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Steroid and nonsteroidal anti-inflammatory drugs, cognitive decline, and dementia

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Abstract

The aim of this study was to evaluate the effects of anti-inflammatory intake on cognitive function in 7234 community-dwelling elderly persons. Cognitive performance, clinical diagnosis of dementia, and anti-inflammatory use were evaluated at baseline, and 2, 4, and 7 years later. Multivariate logistic regression analyses were adjusted for sociodemographic, behavioral, physical, mental health variables, and genetic vulnerability (apolipoprotein E ε4). Elderly women taking inhaled corticosteroids were at increased risk for cognitive decline over 7 years in executive functioning (odds ratio, 1.76; 95% confidence interval, 1.14–2.71; $p = 0.04$); the effect being increased after continuous use (odds ratio, 3.15; 95% confidence interval, 1.29–7.68; $p = 0.01$) and not found after discontinuation of treatment. In men, no significant associations were observed. Corticosteroid use was not significantly associated with an increase risk of incident dementia over 7 years. Nonsteroidal anti-inflammatory drug use was not significantly associated with either dementia incidence or cognitive decline in both sexes. The association may be related to hypothalamic-pituitary-adrenal corticotropic axis dysfunctioning rather than a direct anti-inflammatory mechanism. Long-term use of inhaled corticosteroids may constitute a form of reversible cognitive disorder in elderly women. Physicians should check this possibility before assuming neurodegenerative changes.

Keywords: Corticosteroids; Nonsteroidal anti-inflammatory drugs; Cognitive aging; Alzheimer's disease; Elderly; Apolipoprotein E; Prospective cohort

1. Introduction

In the absence of effective treatment for neurodegenerative disorders, research has focused on the identification of modifiable risk factors to delay cognitive decline and prolong autonomy (Ritchie et al., 2010). There is some evidence that corticosteroids (CS) could be associated with reversible cognitive dysfunction, both experimental and epidemiological research showing that dysregulation of the hypothalamic-pituitary-adrenal (HPA) corticotropic axis, a major component of the stress response system, may lead to, or accelerate hippocampal impairment (Belanoff et al., 2001; Conrad and Bimonte-Nelson, 2010; Lupien et al., 2007). This may be especially important in the aging brain, more vulnerable to stress effects and subject to decrements in cognitive performance due to multiple causes.

Several studies in the elderly have demonstrated a potentially reversible link between elevated endogenous cortisol levels and decline in memory and frontal-executive abilities (Beluche et al., 2010; Egeland et al., 2005; Green-

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dale et al., 2000; Li et al., 2006; O'Hara et al., 2007; Seeman et al., 1997) and dementia (Csernansky et al., 2006; Rasmuson et al., 2002; Umegaki et al., 2000). Associations between short-term CS administration and cognitive impairment have been reported in small experimental and clinical studies in adults (de Quervain et al., 2003; Keenan et al., 1996; Kirschbaum et al., 1996; Lupien et al., 2007; Newcomer et al., 1999; Wolkowitz et al., 2009; Young et al., 1999). The effect of chronic CS administration has, however, never been examined in elderly populations who have high rates of both prescribed and over-the-counter drug use (Hilmer et al., 2007).

Previous studies have failed to take into account the potential confounding effects on cognitive decline of pathologies associated with CS use, e.g., chronic pain and respiratory disorders, or the impact of CS administration mode, oral administration being generally associated with slower absorption and lower biologically active circulating metabolites than inhaled CS. Surprisingly, genetic vulnerability has also not been considered despite a possible interactive effect between cortisol levels and apolipoprotein E (APOE) ε4 allele (Lee et al., 2008). Finally, gender differences have not been examined although they have been reported in relation to both stress response and association between cortisol levels and cognitive decline and neural activity (Beluche et al., 2010; Otte et al., 2005; Sauro et al., 2003; Seeman et al., 1997; Wang et al., 2007) as well as in risk profiles for cognitive impairment and progression to dementia (Artero et al., 2008).

