Nonmelanoma skin cancer is associated with reduced Alzheimer disease risk

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ABSTRACT

Objective: To explore the association of nonmelanoma skin cancer (NMSC) and Alzheimer disease (AD) in the Einstein Aging Study, an epidemiologic study of aging in New York City.

Methods: Community-residing volunteers aged 70 years or older were assessed annually, followed by multidisciplinary diagnostic consensus. Cancer status and type was obtained by self-report. Cox proportional hazards models were used to test associations between NMSC and subsequent risk of developing a neurocognitive disorder. To deduce a biologically specific association between AD and NMSC, we considered 3 nested outcomes groups: only AD (probable or possible AD as the sole diagnosis), any AD (probable AD or possible AD, as well as mixed AD/vascular dementia), and all-cause dementia.

Results: We followed 1,102 adults with a mean age of 79 years at enrollment. Prevalent NMSC was associated with reduced risk of only AD (hazard ratio = 0.21; 95% confidence interval = 0.051–0.87; p = 0.031) among subjects after adjustment for demographics, hypertension, diabetes, and coronary heart disease. APOE ε4 genotypes were available in 769 individuals. The association was similar in magnitude, but nonsignificant, when the number of APOE ε4 alleles was included in the model. No significant association was found between NMSC and subsequent development of any AD or all-cause dementia.

Conclusions: This population-based longitudinal study shows that individuals older than 70 years with NMSC have a significantly reduced risk of developing AD compared with individuals without NMSC. We deduce Alzheimer-specific neuroprotection, because the effect is attenuated or eliminated when considering less-specific diagnoses such as AD with another diagnosis (any AD) or all-cause dementia. *Neurology*® 2013;80:1966–1972

GLOSSARY

AD = Alzheimer disease; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **EAS** = Einstein Aging Study; **HR** = hazard ratio; **NMSC** = nonmelanoma skin cancer; **VaD** = vascular dementia.

Previous studies observed an inverse relationship between Alzheimer disease (AD) and cancer. The Washington University AD Research Center showed reduced incidence of cancer in participants with prevalent AD, and a nonsignificant trend toward lower incidence of AD in persons with history of cancer at baseline.[1] Skin cancer specifically accentuated the protective effect against dementia and AD.[2] Data from the Cardiovascular Health Study found that AD, but not vascular dementia (VaD), was associated with a reduced risk of future cancer hospitalization.[3] In whites, a previous cancer diagnosis conferred a reduced risk of AD, but in African Americans with cancer, an increased AD risk was reported. There was no significant association between a previous diagnosis of cancer and future VaD.[3]

Other research has suggested that skin cancer in particular may have specific effects. In a clinical trial, patients with AD treated with a γ-secretase inhibitor had increased rates of nonmelanoma skin cancer (NMSC).[4] NMSC is the most common malignancy in the United States, with an estimated 2007 prevalence of approximately 13 million whites.[5] Herein, we explore the association of NMSC and AD in the Einstein Aging Study (EAS), a longitudinal

epidemiologic study of aging in New York City. We hypothesized that a history of NMSC would be associated with reduced Alzheimer risk, and that the effect would not apply to other causes of dementia.

METHODS **Design.** The EAS is a cohort study that follows community-residing, systematically sampled, dementia-free older adults in the Bronx, NY, with annual neurocognitive assessments. In the present study, we followed persons with and without a history of NMSC, assessing time to clinical dementia diagnosis. To deduce a biologically specific association between AD and NMSC, we considered nested subsets according to diagnostic subtype: only AD (probable or possible AD as the sole diagnosis), any AD (probable AD or possible AD, as well as mixed AD/VaD), and all-cause dementia.

Study population. EAS design, enrollment procedures, and follow-up methods have been previously described.[6] Inclusion criteria required that participants be aged 70 years or older, noninstitutionalized, speak English, and reside in the Bronx. Exclusion criteria included sensory impairment that would hinder neuropsychological testing, nonambulatory status, psychiatric symptomatology or substance use that would impede assessment, and prevalent dementia. Between 1993 and 2004, the population sample was derived from Health Care Financing Administration/Centers for Medicare & Medicaid Services lists and from New York City Board of Elections voter registration lists after 2004. Potential participants were systematically recruited through the use of letters explaining the study. Follow-up telephone calls were conducted to further explain the study, receive verbal consent, complete a brief medical history questionnaire, and perform a brief cognitive screening test to prevent the enrollment of prevalent dementia cases in the study.[6] Eligible persons based on the telephone interview were assessed in person at the EAS clinic where final study eligibility was determined.

