Synergistic Effect of β-Amyloid and Neurodegeneration on Cognitive Decline in Clinically Normal Individuals

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IMPORTANCE Assessing the ability of Alzheimer disease neuroimaging markers to predict short-term cognitive decline among clinically normal (CN) individuals is critical for upcoming secondary prevention trials using cognitive outcomes.

OBJECTIVE To determine whether neuroimaging markers of β-amyloid (Aβ) and neurodegeneration (ND) are independently or synergistically associated with longitudinal cognitive decline in CN individuals.

DESIGN, SETTING, AND PARTICIPANTS Academic medical center longitudinal natural history study among 166 CN individuals (median age, 74 years; 92 women).

MAIN OUTCOMES AND MEASURES The Aβ status was determined with Pittsburgh Compound B–positron emission tomography, while ND was assessed using 2 a priori measures, hippocampus volume (magnetic resonance imaging) and glucose metabolism (positron emission tomography with fludeoxyglucose F 18), extracted from Alzheimer disease–vulnerable regions. Based on imaging markers, CN individuals were categorized into the following preclinical Alzheimer disease stages: stage 0 (Aβ−/ND−), stage 1 (Aβ+/ND−), stage 2 (Aβ+/ND+), and suspected non-Alzheimer disease pathology (Aβ−/ND+). Cognition was assessed with a composite of neuropsychological tests administered annually.

RESULTS The Aβ+ CN individuals were more likely to be classified as ND+: 59.6% of Aβ+ CN individuals were ND+, whereas 31.9% of Aβ− CN individuals were ND− (odds ratio, 3.14; 95% CI, 1.44-7.02; P = .004). In assessing longitudinal cognitive performance, practice effects were evident in CN individuals negative for both Aβ and ND, whereas diminished practice effects were observed in CN individuals positive for either Aβ or ND. Decline over time was observed only in CN individuals positive for both Aβ and ND, and decline in this group was significantly greater than that in all other groups (P < .001 for all). A significant interaction term between Aβ and ND confirmed that this decline was greater than the additive contributions of Aβ and ND (P = .04).

CONCLUSIONS AND RELEVANCE The co-occurrence of Aβ and ND accelerates cognitive decline in CN individuals. Therefore, both factors are important to consider in upcoming secondary prevention trials targeting CN individuals at high risk for progression to the symptomatic stages of Alzheimer disease.
Accumulation of β-amyloid (Aβ) is thought to be a key feature of Alzheimer disease (AD). Furthermore, Aβ accumulation is found in many clinically normal (CN) older individuals, suggestive of a preclinical AD stage. Although some models suggest that neurodegeneration (ND) occurs downstream to initiating Aβ accumulation, the results of other studies suggest that pathways promoting Aβ and ND may initially occur independently.

Regardless of whether ND initially occurs downstream to or is independent of Aβ accumulation, the co-occurrence of these processes is associated with increased risk for functional progression to mild cognitive impairment and on the Clinical Dementia Rating Scale. It is possible that the convergence of 2 independent processes heightens risk in CN individuals, or Aβ may further accelerate downstream brain changes. However, it is unclear whether these markers have similar effects on cognitive decline during short follow-up periods. This question is of particular interest given upcoming secondary prevention trials that will use cognitive outcomes in assessing anti-Aβ therapies in high-risk CN individuals. A remaining question that may inform the mechanisms underlying cognitive decline is whether Aβ and ND are additive or synergistic: do Aβ+/ND+ CN individuals experience decline equal to the additive effects of each risk factor, or do Aβ+/ND+ CN individuals show decline greater than what is predicted by the contributions of each risk factor? If Aβ and ND are additive risk factors, then Aβ and ND likely have distinct influences that are merely superimposed in Aβ+/ND+ CN individuals. However, if Aβ and ND interact synergistically, then this would imply that their convergence is a key component of imminent cognitive decline.

Overall, the objective of the present study was to investigate the associations of Aβ and ND markers with each other and relative to cognitive decline during a short follow-up period. We also sought to determine whether these factors contribute independently or synergistically to cognitive decline in a group of well-characterized CN individuals participating in the Harvard Aging Brain Study.

