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Association of β-Amyloid Level, Clinical Progression, and Longitudinal Cognitive Change in Normal Older Individuals

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Abstract

Objective
To determine the effect of β-amyloid (Aβ) level on progression risk to mild cognitive impairment (MCI) or dementia and longitudinal cognitive change in cognitively normal (CN) older individuals.

Methods
All CN from the Australian Imaging Biomarkers and Lifestyle study with Aβ PET and ≥3 years follow-up were included (n = 534; age 72 ± 6 years; 27% Aβ positive; follow-up 5.3 ± 1.7 years). Aβ level was divided using the standardized 0–100 Centiloid scale: <15 CL negative, 15–25 CL uncertain, 26–50 CL moderate, 51–100 CL high, >100 CL very high, noting >25 CL approximates a positive scan. Cox proportional hazards analysis and linear mixed effect models were used to assess risk of progression and cognitive decline.

Results
Aβ levels in 63% were negative, 10% uncertain, 10% moderate, 14% high, and 3% very high. Fifty-seven (11%) progressed to MCI or dementia. Compared to negative Aβ, the hazard ratio for progression for moderate Aβ was 3.2 (95% confidence interval [CI] 1.3–7.6; p < 0.05), for high was 7.0 (95% CI 3.7–13.3; p < 0.001), and for very high was 11.4 (95% CI 5.1–25.8; p < 0.001). Decline in cognitive composite score was minimal in the moderate group (−0.02 SD/year, p = 0.05), while the high and very high declined substantially (high −0.08 SD/year, p < 0.001; very high −0.35 SD/year, p < 0.001).

Conclusion
The risk of MCI or dementia over 5 years in older CN is related to Aβ level on PET, 5% if negative vs 25% if positive but ranging from 12% if 26–50 CL to 28% if 51–100 CL and 50% if >100 CL. This information may be useful for dementia risk counseling and aid design of preclinical AD trials.


Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

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β-amyloid (Aβ) deposition begins decades prior to dementia due to Alzheimer disease (AD) and is an important predictor of mild cognitive impairment (MCI) or dementia in cognitively normal (CN) individuals. Preventative treatments should target this early stage of the disease and identifying those at highest risk of decline would allow faster clinical trials.

In most current clinical practice and research settings, Aβ PET scans are classified as positive or negative, but limited data suggest that the risk of progression is related to the level of Aβ in individuals with a positive scan.

The Centiloid (CL) scale was developed to standardize Aβ imaging measures and to aid the adoption of widely applicable thresholds for PET Aβ levels that correspond with histopathologic classification and correlate with prognosis. Zero CL corresponds to the mean scan measure of healthy young adults without Aβ deposition and 100 CL corresponds to the mean scan measure of patients with mild AD dementia. Twenty-five CL corresponds approximately with the discrimination between a positive vs a negative scan by an expert visual reader, and with most standardized uptake value ratio (SUVR) thresholds.

The objective of this study was to determine the effect of Aβ level expressed in CL on the progression risk to MCI or dementia in CN individuals. We further examined associations between Aβ burden and longitudinal change in cognition.

**Methods**

**Participants**

A total of 534 CN individuals from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study with at least 3 years of clinical follow-up after an Aβ PET scan were identified. They underwent a screening visit consisting of a clinical and neuropsychological assessment, APOE genotyping, and Aβ PET and MRI scans. Participants were followed longitudinally at approximately 18-month intervals. After each visit, a clinical panel reviewed the neuropsychological information of the participants blinded to all imaging findings and the participants were classified as CN or were diagnosed with MCI, AD, or other dementia. Diagnosis was based on standard clinical criteria for MCI and AD. Participants diagnosed with MCI or any type of dementia during the follow-up period were classified as progressors and participants not meeting any criteria for MCI or dementia were classified as clinically stable.

Genotyping of APOE was determined by direct sequencing at baseline. Participants with at least 1 APOE ε4 allele were classified as APOE ε4 carriers.

**Imaging Methods and Analysis**

Aβ PET imaging was conducted using Aβ tracers: 11C–Pittsburgh compound B (PiB), 18F-florbetapir, or 18F-flutemetamol. As described previously, PET acquisitions were performed 40–70 minutes post-tracer injection (PI) for 11C-PiB, 50–70 minutes PI for 18F-florbetapir, and 90–110 minutes PI for 18F-flutemetamol. PET images were not corrected for partial volume correction. All Aβ PET scans were quantified using CapAIBL and the Aβ level was expressed in CLs as described by Klunk et al. and Bourgeat et al. Aβ level was classified according to 5 categories: <15 CL negative, 15–25 CL uncertain, 26–50 CL moderate, 51–100 CL high, >100 CL very high. The category limits were chosen prior to data analysis based on published CL information. Notably, studies reporting CL findings in younger controls aged under 45 years give an average of 11 CL as the 2 SD upper limit above the mean of 0 CL, while postmortem correlation studies indicate

**Neuropsychological Evaluation**

All participants received the AIBL neuropsychological test battery as previously described in detail.

