Clinical Endocrinology (2007) **67**, 398–406 doi: 10.1111/j.1365-2265.2007.02900.x

ORIGINAL ARTICLE

Relationship between cortisol and physical performance in older persons

G. M. E. E. Peeters*, N. M. van Schoor*, M. Visser*†, D. L. Knol*‡, E. M. W. Eekhoff§, W. de Ronde§ and P. Lips*§

**EMGO Institute, VU University Medical Center, Amsterdam, †Department of Nutrition and Health, Faculty of Earth and Life Sciences, VU University, Amsterdam, ‡Department of Clinical Epidemiology and Biostatistics, §Department of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands*

Summary

Objective Hypercortisolism is associated with muscle weakness. This study examines the relationship between cortisol and physical performance in older persons.

Design/patients The study was conducted within the Longitudinal Aging Study Amsterdam (LASA), an ongoing cohort study in a population-based sample of healthy older persons in the Netherlands. Data from the second (1995/1996) and fourth (2001/2002) cycle were used pertaining to 1172 (65–88 years) and 884 (65–94 years) men and women, respectively.

Measurements Physical performance was measured by adding up scores on the chair stands, tandem stand and walk test (range 0–12). In the second cycle serum total and calculated free cortisol were assessed; in the fourth cycle evening salivary cortisol was assessed. Regression analysis (stratified for sex, adjusted for age, body mass index, alcohol use, physical activity and region) was performed to examine the cross-sectional relationship between cortisol and physical performance.

Results Women with higher calculated free cortisol scored less well on physical performance (b = –0·28 per SD higher cortisol, $P = 0{\cdot}016$), which was mainly explained by poorer performance on the tandem stand (OR = 1·32 for a lower score per SD higher cortisol, $P = 0{\cdot}003$). Men with higher salivary cortisol scored less well on physical performance (b = –0·90 in the highest *vs.* the lowest quartile, $P = 0{\cdot}008$), which was mainly explained by poorer performance on the chair stands and walk test (OR = 1·88, $P = 0{\cdot}020$ and OR = 1·81, $P = 0{\cdot}027$, respectively, in the highest *vs.* the lowest quartile).

Conclusion Physical performance is negatively associated with high cortisol levels in older persons.

(Received 27 September 2006; returned for revision 1 November 2006; finally revised 4 April 2007; accepted 4 April 2007)

Correspondence: P. Lips, Department of Endocrinology, VU University Medical Center, Postbus 7057, 1007 MB Amsterdam, the Netherlands. Tel.: +31 20 4440614; Fax: +31 20 4440502; E-mail: p.lips@vumc.nl

Introduction

Cortisol is known to stimulate degradation and inhibit synthesis of muscle proteins.[1,2] Hypercortisolism, as occurs in Cushing's syndrome or glucocorticoid therapy, is associated with muscle atrophy and weakness.[3,4] One study found that variations in serum cortisol within the normal range are negatively related to muscle strength of the knee extensors.[5] However, it is not known whether similar associations exist between cortisol and physical performance, including strength, balance and coordination in the lower extremities.

During ageing muscle tissue is gradually lost, contributing to reduced muscle strength.[6,7] Loss of muscle strength is associated with loss of physical function, which may lead to falls, fractures, loss of independence and nursing home admission.[8–10] Age-related hormonal changes, including cortisol, may partly cause these muscular changes.[1,2,6,11] Several studies have investigated the relationship between ageing and cortisol. Although there are conflicting results, the majority of the studies measuring morning or 24-h plasma cortisol concentrations in large samples show that basal cortisol levels increase with age.[12–14] Furthermore, in older persons, both morning and 24-h plasma cortisol levels are higher in women than in men.[12,13,15]

To our knowledge, the relationship between cortisol and physical performance has not been investigated. This study examines the relationship between cortisol and physical performance in older persons. It is hypothesized that high cortisol levels are associated with poorer physical performance. The results of this study add to the understanding of mechanisms in ageing that influence physical functioning.

Methods

Subjects

The study was performed within the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in physical, cognitive, emotional and social functioning in older persons.[16] A random sample of older men and women stratified for age, sex and expected 5-year mortality rate was drawn from the population registry of 11 municipalities in areas in the west, northeast and south of the Netherlands. The sample was representative for the older Dutch population with

