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Cortisol and physical performance in older populations: Findings from the international mobility in aging study (IMIAS)

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ABSTRACT

Objective: To compare diurnal cortisol profiles across samples of older adults from diverse populations and to examine if differences in circadian cortisol secretion are associated with poor physical performance (SPPB<9).
Methods: Data were collected during the baseline survey of the International Mobility in Aging Study conducted in 2012 in Kingston (Canada), Saint-Hyacinthe (Canada), Tirana (Albania) and Manizales (Colombia). Salivary cortisol was collected from a subsample of 309 participants instructed to collect saliva on two consecutive days, and 5 different intervals each day: upon awakening (M1), 30 min (M2) and 60 min after awakening, at 15:00 h and before bedtime (E). Cortisol was analyzed using enzyme immunoassay kits. Physical performance was measured by the Short Physical Performance Battery (SPPB). Mixed linear models were fit to assess the associations between cortisol diurnal output and physical performance, adjusting for potential confounders.
Results: Kingston, Saint-Hyacinthe and Tirana residents had significantly higher cortisol values than their Manizales counterparts, with the population from Tirana showing the highest levels. Attenuated morning cortisol peak (M2) ($p = 0.025$), higher cortisol bed time (E) ($p = 0.005$), and lower M2/E ratio ($p < 0.001$) were found among those with SPPB<9 compared with those with good physical performance (SPPB ≥ 9). These results were not altered after adjustment by potential confounders.
Conclusion: Cortisol profiles varied across four diverse populations of older adults. Circadian cortisol secretion is associated with physical performance as an attenuated morning response and higher bed time values were observed in older adults with SPPB < 9.

1. Introduction

Cortisol is a hormone secreted by the neuroendocrine system through the hypothalamic-pituitary-adrenocortical (HPA) axis, known to be activated by experiences of common challenges throughout the life span, including old age (Wrosch, Miller, & Schulz, 2009). Cortisol is the product of the HPA axis and sustained HPA axis activation might expose the body to excessive amounts of stress hormones with effects on the immune and cardiovascular systems, as well as on metabolism (Carpenter et al., 2007; Sapolsky, Romero, & Munck, 2000).

Given the important regulatory influence of cortisol on the metabolic, immune, skeletal, nervous and circulatory systems, it has been proposed that stress-related disturbances could increase a person's likelihood of developing a variety of health problems (Taylor, Lerner, Sage, Lehman, & Seeman, 2004; Wrosch et al., 2009). Studies indicate that individuals with elevated patterns of cortisol secretion are more prone to increased morbidity and mortality (Kumari et al., 2010; Peeters, van Schoor, van Rossum, Visser, & Lips, 2008; Wrosch et al., 2009).

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Cortisol output is related to chronic stress accumulated through environmental challenges and social and economic adversity during life (Desantis, Kuzawa, & Adam, 2015). The influence of life course socioeconomic trajectories on cortisol response has been a topic of interest in aging research (Agbedia et al., 2011; Gustafsson, Janlert, Theorell, & Hammarstrom, 2010; Wright & Steptoe, 2005). Most of the studies on the relationship between socioeconomic status (SES) and cortisol have shown blunted salivary cortisol patterns during the day in lower SES populations (Agbedia et al., 2011). In a recent study of older adults using a life course developmental perspective, chronically low SES from infancy through to early adulthood predicted flatter cortisol rhythms between waking up and bedtime in old age better than socioeconomic status at any single period of life (Desantis et al., 2015).

In a meta-analysis of five European cohorts of older adults (Gardner et al., 2013), a larger diurnal drop was associated with faster walking speed and a shorter chair standing time, and a blunted cortisol response was associated with poorer physical function in a cohort of older women evaluated in the United States (Varadhan et al., 2008). Several studies have suggested that dysregulation of cortisol levels is associated with worse physical performance and with mobility disability (Gardner et al., 2011; Peeters et al., 2008, 2007).

Few international comparisons of cortisol diurnal patterns in older adults have been published and results are inconsistent. A study comparing healthy older adults in Sao Paulo (Brazil) and Montreal (Quebec) recently reported that the older Brazilian adults had higher morning concentrations and steeper diurnal declines than their Canadian counterparts (Souza-Talarico, Plusquellec, Lupien, Fiocco, & Suchecki, 2014). However, a previous study comparing older adults from Santa Cruz, a city in a rural area of North East Brazil, and Saint Bruno, a suburban area of Quebec, reported a blunted diurnal cortisol curve, characterized by significantly lower awake value and lower diurnal slope among the Santa Cruz population (Tu, Zunzunegui, Guerra, Alvarado, & Guralnik, 2013).