Thus, while there is accumulating evidence to suggest that CS treatment may increase risk of cognitive decline and dementia in the elderly, this hypothesis remains to be tested within a large study able to take into account multiple competing causes of cognitive decline. This prospective study aims to examine the relationship between CS use and cognitive decline and dementia onset in community-dwelling elderly taking into account gender, genetic vulnerability, and reasons for CS use. The cognitive effects of other nonsteroidal anti-inflammatory drugs (NSAIDs) were also examined.

2. Methods

2.1. Study population

Subjects were recruited as part of a multisite cohort study of community-dwelling persons aged 65 years and over from the electoral rolls of 3 French cities between 1999 and 2001 (The 3C Study Group, 2003). The study protocol was approved by the Ethical Committee of the University-Hospital of Bicêtre (France). Written informed consent was obtained from each participant. Participants were administered standardized questionnaires by trained staff and underwent clinical examinations at baseline and at each 2-, 4-, and 7-year follow-up. Of the 9080 dementia-free participants included, 629 died (378 having only 1 cognitive evaluation at baseline and 251 with missing data for covariates), 704 were alive at the end of the follow-up but did not have repeated cognitive testing, and 513 had missing data for at least 1 adjustment variable. The present analyses were conducted on 7234 subjects. The mean (SD) age was 73.6 (5.3) for men and 73.8 (5.2) for women. The average follow-up (median, interquartile range [IQR]) was 6.7 (3.8–7.2) years. Subjects not included in the analysis were significantly older, with lower education levels, and worse physical and mental health, lower baseline cognitive scores, and were more frequently CS users.

2.2. Cognitive measures and dementia

The Isaacs Set Test (Isaacs and Kennie, 1973) provided a measure of verbal fluency or semantic access. The Benton Visual Retention Test (Benton, 1965) assessed visual memory and the Trail Making Tests (TMT) A and B psychomotor speed and executive function respectively (Reitan, 1965). The Mini Mental State Examination (MMSE) was used as a global measure of cognitive function (Folstein et al., 1975). All tests were administered at baseline, and waves 1, 2, and 3 of the follow-up, except the TMT which was not given in wave 1. Consequently, analyses relating to these tasks involved only 6085 participants.

A preliminary diagnosis and classification of dementia at each follow-up examination was made by the study clinical investigators according to *Diagnostic and Statistical Manual of Mental Disorders* revised criteria (DSM-IV; American Psychiatric Association, 1994) and independently validated by a national panel of neurologists (The 3C Study Group, 2003). The onset of dementia was the date of the follow-up interview when dementia was diagnosed.

2.3. Corticosteroid and NSAID use

All prescription and over-the-counter drugs used more than once a week over the preceding month were recorded in a standardized interview. Medical prescriptions and the medications themselves were checked by the interviewer. Oral and inhaled but not topical applications were considered in this analysis.

2.4. Sociodemographic and clinical variables

The standardized interview included questions on sociodemographic and lifestyle characteristics with evaluation of hypertension, hypercholesterolemia, and diabetes. Fasting blood samples were taken at baseline for lipid and glucose levels and APOEε4 genotyping (Ritchie et al., 2007). History of ischemic pathologies (stroke, angina pectoris, myocardial infarction, and cardiovascular surgery) was established according to standardized questions. Chronic bronchitis (daily sputum or mucus production or cough for at least 3 consecutive months/year), other chronic respiratory disorders including wheezing, tachypnea, and asthma attacks (over the last 12 months) were self-reported as well as chronic/regular joint or back pain. Depressive symptomatol-

ogy was assessed by the Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977) with a 16 cutoff point.