A total of 1,791 participants were enrolled in the EAS between October 1993 and December 2009. Participants with no follow-up (n = 679) were excluded from this study. Therefore, a total of 1,102 participants were included in this study. At baseline and at annual follow-up visits, participants were assessed via demographic and health questionnaires, psychosocial histories, neuropsychological testing, neurologic and medical evaluation, and physical measures.

Standard protocol approvals, registrations, and patient consents. Verbal informed consent was obtained during all telephone calls and written informed consents were obtained during all clinic visits according to study protocols approved by the Committee on Clinical Investigation, the institutional review board of the Albert Einstein College of Medicine. Additionally, the Committee on Clinical Investigation approved the use of human subjects for this study.

Criteria for dementia diagnosis. Dementia status for EAS participants was ascertained at case conferences with neuropsychology and neurology input. Dementia diagnosis was dichotomously classified and fulfilled standardized clinical criteria from the *DSM-IV*.[7] Criteria included memory impairment plus impairment in at least one additional cognitive domain, with evidence of functional decline. Dementia was subtyped according to criteria for probable or possible AD as determined by the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.[8] The diagnosis of probable, possible, or mixed VaD was based on criteria set forth by the State of California Alzheimer's Disease Diagnostic and Treatment Centers.[9] For participants with incident dementia, date of incident dementia was assigned to the office visit before consensus case conference. These were strictly clinical diagnoses, informed by comprehensive review of cognitive testing, neurologic signs and symptoms, and functional status. EAS clinical-pathologic studies demonstrated that the diagnosis of AD has a positive predictive value of 78.5% and a negative predictive value of 82.3% for pathologically verified AD (unpublished data).

Criteria for cancer diagnosis. Participants were asked at every assessment whether he or she ever had any form of cancer. A response of "yes" would prompt additional questions ascertaining cancer type, date, and treatment. Individuals who indicated skin cancer and did not specify skin cancer of the melanoma type were classified as having NMSC. For the purposes of our study, we chose to examine only the NMSC type to clarify the specific protective effect suggested in past studies.[1,2]

Statistical analysis. Cox regression models using age as the time scale, with a time-dependent predictor variable NMSC status, were then used to test the association of NMSC diagnosis (yes/no) on risk of dementia (only AD, any AD, or all-cause dementia). Study participants were classified as either prevalent NMSC or no NMSC at baseline. For participants with prevalent NMSC, persons were considered at-risk from the date of study entry to the date of either the first dementia diagnosis or to the end of the participant's follow-up, whichever was earlier, and NMSC status was positive for the entire follow-up period. Participants who did not have NMSC at baseline and who did not develop NMSC during the course of the study were considered free of NMSC for the entire follow-up period. For participants who did not have NMSC at baseline, but who developed incident NMSC during the study follow-up period, the time-dependent predictor NMSC status was derived as follows: person-time participants were considered free of NMSC before diagnosis and were considered exposed subsequent to diagnosis until the date of dementia diagnosis or to the end of the participant's follow-up period, whichever was earlier. For example, a participant followed for 3 years before and 2 years after a diagnosis of NMSC would have had an NMSC-negative status for 3 years and an NMSC-positive status for 2 years.

Four different models were used for this analysis to correct for potential confounders. The first model included sex as a covariate. The second model included demographic factors (sex and education) as covariates. The third model included the demographic factors with the addition of occupation and also risk factors associated with VaD (history of hypertension, diabetes, and coronary heart disease). The fourth model included the demographic factors and also risk factors associated with AD and VaD (number of *APOE* ε4 alleles, history of hypertension, diabetes, and coronary heart disease); however, *APOE* data were available for only 769 individuals. Education is a continuous variable that indicates years of schooling. Comorbid medical conditions were self-reported based on yes or no questions. Because NMSC is very rare among African Americans,[10] this analysis was repeated using only white participants to eliminate a potential confounder. These analyses were then repeated with any diagnosis of cancer (all-cause) rather than NMSC as the primary predictor of interest.