These inconsistencies suggest that more research is needed comparing diurnal cortisol regulation in populations from different social contexts. The International Mobility in Aging Study (IMIAS) is an international study conducted in older populations residing in five cities in Brazil (Natal), Canada (Saint Hyacinthe and Kingston), Colombia (Manizales) and Albania (Tirana), and provides an opportunity to compare diurnal cortisol curves and examine the associations between HPA regulation and physical performance in old age (Zunzunegui et al., 2015).

The present study examines the associations between daily cortisol output and physical performance in diverse populations of older adults. We hypothesized that: 1) in accordance with the literature, life course socioeconomic adversity should be associated with flatter cortisol rhythms between wake up and bedtime, cortisol diurnal concentrations would have lower morning values and lower diurnal decline in older populations from cities in Colombia and Albania compared with older populations from Canadian cities; 2) as poor physical performance indicates compromised physical health, those with poor physical performance would have an attenuated morning response and higher bedtime values (i.e., flatter profiles) compared with those with high physical performance, adjusting for research city and relevant covariates.

2. Material and methods

2.1. Ethics statement

The study was approved by the ethics committees of Queens University and the Centre hospitalier de l'Université de Montreal in Canada, the Albanian Institute of Public Health, and the University of Caldas in Colombia. All participants gave written informed consent.

2.2. Population and sample

IMIAS is a population-based longitudinal study and was conducted in the five cities mentioned above: Natal, Manizales, Tirana, Saint-Hyacinthe and Kingston. Those cities were selected because they provide a wide range of life course exposures to socioeconomic adversity and physical performance outcomes in old age. Although United Nations Human Development Indexes are only available at the country level, they are useful for a general comparison on living conditions (http://hdr.undp.org/en/content/table-1-human-development-index-and-its-components). Among 187 countries, Canada ranked eighth in the 2014 Human Development Index, Brazil occupied the 79th ranking, while Albania ranked 95th, and Colombia 98th. In addition, life expectancy for men born in 1950–1954 (the first period with life expectancy data available on the United Nations website) was 49 in Brazil and Colombia, 54 in Albania, and 67 for Canada; similar figures for women were 53 in Brazil and Colombia, 56 in Albania and 72 for Canada. Participants in IMIAS were born between 1938 and 1947, but life expectancy is not available for those birth cohorts on the United Nations Development Program website. The study cities are middle-sized cities with older adults who have experienced little outward or inward immigration, assuring relatively homogeneous life course exposures within each city while maximizing variability across cities.

In 2012, IMIAS recruited 1995 community dwelling participants (about 200 men and 200 women in each study city) aged 65 to 74 years. In this report, we use data from Manizales (Colombia), Tirana (Albania), Saint-Hyacinthe (Quebec, Canada) and Kingston (Ontario, Canada), as saliva samples were not obtained in Natal (Brazil). A random sample was selected in Tirana and Manizales through neighborhood primary care center registries and participants were approached directly at their homes by our interviewers to invite them to participate. In Kingston and Saint-Hyacinthe, potential participants received a letter from their primary care physicians inviting them to contact our field coordinator, who then arranged for interviews at the volunteer's home. Two different recruitment methods were needed because Canadian ethics committees do not allow direct invitations to potential participants. In Canada and in Albania more than 90% of older adults in the age group 65–74 are registered at the local neighborhood health center belonging to their universal coverage National Healthcare Systems. In Manizales, 82% of older adults in this age group are registered at the Public Health Insurance system.

Participants were excluded if they had four or more errors in the orientation scale of the Leganes Cognitive Test (LCT), a screening test for dementia (De Yebenes et al., 2003). The number of excluded people was zero in Kingston, one in Saint-Hyacinthe and Tirana, and two in Manizales. More information relative to recruitment, pilot study and a detailed description of research sites and procedures can be seen in previous IMIAS publications (Sousa et al., 2014). Due to budgetary limitations, saliva collection was offered to a random subsample of 100 participants from Kingston, Saint-Hyacinthe and Manizales, and to 60 participants from Tirana. Response rates were high for all sites, being 81% in Kingston and Saint-Hyacinthe, 90% in Manizales and 95% in Tirana.

2.3. Cortisol measures

2.3.1. Saliva collection

Participants were instructed to collect saliva samples on two consecutive days through active drool at five different times on

each day: upon awakening, 30 min after awakening, 60 min after awakening, at 15:00 h, and at bedtime. Participants were required to refrain from drinking, eating and brushing their teeth within the hour prior to saliva collection. Participants completed a questionnaire at each time of cortisol collection; it included the time of the day and questions on eating, drinking, exercising or taking medication in the half hour before saliva collection (saliva collection protocol available upon request). All data were revised for adherence to the protocol. Samples deviating by more than 15 min from their planned sampling time were excluded from data analyses.

