

Author's response to reviews

Title: Effect of Sunlight Exposure on Cognitive Function: a Cross-Sectional Study

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Author's response to reviews: see over



SCHOOL OF
PUBLIC HEALTH

Department of Biostatistics

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Kathleen B. Drennan, Editor-in-Chief
Christopher Cahill, Managing Editor
211 East Chicago Avenue, Suite 1450
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Dear Drs. Drennan and Cahill,

Attached along with this cover letter and revision is the revised manuscript now named: "Effect of Sunlight Exposure on Cognitive Function Among Depressed and Non-Depressed Participants: a REGARDS Cross-Sectional Study" for consideration for publication in *Environmental Health*. All authors accept submission of this manuscript for publication and have no competing interests. This manuscript is not currently under consideration for publication elsewhere and is original, unpublished work.

This study is the first to examine the effects of two-week exposure to natural sunlight on cognition, as well as the first to look at solar effects on cognition in a large cohort study. Our innovative sunlight measurement methods used NASA satellite data, which has not been previously used in epidemiological studies.

The following pages in this document have the point-by-point response to the three reviewers.

We appreciate your consideration,

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Reviewer #1

Is there information on the type of depression (% of SAD etc)? It may be interesting to examine whether the associations apply to all types of depression or to SAD only.

It may also be important to examine associations between insolation and depression symptoms in a continuous form. Medications used for depression (or other central nervous system acting drugs) should be considered. Actually the above may constitute an important confounder: could it be that among depressed subjects those with worse depression (i.e. those who endorse more depressive symptoms or take more antidepressant medications etc) happened to live in areas with lower insolation (and hence have worse cognition)?

The reviewer mentions important confounders and interactions which unfortunately could not be further explored in this manuscript, as these variables were not available to us. We have added text in the conclusion to indicate this limitation: “**In addition to the imprecision or bias that may be present in any measurement, we could not account for specific psychiatric diagnoses or medicine consumption.**”

In addition, because the CESD score distribution was extremely skewed with a median score of 0, we performed Mann-Whitney-Wilcoxon rank-sum test to look at the relationship between insolation and continuous CESD score. The results did not indicate any significant relationships or strong dose-response patterns ($p=0.55$).

The cognitive instrument should be described. Is immediate or long term recall assessed? The short length of the instrument is necessitated by the epidemiological large scale nature of the study but can only provide limited information regarding cognitive status. Which elements of the cognitive instrument relate more to the insolation and depression, the memory or orientation ones?

The reviewer has noted the need to better understand what information the cognitive screener is providing. We have now noted in the Methods section that the instrument assesses short-term recall. We have also performed additional analyses to assess the relationship between solar insolation and the two specific components of the SIS (recall and temporal orientation). The following has been added to the Methods section: “**Finally, the cognitive screener was divided into two components, the three points that measure short-term recall and the three points that measure temporal orientation. Each of these components was used to explore individual relationships with insolation. Univariate relationships were analyzed using chi-square tests and multivariable relationships were evaluated by taking the final logistic regression model obtained above and replacing the summary measure of cognitive impairment with each of the individual components of the six-item screener. For these analyses, the three**

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point component measures were dichotomized, with one missing point indicating a deficit in either orientation or recall. The measures were also analyzed continuously, so that each component would be equal to the number of points obtained (0, 1, 2, or 3).” The results of this analysis are indicated at the end of the Results section: “Relationships between temporal orientation and short-term recall components of the six-item screener did not reveal any significant univariate or multivariable relationships with insolation, indicating that no single component was likely responsible for the observed overall relationship between cognitive function and insolation.”

The association of insolation with the covariates needs to be presented either in a text or table form. Is insolation related to depression per se? Given the known associations between depression and cognition and depression and sunlight, the most parsimonious explanation for the findings is an effect of insolation to depression with a subsequent effect on cognition.