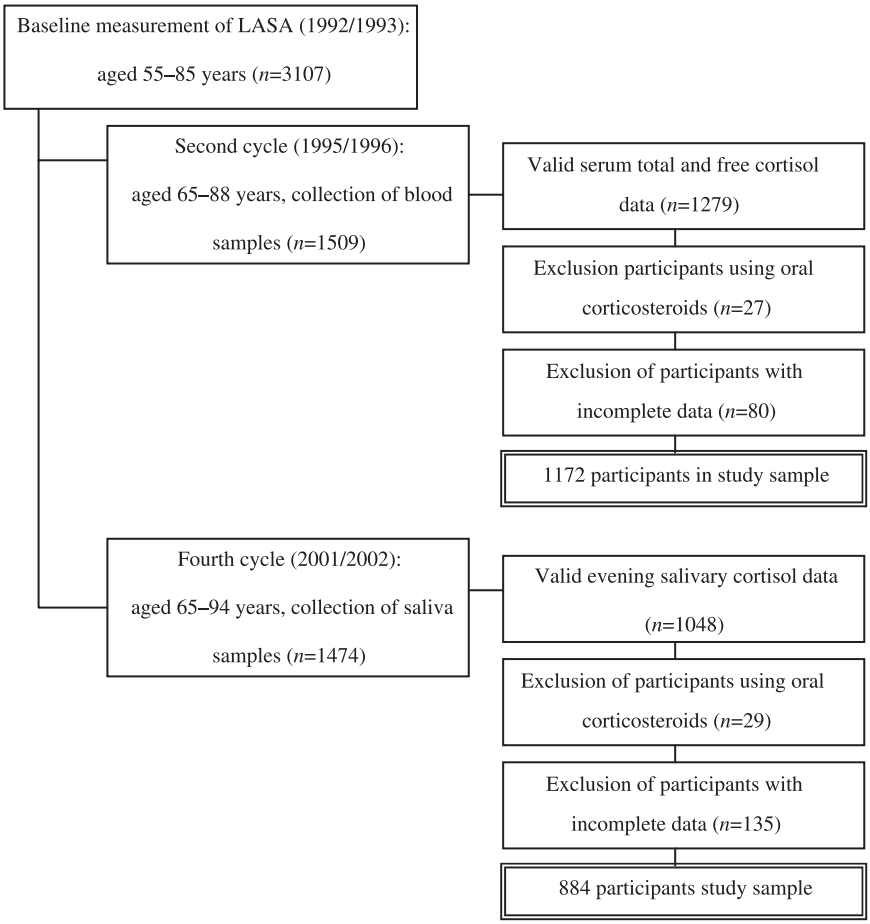

Fig. 1 Design of study sample.

respect to geographical region and degree of urbanization. The sampling and data collection procedures have been described in detail elsewhere.[17] The sample for this study consisted of participants who took part in the main and medical interview of the second (1995/1996) and/or fourth cycle (2001/2002) of LASA. The design of the study sample is presented in Fig. 1. The medical ethics committee approved the study and all participants signed informed consent.

Second cycle. Participants who were born before 1930 (aged 65 and over as of a 1 January 1996) and for whom a valid serum cortisol value was obtained were included ($n = 1279$). Participants using oral corticosteroids ($n = 27$) or having an incomplete dataset ($n = 80$) were excluded. The total number of participants included in the serum cortisol analysis was 1172. Respondents included in the study were significantly younger, took more alcohol, had less chronic diseases, were more often able to walk and more often lived in Amsterdam or in its vicinity than excluded respondents.

Fourth cycle. Participants who were born before 1936 (aged 65 and older as of 1 January 2002) and of whom valid salivary cortisol values were obtained were included ($n = 1048$). Five participants had cortisol levels over 100 nmol/l. These extreme levels were considered to be outliers and were excluded. Participants using oral corticosteroids ($n = 29$) or having an incomplete dataset ($n = 135$) were excluded. The total number of participants included in the salivary cortisol analysis was 884. Respondents included in the study were significantly younger, took more alcohol, had less chronic diseases, were less depressed, were more often able to walk (without walking aids) and were more physically active than excluded respondents. In total, 499 participants took part in both cycles (42% of the second and 56% of the fourth cycle). Therefore, the samples were partly dependent.

Measurements

In the second cycle cortisol was determined in serum, whereas in the fourth cycle, cortisol was measured in saliva. All other variables, including physical performance, were assessed using identical methodology and equipment in all cycles.

Serum total cortisol, corticosteroid binding globulin and calculated free cortisol

Participants were invited to a health care centre near their homes where blood samples were collected in the morning; participants were allowed to take tea and toast before, but no dairy products. Although the exact time of blood collection was not recorded, most participants had their blood samples taken before 10·00 hours. The blood samples were centrifuged and serum was stored at –70 °C until processing in 2002/2003. The serum levels of cortisol were determined in singlicate using a competitive immunoassay (ACS: centauer, Bayer

Diagnostics, Mijdrecht, the Netherlands). The lower limit for accurate detection of cortisol was 30 nmol/l and the interassay coefficients of variation (CV) were 6% at 150 nmol/l and 8% at 1000 nmol/l.

Corticosteroid binding globulin (CBG) levels were determined using a radioimmunoassay (Medgenix Diagnostics, Fleunes, Belgium) method independent of serum total cortisol. The lower limit for accurate detection of CBG concentrations was 11 mg/l and the interassay CVs were 8% at 30 mg/l and 5% at 110 mg/l. Concentrations of cortisol or CBG did not fall below the lower detection limits in any of the samples. Calculated free cortisol was computed according to the free cortisol index: serum total cortisol (nmol/l) divided by CBG (mg/l).[18]

Evening salivary cortisol

Saliva samples were collected using cotton balls. Participants were asked to rinse their mouth with water and wait 10 min before starting to chew the cotton ball. Gums had to be prevented from bleeding previous to and during the collection of saliva. The cotton balls were chewed at around 23·00 hours for approximately 1·5 min and then put in a tube. The samples were kept refrigerated until processing. Radioimmunoassay-coated tubes (Spectria Orion Diagnostics, Turku, Finland) were used to determine evening salivary cortisol (in duplicate). The lower limit for accurate detection was 1·5 nmol/l. None of the measured salivary cortisol concentrations fell below the lower detection limit. The intra- and interassay coefficients of variation (CV) were less than 19%.