Methods

Participants

Study protocols were approved by the Partners Healthcare Institutional Review Board, and all participants provided written informed consent. The Harvard Aging Brain Study participants undergo annual neuropsychological testing and multiple imaging sessions during their first year.

Participants were included if they had a score of less than 11 on the Geriatric Depression Scale at baseline, had a score of 0 on the Clinical Dementia Rating Scale, had a score of greater than 25 on the Mini-Mental State Examination, and performed within education-adjusted norms on the Logical Memory delayed recall (>10 for ≥16 years of education, >6 for 8-15 years of education, and >4 for <8 years of education), as well as completed 2 or more annual neuropsychological visits (among 166 participants, 41 completed 2 visits, 95 completed 3 visits, and 30 completed 4 visits). The median age of the participants was 74 years (interquartile range [IQR], 68-79 years), and their median educational level was 16 years (IQR, 14-18 years). Ninety-two participants (55.4%) were women. The global Pittsburgh Compound B (PiB) median standard uptake value ratio was 1.046 (IQR, 1.004-1.259), and the median baseline PiB imaging delay was 0.33 years (IQR, 0.23-0.49 years). The median follow-up period (the total time between the first and last neuropsychology testing visit) was 2.09 years (IQR, 1.90-2.31 years).

Structural Magnetic Resonance Imaging

Magnetic resonance imaging was performed at the Massachusetts General Hospital Athinoulia A. Martinos Center for Biomedical Imaging on a 3-T imaging system (TIM Trio; Siemens) with a 12-channel head coil. Structural T1-weighted volumetric magnetization–prepared rapid-acquisition gradient-echo images were collected (repetition time, echo time, and inversion time, respectively, 6400, 2.8, and 900 milliseconds; flip angle, 8°; and 1 × 1 × 1.2-mm resolution).

Region of interest (ROI) labeling was implemented using a software program (FreeSurfer version 5.1; http://surfer.nmr.mgh.harvard.edu/). The resulting whole-cerebellum ROI was used as the PiB reference region, whereas multiple cortical ROIs were used to derive a global Aβ value. Hippocampus volume (HV) was collapsed across hemispheres and adjusted for estimated total intracranial volume (eTIV) using the following equation:

Adjusted HV = Raw HV − b (eTIV − Mean eTIV),

where b indicates the regression coefficient when HV is regressed against eTIV. Total cortical gray matter volume was also adjusted by eTIV and used as a covariate in subsequent analyses.

PiB–Positron Emission Tomography

Pittsburgh Compound B–positron emission tomography (PET) was performed at the Massachusetts General Hospital PET facility. Carbon 11–PiB was synthesized using a previously published protocol, and imaging was performed using a PET system (ECAT EXACT HR+; Siemens). Before injection, 10-minute transmission images for attenuation correction were collected. After injection of 3.15 × 10⁸ to 5.55 × 10⁸ Bq of PiB, 60 minutes of dynamic data were acquired in 3-dimensional acquisition mode.

Determination of Aβ status is described elsewhere. In brief, PiB data were analyzed as standard uptake value ratios, and a gaussian mixture modeling approach was used to classify the Harvard Aging Brain Study CN individuals as Aβ+ or Aβ− (cutoff value, 1.196).

PET With Fludeoxyglucose F 18

The PET with fludeoxyglucose F 18 (FDG-PET) was performed at the Massachusetts General Hospital PET facility. Before injection, 10-minute transmission images for attenuation correction were collected. Intravenously, 1.85 × 10⁸ to 3.70 × 10⁸ Bq was injected, and after a 45-minute uptake period, FDG-PET images were acquired for 30 minutes in 3-dimensional acquisition mode.
The FDG-PET data were realigned, summed, and normalized to a template using a software program (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The FDG was extracted from a meta-ROI reflecting AD-vulnerable regions (lateral parietal, lateral inferior temporal, and posterior cingulate cortices) and was normalized by the mean from the top 50% of voxels from a pons-vermis reference region.14