2.3.2. Analyses of cortisol in saliva samples

Samples were stored in the refrigerator at the participant's home before the research team collected them and stored them at −20 °C. Samples from Manizales, Kingston and Saint Hyacinthe were shipped to the Douglas Mental Health University Institute in Verdun, Canada, where they were analyzed in duplicate by a sensitive enzyme immunoassay kit (Salimetrics, State College, PA). The samples from Tirana were analyzed in the Neo Style Laboratory under the supervision of the research team, using a highly sensitive salivary cortisol enzyme immunoassay kit (by Salimetrics, Europe Ltd.). These two Salimetrics tests are very similar, but not identical. The inter-assay coefficient of variation was 9.7% across 3 different assays.

2.4. Physical performance

Physical performance was measured by the Short Physical Performance Battery (SPPB) that includes three timed lower body function tests: a hierarchical standing balance test, a four meter walk at usual pace, and five repetitive chair stands. Each SPPB component test (balance, gait and chair stand) is scored from 0 to 4, with a score of 0 representing inability to perform the test, and a score of 4 representing the highest performance level. A summary performance score (range 0 – 12) was obtained by adding the scores of each individual SPPB component, with higher scores indicating better lower body function (Guralnik et al., 1994; Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Vasunilashorn et al., 2009). For analyses we compared those with low performance (SPPB < 9) to those with higher performance (SPPB ≥ 9) using a previously validated cut-off for frailty in our populations (da Camara, Alvarado, Guralnik, Guerra, & Maciel, 2013).

2.5. Covariates

Based on current literature on cortisol and physical performance, we considered the following covariates as possible confounders: sex, depression, body mass index, physical activity, smoking and anti-depressant, anxiolytic and analgesic medications taken during the last two weeks, as well as city of residence.

Sex was coded as binary (0 = women; 1 = men). The self-reported 20-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depression symptoms experienced over the preceding week. Scores range from 0 to 60. A score of 16 and over was indicative of probable depression. Weight was measured using an electronic scale and height was assessed with a stadiometer. Body Mass Index (BMI) was calculated by dividing participant weight (Kg) by the square of his/her height (m^2). Physical activity was assessed by minutes the participants walked in a regular week; this was calculated as the days per week the person reported walking and the duration of their walk. Physical activity was categorized as more than 30 min, or less or equal to 30 min. Participants who smoked at the time of the survey were classified as current smokers.

Use of medical medication was obtained by asking the participant to show the containers of all medication taken during the last two weeks. Commercial names were recoded using the Anatomic, Therapeutic and Chemical (ATC) classification. Three variables were created to indicate use of psychotropic medication: anti-depressants, anxiolytics and the last group made up of codes N02, N03 or N04 (analgesics, anti-Parkinson or anti-epileptics, respectively).

The city indicator represents the average chronic stress due to environmental challenges and economic adversity to which residents of each city have been exposed to during their life course, representing the average living conditions for that context and that age cohort, corresponding to those born between 1938 and 1947 and who were alive in 2012, the year of the survey. As shown in a previous paper, the father being unemployed, hunger and low socioeconomic status of the family before age 15 were higher in Manizales and Tirana than in Kingston and Saint Hyacinthe (Sousa et al., 2014). More specifically, percentages of subjects with one or more of these three indicators of economic disadvantage in those IMIAS populations were: 5.8, 8.9, 0.5 and 0.8, respectively. Concerning their current economic situation, 71% of those living in Manizales, 21% of those living in Tirana, 7.5% of those participants in Saint-Hyacinthe and 5.3% of those at Kingston reported to have insufficient income to cover basic needs (Sousa et al., 2014).

2.6. Statistical analyses

Cortisol concentrations in micrograms/dL were multiplied by 100 and log transformed (decimal log) in following previous research (Marchand, Durand, Juster, & Lupien, 2014) to improve convergence of the algorithms and to normalize distribution.

Then we applied multilevel regression models by adjusting two sets of mixed models using the five cortisol measures as dependent variables in the repeated measures model. In the first set of models, we tested the hypothesis that there was an interaction between cortisol collection time and physical performance. The initial model included an indicator to adjust for variations between day 1 and 2, dummy indicators for the study city, the wake up time, a dummy variable for each cortisol time, the indicator of poor physical performance (SPPB <9) and the product term to represent cortisol collection time and poor physical performance interactions. Each individual predictor was tested for significance using a bilateral Z test with $p < 0.05$. We entered sex and depression in the fully adjusted model, as both variables have been related to altered cortisol response (Marchand et al., 2014; Tu et al., 2013) and SPPB (Gardner et al., 2013), and several potential confounders as identified in previous research (Gardner et al., 2013; Marchand et al., 2014): BMI, smoking, physical activity and three types of psychotropic medication. As physical activity was not significantly associated with cortisol diurnal patterns in a bivariate model and there were 26 subjects with missing physical activity, we excluded physical activity from further analyses in order to preserve the original sample size based on saliva availability. Thus, models were not adjusted for physical activity.

