.1)	18 (8.0)	40 (10.8)
3 (N, %)	39 (26.7)	57 (25.4)	96 (25.9)
4 (N, %)	65 (44.5)	106 (47.3)	171 (46.2)
5 (N, %)	16 (11.0)	27 (12.1)	43 (11.6)
- (N, %)	2 (1.4)	14 (6.3)	16 (4.3)
Current smoker (N, %)	10 (6.9)	24 (10.7)	34 (9.2)
Current smoking; cigs/day (M, SD)	13.5 (7.5)	15.0 (8.0)	14.6 (7.8)
Body mass index (M, SD)	27.4 (4.4)	27.0 (4.2)	27.2 (4.3)
HADS anxiety score (M, SD)	4.0 (3.3)	3.8 (3.0)	3.8 (3.1)
HADS depression score (M, SD)	2.4 (2.2)	2.4 (1.8)	2.4 (1.9)
Childhood MHT IQ (M, SD)	112.4 (10.0)	111.6 (10.1)	111.9 (10.0)
Raven's SPM score (M, SD)	34.1 (7.4)	32.2 (7.9)	32.9 (7.8)
SDMT score (M, SD)	43.4 (9.2)	41.6 (8.9)	42.2 (9.1)
RAVLT score (M, SD)	47.4 (10.9)	45.9 (11.6)	46.4 (11.4)
Semantic fluency (M, SD)	18.8 (5.1)	18.3 (5.3)	18.5 (5.2)
NART score (M, SD)	35.7 (7.8)	33.6 (8.3)	34.4 (8.2)
Waking cortisol; nmol/L (M, SD)	24.1 (12.1)	28.7 (14.9)	26.9 (14.0)
Peak cortisol; nmol/L (M, SD)	25.6 (11.4)	30.9 (14.1)	28.8 (13.3)
Evening cortisol; nmol/L (M, SD)	4.4 (3.5)	6.1 (5.5)	5.4 (4.9)

*Note.* HADS = Hospital Anxiety and Depression Scale; MHT = Moray House Test; SPM = Standard Progressive Matrices; SDMT = Symbol Digit Modalities Test; RAVLT = Rey Auditory Verbal Learning Test; NART = National Adult Reading Test. Descriptive statistics are provided for 36-Day Sample participants involved in the 6-Day Sample and subsequent 30-Day Sample follow-up studies, and for the combined follow-up sample included in the present study. Current smoking reported for current smokers only

**Table 2**

*Associations between older-age cortisol measures and childhood IQ, older-age cognitive ability and lifelong cognitive change, controlling all covariates*

	Childhood MHT IQ	Raven's SPM	Symbol-Digit Modalities Test	RAVLT	Semantic Fluency	National Adult Reading Test	General factor	Cognitive Change
Waking cortisol	-.06 [-.17, .05]	-.00 [-.11, .11]	<b>.11 [.00, .23]</b>	.07 [-.04, .18]	-.09 [-.21, .02]	-.03 [-.13, .08]	.04 [-.06, .15]	.09 [-.03, .21]
Peak cortisol	.09 [-.02, .20]	.02 [-.09, .13]	<b>.13 [.01, .24]</b>	.02 [-.09, .13]	<b>-.12 [-.23, -.01]</b>	<b>.11 [.01, .22]</b>	.08 [-.03, .19]	.02 [-.09, .14]
Evening cortisol	-.07 [-.18, .04]	-.08 [-.18, .03]	-.10 [-.21, .01]	.04 [-.07, .15]	-.02 [-.13, .09]	-.10 [-.20, .01]	-.10 [-.21, .00]	-.08 [-.20, .03]
CAR	<b>.12 [.00, .24]</b>	.01 [-.10, .13]	-.01 [-.13, .10]	-.03 [-.14, .08]	-.01 [-.12, .11]	<b>.12 [.01, .23]</b>	.02 [-.09, .14]	-.06 [-.18, .06]
Diurnal slope	.01 [-.10, .13]	-.03 [-.14, .08]	<b>-.15 [-.26, -.04]</b>	-.05 [-.16, .06]	.06 [-.06, .17]	-.04 [-.14, .07]	-.09 [-.20, .02]	<b>-.13 [-.24, -.01]</b>
Mean cortisol	.00 [-.11, .11]	-.01 [-.12, .09]	.11 [-.00, .22]	.03 [-.08, .14]	<b>-.16 [-.27, -.05]</b>	.01 [-.10, .11]	.03 [-.08, .13]	.02 [-.10, .13]