Physical performance

Three standardized performance tests were conducted: chair stands, tandem stand and walk test. The chair stands mainly measure proximal leg strength and the tandem stands mainly balance. The walk test mainly measures proximal leg strength, balance and coordination. During the chair stands test the participant stands up from a chair and sits down five consecutive times as fast as possible with the arms folded. The walk test is a test in which the participant walks 3 m along a line, turns 180° and walks back as fast as possible without running. During the tandem stand test the participant stands with one foot behind the other (heel against toe) for 10 s. The scores of the chair stands and walk test range from 1 (slowest) to 4 (fastest), corresponding to the quartiles of time required in the total population at baseline. The score of 0 was assigned when the participant was unable to complete the test. For the tandem stand, 0 points were assigned when the participant was unable to perform the test, 2 points when able to hold for 3–9 s, and 4 points when able to hold for 10 s or more. Physical performance was computed by adding up the scores on the three tests (range 0–12) and a high score indicated a good performance.[19] In large cohort studies, this score has been a valid measure for physical functioning. It is associated with disability, the onset of disability and other health-related factors in older persons.[20–22]

Potential effect modifiers

Gender was derived from the municipal registries. Gender differences have been reported in both the basal activity of the hypothalamic–pituitary–adrenal (HPA) axis[13] and the response of the HPA axis to challenge.[23] Furthermore, other hormones are known to have different effects in women and men. Similarly, cortisol may have a different effect in women and men. Therefore, gender was considered as a potential effect modifier in the relationship between cortisol and physical performance.

Potential confounders

Age was derived from the municipal registries. Region was assessed as living in the west (Amsterdam and vicinity), northeast (Zwolle and vicinity) or south (Oss and vicinity) of the Netherlands. Body weight was measured without clothes on the top half of the body and shoes using a calibrated balance beam scale. Body height was measured using a stadiometre. Body weight and height were used to compute the body mass index [BMI = mass (kg)/length $(m)^2$]. Alcohol consumption (drinking alcohol, 0 *vs.* 1–14 *vs.* 15 glasses or more per week), smoking (current smoker, yes/no), use of a walking aid (yes/no), dizziness (yes/no), and hypertension (yes/no) were assessed. The presence of chronic diseases was assessed using a questionnaire on self-reported chronic diseases, which included chronic obstructive pulmonary disease (COPD), cardiac diseases, vascular diseases, stroke, diabetes mellitus, malignant neoplasms and joint disorders (i.e. osteoarthritis and rheumatoid arthritis). The number of present chronic diseases was counted (range 0–7). Depressive symptoms were assessed using the Center for epidemiologic studies-depression scale (CES-D). The CES-D is a 20-item self-report scale designed to measure depressive symptoms in the community. The score ranges from 0 to 60 and a score of 16 or higher was interpreted as the presence of clinically relevant depressive symptoms.[24] Medication use was assessed by recording the use of medications of the participant directly from the containers. Level of physical activity was measured using the LASA physical activity questionnaire (LAPAQ).[25] The LAPAQ is an interviewer-mediated questionnaire in which the frequency and duration of participation is estimated for six activities during the previous 2 weeks. The activities are walking, cycling, light and heavy household work, and a first and second sport. The number of minutes of participation in each of the activities per day was added up to create a physical activity score. Because renal function and liver function may influence cortisol metabolism, creatinine ($n = 1172$) and gamma GT ($n = 353$, only measured in Zwolle and vicinity) were determined in the second cycle using routine laboratory methods; coefficients of variation were 3 and 1·2%, respectively.

Statistical analysis

All analyses were conducted using SPSS software version 12·0·1 (SPSS Inc., Chicago, IL). To examine the relationship between any of the cortisol measures and physical performance five steps were performed in the analyses. First, the independent variables were tested for linearity. Both serum total and calculated free cortisol were linearly related to the outcome and therefore included continuously. Evening salivary cortisol was not linearly related to physical performance and therefore included in quartiles. Cut-off points for quartiles were 2·3, 3·0 and 4·3 nmol/l, in both women and men. To improve the comparability between the models, serum total and calculated free cortisol were also studied in quartiles. Cut-off points for serum total cortisol quartiles were 355, 453 and 585 nmol/l in women and

407, 498 and 617 nmol/l in men. Cut-off points for calculated free cortisol quartiles were 7·88, 10·14 and 13·50 in women and 10·75, 16·53 and 16·84 in men. The variables BMI and level of physical activity were not linearly related to physical performance. Therefore, BMI was included in quartiles and physical activity was included in sixtiles (which modelled the nonlinear pattern of the relationship more adequately than quartiles). Second, the interaction with gender was tested for significance ($P < 0{\cdot}10$). Third, simple linear regression was conducted. Fourth, multiple linear regression was performed with adjustment for those confounders that led to a change in the regression coefficient of the association between cortisol and performance of more than 10%. This was the case when age, alcohol use, physical activity, BMI and region were added to the model (in all cortisol measures). Fifth, to test which of the individual performance tests had the strongest relationship with cortisol, cumulative logistic ordinal regression was used, which has the feature of proportional odds (SPSS, PLUM).[26,27] *P*-values were based on two-sided tests and were considered statistically significant at $P < 0{\cdot}05$.

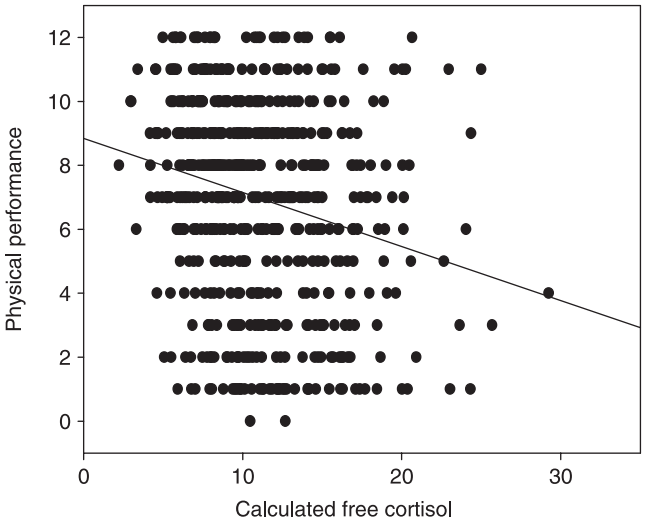

Fig. 2 Relationship between calculated free cortisol and physical performance in women. The graph shows the scatter plot of the continuous data and (unadjusted) regression line for the relationship between calculated free cortisol (*x*-axis) and physical performance (*y*-axis) in women.

