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# Intense solar activity reduces urinary 6-sulfatoxymelatonin in patients with COPD

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## Abstract

**Background** Little is known about the link between solar activity and variations in melatonin. In this study, we investigated if melatonin's major urinary metabolite, urinary 6-sulfatoxymelatonin (aMT6s), is lowest under periods of intense solar activity.

**Methods** We investigated associations between high-energy solar particle events [Coronal Mass Ejection (CME) mass, speed and energy] on creatinine-adjusted aMT6s (aMT6sr) concentrations in 140 patients with chronic obstructive pulmonary disease (COPD) using up to four seasonal urine samples (n = 440). Mixed effect models with a random intercept for each subject were used to estimate associations, including effect modification attributable to diabetes, obesity, and reduced pulmonary function.

**Results** Higher values of CME were associated with reduced aMT6sr concentrations, with stronger associations in patients with diabetes. An interquartile range (IQR) increase in natural log CME<sub>speed</sub> averaged through two days before urine collection was associated with a reduction of 9.3% aMT6sr (95%CI: - 17.1%, - 0.8%) in aMT6sr. There was a greater reduction in aMT6sr in patients with diabetes (- 24.5%; 95%CI: - 35.9%, - 11.6%). In patients without diabetes there was no meaningful association (- 2.2%; 95%CI: - 12%, 8.4%). There were similar associations with CME<sub>energy</sub> and CME<sub>mass</sub>. There was no effect modification attributable to reduced pulmonary function or obesity.

**Conclusions** This is the first study in patients with COPD to demonstrate strong detrimental impact of high-energy solar particle events on aMT6sr, with greater associations in patients with diabetes. Since melatonin is an anti-oxidant, it is possible that adverse effects of intense solar activity may be attributable to a reduction in circulating melatonin and that patients with both COPD and diabetes may be more susceptible.

**Keywords** Intense solar activity, Urinary 6-sulfatoxymelatonin levels, Pulmonary disease, Circadian rhythm disruption, And diabetes mellitus

## Background

Melatonin (*N*-acetyl-5-methoxytryptamine) is a potent nocturnal antioxidant hormone and efficient immunoinflammatory regulator, which is primarily synthesized in the pineal gland [1]. Melatonin is also produced by other organs such as the retina and the gastrointestinal tract [1]. It is well known that pineal gland function and melatonin secretion are modulated by the environmental light/dark cycle via the suprachiasmatic nucleus (SCN) in the hypothalamus [2]. SCN is the “master clock” that regulates the 24 h-circadian rhythm, including melatonin/cortisol rhythms, gene expression, and

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autonomic nervous system (ANS) function [2–8]. The disruption of 24-h circadian rhythm with concomitant reduction of melatonin synthesis and serum levels seem also to be modulated by solar and geomagnetic activity (SGA)-related visible and non-visible electromagnetic radiation [3]. This may be relevant clinically, as we have previously described reductions in pulmonary function attributable to SGA [9]. We have also observed additional adverse effects of SGA that include increases in blood pressure, atrial and ventricular arrhythmias, and increases in circulating biomarkers of systemic inflammation [10–13]. In this study, we hypothesize that intense solar activity reduce levels of urinary 6-sulfatoxymelatonin (aMT6s), thereby providing a biologic pathway with the potential to contribute to the adverse effects of SGA.

Circulating melatonin has a short half-life (~ up to 45 min) and is rapidly metabolized in the liver with the major enzymatic metabolite of melatonin (aMT6s), which highly correlates with plasma melatonin levels [13, 14]. Studies in animals have suggested a link between seasonal rhythmicity of aMT6s levels and ~11-year solar cycles [8]. Melatonin levels can also be affected by genetic factors, sex, pineal gland size, and modifiable factors such as seasonal changes, latitudinal locations, medications (e.g.,  $\beta$ -blockers and non-steroidal anti-inflammatory drugs), sleep quality, depression, smoking status, and comorbidities including diabetes and cancer [2, 13–20]. Levels of melatonin vary throughout life, reaching highest levels in children younger than 4 years, and declining within age [2, 19]. In the lung, melatonin may mitigate respiratory disease severity by modulating pro-inflammatory cytokines such as interleukin1 $\beta$  and 6, and TNF- $\alpha$ , reducing oxidative stress [1, 13, 16]. A reduction in melatonin also can increase the risk of the development of type 2 diabetes mellitus by impairing insulin sensitivity and glucose tolerance [6, 7].