2.5. Statistical analyses

We used logistic regression analyses to determine whether baseline anti-inflammatory use was associated with odds of cognitive decline. Men and women were examined in separate analyses as they differed in both anti-inflammatory drug use and profiles of cognitive ability. The χ^2 test was used to identify gender-related differences. After gender stratification, odds ratios (ORs) were adjusted for center, age, educational level, and baseline cognitive performance (minimally adjusted model). Multivariate adjusted logistic regression further included covariates associated with cognitive decline (at $p < 0.15$); depression, diabetes, hypercholesterolemia, caffeine, smoking, APOEε4, ischemic pathologies, chronic joint or back pain, bronchitis, asthma, and other chronic respiratory disorders. Due to the skewed distribution of cognitive scores, a substantial decline in cognitive function over follow-up was defined as the lowest quintile of the difference between either follow-up visit and baseline score except for response time recorded for the TMT, for which the highest quintile of the difference was considered (Ritchie et al., 2007). We also used random-effect models to analyze the association between CS use and 7-year change on cognitive scores taken as continuous variables. In order to normalize the distribution, variables were transformed using $(15 - \text{Benton})^{1/2}$, $(30 - \text{MMSE})^{1/2}$, and logTMT (Jacqmin-Gadda et al., 1997). Each model included time, CS, time/CS interaction, and covariates. The term CS represents the cross-sectional association between CS and baseline cognitive score. The term time indicates the linear evolution per year on the cognitive test. The term for interaction represents the additional annual modification on the selected cognitive tests for CS use. A Cox model with delayed entry was used in the analysis of dementia incidence taking age as the basic time scale and birth as the time origin (Commenges et al., 1998). This analysis was undertaken on 7486 subjects without missing data for baseline adjustment variables but with possibly missing repeated cognitive testing. Analyses were carried out using SAS software (version 9.1, SAS Institute, Inc., Cary, North Carolina, USA).

3. Results

3.1. Subject characteristics

Within this elderly community-dwelling sample, 352 of the 7234 subjects (4.9%) were taking CS at baseline, of whom 112 (1.6%) used oral and 240 (3.3%) inhaled preparations. Oral CS principally consisted of prednisone (16.2% of CS users), prednisolone (4.9%), methylprednisolone (2.8%), and hydrocortisone (2.3%). The main inhaled CS were beclometasone (27.4%), budesonide (20.5%), fluticasone (12.1%), and triamcinolone (5.9%) (Supplementary Table 1). Fifteen subjects were taking simultaneously inhaled and oral CS. Both oral and inhaled prednisolone and triamcinolone were used, the former being predominantly by oral administration and the latter inhaled. Women used more frequently oral (1.7%) and less frequently inhaled (3.0%) CS than men (1.3% and 3.9%, respectively; $p = 0.04$). Men and women were found to significantly differ on all other characteristics at baseline except APOEε4. A higher proportion of women showed low scores on the MMSE, Benton, and TMTA and TMTB but not on the Isaacs test (data not shown).

For both men and women, CS use was higher in subjects with chronic joint or back pain and respiratory disorders ($p < 0.0001$) (Table 1). Men with lower education level and low MMSE and Isaacs scores at baseline were more frequent CS users ($p < 0.05$), whereas women using CS tended to have lower performance on TMTB ($p = 0.06$).

3.2. CS use and cognitive decline

Logistic regression analysis adjusted for age, center, education level, and baseline cognitive performance indicated that women reporting use of inhaled but not oral CS at baseline showed greater decline over 7 years on the TMTB (OR, 1.65; 95% confidence interval [CI], 1.10–2.47) (Table 2). The association persisted in the complete model further adjusted for other confounders including pathologies associated with CS prescription (chronic pain and respiratory disorders, etc.) (OR, 1.76; 95% CI, 1.14–2.71). No significant interactions were found for decline on TMTB in women between CS use and age ($p = 0.12$) or APOE ($p = 0.38$). No significant effect was observed in men regardless of the cognitive domain. Performing multivariate-adjusted random-effect linear models with the cognition score as the continuous variable led to the same results; the only significant association being found between CS use and performance on the TMTB in women (interaction between time and inhaled CS $p = 0.003$, slope of log (TMTB) increased by 0.008 compared with no CS use). Similar findings were observed when executive function was assessed using score differences such as time on TMTB minus time on TMTA (data not shown).