In the second set of models, we tested the hypothesis of an elevated cortisol value at 30 min after waking up (M2) and a lower cortisol value at bed time (E) in the high performance group (SPPB ≥ 9), along with no morning peak and a higher cortisol value at bed time in the poor performance group (SPPB < 9). These interactions were represented by two product terms between SPPB level at 30 min after waking up and at bedtime. Here, we show results adjusting for all potential confounders, even if the model is over-adjusted to illustrate that extensive controlling for potential confounders does not change the results in the differences in

Table 1
Sample descriptive statistics in the four studied cities.

Variables	Kingston (N = 81)	Saint-Hyacinthe (N = 81)	Tirana (N = 57)	Manizales (N = 90)	p-value
Age [mean ± SD]	69.01 ± 2.47	68.37 ± 2.57	69.46 ± 3.43	68.93 ± 2.77	0.153
Male (%)	33.3	46.9	61.4	45.6	0.013
Smoker (%)	6.2	4.9	10.5	10.0	0.489
CES-d > 16 (%)	8.6	5.2	21.1	24.4	0.005
BMI [mean ± SD]	27.64 ± 5.50	28.54 ± 5.14	28.73 ± 5.36	26.19 ± 3.98	0.005
Walk <30 min by day (%)	58.6	84.0	50.9	75.0	<0.001
Anxiolytics (%)	7.4	11.1	1.8	0	0.005
Anti-depressant (%)	19.8	8.6	0	6.7	0.001
Analgesics (%)	14.8	14.8	12.3	8.9	0.604
SPPB < 9 (%)	13.6	11.1	17.5	19.8	0.422
SPPB [mean ± SD]	9.90 ± 2.15	10.48 ± 1.47	9.98 ± 1.75	9.79 ± 1.74	0.075

cortisol response associated with high and low physical performance.

The joint contribution of the covariates was assessed by a likelihood ratio test following a Chi-squared test with degrees of freedom equal to the difference in parameters.

Lastly, following previous work by Johar et al. (Johar et al., 2015), the ratio of M1 to E (M1/E) and M2 to E (M2/E) log-transformed were used as dependent variables in mixed models with two measurements per subject corresponding to the two days of data collection. We tested the hypothesis that these ratios would be lower in those with poor physical function. All analyses were done with SPSS v21.0.

Figures were constructed illustrating diurnal cortisol profiles using regression coefficients obtained in the multi-level regression analysis of the model, and including interactions between 30 min after waking up and bed time for those with good physical performance (SPPB ≥ 9), and worse (SPPB < 9) for: a woman in Manizales who is not depressed, has average BMI, does not smoke and takes no psychotropic medication. These characteristics were chosen because they showed the lowest cortisol level profiles without confounders. Scores were converted into the micrograms/dL scale to ease interpretation and comparison.

3. Results

Characteristics of the study samples are shown in Table 1. Some statistical differences were observed in the distribution of these selected variables across study sites. Anxiolytic and anti-depressant medication use was more frequent in the Canadian cities. The proportion with poor physical performance was lower in the Canadian samples, but the mean value of SPPB was not statistically different across cities. Table 2 shows the mean values and standard deviations of cortisol at each time of day for the two days and by study city.

Table 3 shows the results of the fully adjusted repeated measures model (Model 1) to examine the associations between diurnal cortisol concentrations as dependent variables and SPPB < 9. In the basic model (results not shown), adjusting only for city, day of saliva collection and wake up hour, the cortisol concentration at 30 min after waking up was significantly higher among participants with SPPB ≥ 9, followed by a decline at 60 min for cortisol concentrations similar to those at the wake up time. Further significant declines were observed at 15:00 h and at bed time. At the wake up time, cortisol was not different among those with high and low physical performance.

Poor physical performance was associated with a significant decrease in cortisol levels at 30 min compared to those with good physical performance. Using Manizales as a reference, Canadian cities had significantly higher concentrations of cortisol, while Tirana had the highest values at all times: waking up, 30 min after, 60 min after, at 15:00 h and at bed time. We controlled for all covariates in the fully adjusted model. Concerning physical performance, coefficients for this fully adjusted model were very similar to the basic Model 0 (adjusting only for city, day of saliva collection and wake up hour); those with poor physical performance showed a significantly lower cortisol concentration 30 min after waking up compared to those with good physical performance (Table 3).

As explained in the methods section, this model is probably over-adjusted since most covariates were not significantly associated with cortisol concentrations. However, we decided to show the coefficients for illustration purposes. Out of all potential confounders, only differences across cities remained significant; Canadian cities showed higher values than Manizales, and Tirana had the highest values at every time. We tested the interaction between cities and time at which cortisol was measured and it was non-significant.