RESULTS We followed 1,102 persons initially free of dementia for an average of 3.7 years and median of 3.0 years (maximum 15.5 years). At baseline, 109 of the 1,102 persons had a history of NMSC. Additionally, during the course of the study, 32 participants developed incident NMSC (table 1). Accordingly, these 141 individuals contributed a total of 509 NMSC-positive

Table 1 Demographic and neurocognitive profile of study participants by nonmelanoma skin cancer status at baseline and follow-up

	NMSC at baseline	Incident NMSC during follow-up	NMSC-free throughout follow-up
No.	109	32	961
Female, n (%)	59 (54.1)	17 (53.1)	593 (61.7)
White, n (%)	106 (97.3)	32 (100)	643 (66.9)
African American, n (%)	2 (1.8)	0	270 (28.1)
Other, n (%)	1 (0.9)	0	48 (5.0)
Age at baseline, y (SD)	79.4 (5.1)	78.0 (4.8)	78.9 (5.5)
Range, y	68.7–93.7	70.8–89.7	66.2–100.4
Mean follow-up before NMSC, y (SD)	NA	3.7 (2.0)	3.6 (2.5)
Mean follow-up after NMSC, y (SD), range	3.8 (2.5), 0.3–10.9	3.1 (1.9), 1.2–10.7	NA
Deaths, n (%)	26 (23.9)	8 (25)	311 (31.3)
Education at baseline, y (SD)	15.1 (3.3)	13.4 (4.2)	13.2 (3.5)
Range, y	8–21	5–20	2–24
Blessed score (max 33) (SD)	1.4 (1.5)	2.2 (2.2)	2.6 (2.4)
FCSRT (free recall, max 48) (SD)	31.7 (5.7)	31.7 (4.5)	30.3 (6.3)
FCSRT (total recall, max 48) (SD)	47.8 (0.8)	47.9 (0.4)	47.4 (2.7)
Boston Naming (max 15) (SD)	12.3 (2.4)	12.0 (2.8)	11.6 (2.7)
WAIS-III Info (max 28) (SD)	22.8 (5.3)	23.2 (5)	20.3 (5.8)
WAIS-III Vocab (max 66) (SD)	52.1 (12.8)	51.4 (12.1)	46.3 (13.6)
WAIS-III Digit span (max 30) (SD)	14.5 (3.6)	13.3 (3.2)	13.3 (3.6)
WAIS-III Digit symbol (max 133) (SD)	43.7 (11.4)	42.2 (12.9)	37.9 (13.7)
WAIS-III Block design (max 68) (SD)	24.2 (8.2)	21.6 (7.7)	20.1 (9.2)
VIQ (SD)	116.6 (16.9)	112.8 (14.3)	107.1 (15.5)
FAS (SD)	38.2 (12.8)	37.9 (12.7)	33.8 (12.8)
Trails A, s (SD)	52 (16.8)	55.9 (22.9)	69.2 (192.3)

Abbreviations: FAS = Controlled Oral Word Association Test; FCSRT = Free and Cued Selective Reminding Test; Info = Information; max = maximum; NA = not applicable; NMSC = nonmelanoma skin cancer; VIQ = Verbal IQ; Vocab = Vocabulary; WAIS = Wechsler Adult Intelligence Scale.

person-years to the NMSC history cohort, and 993 individuals contributed 3,543 NMSC-negative person-years to the cohort.