3.3. Cognitive decline according to the pattern of CS use during follow-up

Of the 3736 women with a TMT evaluation, 3171 (84.9%) did not report CS use (oral or inhaled) at baseline and during the 7-year follow-up, 38 (1.0%) reported inhaled CS use only at baseline or after the first 2-year follow-up, but not at either 4- or 7-year follow-up ("discontinuing" group), and 22 (0.5%) reported inhaled CS use both at baseline and at least at the 2- and 4-year examination (3 consecutive examinations, "continuing" group). Other subjects having reported inhaled CS use intermittently during the follow-up or having taken oral CS at baseline or during the follow-up ($n = 505$) were not considered in the following analyses.

Compared with women who had never used CS, women having continuously used inhaled CS were at higher risk of

Table 1
Characteristics of the study population as a function of corticosteroid use at baseline

Characteristic	Men			Women		
	CS drugs			CS drugs		
	No, % (n = 2686)	Yes, % (n = 147)	p	No, % (n = 4196)	Yes, % (n = 205)	p
Age			0.17			0.3
65–69	26.3	21.8		25.2	20.5	
70–74	35.1	31.3		32.5	34.1	
75–80	24.5	27.2		28.1	32.7	
80+	14.1	19.7		14.2	12.7	
Education			0.03			0.47
5 Years	21.5	24.5		25.4	25.4	
9 Years	30	38.1		39.9	43.4	
12 Years	19.8	11.6		20.8	21	
12+	28.7	25.8		13.9	10.2	
Marital status			0.32			0.54
Married	82.6	80.8		45.8	41.9	
Single or divorced	7.7	11		18.9	21	
Widowed	9.7	8.2		35.3	37.1	
Depressive symptoms (CES-D ≥ 16)[a]	13.4	18.4	0.09	28.3	31.2	0.37
Ischemic pathologies[b]	21.8	25.9	0.25	12.2	15.6	0.14
BMI			0.59			0.2
Normal	38	34.3		53.6	50.7	
Overweight	49.1	53.4		33.2	31.7	
Obese	12.8	12.3		13.2	17.6	
Diabetes[c]	12.6	15	0.41	6.7	10.2	0.05
Chronic bronchitis[d]	3.8	21.1	< 0.0001	2.2	12.2	< 0.0001
Asthma [e]	1.5	14.3	< 0.0001	1.9	23.9	< 0.0001
Hypertension[f]	59.9	60.5	0.87	53.4	59.5	0.09
Hypercholesterolemia[g]	83.4	80.3	0.32	68	63.4	0.17
Alcohol			0.75			0.29
0	8	7.5		26.9	31.7	
1–36 g/day	73.2	71.2		71.5	67.3	
> 36 g/day	18.8	21.2		1.6	1	
Smoking			0.14			0.27
Never	30.5	23.8		81.4	79	
Former	61.3	69.4		14.9	18.6	
Current	8.2	6.8		3.7	2.4	
NSAID use	6.2	9.5	0.11	10.3	9.8	0.8
Self-report chronic joint or back pain	9.6	20.4	< 0.0001	16.6	26.3	0.0003
Caffeine consumption per day[h]			0.07			0.32
0–1 Unit	27.2	35.4		25.1	29.8	
1–3 Units	59.5	50.3		58.5	55.1	
> 3 Units	13.3	14.3		16.4	15.1	
Carrier of the APOEε4 allele	20.8	17	0.27	19.6	16.6	0.29
Global cognitive functioning (MMSE score < 26)[i]	11.4	17.7	0.02	15.7	14.6	0.68
Verbal fluency (Isaacs set test score < 39)[i]	19.7	26.5	0.04	20.4	20	0.9
Visual memory (Benton score < 10)[i]	23.3	25.2	0.61	30.6	34.2	0.29
Psychomotor speed (TMTA score > 70)[i]	16.6	20.7	0.2	21.5	26.9	0.07
Executive function (TMTB score > 140)[i]	17.9	17.6	0.94	21	26.8	0.06

Key: APOE, apolipoprotein E; BMI, body mass index; CS, corticosteroid; MMSE, Mini Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; TMTA, Trail Making Task A; TMTB, Trail Making Task B.

[a] The presence of depressive symptoms was assessed using the Center for Epidemiological Studies-Depression Scale (CES-D) (Radloff, 1977) with a cutoff of ≥ 16.

[b] History of stroke, myocardial infarction, angina pectoris, or arteritis and cardiovascular surgery.