In Table 4, the fully adjusted model is shown after inclusion of two interaction product terms to examine the hypothesis of an elevation in cortisol at 30 min after waking up and lower bed time values among those with high physical performance versus an attenuated morning peak and higher bedtime cortisol among those with poor physical performance. Both interaction terms were significant, with p-values = 0.027 and 0.005, respectively. Table 4

Table 2
Distribution of cortisol (μg/dL) by studied city.

	Kingston		Saint-Hyacinthe		Tirana		Manizales	
Cortisol [mean ±SD]	DAY 1	DAY 2	DAY 1	DAY 2	DAY 1	DAY 2	DAY 1	DAY 2
Awake	0.31 ± 0.21	0.31 ± 0.16	0.32 ± 0.27	0.31 ± 0.18	0.52 ± 0.38	0.53 ± 0.49	0.27 ± 0.21	0.29 ± 0.35
+30 min	0.39 ± 0.34	0.41 ± 0.33	0.41 ± 0.25	0.36 ± 0.20	0.65 ± 0.39	0.65 ± 0.50	0.29 ± 0.15	0.35 ± 0.32
+60 min	0.31 ± 0.24	0.30 ± 0.17	0.33 ± 0.26	0.28 ± 0.19	0.49 ± 0.27	0.59 ± 0.65	0.25 ± 0.19	0.29 ± 0.25
15:00 h	0.12 ± 0.15	0.10 ± 0.07	0.12 ± 0.21	0.12 ± 0.15	0.21 ± 0.17	0.23 ± 0.18	0.08 ± 0.07	0.09 ± 0.07
Bed Time	0.06 ± 0.06	0.06 ± 0.05	0.08 ± 0.27	0.06 ± 0.06	0.11 ± 0.86	0.11 ± 0.07	0.05 ± 0.05	0.05 ± 0.06

Table 3
Regression coefficients of models using log (Cortisol concentration in μg/dL *100) according to low (< 9) SPPB (versus high (≥9) SPPB): Testing for differences at each time of cortisol output.

Fixed part	Coefficient	SE(coefficient)
Constant	1.353[a]	0.110
Day 1 vs day 2	−0.001	0.008
Cortisol awakening time	0.000002	0.000002
+30 min	0.105[a]	0.014
+ 60 min	0.003	0.014
15:00 h	−0.460[a]	0.014
Bedtime	−0.760[a]	0.014
SPPB < 9 (Wake up)	−0.003	0.040
SPPB < 9 (+30 min)	−0.105[a]	0.037
SPPB < 9 + (60 min)	−0.067	0.037
SPPB < 9 (15:00 h)	−0.040	0.037
SPPB < 9 + (Bedtime)	0.050	0.037
Kingston vs Manizales	0.102[b]	0.033
Saint-Hyacinthe vs Manizales	0.085[b]	0.031
Tirana vs Manizales	0.336[a]	0.036
Men vs Women*	0.017	0.023
Depression No vs Yes*	−0.046	0.029
BMI	−0.0002	0.003
Smoking (No vs Yes)	0.034	0.044
Anxiolytics (No vs yes)	−0.041	0.053
Anti-depressants (No vs yes)	−0.055	0.042
Analgesics (No vs yes)	0.010	0.036
Random Parameters		
Inter-Subject	0.034567[a]	0.003308
Residual	0.053969[a]	0.001464
Fit statistics		
Model χ2 (df)	513.84(24)	
Interaction SPPB-time (df)	0.73 (4)	

Fit Statistics for Table 3 Multi-level Regression Models	Chi-square	df	Change in Chi-square	p-value
Model 0 (adjusting for awakening time and city)				
Without interaction SPPB*time	480.68			
With interaction SPPB*time at each time point	480	4	0.68	0.954
Model 1 (with full adjustment by relevant covariates)				
Without interaction SPPB*time	513.84			
With interaction SPPB*time at each time point	513.11	4	0.73	0.948

[a] P < 0.001.
[b] P < 0.01.

shows the coefficients of the final fully adjusted model (Model 1). Coefficient estimates for all covariates were very similar to those estimated in Model 0, adjusting only for city, day of saliva collection and wake up hour.

Next, we examined the Chi-squared statistics comparing the overall fit of the two models, with and without adjustment for all above mentioned covariates (Table 4). The models including the two interaction terms for the 30 min after waking up and bed time significantly improved the model fit, as indicated by the significant improvement value in the log of likelihood functions.

For illustrative purposes, Fig. 1 shows the cortisol means and standard deviations for high and low physical performance based on the fully adjusted model. Fig. 1 shows the attenuated mean morning peak (M2) and highest mean evening level for a Manizales woman who does not smoke, has no depression and does not take psychotropic medication with low physical function compared with a similar woman with high physical performance.