*Note.* CAR = cortisol awakening response; MHT = Moray House Test; SPM = Standard Progressive Matrices; RAVLT = Rey Auditory Verbal Learning Test. General factor (g) derived by factor analysis of five older-age cognitive measures; cognitive change derived by regressing older-age g over childhood IQ. Standardised  $\beta$  coefficients are reported, with 95% confidence intervals in brackets. All analyses controlled for age, sex, body mass index, current smoking, Hospital Anxiety and Depression Scale scores, years of education and social class. Participants reporting a diagnosis of dementia, scoring 20 or below on the adapted Mini Mental State Examination, or currently taking steroid-based medications were excluded from all analyses. Significant results at  $p < .05$  are highlighted in bold; none remained significant after correcting for multiple comparisons.

**Table S1**

*Associations between older-age cortisol measures and childhood IQ, older-age cognitive ability and lifelong cognitive change, controlling age and sex*

	Childhood MHT IQ	Raven's SPM	Symbol-Digit Modalities Test	RAVLT	Semantic Fluency	National Adult Reading Test	General factor	Cognitive Change
Waking cortisol	-.01 [-.12, .10]	.01 [-.10, .12]	<b>.13 [.02, .24]</b>	.10 [-.00, .21]	-.08 [-.19, .03]	-.00 [-.11, .11]	.07 [-.04, .18]	.11 [-.01, .22]
Peak cortisol	.11 [-.00, .22]	.02 [-.09, .13]	<b>.12 [.01, .23]</b>	.04 [-.07, .15]	-.11 [-.22, .00]	.10 [-.01, .21]	.08 [-.04, .19]	.02 [-.10, .14]
Evening cortisol	-.05 [-.15, .06]	-.03 [-.14, .08]	-.08 [-.19, .04]	.05 [-.06, .16]	-.02 [-.13, .09]	-.09 [-.20, .02]	-.07 [-.18, .05]	-.05 [-.17, .06]
CAR	.09 [-.02, .20]	.01 [-.11, .12]	-.03 [-.14, .09]	-.05 [-.16, .06]	-.02 [-.13, .10]	.09 [-.03, .20]	-.00 [-.12, .11]	-.08 [-.20, .04]
Diurnal slope	-.02 [-.13, .09]	-.02 [-.13, .09]	<b>-.15 [-.26, -.04]</b>	-.07 [-.18, .04]	.04 [-.07, .16]	-.05 [-.17, .06]	-.10 [-.21, .01]	<b>-.13 [-.25, -.01]</b>
Mean cortisol	.06 [-.05, .16]	.01 [-.10, .12]	<b>.13 [.02, .24]</b>	.06 [-.04, .17]	<b>-.13 [-.24, -.03]</b>	.02 [-.09, .13]	.06 [-.05, .17]	.05 [-.06, .16]

*Note.* CAR = cortisol awakening response; MHT = Moray House Test; SPM = Standard Progressive Matrices; RAVLT = Rey Auditory Verbal Learning Test. General factor (g) derived by factor analysis of five older-age cognitive measures; cognitive change derived by regressing older-age g over childhood IQ. Standardised  $\beta$  are coefficients reported, with 95% confidence intervals in brackets. All analyses controlled for age and sex. Participants reporting a diagnosis of dementia, scoring 20 or below on the adapted Mini Mental State Examination, or currently taking steroid-based medications were excluded from all analyses. Significant results at  $p < .05$  are highlighted in bold; none remained significant after correcting for multiple comparisons.

**Table S2**

*Associations between older-age cortisol measures and childhood IQ, older-age cognitive ability and lifelong cognitive change, excluding high HADS subscale scores*