[c] Diabetes defined as glucose ≥ 7 mmol/L or treated.

[d] Chronic bronchitis (with daily sputum or mucus production or cough for at least 3 consecutive months a year).

[e] Asthma attacks and other chronic respiratory disorders including wheezing, tachypnea (over the last 12 months).

[f] Systolic blood pressure ≥ 160 or diastolic blood pressure ≥ 95 mm Hg or intake of antihypertensive drugs.

[g] Total cholesterol level ≥ 6.2 mmol/L or treated by lipid lowering agents.

[h] One unit = 100 mg caffeine.

[i] The percentage of subjects with lowest cognitive performance at baseline are reported (lowest quintile except for TMT highest quintile). The numbers of subjects completing the TMT tests were for women, 3573 non-CS users and 163 users; and for men, 2242 non-CS users and 107 users (see Methods for detail).

Table 2
Baseline corticosteroid (CS) use and cognitive decline [a] over the 7-year follow-up period

	Men (n = 2833) [b]		Women (n = 4401) [b]	
	OR (95% CI) [b]	Global p-value	OR (95% CI) [b]	Global p-value
Minimally adjusted [c]				
ΔMMSE ≤ −2		0.62		0.15
Oral CS	1.18 (0.60–2.33)		1.05 (0.65–1.70)	
Inhaled CS	1.20 (0.80–1.79)		0.68 (0.47–1.01)	
ΔBenton ≤ −2		0.55		0.36
Oral CS	1.08 (0.54–2.18)		1.19 (0.72–1.97)	
Inhaled CS	0.79 (0.52–1.21)		1.29 (0.87–1.91)	
ΔIsaacs ≤ −6		0.61		0.34
Oral CS	1.42 (0.70–2.87)		1.14 (0.70–1.87)	
Inhaled CS	1.05 (0.69–1.60)		0.76 (0.51–1.13)	
ΔTMTA ≥ 15		0.87		0.58
Oral CS	1.17 (0.54–2.57)		1.03 (0.56–1.90)	
Inhaled CS	1.09 (0.65–1.83)		0.78 (0.49–1.25)	
ΔTMTB ≥ 41		0.74		0.05
Oral CS	0.92 (0.39–2.15)		1.02 (0.56–1.84)	
Inhaled CS	0.81 (0.46–1.40)		1.65 (1.10–2.47)	
Fully adjusted [d]				
ΔTMTB ≥ 41				0.04
Oral CS			1.02 (0.56–1.86)	
Inhaled CS			1.76 (1.14–2.71)	

Key: CI, confidence interval; MMSE, Mini Mental State Examination; OR, odds ratio; TMTA, Trail Making Task A; TMTB, Trail Making Task B.
[a] This corresponded to lowest quintile of performance, i.e., a decrease from baseline of at least 6 points on the Isaacs total score or at least 2 points on the Benton test and the MMSE and an increase from baseline of at least 15 (TMTA) or 41 seconds (TMTB).
[b] Except for TMTA and TMTB, where n = 2349 for men and 3736 for women.
[c] Adjusted for center, age, education, and baseline cognitive performance.
[d] Adjusted for center, age, education, baseline cognitive performance, depression, ischemic pathologies, diabetes, hypercholesterolemia, caffeine, smoking, APOEε4, chronic joint or back pain, chronic bronchitis, asthma, and other chronic respiratory disorders.

cognitive decline on the TMTB in fully-adjusted models (OR, 3.15; 95% CI, 1.29–7.68; p = 0.01) (Table 3). The association was not significant for women in the "discontinuous" group (OR, 1.41; 95% CI, 0.69–2.89; p = 0.35).

3.4. NSAID and cognitive decline

A total of 180 men (6.4%) and 452 women (10.3%) were taking NSAID at baseline. Thirty-four (0.5%) were taking both NSAID and CS. NSAID principally consisted of diacerein (23.1% of users), diclofenac (14.5%), piroxicam (14.2%), ketoprofen (9.9%), ibuprofen (8.6%), and 6.8% were taking coxibs (Supplementary Table 2). There was no significant association between NSAID use at baseline and cognitive decline in men and women (Table 4). Examining cognitive decline according to the pattern of NSAID use during follow-up, we only observed a nonsignificant association with an increased risk of decline on the Isaacs' task in the 100 women having used NSAID continuously (multiadjusted OR, 1.50; 95% CI, 0.96–2.35; p = 0.08].