In Table 5, results from the mixed models regressing the log transformed ratios of M1/E and M2/E are shown. While the M1/E ratios are not significantly different among those with high and low physical performance, the M2/E ratios are significantly lower among those with SPPB <9 compared with those with SPPB ≥9, even after fully adjustment by all covariates. These results are in agreement with results shown in Table 4.

4. Discussion

In this study, we found that there were clear differences in cortisol diurnal output by research site and we can only hypothesize as to why this is the case. We propose that the city of residence reflects the physical and socioeconomic context to which participants have been exposed during their life course and that life course adversity could be one of the causes for the difference in diurnal cortisol concentrations across study sites.

We found lower cortisol diurnal concentrations of older subjects from Manizales compared with the two Canadian cities (Kingston and Saint Hyacinthe), using the same methods for saliva collection and the same laboratory for cortisol determinations. Cortisol concentrations in older adults from Tirana showed the highest values at all times of data collection, but comparability cannot be assured since differences between the two laboratories (Tirana and Montreal) could also explain the difference in results, even though similar Salimetric kits were used. Thus, these results partially confirm our first hypothesis since the results are as hypothesized when comparing the Canadian (Kingston and Saint-Hyacinthe) data with the Manizales data; however, diurnal cortisol output from Tirana does not support our first hypothesis.

Manizales had lower cortisol concentrations compared with Kingston and Saint Hyacinthe. This is in agreement with our

Table 4
Regression coefficients of models using log (Cortisol concentration in μg/dL *100) according to low (<9) SPPB (versus high (≥9) SPPB): Testing for differences at 30 min and at bed time.

Fixed part	Coefficient	SE(coefficient)
Constant	0.217[a]	0.115
Day 1 vs day 2	−0.001	0.008
Cortisol awakening time	0.000002	0.000002
+30 min	0.100[a]	0.0141
+ 60 min	−0.007	0.0133
15:00 h	−0.466[a]	0.0134
Bedtime	−0.765[a]	0.014
SPPB < 9 (Awakening)	0.023	0.05
SPPB < 9 (+30 min)	−0.070[b]	0.030
SPPB < 9 (Bedtime)	0.085[a]	0.030
Kingston vs Manizales	0.102[b]	0.033
Saint-Hyacinthe vs Manizales	0.095[b]	0.034
Tirana vs Manizales	0.336[a]	0.036
Man vs Woman*	0.019	0.024
Depression (No vs Yes)*	−0.045	0.034
BMI	−0.0001	0.002
Smoking (No vs Yes)	0.034	0.044
Anxiolytics (No vs yes)	−0.041	0.053
Anti-depressants (No vs yes)	−0.058	0.042
Analgesics (No vs yes)	0.012	0.036
Random Parameters		
Inter-Subject	0.0346[a]	0.0033
Residual	0.0545[a]	0.0015
Fit statistics		
Model $\chi 2$ (df)	513.84 (20)	
Interaction SPPB−30 min and bed times (df)[c]	7.23 (2)	

Fit Statistics for Table 4 Multi-level Regression Models	Chi-square	df	Change in Chi-square	p-value
Model 0 (adjusting for awakening time and city)				
Without interaction SPPB*time	480.68			
With interaction SPPB*time at 30 min and bed time	473.45	2	7.23	0.027
Model 1 (with full adjustment by relevant covariates)				
Without interaction SPPB*time	513.84			
With interaction SPPB*time at 30 min and bed time	506.61	2	7.23	0.027

[a] $P < 0.001$
[b] $P < 0.01$
[c] $p < 0.05$

previous study. We showed that cortisol concentrations in a rural North East Brazilian population of older adults were lower than in a suburban population of Quebec, using the same methodology and the same reference laboratory (Tu et al., 2013). These results are also in agreement with a recent US study showing that the African American population had lower awakening cortisol and slower afternoon decline when compared with Caucasians; based on current research and previous evidence, the authors of this research propose that slower afternoon decline be used as a marker of biological aging (Samuel, Roth, Schwartz, Thorpe, & Glass, 2016).

As stated in the introduction, conflicting results from a recent study comparing volunteer populations of Sao Paulo and Montreal have been reported (Souza-Talarico et al., 2014). These discordant findings could be explained by two selection criteria used in that study: 1) the older Sao Paulo adults were healthy volunteers with relatively high education living in a cosmopolitan city of Brazil; 2) the Sao Paulo-Montreal researchers applied exclusion criteria based on health conditions. Joining the evidence from our current study with our previous research on a random sample of older adults in Santa Cruz (a city of the interior in the North East region of Brazil), where life conditions used to be extremely difficult and still continues to be difficult for older adults, we suggest that populations of older adults in Manizales and in Santa Cruz who have survived to age 65 may have an attenuated response to daily challenges, likely due to the many deprivations along their life course (Zunzunegui, Alvarado, Beland, & Vissandjee, 2009). The biological consequences of this HPA axes dysregulation need to be examined.