Understanding the impact of solar activity on melatonin levels is critical to understanding natural exposures that may affect health outcomes, particularly in association with oscillations of 11-solar cycles, even though the relationship between variation in solar activity and melatonin levels in humans has not been well established. To investigate this, we took advantage of previously collected urine samples in a cohort of patients with COPD [21, 22] to assess the link between short-term variation in solar activity intensity and melatonin excretion, using aMT6s concentrations to estimate melatonin levels. We also assessed effect modification of comorbidities (diabetes mellitus, obesity, and reduced pre-bronchodilator pulmonary function) on aMT6s.

## Methods

### Study subjects

Between 2013 and 2017, 143 patients with chronic obstructive pulmonary disease (COPD) were recruited at Veterans Affairs (VA) Boston Healthcare System from Eastern Massachusetts and vicinity to investigate the impact of particulate air pollution exposures [20–22]. Participants had up to 4 seasonal visits scheduled at least 2 weeks after therapy for a COPD exacerbation. Participants were former smokers with 10 pack-years or more of lifetime smoking, and had a ratio of post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV<sub>1</sub>/FVC) of <0.70 at a screening visit or emphysema on chest computed tomography. Individuals with malignancies other than local skin or stable prostate cancer, a systemic inflammatory disease such as rheumatoid arthritis; or with unstable heart disease, were excluded. By study design, in order to substantially reduce exposure to sources of indoor combustion, we excluded patients who were current smokers or lived with a current smoker, or who had a major source of indoor air pollution (e.g., wood stove or fireplace, frequent burning of incense or candles). At each study visit spirometry pre- and post-bronchodilator was conducted [23], medication use was reviewed, and height and weight were measured. At study entry, participants were asked if they had ever being told by doctor that they had sleep apnea or diabetes. The study protocol was approved by Institutional Review Boards at VA Boston and Harvard Medical School. We obtained informed consent from all participants prior to study procedures.

### Urinary 6-sulfatoxymelatonin (aMT6s) assessment

Study visits occurred during daylight hours where the time of urine sample collection was noted [median 11:22 AM (interquartile range (IQR): 2 h 34 min), mean 11:35 AM (standard deviation: 1 h 51 min)]. Samples were put on ice and transported to the VA Boston core laboratory and frozen at – 80 °C. For this analysis aMT6s (ng/ml) was measured in these stored samples in duplicate by an ELISA assay (Alpco, Salem, NH) in the Department of Laboratory Medicine, Boston Children's Hospital, Boston, MA, USA. The day-to-day variabilities of the assay at concentrations of 6.8, 95 and 248 ng/mL are 11.0, 6.3 and 5.2%, respectively. The assay is sensitive to 1.0 ng/mL. To account for differences in urinary dilution, we measured urinary creatinine (mg/ml), using the ratio of aMT6s and creatinine (aMT6sr) as the study outcome (in ng/mg creatinine).

### Solar activity parameters

Parameters of solar activity events [corona mass ejection (CME)] were obtained from the NASA SOHO/LASCO

CME ([https://cdaw.gsfc.nasa.gov/CME\\_list/](https://cdaw.gsfc.nasa.gov/CME_list/)). CME is high-energy plasma ejected from the outer surface of the Sun that interacts with the earth's magnetic field, producing geomagnetic disturbances and increased electromagnetic phenomena in the earth's systems (e.g. atmosphere, geosphere). CME can take hours to days to reach earth depending on its energy, mass and speed. We converted hourly CME data in UTC time to local Boston time, and created daily averages. Daily CME data included the mean of  $CME_{mass}$  (grams of solar mass),  $CME_{energy}$  [in erg, unit of energy equal to  $10^{-7}$  J (100 nJ)], and  $CME_{speed}$  (km/s). CME can occur many times per day or none, depending on the intensity of solar activity (higher intensity of solar activity results in an increased number of CME events). Because the CME values can range from negligible to trillions of units of  $CME_{mass}$ , energy and speed, we used the natural log of CME variables.