3.5. Dementia incidence

Within the 7486 subjects included in the analysis 527 incident cases were diagnosed during the 7-year follow-up, of whom 360 had Alzheimer's disease (AD). Adjusted Cox

Table 3
Cognitive decline in executive function in women according to pattern of inhaled corticosteroid use during the follow-up period (n = 3231 [a])

	Minimally adjusted [b]		Fully adjusted [c]	
	OR (95% CI)	p	OR (95% CI)	p
ΔTMTB ≥ 41				
None [d]	1		1	
Discontinuing	1.39 (0.69–2.77)	0.36	1.41 (0.69–2.89)	0.35
Continuing	3.01 (1.24–7.26)	0.01	3.15 (1.29–7.68)	0.01

Key: APOE, apolipoprotein E; CI, confidence interval; OR, odds ratio; TMTB, Trail Making Task B.
[a] The 505 women having taken inhaled CS intermittently during the follow-up or having taken oral CS at baseline or during the follow-up were not considered in this analysis.
[b] Adjusted for center, age, education, and baseline cognitive performance.
[c] Adjusted for center, age, education, baseline cognitive performance, depression, ischemic pathologies, diabetes, hypercholesterolemia, caffeine, smoking, APOEε4, chronic joint or back pain, chronic bronchitis, asthma, and other chronic respiratory disorders.
[d] Nonusers of oral and inhaled corticosteroids during 7 years.

Table 4
Baseline NSAID use and cognitive decline over the 7-year follow-up period

	Men (n = 2833 [a])		Women (n = 4401 [a])	
	OR (95% CI) [b]	p	OR (95% CI) [b]	p
ΔMMSE ≤ −2	1.11 (0.81–1.53)	0.52	0.92 (0.75–1.14)	0.45
ΔBenton ≤ −2	1.07 (0.76–1.49)	0.71	0.99 (0.80–1.24)	0.95
ΔIsaacs ≤ −6	0.92 (0.66–1.29)	0.64	1.17 (0.95–1.44)	0.15
ΔTMTA ≥ 15	1.09 (0.74–1.59)	0.67	1.09 (0.86–1.39)	0.47
ΔTMTB ≥ 41	1.04 (0.70–1.54)	0.84	1.12 (0.89–1.42)	0.34

Key: CI, confidence interval; MMSE, Mini Mental State Examination; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; TMTA, Trail Making Task A; TMTB, Trail Making Task B.
[a] Except for TMTA and TMTB, where n = 2349 for men and n = 3736 from women.
[b] Adjusted for center, age, education, and baseline cognitive performance.

models failed to find a significant association between the incidence of dementia or AD and CS or NSAID use at baseline (Table 5).

4. Discussion

4.1. CS use and cognitive decline

Our results indicate a 1.8-fold increased risk of decline in a cognitive task sensitive to alterations in psychomotor speed and frontal executive functioning in women only. The same results were obtained in the minimally and the fully adjusted model, which was further adjusted for the pathologies associated with CS treatment (such as chronic pain and respiratory disorders) (Belanoff et al., 2001) and using 2 different models (logistic regression and random-effect models). This underlines the consistency of these associations, in spite of an eventual risk of overadjustment and suggests that the cognitive decline was more likely related to the CS themselves rather than the underlying burden of illness, making unlikely an eventual prescription bias. This is also supported by the observation that risk of cognitive decline nearly doubled (OR, 3.2; p = 0.01) with longer treatment and continuous use, and was nonsignificant after discontinuation.