Results

In the second cycle, 600 women and 572 men were included with mean serum total cortisol concentrations of 480·0 nmol/l (standard deviation = 173·4) and 517·8 nmol/l (SD = 161·4) and mean calculated free cortisol concentrations of 10·9 (SD = 4·1) and 14·0 (SD = 4·4), respectively. In the fourth cycle, 464 women and 420 men were included. The median evening salivary cortisol concentration was 3·0 nmol/l (interquartile range = 1·2–4·8) in women and 3·0 nmol/l (IQR = 1·0–5·0) in men. Table 1 shows the characteristics of the participants in both cycles. Figure 2 shows that, over the full range of calculated free cortisol values measured, physical performance decreased by more than 2 points in women.

In the second cycle, an interaction with gender was found for calculated free cortisol ($P = 0{\cdot}001$) but not for serum total cortisol ($P = 0{\cdot}13$). To enhance the comparability, all models were analysed for men and women separately. In women, an unadjusted relationship was found between both serum total and calculated free cortisol and physical performance (Table 2). After adjustment, only the

Table 1. Baseline data for men and women in the second and fourth cycle

	Second cycle		Fourth cycle	
Variables	Women ($n = 600$)	Men ($n = 572$)	Women ($n = 464$)	Men ($n = 420$)
Age	75·1 (6·4)	75·3 (6·5)	75·1 (6·7)	75·1 (6·8)
Body mass index	27·6 (4·7)	26·1 (3·3)	27·8 (4·7)	26·7 (3·3)
Alcohol (% ≥ 15 glasses/week)	11·0	31·1	12·5	29·4
Smoking (% yes)	12·5	24·1	9·9	20·5
Number of chronic diseases	1·2 (1·1)	1·2 (1·1)	1·4 (1·0)	1·3 (1·1)
Depression (% CES-D > 16)	20·3	7·2	16·6	9·9
Use of walking aid (% yes)	3·8	2·3	2·9	1·4
Physical activity (min/day)*	163·7 [50·9–276·5]	106·4 [0–218·0]	161·3 [39·9–282·7]	107·0 [3·9–210·1]
Region (% Amsterdam)	47·0	46·7	43·7	43·4
Walk test*	2 [0·0–4·0]	3 [1·0–4·0]	2 [0–4]	2 [0–4]
Chair stands	1·9 (1·2)	2·3 (1·1)	2·1 (1·1)	2·3 (1·1)
Tandem stand (% able ≥ 10 s)	61·0	72·7	70·2	80·7
Physical performance	7·0 (3·2)	8·1 (2·8)	7·4 (3·0)	8·1 (2·7)
Serum total cortisol†	480·0 (173·4)	517·8 (161·4)	–	–
CBG*†	43·7 [32·7–54·7]	36·4 [28·4–44·4]	–	–
Calculated free cortisol†	10·9 (4·1)	14·0 (4·4)	–	–
Evening salivary cortisol*‡	–	–	3·0 [1·2–4·8]	3·0 [1·0–5·0]

All variables are presented as mean (standard deviation) unless stated otherwise. *Results are presented as median [interquartile range]. †Calculated free cortisol = serum total cortisol (nmol/l)/CBG (mg/l); nmol/l = 27·5*μg/dl. ‡Salivary cortisol is presented in nmol/l.

Table 2. Relationship between serum cortisol and total physical performance score

		Women		Men	
Physical performance		b*	*P*-value	b*	*P*-value
Continuous					
Serum total cortisol†		–0·39	0·002††	–0·11	0·36
Serum total cortisol (adjusted)†‡		–0·17	0·13	–0·05	0·64
Calculated free cortisol†		–0·69	<0·001††	–0·14	0·23
Calculated free cortisol (adjusted)†‡		–0·28	0·016**	0·09	0·43
Quartiles§					
Serum total cortisol	Q1¶	0	0		
	Q2	–0·35	0·34	–0·59	0·08
	Q3	–0·53	0·14	–0·57	0·09
	Q4	–1·25	0·001††	–0·54	0·10
Serum total cortisol (adjusted)‡	Q1¶	0	0		
	Q2	–0·20	0·51	–0·37	0·23
	Q3	–0·20	0·52	–0·16	0·60
	Q4	–0·61	0·05	–0·41	0·19
Calculated free cortisol	Q1¶	0		0	
	Q2	–1·08	0·003††	–0·69	0·04*
	Q3	–1·40	<0·001††	–0·19	0·57
	Q4	–1·98	<0·001††	–0·78	0·02*
Calculated free cortisol (adjusted)‡	Q1¶	0	0		
	Q2	–0·49	0·11	–0·34	0·27
	Q3	–0·38	0·23	0·19	0·55
	Q4	–0·88	0·007††	–0·01	0·96

*Unstandardized regression coefficients; †regression coefficients expressed per SD higher serum cortisol: women $SD_{total\ cortisol}$ = 173·4 nmol/l, $SD_{free\ cortisol}$ = 4·1, Men $SD_{total\ cortisol}$ = 161·4 nmol/l, $SD_{free\ cortisol}$ = 4·4; ‡Adjusted for age, alcohol use, body mass index, physical activity and region; §Quartile (cut-off points are mentioned in the method); ¶Reference quartile; **significant at the 0·05 level (two-tailed); ††significant at the 0·01 level (two-tailed).