Classification Into ND Groups
Determination of neurodegeneration status was based on adjusted HV and meta-ROI-FDG14 as described by investigators at the Mayo Clinic, Rochester, Minnesota.15 Clinically normal individuals were divided into ND+ and ND− groups based on cutoffs derived in Alzheimer’s Disease Neuroimaging Initiative patients with AD of 1.249 for meta-ROI–FDG and 6723 mm3 for adjusted HV (eMethods 1 and eFigures 1, 2, and 3 in the Supplement). Clinically normal individuals were considered ND− if they fell below either cutoff value.15

Classification Into Preclinical Stages
A National Institute on Aging-Alzheimer’s Association1 work was proposed a staging criteria for preclinical AD: stage 0 is defined as Aβ−/ND−, stage 1 is defined as Aβ+/ND−, and stage 2 is defined as Aβ+/ND+. The Aβ+/ND− CN individuals were initially not anticipated and were subsequently classified as having “suspected non-AD pathophysiology” (SNAP) by Jack and colleagues.15 Although multiple groups have implemented these staging criteria,7,9,15 differences among studies include derivation of Aβ cutoffs, markers of ND (cerebrospinal fluid t-tau and p-tau181), and the use of subtle cognitive decline as a categorization variable. Given our interest in determining the association between preclinical stages and cognition, we excluded subtle cognitive change as a categorizing variable.

Neuropsychological Testing
Given that previous work examining Aβ and longitudinal decline in CN individuals has revealed associations with global cognitive function,16-19 we examined a single global cognitive composite using the following 8 neuropsychological tests: (1) Logical Memory delayed recall20; (2) 6-Trial Selective Reminding Test delayed recall21; (3) Face-Name Associative Memory Exam cued recall of names22; (4) the number of words produced in 60 seconds for the letters f, a, and s24; (5) the number of words produced for animal, vegetable, and fruit categories25; (6) Trail Making Test A and B26; (7) Digit Symbol Substitution Test total27; and (8) Mini-Mental State Examination total.28 Measures were z score transformed based on the mean (SD) from baseline data and averaged.

Statistical Analysis
Analyses were performed using statistical software (R version 3.0; http://www.r-project.org/). Logistic regression was used to assess the associations between Aβ and ND status. Differences in demographics across preclinical stages were examined with Wilcoxon rank sum tests for continuous variables and χ2 tests for dichotomous variables.

Longitudinal cognitive change was examined with a hierarchical linear mixed regression modeling approach (eMethods 2 in the Supplement), with (1) inclusion of interactions of Aβ with time and ND status with time in the same model and (2) inclusion of interactions of Aβ with time and ND status with time along with their joint interaction with time. All models included a random intercept for each participant. In addition, we examined the pattern of cognitive change across preclinical groups (stage 0, stage 1, stage 2, and SNAP) and contrasted all pairwise combinations. All P values were 2-sided, and no multiple comparisons correction was performed.

All models controlled for age, sex, and educational level (as well as their interaction with time in linear mixed regression models). In addition, follow-up analyses controlled for total gray matter and APOE4 (dichotomized by the presence of an APOE4 allele). Four APOE4/2 individuals and 7 CN individuals who were not genotyped were excluded from analyses controlling for APOE4.

Results
Preclinical AD Stages
The Aβ+ CN individuals were more likely to be classified as ND+ compared with Aβ− CN individuals (59.6% of Aβ+ CN individuals were ND+, whereas 31.9% of Aβ− CN individuals were ND+ [P = .004]; odds ratio, 3.14; 95% CI, 1.44-7.02) (eFigure 4 in the Supplement). This association remained significant after controlling for total gray matter (P = .003) and APOE4 status (P = .01).

Stage 2 participants were older than stage 0 (P < .001) and stage 1 (P = .03) participants, whereas SNAP participants were older than stage 0 (P < .001) and stage 1 (P = .005) participants. The SNAP participants had a greater proportion of men compared with stage 0 (P = .04) and stage 2 (P = .01) participants. Finally, stage 1 participants had a higher proportion of APOE4 carriers than stage 0 (P = .002) and SNAP (P = .009) participants. Likewise, stage 2 participants had a higher proportion of APOE4 carriers than stage 0 (P < .001) and SNAP (P = .004) participants (Table 1).