Systemic toxicity is known to be a major concern with long-term use of high-dose glucocorticoids. In our study, the deleterious effect on cognitive function was only observed for inhaled CS. This may be linked to differences in the active substances and/or pharmacodynamic properties related to administration mode; oral administration being generally associated with slower absorption/distribution, higher metabolism due to hepatic first-pass effect, and lower biologically active circulating metabolites. Adrenal insufficiency and Cushing's syndrome have also been reported in patients treated with inhaled CS (Molimard et al., 2008). In our study, however, the small number of subjects taking CS using either mode did not allow us to examine the effect of administration method. We also did not have any information on patient conformity to prescription; inhaled CS being more likely to be overdosed.

Only a few small experimental studies in healthy young or adult participants have examined the link between acute or short-term glucocorticoid administration and cognitive impairment. Cognitive assessment has principally focused on changes in declarative memory consistent with deficiencies in hippocampus-dependent activity, although recent studies have also noted impairments in prefrontal cortex processing (Franz et al., 2011; Lupien et al., 2007; Wolkowitz et al., 2009); both structures having a relatively high density of gluco- and mineralocorticoid receptors. These associations may be transient and dose-dependent (de Quer-

Table 5
Baseline CS and NSAID use and 7-year incidence of dementia (Cox model with delayed entry)

	Women (n = 4573)		Men (n = 2913)	
	HR [a] (95% CI)	p	HR [a] (95% CI)	p
CS				
All dementia [b]	1.22 (0.72–2.06)	0.45	0.91 (0.50–1.67)	0.76
Alzheimer's disease [c]	1.21 (0.64–2.28)	0.55	0.74 (0.33–1.63)	0.45
NSAID				
All dementia [b]	1.27 (0.88–1.83)	0.20	0.88 (0.48–1.63)	0.69
Alzheimer's disease [c]	1.32 (0.86–2.03)	0.21	1.01 (0.49–2.09)	0.97

Key: APOE, apolipoprotein E; CI, confidence interval; CS, corticosteroid; HR, hazard ratio; NSAID, nonsteroidal anti-inflammatory drug.
[a] Adjusted for gender, center, age, education, depression, ischemic pathologies, diabetes, hypercholesterolemia, caffeine, smoking, APOEε4, chronic joint or back pain, chronic bronchitis, asthma, and other chronic respiratory disorders.
[b] Three hundred twenty women and 207 men were diagnosed with incident dementia.
[c] Two hundred twenty-six women and 134 men had incident Alzheimer's disease. The 94 women and 73 men with other types of dementia were excluded from this analysis.

vain et al., 2003; Keenan et al., 1996; Kirschbaum et al., 1996; Newcomer et al., 1999; Young et al., 1999). A lower sensitivity of verbal memory skills compared with other cognitive functions has been reported in young adults after acute CS administration (Lupien et al., 2007) and recently in older adults, in a large study using an extensive cognitive battery; high cortisol levels being specifically associated with poor frontal-executive functions (Franz et al., 2011). No such studies have been performed in the elderly.

In our study poor performance is only seen on the TMTB and not on the TMTA trial (the A trial not involving the cognitive switching task) and similar results were observed when executive function was assessed using score differences. This thus suggests that executive performance is affected rather than psychomotor speed. Neuropsychological tests requiring intact prefrontal cortical activity such as the TMTB may thus be especially vulnerable to chronic inhaled CS use in elderly women. A "two-factor model of brain aging" which posits that endocrine-related aging, like normal aging, may primarily involve loss of frontal-striatal circuits with associated executive function changes, whereas pathological cognitive aging (e.g., AD) is more strongly associated with hippocampal abnormalities appears to support our observations but remains speculative (Buckner, 2004; Franz et al., 2011; Hedden and Gabrieli, 2004).