The reviewer’s suggestion of presenting the analyses between insolation and the covariates gave interesting results and is now described in the Results “CMH chi-squared tests indicated that gender, age, region, population density, season, BMI, PCS-12, and weekly exercise had dose-response relationships with ordinaly categorized insolation, but education, diabetes, hypertension, high cholesterol, smoking (data not shown), and depression (Table 2) did not. Dose-response relationships of income ($p=0.0956$) and alcohol use ($p=0.0650$) with insolation were marginal (data not shown).” This is also addressed near the end of the conclusion: “That insolation had a relationship with cognitive function but not depression, and that the effect of insolation on cognition is shown among depressed, but not non-depressed participants indicates that insolation may have a relationship with cognition that is independent of, but modified by, depression.”

Some more practical interpretation – examples of insolation should be presented. For example what does 10000 J/ m² correspond to (i.e. how many hours of sunlight without clouds under what regional or other climatic conditions)?

It is important that a more practical and everyday understanding be attempted for scientific measurements. In order to clarify what the insolation is measuring in everyday terms, we have added the following to the Methods: “As a point of reference, under clear skies in late spring or early summer, a typical daily insolation value in the central U.S. is approximately 25,000-30,000 KJ/m². In late fall or early winter, a typical daily value is approximately 8,000-10,000 KJ/m².”

In addition to the addressing the comments above, we found a critical mistake was made in the insolation units. In the Methods and Results sections we have changed all references of “joules” to “kilojoules”.

Given the literature on temperature and insolation and temperature and cognition, should or could temperature be considered as a confounder? The effect of season is simultaneously interesting and puzzling. The authors should include some literature review and attempt to offer some explanations for the finding.

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The effect of season was inadequately described in the manuscript. We have now added text to the Methods explaining that: “**Since other factors related to seasonality besides insolation may be related to cognitive function, such as temperature, activity level, allergies, and stress, the final model was run both with and without season as a covariate**” The reviewer justifiably expresses concern over the effect of temperature on this relationship. Unfortunately, we do not have this data available at this time. However, we have now mentioned it as a possible confounder and have noted this in the Conclusion: “**Also, environmental temperature may be related to cognitive function, although temperature fluctuations are partially controlled for by season, exercise, cardiovascular factors, and other possible correlates of temperature.**”

Is there information on the type of depression (% of SAD etc)? It may be interesting to examine whether the associations apply to all types of depression or to SAD only. It may also be important to examine associations between insolation and depression symptoms in a continuous form.

The reviewer’s points regarding clinical measurements of type of depression and continuous depression measurements have been addressed in the first comment, above.

At the end of the 2nd paragraph of page 11 an incorrect attribution of cerebral blood flow as a potentially contributing factor for Alzheimer’s disease and Lyme disease are not explicitly stated but suggested. Although clearly lowering cerebral blood flow can be the cause of cognitive dysfunction (usually taking the form of delirium - encephalopathy or stroke-related cognitive dysfunction) current thinking considers low cerebral blood flow as the result of Alzheimer’s type pathological cerebral changes.

The reviewer is correct in stating that our description of the involvement of cerebral blood flow insinuates a causality that may be in an opposite direction than the evidence shows. The text has been changed to to indicate a correlation, rather than causation: “Inadequate cerebral blood flow has been **found to be a likely cause or result of** decreasing cognitive functions **among those with cardiovascular diseases, as well as correlated with** age-related diseases such as Alzheimer’s and non-age related diseases such as Lyme disease.”

The issue of time spent indoors or away of the residence may be partially addressed by considering physical disability, arthritis, ability for transportation as recorded in functional ability scales (some of this information must be available in the REGARDS study).

The reviewer is correct in noting that the analysis is lacking a measurement of time spent indoors. We tried to partially account for this by the possible inclusion of “weekly exercise” as a covariate, which was removed during the backwards selection procedure. In response to the statement above, we have also added in the Statistical Analyses section the following **red** text: “Due to prior evidence regarding relationships with cognitive function, we considered the following as potential confounders: sex, geographic region (stroke belt, stroke buckle, or non-