Table 1. Clinically Normal Individuals Classified Into Preclinical Stages

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage 0 (n = 81)</th>
<th>Stage 1 (n = 19)</th>
<th>Stage 2 (n = 28)</th>
<th>SNAP (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>70 (67-76)</td>
<td>73 (69-77)</td>
<td>77 (73-82)</td>
<td>79 (75-82)</td>
</tr>
<tr>
<td>Educational level, median (IQR), y</td>
<td>17 (14-18)</td>
<td>16 (14-18)</td>
<td>16 (15-18)</td>
<td>16 (14-18)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>59.3</td>
<td>52.6</td>
<td>71.4</td>
<td>36.8</td>
</tr>
<tr>
<td>APOE4+, %</td>
<td>18.7</td>
<td>58.8</td>
<td>57.7</td>
<td>18.9</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; SNAP, suspected non-Alzheimer disease pathology.
Table 2. Decline Across Preclinical Groups

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Estimate (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAP vs stage 0</td>
<td>-0.069 (0.032)</td>
<td>.03</td>
</tr>
<tr>
<td>SNAP vs stage 1</td>
<td>-0.031 (0.041)</td>
<td>.44</td>
</tr>
<tr>
<td>Stage 1 vs stage 0</td>
<td>-0.038 (0.038)</td>
<td>.32</td>
</tr>
<tr>
<td>Stage 2 vs stage 0</td>
<td>-0.215 (0.032)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage 2 vs stage 1</td>
<td>-0.177 (0.042)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage 2 vs SNAP</td>
<td>0.146 (0.035)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trend test stage 0-2</td>
<td>-0.106 (0.015)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: SNAP, suspected non–Alzheimer disease pathology.

Figure. Cognitive Decline Across Preclinical Stages

Beta estimates from a linear mixed model examining decline across preclinical stages are plotted. Practice effects are observed in stage 0 and are diminished in stage 1 and suspected non–Alzheimer disease pathology (SNAP), whereas decline is observed in stage 2. Plotted lines extend to the maximum follow-up period of 3 years, while the median follow-up period across all participants was 2.09 years. Although there is a lower estimated baseline value in the SNAP group than in the other groups, this effect did not reach statistical significance (P = .44 for SNAP vs stage 0, P = .63 for SNAP vs stage 1, and P = .55 for SNAP vs stage 2). Stage 2 showed significantly greater decline over time than all other groups (P < .001 for all).

Contributions of Aβ and ND to Longitudinal Cognition

The Aβ status and ND status were independently associated with longitudinal cognitive change (P < .001 for both). An interaction term between Aβ and ND was added to this model and revealed a significant effect, such that Aβ+/ND− CN individuals showed decline greater than the additive contributions of Aβ and ND (P = .04) (eTable in the Supplement). This interaction term remained significant when also controlling for total gray matter (P = .03) and APOE4 status (P = .02). Examination of cognitive change across preclinical groups revealed a practice effect in stage 0 participants (Aβ+/ND−) and a diminished practice effect in stage 1 (Aβ+/ND+) and SNAP (Aβ+/ND+) participants. Decline was only observed in stage 2 participants (Aβ+/ND+), and this decline was significantly greater than that of all other groups (P < .001 for all) (Table 2 and Figure).

Associations With Subthreshold Aβ Levels

To determine whether subthreshold levels of Aβ were associated with ND status and cognitive change, we performed follow-up analyses in the Aβ+ group (stage 0 and SNAP participants combined). A logistic regression model predicting ND status revealed a trend-level association between continuous Aβ and ND status in Aβ+ CN individuals, such that higher levels of subthreshold Aβ were associated with greater odds of being ND+ (β = 6.89, P = .08). Likewise, a linear mixed model predicting cognitive change revealed a trend for greater cognitive change with higher levels of subthreshold Aβ (β = −0.40, P = .07) controlling for change related to ND status). This model revealed that an Aβ− CN individual with an Aβ index value of 1.025 (the median value of the Aβ+ group) had a positive slope of 0.10 z score units per year, whereas an Aβ+ CN individual with an Aβ index value of 1.19 (the maximum value in the Aβ+ group) had a positive slope of 0.04 z score units per year. Therefore, slightly elevated values in the Aβ+ group were associated with a reduced practice effect on repeat cognitive testing. The Aβ+ group (stage 1 and stage 2 combined) revealed no association between suprathreshold levels of Aβ and ND status (β = 1.07, P = .53) (eFigure 5 in the Supplement) or with cognition over time (β = −0.01, P = .95) (eFigure 6 in the Supplement).