To assess cognitive performance longitudinally, 3 measures were used: Clinical Dementia Rating Sum of Boxes (CDR-SoB), California Verbal Learning Test II long delay free recall (CVLT-II LDFR), and a cognitive composite score called the AIBL–Preclinical AD Cognitive Composite (PACC). The AIBL-PACC is based on the ADCS-PACC derived by Donohue et al. and has been shown to be sensitive for deterioration in cognition in clinically normal older cohorts. The AIBL-PACC consists of the Mini-Mental State Examination, Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale, CVLT-II LDFR, and Logical Memory IIA subtest from the Wechsler Memory Scale. For each individual, the Z scores of each of the 4 test scores were mean averaged to give a PACC Z score.
Consortium to Establish a Registry for Alzheimer’s Disease (CERAD)—classified moderate neuritic plaque density may be found at 15 CL but usually is associated with >25 CL. Consequently, we set <15 CL as negative, 15–25 as uncertain, and then, to reflect categories that may be useful to a clinician for determining individual prognosis, divided the traditionally positive scans into the 3 categories of moderate, high, and very high.

3T MRI 3D magnetization-prepared rapid gradient echo was used to measure hippocampal volume (HV) corrected for whole brain volume. Using the HV of the AIBL CN and AD groups, the Youden Index was applied to determine optimal HV cutoff value for hippocampal atrophy (HA), yielding HA ≤ 2.74 cm³ for sensitivity 85%, specificity 86%.

### Statistical Analyses

Statistical analyses were performed using RStudio, version 3.5.3, with statistical significance at $p < 0.05$. Differences between the progressors and the clinically stable group were assessed with independent $t$ test for continuous data (age, years of education, and length of follow-up), $\chi^2$ testing for categorical data (sex, APOE $\varepsilon$4 status, and HA), and Fisher exact test (Aβ categories).

Cox proportional hazards analysis was used to examine the effect of the Aβ levels and other measures (age, sex, years of education, APOE $\varepsilon$4 status, low baseline memory performance, and HA) on clinical progression to MCI or dementia. The visit with the first PET scan was identified as the baseline visit and the event was classified as the progression to MCI or dementia. Survival was defined as the time between baseline and the event, or withdrawal, or the last available follow-up examination. We also analyzed the data truncated at the 4.5-year follow-up due to concern about the relatively small number of at risk Aβ-positive individuals beyond this point.

Linear mixed effects models were performed to examine the association between Aβ level and the longitudinal change in cognitive performance. Three models were created for the following variables: AIBL-PACC, CVLT-II LDFR, CDR-SoB. Time from baseline (years), Aβ level, and their interaction were included as fixed effects. Participant identification

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**Table 1** Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All (n = 534)</th>
<th>Progressors (n = 57)</th>
<th>Clinically stable (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 ± 6 (56–90)</td>
<td>74 ± 6 (62–88)</td>
<td>72 ± 6 (56–90)</td>
</tr>
<tr>
<td>Female</td>
<td>295 (55)</td>
<td>27 (47)</td>
<td>268 (56)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13 ± 3 (6–22)</td>
<td>13 ± 3 (6–22)</td>
<td>13 ± 3 (6–22)</td>
</tr>
<tr>
<td>Tested for APOE $\varepsilon$4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APOE $\varepsilon$4 carrier</td>
<td>140 (28)</td>
<td>30 (55)</td>
<td>110 (24)</td>
</tr>
<tr>
<td>Tested for memory impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory impairment$^d$</td>
<td>81 (15)</td>
<td>22 (39)</td>
<td>59 (12)</td>
</tr>
<tr>
<td>Tested for hippocampal atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal atrophy</td>
<td>88 (20)</td>
<td>19 (40)</td>
<td>69 (18)</td>
</tr>
<tr>
<td>β-amyloid level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>337 (63)</td>
<td>17 (30)</td>
<td>320 (67)$^c$</td>
</tr>
<tr>
<td>Uncertain</td>
<td>52 (10)</td>
<td>4 (7)</td>
<td>48 (11)</td>
</tr>
<tr>
<td>Moderate</td>
<td>51 (10)</td>
<td>6 (11)</td>
<td>45 (9)</td>
</tr>
<tr>
<td>High</td>
<td>76 (14)</td>
<td>21 (37)</td>
<td>55 (12)$^c$</td>
</tr>
<tr>
<td>Very high</td>
<td>18 (3)</td>
<td>9 (16)</td>
<td>9 (2)$^c$</td>
</tr>
<tr>
<td>Time to progression, y</td>
<td>3.6 ± 1.8 (1.4–7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of follow-up, y</td>
<td>5.3 ± 1.7 (2.7–8.0)</td>
<td>5.0 ± 1.7 (2.8–8.0)</td>
<td>5.4 ± 1.7 (2.7–8.0)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD (range) or n (% of column total).