Table 3. Relationship between serum cortisol (continuous) and the individual performance tests

		Tandem stand		Walk test		Chair stands	
	Performance tests	OR*	*P*-value	OR*	*P*-value	OR*	*P*-value
Women	Serum total cortisol	1·47	<0·001§	1·11	0·16	1·04	0·63
	Serum total cortisol (adjusted)†	1·28	0·007§	1·05	0·54	1·04	0·63
	Calculated free cortisol	1·67	<0·001§	1·26	0·002§	1·21	0·008§
	Calculated free cortisol (adjusted)†	1·32	0·003§	1·09	0·33	1·05	0·52
Men	Serum total cortisol	1·12	0·20	1·05	0·54	0·98	0·79
	Serum total cortisol (adjusted)†	1·04	0·67	1·11	0·19	1·01	0·95
	Calculated free cortisol	1·16	0·12	1·08	0·30	0·97	0·73
	Calculated free cortisol (adjusted)†	1·02	0·86	1·01	0·86	1·08	0·31

*OR for a poorer test result, expressed per SD higher serum cortisol: Women $SD_{total\ cortisol}$ = 173·4 nmol/l, $SD_{free\ cortisol}$ = 4·1, Men SD_{total} cortisol = 161·4 nmol/l, SDfree cortisol = 4·4; †Adjusted for age, alcohol use, body mass index, physical activity and region; §Significant at the 0·01 level (two-tailed).

relationship between calculated free cortisol (both continuously and in quartiles) and physical performance remained significant. A value of 1-SD-higher calculated free cortisol level (continuous) was associated with a poorer physical performance score of 0·28 points ($r^2 = 0·35$). The most important confounders were age and alcohol use (range 0–2) with regression coefficients of –0·21 points per year and 0·60 points per category, respectively. Women in the highest quartile of calculated free cortisol had a 0·88-points poorer physical performance score than those in the lowest quartile. In men, no significant relationships were found after adjustment for confounding.

In women, ordinal regression showed that there was a relationship between both serum total and calculated free cortisol (continuous) and the tandem stand (Table 3). These relationships remained significant after adjustment for confounding. The cumulative odds for

Table 4. Relationship between evening salivary cortisol and total physical performance score

Physical performance		Women		Men	
		b*	*P*-value	b*	*P*-value
Evening salivary cortisol	Q1‡	0	0		
	Q2	–0·36	0·37	–1·10	0·003¶
	Q3	0·23	0·56	–0·74	0·05
	Q4	–1·32	0·001¶	–1·40	<0·001¶
Evening salivary cortisol (adjusted)†	Q1‡	0	0		
	Q2	–0·39	0·25	–0·79	0·016§
	Q3	0·37	0·27	–0·48	0·15
	Q4	–0·79	0·026§	–0·90	0·008¶

*Unstandardized regression coefficients; †Adjusted for age, body mass index, physical activity, alcohol use and region; ‡reference quartile; §significant at the 0·05 level (two-tailed); ¶significant at the 0·01 level (two-tailed).

Table 5. Relationship between evening salivary cortisol and the individual performance tests

	Performance tests		Tandem stand		Walk test		Chair stands	
			OR*	*P*	OR*	*P*	OR*	*P*
Women	Evening salivary cortisol	Q1‡	1		1	1		
		Q2	1·71	0·08	0·83	0·44	1·29	0·28
		Q3	1·12	0·72	0·69	0·12	0·99	0·97
		Q4	2·79	0·001¶	1·41	0·17	1·77	0·021§
	Evening salivary cortisol (adjusted)†	Q1‡	1		1	1		
		Q2	1·92	0·05	0·77	0·30	1·34	0·23
		Q3	1·02	0·96	0·62	0·06	0·88	0·61
		Q4	2·42	0·008¶	1·09	0·75	1·43	0·16
Men	Evening salivary cortisol	Q1‡	1		1	1		
		Q2	1·86	0·10	1·98	0·006¶	1·92	0·09
		Q3	1·50	0·29	1·44	0·15	1·59	0·07
		Q4	2·00	0·07	2·33	0·001¶	2·15	0·003¶
	Evening salivary cortisol (adjusted)†	Q1‡	1		1	1		
		Q2	1·34	0·48	1·61	0·07	1·62	0·06
		Q3	1·15	0·75	1·29	0·33	1·54	0·09
		Q4	1·20	0·66	1·88	0·020§	1·81	0·027§

*OR for a poorer test result; †Adjusted for age, body mass index, physical activity, alcohol use and region; ‡reference quartile; §significant at the 0·05 level (two-tailed); ¶significant at the 0·01 level (two-tailed).

a lower score on the tandem stand test became 1·28 times greater when serum total cortisol increased by 1 SD-value and 1·32 times greater when calculated free cortisol increased by 1 SD-value. Furthermore, a relationship was found between calculated free cortisol and the chair stands and walk test, respectively. However, after adjustment for confounding, the latter associations were no longer statistically significant. No significant relationships were found in men between serum total or calculated free cortisol and any of the physical performance tests. The results were similar when serum total and calculated free cortisol were included in quartiles (data not shown).

In the fourth cycle, no interaction with gender was found ($P = 0{\cdot}70$). However, to enhance the comparability, results are presented for men and women separately. Both unadjusted and adjusted relationships between evening salivary cortisol and physical performance were found in women as well as in men (Table 4). Women and men in the highest quartile of salivary cortisol had 0·79- and 0·90-points poorer physical performance scores, respectively, compared with the lowest quartiles. The most important confounders in women were age and alcohol use (range 0–2), with regression coefficients of –0·17 points per year and 0·70 points per category, respectively. In men, the most important confounder was age, with a regression coefficient of –0·16 points per year.