### Statistical analysis

We used mixed effect models with random intercept for each subject to analyze the association of solar activity on the natural log transformed aMT6sr to normalize its distribution and meet model assumptions. As CME can take hours to days to reach Earth, we analyzed five windows of moving averages of exposure from the day of urine collection (day 0) to up to 4-days (day 4) prior to the urine sample collection.

The primary models included a single exposure variable (corona mass ejection energy, speed or mass) and covariates. Melatonin can be affected by sex, seasonal changes, medications (including  $\beta$ -blockers and non-steroidal anti-inflammatory drugs), sleep apnea, and comorbidities including diabetes [2, 13–20]. Therefore, model covariates included a priori were race (white vs. other), sex (male/female), age, body mass index (BMI), beta blocker use and non-steroidal anti-inflammatory medication use within 1 day of urine collection, diabetes, time of urine collection, history of sleep apnea, and season (winter, spring, summer, fall), and BMI.

$$\begin{aligned} aMT6sratio_{ID} \sim & X_1 CME_{[X]} + X_2 urine_{season} + X_3 sex \\ & + X_4 bmi + X_5 age + X_6 race + X_6 med1(NSAID) \\ & + X_7 med2(beta\text{blockers}) + X_8 baseline_{diabetes} \\ & + X_9 baseline_{apnea} + X_{10} urine_{time}, \end{aligned}$$

where:  $aMT6sratio_{ID}$  is the natural log of aMT6s/creatinine per visit;  $X_1$  is the natural log CME mass, energy or speed.

Visits where persons reported melatonin use the night before urine collection were excluded in addition to when the aMT6sr was above the upper 95th percentile ( $aMT6sr > 77.8$ ), suggesting unreported melatonin use

(from 143 patients, 3 were excluded). That is consistent with the upper limit of physiologic levels reported in the literature [12]. We assessed the effect modification by obesity ( $BMI > 30$ ), diabetes, and %-predicted pre-bronchodilator  $FEV_1 < 50\%$  and  $\geq 50\%$  predicted using multiplicative interaction terms and stratified effect estimates. Effects on aMT6sr were calculated by multiplying each beta and corresponding 95% confidence interval values by log IQR of CME mass, speed and energy and exponentiating. After subtracting 1 from each estimate and multiplying by 100, the results are expressed as percent increase in aMT6sr per log IQR of each exposure. We assessed the correlation among the exposure variables (Additional file 1) by calculating Pearson and Spearman correlation coefficients (Additional file 1). We also examined each model residuals to assess model fit. We performed all analyses using SAS 9.4 software.

## Results

### Characteristics of the study population

After excluding visits with aMT6sr above the upper 95th percentile, there were 140 participants with 440 visits (75 patients with 4 visits, 25 patients with 3 visits, 25 patients with two visits, and 15 patients with only one visit) and approximately 95% of the visits were completed over one year. The clinical characteristics of the patients are showed in the Table 1. Most of them were elderly white men, having a mean age of 72.7 (SD = 8.2) years. Thirty-six percent (25.7%) reported diabetes, and 66(47.2%) were obese at study entry. There were 73 (52.1%) patients using beta blockers, and 21(15%) using non-steroidal taking anti-inflammatory medication (Table 1). aMT6sr levels varied widely among study participants [mean = 14.8 (SD = 11.4); median = 11.2 (IQR = 11.7)]. There was a strong correlation among CME parameters ( $R > 0$ ;  $p$ -value  $> 0.05$ ) (details in the Additional file 1).

### Primary analysis

There was inverse relationship between each CME parameter moving average (from day 0 to 4 days prior to the urine collection) and creatinine-adjusted melatonin, consistent with an association between intense solar particle events and reduction in aMT6sr (Fig. 1). The point estimates for  $CME_{speed}$  were more negative than those of the other CME parameters, indicating a slightly greater reduction (Fig. 1). For an increase of an IQR of 1.1 (2.1 km/s) in natural log  $CME_{speed}$  two days prior to the day of examination, there was a reduction of 9.3% (95%CI: - 17.1%, - 0.8%;  $p$ -value: 0.02) or - 0.1 units (95%CI: - 0.2; - 0.01) of natural log-transformed aMT6sr levels (Fig. 1; Additional file 1).