Comparison of baseline characteristics by NMSC status. Table 1 shows a comparison of the samples with NMSC at baseline, those with incident NMSC, and those who remained NMSC-free throughout follow-up. These 3 groups did not differ in sociodemographic characteristics other than race, as African Americans had far less skin cancer. There were, however, differences over a range of baseline cognitive assessments. These are only descriptive comparisons, and no formal statistical tests were performed, for nonsignificant differences between groups can still result in confounding. These differences were in global mental status (Blessed Information–Memory-Concentration Test,[11] which assesses memory, attention, concentration, and the ability to complete activities of daily living) as well as a range of neurocognitive instruments assessing memory, language, visuospatial, and executive functions: Free and Cued Selective Reminding Test[12]; Boston Naming Test[13]; FAS letter fluency[14]; and WAIS-III (Information, Vocabulary, Digit Span, Block Design, Digit Symbol, and Verbal IQ).[15]

Comparison of baseline characteristics by dementia status. During the course of the study, 958 people remained dementia-free throughout follow-up and 126 developed dementia, the all-cause dementia group. Of the incident dementia cases, 76 had only AD; 24 had mixed AD/VaD resulting in a total of 100 people with any AD. In addition, 26 subjects met criteria for dementia but did not have an AD diagnosis. The most common diagnoses in the other dementia group included VaD and frontotemporal dementia (table 2).

Development of a neurocognitive disorder as a function of NMSC status. All Cox regression models used in the analyses apply age as the time scale. The results of

Table 2 Baseline characteristics of study participants by dementia status at last follow-up

	Dementia-free	All-cause dementia[a]	Any AD	Only AD
No.	958	126	100	76
Female, n (%)	575 (60.0)	81 (64.3)	65 (65)	51 (67.1)
White, n (%)	684 (71.4)	85 (67.5)	67 (67)	48 (63.2)
African American, n (%)	231 (24.1)	36 (28.6)	29 (29)	24 (31.6)
Other, n (%)	43 (4.5)	5 (4.0)	4 (4)	4 (5.3)
Age, y (SD)	78.6 (5.4)	80.7 (5.4)	81.5 (5.4)	81.4 (5.6)
Range, y	66.2–100.4	70.0–97.0	70.7–97.5	70.7–96.2
Education, y (SD)	13.5 (3.5)	12.8 (3.6)	12.7 (3.6)	12.6 (3.7)
NMSC, n (%)	129 (13.4)	10 (7.9)	6 (6)	2 (2.6)

Abbreviations: AD = Alzheimer disease; NMSC = nonmelanoma skin cancer.
[a] The all-cause dementia subgroup consisted of 76 with only AD, 24 with mixed AD/vascular dementia, and 26 others (3 frontotemporal dementia, 18 vascular dementia, 5 dementia not otherwise specified).

model 1 (adjusting for sex), model 2 (adjusting for sex and education), model 3 (adjusting for demographic and vascular risk factors), and model 4 (adjusting for demographic and vascular risk factors and the number of APOE ε4 alleles) are shown in table 3. Model 3 demonstrates that NMSC showed reduced Alzheimer risk (hazard ratio [HR] for developing only AD was 0.21, p = 0.031) (figure). Only 2 individuals with NMSC developed only AD. There was a nonsignificant reduced risk of developing any AD, with an attenuated HR of 0.50 (p = 0.11). When considering the outcome of all-cause dementia, the apparent protective effect was further diminished (HR = 0.68, p = 0.24). When these analyses were repeated using only white participants, NMSC continued to be associated with a reduced risk of developing only AD, albeit with diminished statistical confidence (table e-1 on the *Neurology*® Web site at www.neurology.org). Model 4 shows a substantial but nonsignificant reduced risk of developing only AD (HR = 0.18, p = 0.094), any AD (HR = 0.60, p = 0. 35), and all-cause dementia (HR = 0.75, p = 0.50).

Development of a neurocognitive disorder as a function of cancer status. Model 3 shows that there was no significant effect for reduced risk of developing all-cause dementia (HR = 0.85, p = 0.44), any AD (HR = 0.74, p = 0.23), or only AD (HR = 0.69, p = 0.21) for history of any cancer (table 4). Model 4 shows a nonsignificant increase in the risk of developing all-cause dementia (HR = 1.30, p = 0.91), and a nonsignificant decrease in any AD (HR = 0.93, p = 0.90) and only AD (HR = −0.95, p = 0.90) for history of any cancer. When these analyses were repeated using only white participants, a similar trend was observed.