Differences between progressors and cognitively stable participants were assessed using $^a$independent $t$ test $p < 0.05$, $^b$Pearson $\chi^2$ test $p < 0.01$, $^c$Fisher exact test $p < 0.01$. $^d$Defined by California Verbal Test II delayed free recall Z score as $\leq -1.0$. 
number (intercept) and time from baseline (slope) were included as random factors. Sex, age, years of education, and APOE e4 status were included as covariates. Data from 5 review cycles, approximately equivalent to baseline and 18 months, 36 months, 54 months, and 72 months follow-up, were included in each of the models.

Data Availability
Most baseline data are available on the AIBL subsection of the adni.loni.usc.edu website. Limited follow-up data are available at this site and access to all the data in this article can be requested through an application to the AIBL management committee.

Results
Baseline Findings
Demographic characteristics of the 534 CN participants are shown in tables 1 and 2. At baseline, the mean age was 72 ± 6 years, 55% were women, 28% were APOE e4 positive, and 27% were Aβ scan positive using a threshold of 25 CL. During the follow-up period of 5.3 ± 1.7 years, 57 participants (11%) progressed to MCI or dementia.

Age, APOE e4 status, baseline CVLT-II LDFR, and HA were significantly different between the progressors and clinically stable group (table 1). Aβ level (>50 CL) was more prevalent in the progressor group while Aβ level (<15 CL) was more prevalent in the stable group. HA was more prevalent in the progressor group (table 1).

Table 2 shows that the groups with greater Aβ burden were older and had a higher prevalence of APOE e4 and HA than the Aβ-negative group.

Aβ and Clinical Progression
We assessed the effect of the individual factors on clinical progression to MCI or dementia (table 3). By the 4.5-year follow-up time point, 79 (15%) of the stable participants had withdrawn. Their baseline demographics were no different from the whole cohort. In particular, the proportion in each CL

Table 2 Characteristics of Participants Based on Centiloid Group

<table>
<thead>
<tr>
<th></th>
<th>Negative (n = 337)</th>
<th>Uncertain (n = 52)</th>
<th>Moderate (n = 51)</th>
<th>High (n = 76)</th>
<th>Very high (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71 ± 6</td>
<td>72 ± 4</td>
<td>75 ± 6b</td>
<td>74 ± 6b</td>
<td>76 ± 6b</td>
</tr>
<tr>
<td>Female</td>
<td>191 (57)</td>
<td>25 (48)</td>
<td>26 (51)</td>
<td>44 (58)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13 ± 3</td>
<td>12 ± 3</td>
<td>12 ± 3</td>
<td>13 ± 3</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>Tested for memory</td>
<td>Negative (n = 336)</td>
<td>Uncertain (n = 52)</td>
<td>Moderate (n = 51)</td>
<td>High (n = 76)</td>
<td>Very high (n = 18)</td>
</tr>
<tr>
<td></td>
<td>43 (13)</td>
<td>9 (17)</td>
<td>13 (25)c</td>
<td>12 (16)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>AIBL-PACC</td>
<td>0.21 ± 0.83</td>
<td>0.28 ± 0.78</td>
<td>0.04 ± 1.02</td>
<td>−0.15 ± 0.92a</td>
<td>0.27 ± 1.07</td>
</tr>
<tr>
<td>Tested for APOE e4</td>
<td>Negative (n = 315)</td>
<td>Uncertain (n = 48)</td>
<td>Moderate (n = 50)</td>
<td>High (n = 74)</td>
<td>Very high (n = 17)</td>
</tr>
<tr>
<td></td>
<td>60 (19)</td>
<td>10 (21)</td>
<td>23 (46)c,d</td>
<td>35 (47)c,d</td>
<td>12 (71)c,e</td>
</tr>
<tr>
<td>Tested hippocampal volume</td>
<td>Negative (n = 277)</td>
<td>Uncertain (n = 42)</td>
<td>Moderate (n = 43)</td>
<td>High (n = 65)</td>
<td>Very high (n = 15)</td>
</tr>
<tr>
<td></td>
<td>43 (16)</td>
<td>10 (24)</td>
<td>11 (26)</td>
<td>18 (28)c</td>
<td>6 (40)a</td>
</tr>
</tbody>
</table>

Abbreviations: AIBL-PACC = Preclinical AD Cognitive Composite. Data are presented as mean ± SD or n (% of column total). Statistical differences (p < 0.05) between Centiloid groups were assessed using a independent t test compared to negative, b independent t test compared to uncertain, c Pearson χ2 test compared to negative, d Pearson χ2 test compared to uncertain, e Fisher exact test compared to negative. No other comparisons were significant.

f Defined by California Verbal Test II delayed free recall Z score as ≤−1.0.