**Table 1** Characteristics of patients with COPD between 2013 to 2017

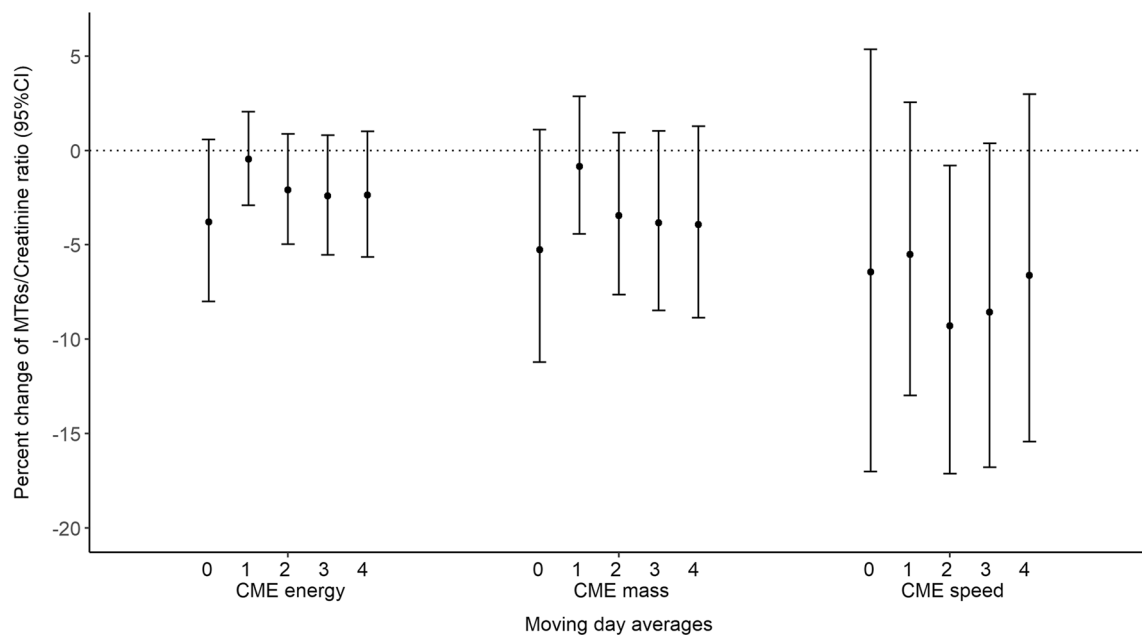
	First visit n = 140	Overall n <sub>obs</sub> = 440
Age (years)	72.7 (8.2)	73.1 (8.3)
BMI (kg/m <sup>2</sup> )	30 (5.7)	30.3 (6.1)
Past lifetime smoking (packyears)	59.9 (5.7)	58.3 (37.1)
Pre-bronchodilator % predicted FEV <sub>1</sub>	64.5 (21.9)*	64.7 (22)**
Pre-bronchodilator % predicted FVC	85.5 (20.2)*	85 (20.5)**
FEV <sub>1</sub> /FVC ratio	0.54 (0.13)*	0.55 (0.12)**
aMT6s (ng/ml)	15.6 (13.9)	17.4 (18.2)
Log-aMT6sr	2.5 (0.7)	2.5 (0.7)
Creatinine (mg/dl)	112.1 (57.4)	120 (68.9)
	<b>N (%)</b>	<b>N (%)</b>
Race		
White	125 (89.3)	390 (88.6)
Non-white	15 (10.7)	50 (11.4)
Sex		
Female	4 (2.8)	11 (2.5)
Male	136 (97.2)	429 (97.5)
Season		
Winter	21 (15)	101 (23)
Spring	35 (25)	103 (23.4)
Summer	48 (34.3)	121 (27.5)
Fall	36 (25.7)	115 (26.2)
<b>Comorbidities</b>	<b>N (%)</b>	<b>N (%)</b>
Reduced lung function (pre-bronchodilator FEV <sub>1</sub> < 50% predicted)***	35 (25.8)	112 (25.9)
Obesity (BMI > 30)	66 (47.2)	209 (47.5)
Diabetes	36 (25.7)	113 (25.7)
Sleep apnea	42 (30)	139 (31.6)
<b>Medications (within 1 day of urine collection)</b>	<b>N (%)</b>	<b>N (%)</b>
Beta blocker	73 (52.1)	232 (52.7)
Non-steroidal anti-inflammatory medication	21 (15)	61 (13.8)
<b>Solar activity assessment [Coronal Mass Ejection (CME)]</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
Log-CME <sub>speed</sub>	7.3 (0.4)	7.2 (0.5)
Log-CME <sub>mass</sub>	35.8 (0.8)	35.6 (0.9)
Log-CME <sub>energy</sub>	70.2 (1.2)	69.9 (1.3)
CME <sub>speed</sub>	1519.4 (627.2)	1503.6 (694.9)
CME <sub>mass</sub>	4.2 × 10 <sup>16</sup> (2.5 × 10 <sup>16</sup> )	3.8 × 10 <sup>15</sup> (2.6 × 10 <sup>15</sup> )
CME <sub>energy</sub>	5.1 × 10 <sup>30</sup> (5.3 × 10 <sup>30</sup> )	4.5 × 10 <sup>30</sup> (5.4 × 10 <sup>30</sup> )