DISCUSSION This population-based longitudinal study shows that individuals older than 70 years with NMSC have a significantly reduced risk of developing AD compared with individuals free of NMSC. We deduce Alzheimer-specific neuroprotection, because the effect is attenuated or eliminated when considering inclusive outcomes such as all-cause dementia. Adjusting for hypertension, diabetes, and coronary heart disease did not significantly change the results. When adjusting for the number of APOE ε4 alleles, the magnitude of the HR is unchanged but statistical significance is lost, possibly because of reduced power.

Repeating the analysis for whites only also did not significantly change the results. Skin cancer is the most common cancer among whites; however, it represents a very small percentage of cancers for African Americans. Additionally, the incidence of skin cancer has been increasing for whites, but remains low among African Americans.[10]

This study focused solely on NMSC. Other studies have found an inverse association between cancer of any type and AD.[1,3] Our results showed nonsignificant trends and therefore can neither substantiate nor refute these findings. It is possible that the putative protective effect of cancer of any type suggested in some studies is driven primarily by the strong influence of NMSC, with its high prevalence in light-skinned populations. For example, in the Washington University study, no
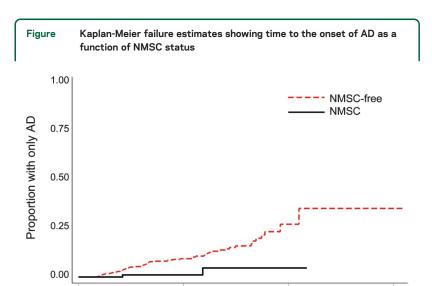
Table 3 Results of Cox proportional hazards models[a] testing time to diagnosis of dementia or AD as a function of history of nonmelanoma skin cancer in all participants (N = 1,134)

Type of dementia diagnosis end point	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
All-cause dementia	0.64	0.34–1.23	0.18	0.66	0.34–1.27	0.22	0.68	0.35–1.31	0.24	0.75	0.32–1.76	0.50
Any AD	0.47	0.21–1.09	0.077	0.49	0.21–1.13	0.096	0.50	0.22–1.17	0.11	0.60	0.21–1.72	0.35
Only AD	0.20	0.048–0.81	0.024	0.21	0.051–0.85	0.029	0.21	0.051–0.87	0.031	0.18	0.024–1.34	0.094

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio.
[a] All models used age as the time scale. Model 1 was adjusted for sex; model 2 was adjusted for sex and education; model 3 is model 2 plus occupation, hypertension, diabetes, and coronary heart disease (angina, myocardial infarction, coronary artery bypass); and model 4 is model 3 plus number of APOE ε4 alleles. Note that APOE data of only 769 individuals contributed to model 4.

Figure Kaplan-Meier failure estimates showing time to the onset of AD as a function of NMSC status

AD = Alzheimer disease; NMSC = nonmelanoma skin cancer.

participants with a history of skin cancer developed dementia during the follow-up period.[2]

Our study has also shown that participants with a history of NMSC perform better than NMSC-free participants on baseline cognitive assessments. This finding is consistent with previous research that has shown that one form of NMSC, basal cell carcinoma, is associated with higher socioeconomic status, income, and education. That study also showed that another form of NMSC, squamous cell carcinoma, is weakly associated with higher income, but not education.[16] Lower education is associated with reduced reporting of medical illness.[17] These baseline cognitive differences suggest that NMSC might be a marker for a factor or factors that protect against the development of AD. In the subset of the sample with no NMSC history at baseline and throughout follow-up, there may be an increased rate of persons with predementia AD. This would account for both the reduced mean performance and higher levels of variability in the NMSC-free subjects.