Discussion

We found that Aβ+ CN individuals were more likely to be classified as ND+ than Aβ− CN individuals. Examination of cognitive change over time revealed that Aβ+/ND− CN individuals (stage 0) demonstrated improvement in cognition over time (suggestive of a practice effect), CN individuals positive for both Aβ or ND (stage 1 and SNAP) showed a diminished practice effect, and Aβ+/ND+ CN individuals (stage 2) demonstrated decline over time. Last, we found that levels of continuous Aβ in the Aβ+ group were associated with ND status and with cognitive change over time, suggesting that slightly elevated levels of subthreshold Aβ may provide a biologically meaningful signal.

Aβ+ CN Individuals More Likely to Be Classified as ND+

We identified an association between Aβ and ND, such that the odds of being classified as ND+ were 3 times greater for Aβ+ CN individuals compared with Aβ− CN individuals. This association is consistent with models suggesting that ND occurs downstream to Aβ+29,30 or that ND initially occurs independently but is accelerated by Aβ.11 Although some studies2,31-35 have identified a similar association in CN individuals, recent work has failed to identify an association between Aβ and ND markers.6,30,36,37 These inconsistencies suggest that the association between Aβ and ND status in CN individuals may be subtle and depend on the examined ND marker. It is also possible that other factors, such as age, APOE genotype, family history, and the length of time that a given individual has harbored Aβ burden, will influence this association. Large cohorts of CN individuals with known Aβ status and multiple ND markers will be essential to clarify the association between Aβ and ND in CN individuals.
Additional Factors Contributing to ND

Although a significant association between Aβ and ND status was present herein, 22.9% of our sample was classified as having SNAP (ND−) CN individuals who were Aβ−, a proportion similar to that in other CN cohorts.9,15,38 This group highlights that multiple factors likely contribute to ND markers.39-40 Additional non-AD pathologic contributors may be infarcts,41 Lewy bodies,41 or hippocampal sclerosis,42 all of which have been identified in CN individuals. Furthermore, a sizable subset of individuals with amnestic mild cognitive impairment demonstrates non-AD pathologic conditions affecting the medial temporal lobe,43 and associations between neuroimaging ND markers and non-AD pathologic conditions have been established.44 It is also possible that normal aging processes, such as synaptic alterations,45 contribute to the signal captured in neuroimaging markers of ND. Finally, subthreshold levels of Aβ accumulation may contribute to ND in CN individuals classified as Aβ−, which was supported by the trend-level association we identified between continuous levels of Aβ and ND status in Aβ− CN individuals. Overall, neuroimaging markers of ND are likely influenced by non-AD pathologic conditions, normal aging processes, and subthreshold levels of Aβ. Nevertheless, the association we identified between Aβ and ND status in the present analysis suggests that Aβ positivity is at least 1 risk factor for ND in CN individuals or is an accelerant of preexisting ND caused by non-Aβ processes.

Co-occurrence of Aβ and ND Promoting Cognitive Decline

We found that Aβ and ND synergistically contributed to cognitive change, suggesting that the co-occurrence of these processes accelerates decline in CN individuals. Notably, decline was present in Aβ+/ND− CN individuals, whereas all other groups (Aβ+/ND+, Aβ+/ND−, and Aβ−/ND−) showed improvement in performance over time, suggestive of practice effect, a pattern often reported in CN individuals.46 Overall, these findings extend the results from other groups that have demonstrated increased risk for functional decline in Aβ+/ND+ CN individuals5-8 by providing evidence that this risk is also reflected in early cognitive change. Our results are relevant for upcoming secondary prevention trials in that the effect of joint Aβ and ND status was observed during a short follow-up period using cognitive outcomes while controlling for effects related to age, sex, educational level, and APOE4 status.