	Childhood MHT IQ	Raven's SPM	Symbol-Digit Modalities Test	RAVLT	Semantic Fluency	National Adult Reading Test	General factor	Cognitive Change
Waking cortisol	-.02 [-.13, .09]	.00 [-.11, .12]	.12 [-.00, .24]	.11 [-.00, .23]	-.08 [-.19, .04]	-.00 [-.11, .11]	.06 [-.05, .18]	.09 [-.03, .22]
Peak cortisol	.09 [-.02, .21]	.04 [-.08, .15]	.12 [.00, .24]	.04 [-.08, .16]	-.09 [-.21, .03]	<b>.13 [.02, .24]</b>	.10 [-.02, .21]	.05 [-.08, .17]
Evening cortisol	-.10 [-.21, .01]	-.09 [-.20, .02]	<b>-.13 [-.25, -.01]</b>	.01 [-.11, .12]	-.06 [-.17, .06]	<b>-.15 [-.26, -.04]</b>	<b>-.14 [-.25, -.03]</b>	-.11 [-.23, .01]
CAR	.08 [-.03, .20]	.02 [-.10, .14]	-.02 [-.15, .10]	-.05 [-.17, .07]	-.00 [-.13, .12]	.10 [-.01, .22]	.01 [-.11, .13]	-.04 [-.17, .09]
Diurnal slope	-.04 [-.15, .08]	-.05 [-.16, .07]	<b>-.16 [-.28, -.04]</b>	-.10 [-.22, .01]	.02 [-.10, .14]	-.08 [-.19, .03]	<b>-.13 [-.25, -.02]</b>	<b>-.14 [-.26, -.02]</b>
Mean cortisol	-.00 [-.11, .11]	-.01 [-.12, .10]	.11 [-.01, .23]	.05 [-.07, .16]	<b>-.15 [-.26, -.03]</b>	.02 [-.09, .13]	.04 [-.07, .15]	.04 [-.08, .16]

*Note.* HADS = Hospital Anxiety and Depression Scale; CAR = cortisol awakening response; MHT = Moray House Test; SPM = Standard Progressive Matrices; RAVLT = Rey Auditory Verbal Learning Test. General factor (g) derived by factor analysis of five older-age cognitive measures; cognitive change derived by regressing older-age g over childhood IQ. Standardised  $\beta$  are coefficients reported, with 95% confidence intervals in brackets. All analyses controlled for age, sex, body mass index, current smoking, years of education and social class. Participants reporting a diagnosis of dementia, scoring 20 or below on the adapted Mini Mental State Examination, or currently taking steroid-based medications were excluded from all analyses, as well as participants scoring eight or above on either of the HADS subscales. Significant results at  $p < .05$  are highlighted in bold; none remained significant after correcting for multiple comparisons.



**Table S3**

*Interactive effect between older-age cortisol measures and childhood IQ on older-age cognitive ability, controlling all covariates*

	Raven's SPM	Symbol-Digit Modalities Test	RAVLT	Semantic Fluency	National Adult Reading Test	General factor
Waking cortisol	.01 [-.12, .14]	-.00 [-.14, .13]	-.04 [-.18, .10]	.05 [-.08, .19]	-.00 [-.11, .10]	-.00 [-.12, .11]
Peak cortisol	<b>.12 [.02, .21]</b>	.06 [-.04, .16]	.02 [-.08, .12]	-.01 [-.11, .09]	-.04 [-.12, .03]	.07 [-.02, .15]
Evening cortisol	.00 [-.08, .09]	-.09 [-.18, .00]	.04 [-.05, .13]	.09 [-.01, .18]	.05 [-.02, .12]	-.02 [-.10, .06]
CAR	.09 [-.00, .19]	.03 [-.07, .13]	.02 [-.08, .12]	-.02 [-.13, .08]	-.04 [-.12, .04]	.04 [-.05, .13]
Diurnal slope	.00 [-.13, .13]	-.08 [-.21, .05]	.06 [-.08, .20]	.04 [-.10, .18]	.09 [-.01, .20]	-.00 [-.12, .11]
Mean cortisol	.08 [-.03, .19]	-.00 [-.12, .12]	-.00 [-.12, .12]	.05 [-.08, .17]	.00 [-.09, .09]	.03 [-.07, .14]

*Note.* CAR = cortisol awakening response; SPM = Standard Progressive Matrices; RAVLT = Rey Auditory Verbal Learning Test. General factor derived by principal component analysis of five older-age cognitive measures. Standardised  $\beta$  are coefficients reported, with 95% confidence intervals in brackets. All analyses controlled for age, sex, body mass index, current smoking, Hospital Anxiety and Depression Scale scores, years of education and social class. Participants reporting a diagnosis of dementia, scoring 20 or below on the adapted Mini Mental State Examination, or currently taking steroid-based medications were excluded from all analyses. Significant results at  $p < .05$  are highlighted in bold; none remained significant after correcting for multiple comparisons.