4.2. Gender specificity

We did not observe a significant association between CS use and cognitive decline for men. This could be due to pharmacodynamic or metabolism differences. In a meta-analysis, Otte et al. reported a 3-fold stronger effect of age on cortisol response in women than in men (Otte et al., 2005). A gender difference in biological response to stress both at a functional and structural level may also be possible (Kudielka et al., 2004; Kumsta et al., 2007; Pruessner et al., 2010). Overall, specific cognitive functions may be affected by cumulative exposure to chronic stress via glucocorticoids released from the HPA axis, but also from gonadal steroids released from the hypothalamic-pituitary-gonadal axis (notably estrogens and testosterone which have distinct cognitive effects in women and men) (Conrad and Bimonte-Nelson, 2010). Interestingly, hypercortisolism and steroid dementia syndrome previously reported in adult patients after glucocorticoid intake at high doses and for extended periods, show some pathophysiological similarities with the cognitive features observed in this study, including durable executive dysfunction, higher incidence in females, dose dependency, and reversibility (Egeland et al., 2005; Lewis and Smith, 1983; Sacks and Shulman, 2005; Wolkowitz et al., 2007, 2009).

4.3. CS use and dementia

We observed no significant association between CS use at baseline and risk of developing dementia over 7 years. To date only 1 randomized controlled trial has examined the effect of 1-year prednisone treatment on cognitive decline in Alzheimer's patients (Aisen et al., 2000) showing no significant difference between CS- and placebo-treated patients. CS dose and exposure duration could also be evoked, but the small number of demented subjects taking CS (n = 28) have precluded exploration of this possibility.

4.4. NSAID use, cognitive decline, and dementia

We did not observe any significant associations between NSAID intake at baseline and cognitive decline and dementia over 7 years. In observational studies, exposure to NSAIDs were possibly associated with decreased risk for cognitive decline and AD, depending on class and dose, longer duration or younger age at intake, and APOEε4 vulnerability (de Craen et al., 2005; Gorelick, 2010; Szekely and Zandi, 2010; Szekely et al., 2004, 2008; Vlad et al., 2008). Conversely, the 3 randomized controlled trials performed using rofecoxib, celecoxib, and naproxen, suggested an increased risk in AD and no consistent association or worsening of cognitive function with naproxen (in global summary scores and verbal fluency) (ADAPT Research Group et al., 2007; ADAPT Research Group et al., 2008; Thal et al., 2005).

Inflammatory processes are complex and may have either reparative or detrimental effects on neurons (Wyss-Coray and Mucke, 2002). In our study, neither CS nor NSAID appeared to be beneficial for cognitive dysfunction or dementia, which does not support the hypothesis that inhibiting inflammation can reduce neurodegenerative processes in the elderly. The different patterns of cognitive change observed in our study between CS and NSAID suggests that deleterious CS effects on executive function may be more likely related to glucocorticoid and HPA axis functioning rather than an anti-inflammatory effect.

4.5. Limitations and strengths

A limitation of our study was the use of some self-reported covariates with eventual subsequent recall bias. Bias could also have been introduced through the exclusion of participants, those lost to follow-up being more likely to have dementia, to be older, and thus with worse physical and mental health, and using CS more frequently. This may limit the generalizability of our results, and associations may have thus been underestimated. We did not consider treatment compliance, which may have caused classification bias. Because we did not have data on precise duration of medication use, we could not definitively address the question of whether prolonged use could precipitate nonreversible dementia. Finally, because multiple analyses have been performed we cannot exclude that some observed associations were due to a chance finding.

The strengths of this study relate principally to its prospective, community-based design, large size, and extensive information obtained on clinical status. CS and NSAID use was verified by examining prescriptions and medications, thus minimizing exposure misclassification and with the

advantage, compared with reimbursement data, of including self-medication (Noize et al., 2009). Finally, we have taken into account a wide range of competing causes of cognitive dysfunction in the elderly, by controlling for sociodemographic, genetic, health, and lifestyle covariates, thus limiting any potential confounding including prescription bias.

In conclusion, findings from this study suggest that inhaled CS use is associated with poorer executive performance in elderly women; the principal clinical and functional implication being that medical practitioners should take chronic CS use into account before making a differential diagnosis of early neurodegenerative disorder.

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Disclosure statement

Drs. Ancelin, Carrière, Helmer, Rouaud, Pasquier, Berr, and Chaudieu report no disclosures. Dr. Ritchie serves on scientific advisory boards for the Biomedical Research Centre, King's College London, and London and MRC Strategic Steering Committee (Longitudinal Health and Aging Research Unit).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neurobiolaging.2011.09.038

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