Ordinal regression showed that there was a relationship between evening salivary cortisol and each of the physical performance tests, both in women and in men (Table 5). After adjustment, the relationships with tandem stand were significant in women. Women in

the highest quartile had 2·42 times higher odds for a poorer score on the tandem stand than women in the lowest quartile, respectively. In men, on the other hand, the relationships between salivary cortisol and both the chair stands and walk test remained significant after adjustment. Men in the highest quartile of salivary cortisol had 1·88 and 1·81 times higher odds for a poorer score on the chair stands and walk test, respectively, than men in the lowest quartile.

Use of oral oestrogens is known to affect CBG. However, excluding these participants ($n = 11$ in the second cycle; $n = 16$ in the fourth cycle) did not affect the results. To increase the power, we did not exclude these participants from the analyses.

Discussion

The results of this study show that in older women there is a relationship between calculated free cortisol and physical performance. This relationship can for the greater part be explained by the relationship between calculated free cortisol and the performance on the tandem stand test. These findings in older women were confirmed by the relationships between evening salivary cortisol and physical performance and in particular the tandem stand. The results also show that in older men there is a relationship between evening salivary cortisol and physical performance. This relationship can for the greater part be explained by the chair stands and walk test.

In our study, relationships between cortisol and physical performance were found both in women and in men, although these relationships were different for the individual performance tests. In women, cortisol was negatively associated with the tandem stand, which mainly measures balance. In one study, a relationship was observed between leg muscle power (force × velocity, the ability to generate force quickly) and tandem gait (forward and backward walking, heel to toe, over a 20-foot distance), while no relationship was found between leg muscle strength and tandem gait.[28] This suggests that leg muscle power explains more of the variance in balance than leg muscle strength. Other investigators found that older women had lower strength and strength development rates than older men.[29] Possibly, decline in muscle power and consequently balance is more pronounced in older women than in older men. Alternatively, older women have less muscular reserve and pass a threshold earlier than older men, resulting in earlier balance upset. Moreover, in older women, cortisol may influence muscle power rather than muscle strength alone.

In men, we found an independent relationship between evening salivary cortisol and performance on the chair stands and walk test. The chair stands test predominantly measures the functional strength of the proximal lower extremity muscles. One of the symptoms of Cushing's syndrome is weakness of the proximal muscles, mainly of the lower extremities.[30] Izquierdo *et al.* found that the cortisol level accounted for 18 and 40% of the variance in maximal isometric knee extension strength in middle-aged and older men, respectively.[5] The current findings support the hypothesis that high cortisol levels affect proximal muscle strength and not general muscle strength. In contrast, no relationships between serum cortisol and the chair stands test were found.

The walk test measures a combination of strength, balance and coordination. In men, a relationship between cortisol and the chair stands (strength) was found, but not between cortisol and the tandem stand (balance). This may imply that the relationship between cortisol level and the walk test in men is explained by strength more than by balance. Coordination was not separately tested in this study.

Calculated free cortisol (i.e. cortisol/CBG) is a rather rough estimate of the actual free cortisol concentration. Particularly at higher cortisol/CBG ratios, cortisol levels exceed CBG binding capacity, and then free cortisol rises steeply. Free cortisol can also be calculated using an algorithm based on the law of mass action, with both CBG and albumin as the binding proteins and the dissociation constants, as described by Lentjes *et al.*[31] Although the relationship between the cortisol/CBG ratio and algorithm-based free cortisol was nonlinear (as expected), the coefficient of correlation was high ($r > 0{\cdot}95$, $P < 0{\cdot}001$). Repeating our analyses using the algorithm-based free cortisol instead of cortisol/CBG ratio did not essentially alter the results.

The foetal origins hypothesis proposes that disease in adult life may originate from permanent changes in the structure, physiology and metabolism of the foetal body as adaptation to undernutrition.[32] Adaptation of the HPA axis may be one such mechanism and associations have been found between low birth weight and elevated morning cortisol concentrations in healthy older men.[33] The relationships found in the current study between cortisol and physical performance may originate in the perinatal period when the HPA axis is programmed.

A strength of this study is that a second population (2001/2002) that only partly overlaps with the first (1995/1996) was used to validate our findings. Some participants of the second cycle died or withdrew from the study and participants younger than 65 in 1996 participated in the fourth cycle in 2002. About 43% of the participants in the second cycle also took part in the fourth cycle and 54% of the fourth cycle had participated in the second cycle. In addition, the sample is representative of the older population in the Netherlands.

Two limitations need to be mentioned. First, the significant results that were observed could be a consequence of multiple testing. However, when a stricter α of 0·01 is used, in women the relationships between calculated free cortisol and physical performance and between any of the cortisol measures and the tandem stand remain significant. Also, in men, the relationship between salivary cortisol and physical performance remains significant. The relationship between salivary cortisol and the walk test and chair stands could be interpreted as a trend.

Second, cortisol was measured only once per cycle, while serum cortisol levels are known to fluctuate strongly during the day and with stress.[13,34,35] A more reliable measure for serum cortisol may be obtained by 24-h measurements or repeated measurement. However, the mean serum cortisol concentrations measured are realistic for the population and time measured.[36] In addition, a relationship was found despite the time-point of sampling and it remained significant after adjustment for confounding. Furthermore, the analyses were conducted using three different measures for cortisol and in two partly different populations. In the second cycle cortisol was measured in serum and in the fourth cycle cortisol was measured in evening saliva. Results for serum total and calculated free cortisol were comparable, although the relationships between calculated free cortisol and physical performance were somewhat stronger. Calculated free

cortisol is believed to be the biologically active part of the serum total cortisol,[37] and is probably a better measure than serum total cortisol to express the relationship with functional outcomes. Salivary cortisol concentrations are believed to be equivalent to calculated free cortisol levels in this respect. Overall, the results found with calculated free cortisol are supported by the results found with evening salivary cortisol. The small differences between the cycles can be explained by the time-point of sampling (morning *vs.* evening) and by the participants measured. Cortisol levels fluctuate highly during the day, with a peak early in the morning and a nadir late in the evening.[13,34,35] The normal range for cortisol levels in the morning is wide. Serum cortisol shows a fluctuating pattern and morning serum cortisol better reflects peak cortisol, while evening salivary cortisol better reflects basal cortisol secretion.