\*N = 136, \*\*N = 433, \*\*\*based on Hankinson et al. [24]

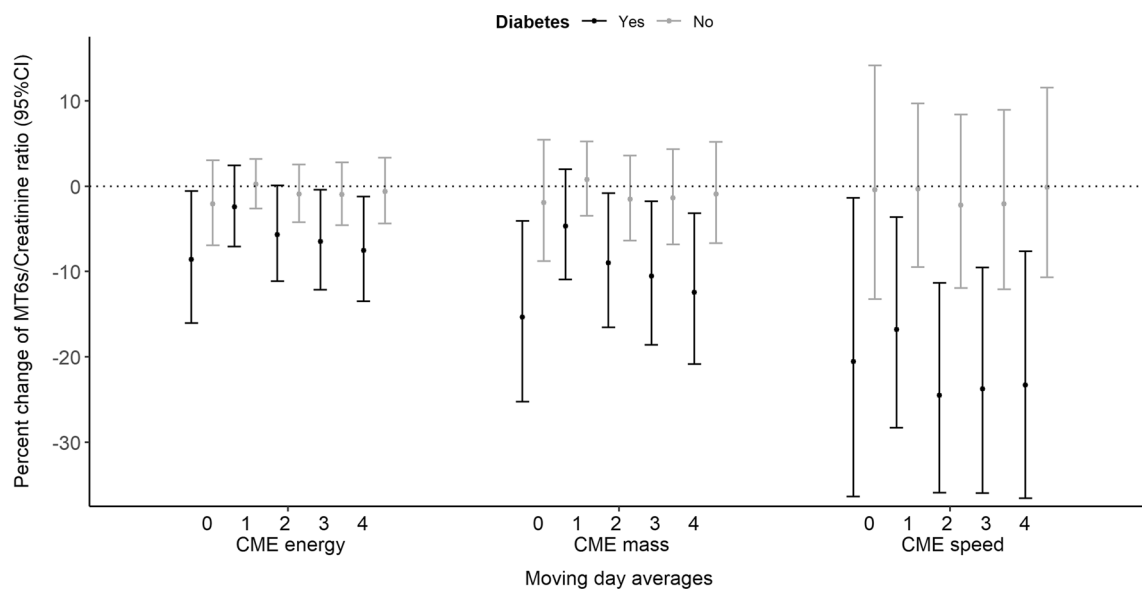
**Effect modification**

There were greater CME-related effects in patients with diabetes mellitus (*p*-interaction=0.006) (Fig. 2; Additional file 1). For example, an IQR of 1.1 (2.1 km/s) natural log CME<sub>speed</sub> two days prior to the sample collection was associated with a reduction of 24.5% (95%CI: − 35.9%, − 11.6%; *p*-value: 0.0006) or − 0.3 units (95%CI:

− 0.5, − 0.1) in natural log aMT6sr levels in patients with diabetes. In patients without diabetes there was no association [aMT6sr: − 2.2% (95%CI: − 12%, 8.4%; *p*-value: 0.66) or − 0.02 natural log units (95%CI: − 0.1, 0.1) (Fig. 2; Additional file 1). There was no evidence of effect modification attributable to obesity and reduced pulmonary function (Additional file 1).