Although the mechanism underlying this synergistic effect of Aβ and ND remains unclear, it is possible that ND renders neurons more susceptible to toxic effects of Aβ. Therefore, either process alone may be insufficient to affect cognition, but the double hit of both processes may result in cognitive decline by overwhelming compensatory processes. It is also possible that ND reflects underlying neurofibrillary tangles (NFTs),47-48 a pathologic condition that has specifically been shown to mediate toxic effects of Aβ.49 Furthermore, the spread of NFTs from medial temporal lobe regions to the neocortex may occur in conjunction with late-life Aβ accumulation,50 consistent with laboratory work suggesting that Aβ exacerbates NFT pathologic conditions.49 Therefore, although accumulation of Aβ and NFT may initially reflect separate processes, late-life Aβ may induce NFT spread, which in turn promotes cognitive decline.

Relevance of Subthreshold Aβ

The selection of Aβ cutoffs is somewhat arbitrary and inconsistent across laboratories. Although our modeling approach confirms the existence of a bimodal distribution for Aβ imaging data from CN individuals (reflecting Aβ− and Aβ+ groups),52 it remains unclear whether subthreshold variation in signal magnitude contains a biologically relevant signal. With the absence of a gold standard to determine whether such variation is relevant, we investigated associations between continuous Aβ and ND, as well as cognitive decline in the Aβ− group. Although only reaching trend-level significance, this analysis revealed that Aβ− CN individuals with slightly elevated Aβ values were more likely to be ND+ and show reduced practice effects over time (whereas no association with Aβ level was present in the Aβ+ group). This pattern suggests that subthreshold levels of Aβ may reflect biologically relevant signal, whereas variability in Aβ magnitude may be less informative after a certain threshold is reached. The results of these analyses suggest that our cutoff value may have been too conservative. However, it is likely that slightly elevated values within the Aβ− distribution represent CN individuals who have early Aβ deposition, as well as CN individuals with slightly elevated values due to methodologic issues (eg, greater white matter spillover, variation within the reference region). Examination of subthreshold levels of Aβ in conjunction with diminished practice effects may indicate which Aβ− CN individuals are most likely to have biologically relevant signal and be at risk for subsequent decline and further Aβ accumulation.4,51

Limitations

Our analyses have several limitations. The median follow-up period was short (2.09 years) and may explain the persistence of practice effects. However, diminished practice effects may be a meaningful marker of underlying disease processes in CN individuals. The present analysis only examined a global measure of cognition, and follow-up analyses will focus on whether measures within specific cognitive domains are more sensitive. We restricted our analyses to a priori markers of ND, which may not capture ND patterns that are most relevant to decline in CN individuals. Last, the Harvard Aging Brain Study participants were highly educated and recruited to participate in a memory study, both of which may bias our sample and limit the generalizability of our findings.

Relevance to Secondary Prevention Trials

Contributions of Aβ and ND to cognitive decline among CN individuals is increasingly relevant given upcoming secondary prevention trials. The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease trial52 will assess the efficacy of an anti-Aβ therapy on cognitive trajectories in Aβ− CN individuals followed up for 3 years. Although our findings suggest that it is relevant to account for ND among Aβ− participants, it is unclear whether anti-Aβ monotherapy may be most effective in Aβ− CN individuals with or without concurrent ND. If mechanisms underlying cognitive decline in CN individuals depend
on the co-occurrence of both Aβ and ND, then anti-Aβ therapy may be effective in CN individuals who are Aβ+/ND−, as well as in CN individuals who are Aβ+/ND+ who may eventually become ND+. However, if mechanisms are temporally uncoupled, such that Aβ accumulation initiates a cascade of ND processes that eventually impairs cognition, then anti-Aβ therapies may only be successful before the point when the ND process has taken hold.

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Author Contributions: Dr Mormino had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: All authors.

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