We found a relationship between cortisol and physical performance in healthy older persons, with cortisol levels fluctuating within the normal range. This relationship was for the greater part explained by the chair stands and walk test in men and by the tandem stand in women. As shown in Fig. 2, over the full range of cortisol values measured, a difference of 2 points in physical performance was observed. A 2-points lower score indicates that the performance was one point lower on two of the three tests (25% reduction in the score on two tests) or two points lower on one of the three tests (a 50% reduction in the score on one test) compared with the higher score. To our knowledge, the clinical or population relevance of a 1-point difference in physical performance in older persons has not yet been discussed in the literature. However, a high cortisol level appears to be a risk factor for a poorer physical performance score, and decline in physical performance is known to predict disability, recurrent falling and other health-related factors in older persons.[21,22,38] In an earlier study conducted at our department, recurrent fallers (mean score = 6·1) scored 1·1 points lower on physical performance than non- and once-fallers (mean = 7·2)[38] indicating that a 1-point difference can have a profound effect on one's health status. Furthermore, it is interesting to see that these relationships were found in a normal older population. It can be expected that the relationships will be even stronger in a less healthy population.

A possible mechanism explaining the effect of cortisol on physical performance is that glucocorticoids stimulate degradation and decrease synthesis of myosin heavy chains, which leads to muscle atrophy.[39] Further research on the relationship between cortisol and muscle strength and the underlying mechanisms, both in men and in women, is needed and may explain the different relationships found in women and men in this study. Furthermore, as performance on the tandem stand is associated with recurrent falling,[40] it might be interesting to examine the association between cortisol and recurrent falling.

In conclusion, high levels of cortisol are negatively associated with physical performance in healthy older persons. This association can for the greater part be explained by balance in women and by proximal leg strength in men.

Acknowledgements

This study is based on data from the Longitudinal Aging Study Amsterdam (LASA) and is financially supported by the Dutch Ministry of Public health, Welfare and Sports.

References

1 Marcell, T.J. (2003) Sarcopenia: causes, consequences, and preventions. *Journals of Gerontology Series A: Biological and Medical Sciences*, **58**, M911–M916.

2 Nieuwenhuijzen Kruseman, A.C., van der Klauw, M.M. & Pijpers, E. (2005) [Hormonal and metabolic causes of muscular weakness and the increased risk of fractures in elderly people]. *Nederlands Tijdschrift voor Geneeskunde*, **149**, 1033–1037.

3 Djaldetti, M., Gafter, U. & Fishman, P. (1977) Ultrastructural observations in myopathy complicating Cushing's disease. *American Journal of Medical Science*, **273**, 273–277.

4 Melby, J.C. (1977) Clinical pharmacology of systemic corticosteroids. *Annual Review of Pharmacological Toxicology*, **17**, 511–527.

5 Izquierdo, M., Hakkinen, K., Anton, A., Garrues, M., Ibanez, J., Ruesta, M. & Gorostiaga, E.M. (2001) Maximal strength and power, endurance performance, and serum hormones in middle-aged and elderly men. *Medicine & Science in Sports & Exercise*, **33**, 1577–1587.

6 Balagopal, P., Rooyackers, O.E., Adey, D.B., Ades, P.A. & Nair, K.S. (1997) Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. *American Journal of Physiology*, **273**, E790–E800.

7 Gallagher, D., Visser, M., De Meersman, R.E., Sepulveda, D., Baumgartner, R.N., Pierson, R.N., Harris, T. & Heymsfield, S.B. (1997) Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *Journal of Applied Physiology*, **83**, 229–239.

8 Rosenberg, I.H. (1997) Sarcopenia: origins and clinical relevance. *Journal of Nutrition*, **127**, 990S–991S.

9 Visser, M., Kritchevsky, S.B., Goodpaster, B.H., Newman, A.B., Nevitt, M., Stamm, E. & Harris, T.B. (2002) Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70–79: the health, aging and body composition study. *Journal of the American Geriatrics Society*, **50**, 897–904.

10 Gillick, M. (2001) Pinning down frailty. *Journals of Gerontology Series A: Biological and Medical Sciences*, **56**, M134–M135.

11 Lamberts, S.W., van den Beld, A.W. & van der Lely, A.J. (1997) The endocrinology of aging. *Science*, **278**, 419–424.

12 Laughlin, G.A. & Barrett-Connor, E. (2000) Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: the Rancho Bernardo Study. *Journal of Clinical Endocrinology and Metabolism*, **85**, 3561–3568.

13 Van Cauter, E., Leproult, R. & Kupfer, D.J. (1996) Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *Journal of Clinical Endocrinology and Metabolism*, **81**, 2468–2473.

14 Purnell, J.Q., Brandon, D.D., Isabelle, L.M., Loriaux, D.L. & Samuels, M.H. (2004) Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women. *Journal of Clinical Endocrinology and Metabolism*, **89**, 281–287.

15 Heuser, I.J., Gotthardt, U., Schweiger, U., Schmider, J., Lammers, C.H., Dettling, M. & Holsboer, F. (1994) Age-associated changes of pituitary–adrenocortical hormone regulation in humans: importance of gender. *Neurobiological Aging*, **15**, 227–231.