**Fig. 1** Associations of natural log CME (energy, mass, and speed) with aMT6s/Creatinine ratio. The primary models included a single exposure variable (log corona mass ejection energy, speed or mass) and model covariates



**Fig. 2** Associations of natural log CME with aMT6s/creatinine ratio modified by diabetes. Effect modification of diabetes. The models included a single exposure variable (log corona mass ejection energy, speed or mass) and model covariates

**Discussion**

To the best of our knowledge, this is the first study to demonstrate a reduction of aMT6sr during periods of intense high-energy solar particle events. The associations were stronger and more robust in patients with diabetes mellitus. Although all CME parameters are strongly correlated and represent the ejection of high energy solar

material, the association between CME speed and MT6sr was greater than other parameters. As CME<sub>speed</sub> parameter seems to play a critical role on the atmospheric photoionization processes and energetic particle precipitation, and on Earth’s magnetic field disturbances, these factors may be linked for the observed impact on melatonin levels [23]. Intense solar activity can impact human

health directly, by the modulation and disruption of the 24 h-circadian rhythm, and indirectly by inducing physicochemical properties and toxicity of atmospheric aerosols [9, 12].

Solar activity continuously emits a broad-spectrum range of electromagnetic radiation that modulates changes in the solar–terrestrial environment over time scales ranging from minutes to millennia. Sun–Earth interaction plays major roles in the radioactive, physicochemical processes and dynamics of Earth systems, which affect the human health possibly by the reduction of melatonin synthesis and ANS dysregulation related to the disruption of the 24 h circadian rhythm located in the SCN [15]. While it is unclear why patients with diabetes were more susceptible to the detrimental impact of intense solar activity on aMT6sr levels, the literature describes a link between aMT6s and diabetes risk [4, 7, 17]. Reduced levels of melatonin can impair diabetes management and disrupt blood sugar control [7], which suggests that diabetic patients may experience periods of poor health during intense solar activity periods.

A bidirectional relationship between melatonin levels and insulin secretion may explain our findings in patients with diabetes. The disruption of the 24 h circadian rhythm with subsequent lower nocturnal melatonin secretion is associated with insulin secretion and resistance [4, 17], which may influence the development and progression of type 2 diabetes [4]. The circadian rhythm regulates the sleep/wake and feeding/fasting cycles through melatonin, impacting glucose homeostasis by influencing the timing of insulin secretion from pancreatic  $\beta$  cells, glucose production by the liver, insulin-dependent glucose GLUT 4 expression in skeletal muscles, among other effects [4]. There is a synchronization between insulin levels and melatonin during the night and day, in which melatonin action is inhibited by insulin release (and reduce glucose tolerance) through its membrane receptors  $MT_1$  and  $MT_2$ , and the secondary messengers 3',5'-cyclic adenosine monophosphate, 3',5'-cyclic guanosine monophosphate, and inositol 1,4,5-trisphosphate [6]. High levels of insulin are observed when melatonin levels are low, and during the night low levels of insulin are observed with high levels of melatonin [6]. Reduction of the melatonin receptor  $MT_2$  may play a role on the development of type 2 diabetes and metabolic diseases [6]. Concomitantly, age-related reduction levels of melatonin accompany an increase of age-related insulin resistance and type 2 diabetes risk [6]. Patients with both diabetes and COPD appear to be more susceptible to solar activity reducing circulating melatonin, and potentially antioxidant effects of melatonin. This finding suggests that differences in the response to solar activity could in part explain a greater susceptibility to effects of illnesses and environmental

exposures that promote oxidative stress in patients with diabetes [25].