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stroke belt), population density (urban, suburban, and rural), income (less than \$20,000, \$20,000 to \$34,999, \$35,000 to \$74,900, or \$75,000 and more), education (less than high school, high school diploma, some college, or college diploma), race (black or white), smoking (current, past, or never), alcohol use (never used or ever used), Body Mass Index (BMI) (underweight, normal, overweight, or obese), hypertension status (SBP \geq 140, DBP \geq 90 or self-reported use of hypertension medications), high cholesterol (cholesterol $>$ 240), diabetes status (fasting glucose \geq 126, non-fasting glucose \geq 200, or self-reported diabetes medications), exercise (weekly or less than weekly), depression status based on the Center for Epidemiologic Studies Depression Scale (CES-D) scale, **physical function as measured by the 100 point scale Physical Components Summary (PCS) in the 12-item Short Form (SF-12)**, and season of phone interview (spring, summer, fall, or winter), and age in years (45-54, 55-59, 60-64, 65-69, 70-74, 75-79, or 80 or more).” in attempt to better account for this factor.

This variable remained in the final model as is now noted in the results and tables. Furthermore, we have also mentioned this as a limitation in the Conclusion section: “**However, this lack of a significant finding may be found due to a number of inadequately controlled for indirect behaviors acting as confounders, since there is previous environmental evidence for both season’s effects on cognition and environmental illumination’s effects on mood and cognition in general populations. Of particular importance, it may be true that those who are non-depressed may spend more time outside, thus receiving a more adequate supply of environmental illumination**”

Which one is the Keller et al 2005 reference in page 12 (the 1st)?

We thank the reviewer for pointing out that a reference is missing in the text. It has now been noted as reference #1.

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Reviewer #2:

Page 11, line 7. The authors' brief mention of "leading theories" mentions melatonin which is but a small measure of circadian rhythmicity and doesn't acknowledge the importance of the underlying control by suprachiasmatic nuclei. An extra sentence and reference or 2 here would be helpful for some readers. Potential references are [1, 2].

Page 12, line 1. The authors' briefly discuss memory and cognition's short wavelength spectral sensitivity without explanation or acknowledgment of the supporting literature elucidating this dependence. The intensity and spectral qualities of natural light make it optimal for enhancing cognitive function and briefly mentioning this will enhance this paper. Reference(s) above could apply here as well

The reviewer notes that the background is missing some of the overall picture regarding the body's control of circadian rhythms. In the introduction, the following was added: "Melatonin, serotonin and other mechanisms involved in circadian rhythms are associated with cognitive functioning, are regulated by the suprachiasmatic nuclei (SCN), which are susceptible to the effects of differing intensities and patterns of environmental illumination". A more extensive discussion of the background is also now in the Conclusions section: "Leonard and Myint, 2006 laid out a paradigm showing how environmental illumination and other stresses might lead to altered serotonin levels, neurodegeneration, depression, cognitive deficits, and ultimately dementia. Both seasonal and non-seasonal depression have been shown to have relationships with environmental illumination. Theories regarding the body's seasonal cycles, which affect depression and may also affect cognition, are mostly based on the regulation of the body's circadian rhythms by the hypothalamic suprachiasmatic nuclei (SCN). The SCN are modulated by various factors such as body temperature and physical activity, but are in particular modulated by light received by retinal sensors at optimal wavelengths close to sunlight's dominant wavelength of 477 nanometers. The SCN regulate the body's sleep cycle, body temperature, blood pressure, digestion, immune system, and various hormonal systems. Dysfunctional circadian rhythms and sleep disorders, which can occur from inadequate environmental light, have been associated with cognitive deficits. One of the SCN's regulatory functions are their inhibition of the pineal gland from turning serotonin into melatonin during the presence of daytime light."

Page 13, line 1. The authors' acknowledge some study limitations but the discussion fails to mention the confounding factor of reduced retinal illuminance which occurs with age due to decreasing crystalline lens transmittance and pupillary area.[2]

The reviewer suggests an important confounder that has not been mentioned. We have now included it in the Conclusion section as a limitation: "Eye function is another possible confounder. Specifically, crystalline lens transmittance and pupillary area have been found affect circadian photoreception, although controlling for age may reduce confounding from these factors."