16 Deeg, D., Knipscheer, C. & van Tilburg, W. (1993) *Autonomy and Well-being in the Aging Population: Concepts and Design of the Longitudinal Aging Study Amsterdam*. Netherlands Institute of Gerontology, Bunnik.

17 Smith, J. & de Vries, M. (1994) Procedures and results of the field work. In: D.J.H. Deeg, M. Westendorp-de Serriere, eds. *Autonomy and Well-Being in the Aging Population I: Report from the Longitudinal Aging Study Amsterdam 1992–93*. VU University Press, Amsterdam, 7–13.

18 le Roux, C.W., Sivakumaran, S., Alaghband-Zadeh, J., Dhillo, W., Kong, W.M. & Wheeler, M.J. (2002) Free cortisol index as a surrogate marker for serum free cortisol. *Annals of Clinical Biochemistry*, **39**, 406–408.

19 Guralnik, J.M., Simonsick, E.M., Ferrucci, L., Glynn, R.J., Berkman, L.F., Blazer, D.G., Scherr, P.A. & Wallace, R.B. (1994) A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *Journal of Gerontology*, **49**, M85–M94.

20 Guralnik, J.M., Seeman, T.E., Tinetti, M.E., Nevitt, M.C. & Berkman, L.F. (1994) Validation and use of performance measures of functioning in a non-disabled older population: MacArthur studies of successful aging. *Aging (Milano)*, **6**, 410–419.

21 Guralnik, J.M., Ferrucci, L., Simonsick, E.M., Salive, M.E. & Wallace, R.B. (1995) Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *New England Journal of Medicine*, **332**, 556–561.

22 Guralnik, J.M., Ferrucci, L., Pieper, C.F., Leveille, S.G., Markides, K.S., Ostir, G.V., Studenski, S., Berkman, L.F. & Wallace, R.B. (2000) Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *Journals of Gerontology Series A: Biological and Medical Sciences*, **55**, M221–M231.

23 Seeman, T.E., Singer, B., Wilkinson, C.W. & McEwen, B. (2001) Gender differences in age-related changes in HPA axis reactivity. *Psychoneuroendocrinology*, **26**, 225–240.

24 Beekman, A.T., Deeg, D.J., Braam, A.W., Smit, J.H. & Van Tilburg, W. (1997) Consequences of major and minor depression in later life: a study of disability, well-being and service utilization. *Psychological Medicine*, **27**, 1397–1409.

25 Stel, V.S., Smit, J.H., Pluijm, S.M., Visser, M., Deeg, D.J. & Lips, P. (2004) Comparison of the LASA physical activity questionnaire with a 7-day diary and pedometer. *Journal of Clinical Epidemiology*, **57**, 252–258.

26 Agresti, A. (2002) *Categorical Data Analysis*, 2nd edn. John Wiley & Sons, Inc, New York.

27 McCullagh, P. (1980) Regression models for ordinal data. *Journal of the Royal Statistical Society Series B*, **42**, 109–142.

28 Bean, J.F., Kiely, D.K., Herman, S., Leveille, S.G., Mizer, K., Frontera, W.R. & Fielding, R.A. (2002) The relationship between leg power and physical performance in mobility-limited older people. *Journal of the American Geriatrics Society*, **50**, 461–467.

29 Thelen, D.G., Schultz, A.B., Alexander, N.B. & Ashton-Miller, J.A. (1996) Effects of age on rapid ankle torque development. *Journals of Gerontology Series A: Biological and Medical Sciences*, **51**, M226–M232.

30 Nieman, L.K. & Ilias, I. (2005) Evaluation and treatment of Cushing's syndrome. *American Journal of Medicine*, **118**, 1340–1346.

31 Lentjes, E.G. & Romijn, F.H. (1999) Temperature-dependent cortisol distribution among the blood compartments in man. *Journal of Clinical Endocrinology and Metabolism*, **84**, 682–687.

32 Barker, D.J.P. (1998) *Mothers, Babies and Health in Later Life*, 2nd edn. Churchill Livingstone, Edinburgh.

33 Phillips, D.I., Barker, D.J., Fall, C.H., Seckl, J.R., Whorwood, C.B., Wood, P.J. & Walker, B.R. (1998) Elevated plasma cortisol concentrations: a link between low birth weight and the insulin resistance syndrome? *Journal of Clinical Endocrinology and Metabolism*, **83**, 757–760.

34 Young, E.A., Abelson, J. & Lightman, S.L. (2004) Cortisol pulsatility and its role in stress regulation and health. *Front Neuroendocrinology*, **25**, 69–76.

35 Raff, H., Raff, J.L. & Findling, J.W. (1998) Late-night salivary cortisol as a screening test for Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism*, **83**, 2681–2686.

36 College voor Zorgverzekeringen. (2003) Diagnostisch kompas 2003. http://www.dk.cvz.nl/testbeschrijvingen/C/Cortisol.asp

37 Mendel, C.M. (1989) The free hormone hypothesis: a physiologically based mathematical model. *Endocrine Reviews*, **10**, 232–274.

38 Stel, V.S., Pluijm, S.M., Deeg, D.J., Smit, J.H., Bouter, L.M. & Lips, P. (2003) A classification tree for predicting recurrent falling in community-dwelling older persons. *Journal of the American Geriatrics Society*, **51**, 1356–1364.

39 Salehian, B. & Kejriwal, K. (1999) Glucocorticoid-induced muscle atrophy: mechanisms and therapeutic strategies. *Endocrine Practice*, **5**, 277–281.

40 Stel, V.S., Smit, J.H., Pluijm, S.M. & Lips, P. (2003) Balance and mobility performance as treatable risk factors for recurrent falling in older persons. *Journal of Clinical Epidemiology*, **56**, 659–668.