Cortisol concentrations in Tirana residents are consistently higher than those of the Canadian and Manizales samples. Older Tirana adults in the age group considered in this study lived under communism until 1992, with considerable social and economic security. Since 1992, Albania has experienced drastic transformations towards capitalism and now older people are aging with insufficient pensions, along with poor access and quality of healthcare (Ylli, 2010). Given the possible differences in laboratory methods, it is not possible to argue whether the elevated cortisol values found in the Tirana sample are due to the differences in the laboratory methods used or to the populations' stress response. It is noticeable that elevated levels of daily cortisol output in Tirana are consistent with the findings, and with the hypothesis of the researchers comparing Sao Paulo with older Montreal adults (Souza-Talarico et al., 2014). A potential explanation for the higher diurnal cortisol concentration of Sao Paulo residents is because those older adults currently live in unstable social conditions which could be related to the higher cortisol levels (Souza-Talarico et al., 2014).

Our second hypothesis was that those with poor physical performance would have an attenuated morning response and higher bedtime values compared with those with high physical performance, adjusted for research city and relevant covariates. Our results support this hypothesis. Researchers have proposed that a more reactive HPA axis (a higher awakening response and a

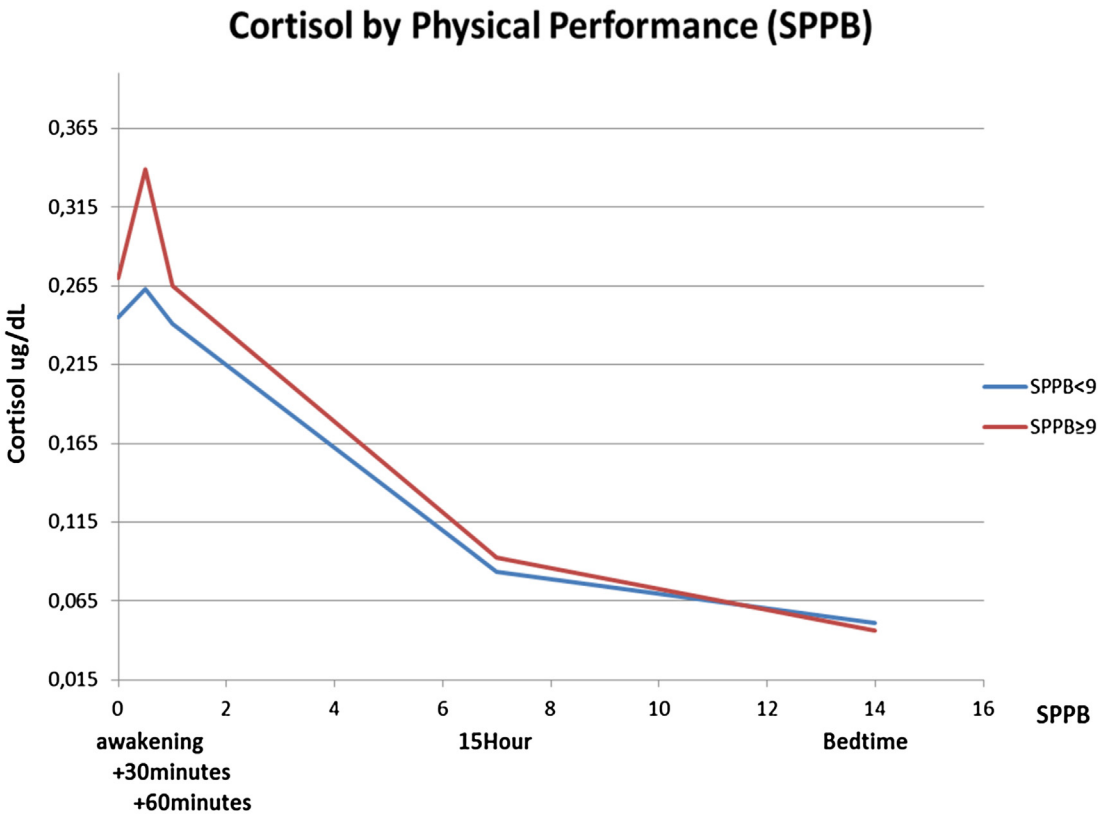

Fig. 1. Diurnal cortisol output by physical performance groups.

faster diurnal decline, with a lower value at night time of cortisol concentrations) is associated with a better functional outcome.