Page 14, line 21-23. The authors state “This study also has an important finding regarding those without an elevated level of depressive symptoms. We did not find that sunlight meaningfully affected the cognitive abilities of these individuals”. This conclusion is strictly true based on a narrow interpretation of the data but probably understates positive effects on mood and cognition for the general population. The incidence of both seasonal and nonseasonal depression are inversely correlated with environmental illumination[3-5] and depression is also linked to cognitive deficits.[6, 7] Both are responsive to bright light therapy.[8] Depressed individuals benefit the most from sunny environments but are typically those whose mental status, work schedules or lifestyle choices provide relatively less illumination. On the other hand, light enhancement has been shown to increase subjective mood in general populations free of depression [9-11] and improve work performance (cognition) of employees without depression.[12] To state that sunlight did not meaningfully affect the cognitive abilities of non-depressive individuals ignores evidence that the depressive-free subjects are possibly those who spend sufficient and relatively more time in natural lighting and therefore possibly avoid both depression and reduced cognition. This possible alternative contingency of adverse selection should be acknowledged.

The reviewer suggests that previous studies indicate that sunlight may affect non-depressed individuals, despite the findings of our study. We agree that this is the case, and thus, this is now included throughout the Discussion section: “Abnormalities and regulation of both the melatonin and serotonin systems have been found to vary according to sunlight and light therapy in SAD, bipolar and schizophrenic patients, and even among those without psychiatric diagnoses” It has also been further addressed near the end of the manuscript: “However, this lack of a significant finding may be found due to a number of inadequately controlled for indirect behaviors acting as confounders, since there is previous environmental evidence for both season’s effects on cognition and environmental illumination’s effects on mood and cognition in general populations. Of particular importance, it may be true that those who are non-depressed may spend more time outside, thus receiving a more adequate supply of environmental illumination.”

Reviewer #3

a) definition of cognitive impairment that is very shaky despite publications on the Six-item screener to identify cognitive impairment. Confounding variables have been considered from the epidemiological viewpoint but not clinical: for instance, medication and time of assessment (diurnal variation) are known to influence some cognitive performances.

The reviewer brings up important variables that we were not able to control for. We have now mentioned some of these clinical variables in the Conclusion section: “**In addition to the imprecision or bias that may be present in any measurement, we could not account for specific psychiatric diagnoses or medicine consumption... Eye function is another possible confounder. Specifically crystalline lens transmittance and papillary area have been found affect circadian photoreception, although controlling for age may reduce confounding from these factors. The interview’s time of the day may also have an effect on cognition; however, the sampling method of REGARDS should result in all participants having an equal chance of being interviewed during a given time resulting in similar time distributions at any given variable level**”

b) Title is misleading. In fact the sunlight exposure has been found related to cognitive performance only among depressed patients, detail that is over sighted. Depression as variable although better described than cognition needs some rewriting, particularly the literature on cognitive impairment in depression. Also it is well known that depressive patients tend to show social withdrawal, and therefore, less light exposure. Authors have to comment that point, which is very clear for a clinician. In that case relationship may be just the oposite: depressives more cognitively impaired tend to show more social withdrawal.

The reviewer indicates that the relationship found in the analysis is not adequately presented in the title and text of the manuscript. We have attempted to remedy this by changing the title to: “**Effect of Sunlight Exposure on Cognitive Function Among Depressed and non-Depressed Participants: a REGARDS Cross-Sectional Study**” to demonstrate that the effect, or lack of effect, of sunlight on cognitive function is modified by depression.

c) Sunlight exposure is different from to lighththerapy. The fact that same day assessment does not show correlation between sunlight and cognition might be related to indirect behaviors rather than direct effect of light.

The reviewer noted that the relationship may be unclear due to the nature of the environmental illumination and behavior and their effects on cognition. This has been further addressed in the conclusion : “**However, this lack of a significant finding may be found due to a number of inadequately controlled for indirect behaviors acting as confounders, since there is previous environmental evidence for both season’s effects on cognition and environmental illumination’s effects on mood and cognition in general populations. Of particular importance, it may be true that those who are non-depressed may spend more time outside, thus receiving a more adequate supply of environmental illumination.**”

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Miscellaneous changes

In addition to the above comments: T-tests, chi-squared, and correlation tests were used to determine preliminary relationships between insolation, cognition, and the covariates. Cochran-Mantel-Haenzel (CMH) chi-squared tests were used to determine if categorized insolation had relationships with categorical predictors.

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