The apparent protective effect of NMSC has several possible explanations. Perhaps NMSC and reduced risk of AD are linked through a confounder such as education.[18] Better education encourages healthier lifestyle choices,[19] including more health checkups,[17] whereby the presence of cancer could be detected. After adjusting for education and occupation, the results remained robust. Other potential confounders include personality, psychosocial variables, and physical activity.[20,21] Physical activity is protective against cognitive decline and dementia.[18] Outdoor physical activity may lead to increased exposure to ultraviolet radiation, which increases skin cancer risk.[22]

It is also possible that the protective effect of NMSC is conferred by biological factors. None of the psychosocial factors discussed above are known to confer a risk reduction near the magnitude we report for NMSC. The protective effect is largest and most robust for the outcome of only AD, a diagnostic group likely to be enriched with Alzheimer biology and pathology. There are several plausible mechanisms. The relationship between cancer and AD may reflect differences in DNA methylation,[23] activity of the tumor suppressor gene *p53*, the enzyme Pin1, or the Wnt signaling pathway.[20] Additionally, NMSC-specific associations with AD can be attributed to mechanisms involving γ-secretase signaling[21,24,25] through a Notch 1 signaling pathway.[26,27]

This study has a number of limitations. First, NMSC diagnoses were identified based on self-report. While collecting cancer data, we did not specifically ask about NMSC; therefore, it is possible that a percentage of our NMSC cohort contains cases of melanoma that were misclassified. Because melanoma is not protective against AD, if this error occurred, it would cause us to underestimate our results. Self-reported cancer histories in the United States are generally accurate,[28,29] although their use in epidemiologic studies[30] has been challenged. In older adults, forgetting prior diagnoses is a possibility and differential forgetting in those who go on to develop AD is plausible. However, we excluded prevalent dementia from the inception cohort. If this

Table 4 Results of Cox proportional hazards models[a] testing time to diagnosis of dementia end point as a function of history of cancer in all participants (N = 1,134)

Type of dementia diagnosis end point	Model 1			Model 2			Model 3			Model 4		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
All-cause dementia	0.86	0.57–1.29	0.47	0.88	0.58–1.32	0.53	0.85	0.56–1.29	0.44	1.03	0.60–1.78	0.91
Any AD	0.75	0.47–1.21	0.24	0.77	0.48–1.25	0.30	0.74	0.45–1.21	0.23	0.93	0.50–1.73	0.82
Only AD	0.66	0.37–1.17	0.16	0.69	0.39–1.22	0.20	0.69	0.39–1.23	0.21	0.95	0.47–1.93	0.90

Abbreviations: AD = Alzheimer disease; CI = confidence interval; HR = hazard ratio.
[a] All models used age as the time scale. Model 1 was adjusted for sex; model 2 was adjusted for sex and education; model 3 is model 2 plus occupation, hypertension, diabetes, and coronary heart disease (angina, myocardial infarction, coronary artery bypass); model 4 is model 3 plus number of *APOE* ε4 alleles. Note that *APOE* data of only 769 individuals contributed to model 4.

effect occurs, it would again attenuate our findings. Diagnostic confirmation of NMSC is problematic because most state and national cancer registries do not track NMSC diagnoses. Future studies in this area should apply more rigorous ascertainment of NMSC status.

Second, we used date of study enrollment and not date of NMSC onset to start calculating person-time for risk of AD in persons who self-reported a history of NMSC at baseline. Although we did ask participants to report a date of diagnosis, such a date would be subject to recall bias, and the follow-up for the purpose of dementia outcomes began with study enrollment, so we elected not to use it. Because most of the NMSC-positive participants were prevalent for the disease, this decision probably served to attenuate our results. Third, we had limited genotype (*APOE* ε4 allele) data on our patients. This served to reduce power in model 4 and attenuated our results.

Fourth, this study utilized clinical neurocognitive diagnosis. Although clinical-neuropathologic correlation in EAS is excellent, some level of misclassification in dementia status is inevitable. This misclassification would be likely to attenuate the reported associations if anything. Lastly, the EAS exclusively studies individuals older than 70 years, and our results may not apply to other samples.

Our study also has a number of strengths. The EAS is a large, population-based, prospective study that uses well-established procedures to ascertain dementia outcomes and achieve excellent retention. Our findings meet several of the criteria for causation,[31] including strength, temporality, specificity, and plausibility. The present study has shown that persons who report a diagnosis of NMSC have a reduced risk of developing Alzheimer dementia. Further investigation is necessary to elucidate the biological and psychosocial basis for the reduced Alzheimer risk associated with NMSC.

AUTHOR CONTRIBUTIONS

R.S. White: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. R.B. Lipton: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. C.B. Hall: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. J.R. Steinerman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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