Our results based on populations from four cities coincide with evidence from single population studies supporting this concept. In a cohort composed of men followed for 20 years, poor morning response and less diurnal decline (blunted cortisol profile) was associated with poorer performance (Gardner et al., 2011). In a recent meta-analysis, walking speed and faster chair standing were associated with higher morning cortisol, larger diurnal drop and larger cortisol awakening response (Gardner et al., 2013). High night time cortisol values were associated with poorer balance, but this association was attenuated after adjustment for relevant confounders (Gardner et al., 2013). Varadhan compared cortisol responses of frail and non-frail women aged 80 to 90 from the Women's Health and Aging study and reported no difference in the awakening levels, followed by a blunted cortisol response and higher evening cortisol values in the frail group, coinciding with our results comparing older adults with poor and high physical performance (Varadhan et al., 2008).

We emphasize that the rate of decline and amplitude are measures of diurnal cortisol variation and reflect the resilience of the hypothalamic-pituitary-drenal axis, and lower values indicate reduced resilience (Varadhan et al., 2008). It is known that lack of resilience prevents muscle recovery and causes sarcopenia (Agbedia et al., 2011; Varadhan et al., 2008), however, hypothesizing the association between lower cortisol levels and physical performance should go beyond musculoskeletal deficiency could be related to fatigue and mental exhaustion (Marchand et al., 2014; Tu et al., 2013). Furthermore, that social and economic adversity during life course could result in stress and soon in HPA axis dysregulation, as shown in previous research (Agbedia et al., 2011; Tu et al., 2013).

Nevertheless, the associations observed in this study were cross-sectional, and reverse causation cannot be ruled out. Therefore, we consider that the biological consequences of cortisol dysregulation need to be examined in longitudinal studies to be better understood.

Potential limitations of this study are related to the limited sample size to examine interactions between sex, physical performance and cortisol diurnal output. Sex-specific analyses of the associations between SPPB and cortisol output showed stronger cortisol differences between high and low SPPB groups in women than in men; however, we lacked the power to examine the three orders of interactions. Secondly, the observed associations are cross-sectional and reverse causation cannot be ruled out. However, previous studies have used longitudinal data from the United Kingdom (Cohort CaPS) and showed that blunted cortisol predicted decline in physical performance. The third limitation

Table 5
Log-transformed ratio of waking up to evening bed time (M1/E) cortisol and the log-transformed cortisol 30-min to evening bed time (M2/E) cortisol.

	Model 1			Model 2		
	Mean	95% CI	p-value	Mean	95% CI	p-value
log (M1/E)						
SPPB < 9	1.63	(1.41;1.84)	0.38	1.61	(1.34;1.88)	0.41
SPPB ≥ 9	1.73	(1.64;1.82)		1.51	(1.18;1.82)	
log (M2/E)						
SPPB < 9	1.61	(1.40;1.82)	<0.001	1.65	(1.32;1.97)	0.005
SPPB ≥ 9	1.98	(1.89;2.07)		1.99	(1.72;2.26)	

Model 1. Adjusted by age, sex, site.
Model 2. Adjusted by age,sex, site, smoking, depression and psychotropic medications

comes from the use of two different laboratories, one in Montreal for Manizales, Kingston and Saint Hyacinthe, and one in Tirana for the Tirana sample.

Although results are suggestive of hypercortisolemia among Tirana residents, more research would be needed to replicate this finding.

This study also has some strengths. First, the use of a common laboratory demonstrated that residents of Manizales have an attenuated cortisol response, thereby contrasting with the Canadian samples. Second, the use of a comprehensive assessment of physical performance is another strength. SPPB is a complete battery of lower extremity functions which requires strength, balance, postural and motor control, and has been validated in our study populations (Freire, Guerra, Alvarado, Guralnik, & Zunzunegui, 2012; Gomez, Curcio, Alvarado, Zunzunegui, & Guralnik, 2013). Third, our results confirm previous findings from North America and European populations on the link between poor physical performance and cortisol dysregulation after extensive control of potential confounders, being at the international level among very diverse populations.

5. Conclusion

This is a preliminary study and we need to be cautious about conclusions. The observed differences between Manizales and the Canadian cities are consistent with previous studies suggesting that chronic life course with low socioeconomic position leads to lower overall cortisol response at every time of the day (Desantis et al., 2015; Tu et al., 2013). The observed cortisol profile in Tirana supports the concept that social stress due to current living conditions may lead to hypercortisolemia along the diurnal cycle. We present this evidence to suggest that past and current stress could have opposite effects on current cortisol response. These ideas could be considered as hypotheses to be explored in future studies.

Our evidence showing that dysregulation of the HPA axis with an attenuated morning peak, higher values at bed time and lower ratios of the morning peak to bed time values, observed among people with low physical performance contributes to previous reports from the United States and the United Kingdom cohorts of older adults. More international research could help to explore these differences in the HPA axis response to life course and current stressful living conditions.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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