This study has limitations and strengths. As the original COPD study was not designed to assess effects linked to melatonin, the time of urine collection was not standardized and there is no information about melatonin determinants such as sleep habits and nocturnal light exposures, and the cohort included mainly white males. However, we improved our estimation by adjusting our models for covariates linked to impaired melatonin secretion, including urine collection time, sleep apnea history and treatment, beta blocker use, and diabetes history as covariates. As melatonin excretion is greatest at night, urine from a first morning void might be more informative, while 24-h urine collection would be ideal to assess overall impact on melatonin secretion. This limitation should bias towards a null result; therefore, the effect that we observed is likely underestimated. As melatonin was assessed at only one time of day, we are unable to comment on the effects of solar activity on circadian rhythm per se, which would require repeated measures across the day. Moreover, our findings may not be generalized to other populations. Our study strengths are the availability of this cohort with stored urine samples for every visit, extensive information regarding personal and clinical characteristics, which created a unique opportunity to test our hypotheses.

## Conclusions

Our findings contribute to understanding relationships between solar activity and susceptibility to disruption to 24 h-circadian rhythm that result in lower levels of melatonin, a circulating anti-oxidant. These results provide evidence for a biologic pathway related to intense solar activity that may be responsible for adverse health effects. Hence, our study findings have critical relevance to understand the impact of the periodicity of solar activity intensity on aMT6sr levels in high risk patients with COPD, which impacts the progression and prognosis of the disease and comorbidities.

## Abbreviations

COPD	Chronic obstructive pulmonary diseases
aMT6s	Urinary 6-sulfatoxymelatonin
aMT6sr	Creatinine-adjusted aMT6s
CME	Coronal mass ejection
$CME_{energy}$	Energy of CME in in <i>erg</i> , unit of energy equal to $10^{-7}$ J
$CME_{mass}$	Mass of CME in grams of solar mass
$CME_{speed}$	Speed of CME in km/s
SCN	Suprachiasmatic Nucleus
SGA	Solar and geomagnetic activity
TNF- $\alpha$	Tumor necrosis factor alpha
VA	Veterans Affairs
FEV1	Bronchodilator forced expiratory volume in one second
FVC	Forced vital capacity
FEV <sub>1</sub> /FVC	FEV <sub>1</sub> /FVC ratio

IQR Interquartile range  
 BMI Body Mass Index  
 ANS Autonomic nervous system  
 MT Melatonin receptors

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-023-02390-w>.

**Additional file 1: Table S1** Supplementary descriptive analysis. **Table S2** Pearson correlation analysis [is this for n=440? Show Pearson for natural log as this is what you use in the models. **Table S3** Associations of log CME with aMT6s/Creatinine modified by pre bronchodilator %-predicted FEV<sub>1</sub>, obesity, and diabetes in patients with COPD. Results expressed as %-change per overall IQR of log CME<sub>speed</sub>, CME<sub>energy</sub>, and CME<sub>mass</sub> for each moving average starting with the day 0, the day of urine collection through 4 days before collection. **Table S4** Associations of log CME with aMT6s/Creatinine modified in patients with COPD. Results expressed as %-change per overall IQR of log CME<sub>speed</sub>, CME<sub>energy</sub>, and CME<sub>mass</sub> for each moving average starting with the day 0, the day of urine collection through 4 days before collection. **Fig. S1**. Associations of CME<sub>speed</sub>, CME<sub>energy</sub>, CME<sub>mass</sub> with MT6s/creatinine modified by obesity (BMI>30). **Fig. S2**. Associations of CME<sub>speed</sub>, CME<sub>energy</sub>, CME<sub>mass</sub> with MT6s/creatinine modified by post-bronchodilator %-predicted FEV<sub>1</sub> <50%.

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## Author contributions

CLZV, EG and PK designed the study; CLZV conducted the statistical analysis and wrote the draft manuscript. ML provided graphics assistance. The manuscript was edited by CLZV, EG, PK and DG. All authors read and approved the final version.

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## Availability of data and materials

Data is available for sharing upon request in the setting of an approved IRB protocol and executed data sharing agreement.

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by Institutional Review Boards at VA Boston and Harvard Medical School. We obtained informed consent from all participants prior to study procedures.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing financial interests.

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