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category was no different (64% negative, 8% uncertain, 10% moderate, 18% high, 0% very high). Beyond the 4.5-year time point, the number at risk in the Aβ-positive groups declined substantially (figure 1). Consequently, progression was assessed at 4.5 years as well as for the full data set. At 4.5 years, carriage of APOE ε4, HA, and positive Aβ scan were associated with significant increase in risk of clinical progression (table 3). Greatest risk was seen with high and very high Aβ levels (HR 5.2 and 8.1, respectively). An uncertain or moderate Aβ PET result did not affect the risk of clinical progression by 4.5 years (HR 1.3 and 0.9, respectively). With the full data set, age greater than 72 years, low baseline memory performance on the CVLT-II LDFR, and moderate Aβ level (26–50 CL) emerged as significant risks. The risk from APOE ε4 carriage was unchanged, the risk from HA declined, and the risk from high and very high Aβ level increased (table 3). Figure 1 illustrates that progression to MCI or dementia in the moderate Aβ level group occurred predominantly after 4.5 years of follow-up.

**Aβ and Cognitive Change**

With sex, age, years of education, and APOE ε4 status as covariates, compared to the negative CL group, the moderate, high, and very high groups showed decline in longitudinal cognitive performance on the AIBL-PACC (moderate −0.02 SD/year, p = 0.05; high −0.08 SD/year, p < 0.001; and very high −0.35 SD/year, p < 0.001) (figure 2). The same was observed for performance on the CVLT-II LDFR (moderate −0.02 SD/year, p = 0.03; high −0.1 SD/year, p < 0.05; and very high −0.24, p < 0.05). On the CDR-SoB, only the high and very high groups performed worse compared to the negative group (high −0.17/y and very high −0.38/y). Practice effects were observed for the negative group on the AIBL-PACC and CVLT-II LDFR (+0.18 SD/year and +0.04 SD/year, respectively). No other significant differences were observed between the groups.

**Discussion**

In this study, we showed that the level of Aβ deposition in the brain could identify CN people at risk for cognitive decline and clinical progression to MCI or dementia and better stratify that risk than binary classification of an Aβ PET scan as just positive or negative. The greatest cognitive decline and rate of clinical disease progression was seen in the participants with an Aβ level higher than 50 CL. Participants with a moderately positive scan of 26–50 CL showed little clinical progression until after 4.5 years of follow-up. We found that the prevalence of MCI or dementia with an average follow-up of 5.3 years was 5% if <15 CL, 7% if 16–25 CL, 12% if 26–50 CL, 28% if 51–100 CL, and 50% if >100 CL. This indicates that the level of Aβ provides important prognostic information.
We have previously reported this observation but only in patients with $^{11}$C-PiB PET quantified with SUVR using in-house–derived regions of interest. Consequently, the findings could not be easily translated into clinical practice. In the present larger study, we used the CL scale to allow inclusion of participants imaged with a variety of Aβ tracers ($^{11}$C-PiB in 44%, $^{18}$F-florbetapir in 27%, $^{18}$F-flutemetamol in 29%) and to stratify the level of Aβ into categories that can be replicated in any clinical or research PET site, purposes for which the CL method was developed.

The close match of our cohort characteristics, including age, prevalence of APOE e4, proportion with positive Aβ PET, and clinical progression rate in the Aβ-positive participants, with other longitudinal studies of older CN cohorts suggests that our findings are widely applicable. For example, in our cohort, the risk of progression to MCI or dementia over a mean of 5.3 years of follow-up was 25% in Aβ-positive CN when defined as >25 CL. This is consistent with progression rates for Aβ-positive CN in the Mayo Clinic Study of Aging (18% at 3.7 years), the Alzheimer’s Disease Neuroimaging Initiative (ADNI) (32% at 4 years), and the Harvard University Knight Alzheimer Disease Research Center (26% at 5 years), and the Harvard Aging Brain Study (20% at 3 years). Our study is unique in that it has demonstrated that the level of Aβ deposition in a positive Aβ scan provides additional prognostic information.

Our findings also have implications for preclinical AD therapeutic trials if slowing or halting cognitive decline is the proposed primary outcome measure. Suitable participants for such trials must be at high risk for detectable cognitive decline over the period of the study. Figure 2 suggests separation of the confidence limits that the groups with high or very high Aβ burden (i.e., >50 CL) have significantly declined compared to the Aβ-negative group on several cognitive measures within 3 years of follow-up. In contrast, those with a moderate Aβ burden declined much less compared to baseline performance, with minimal change and no increased risk of progression to MCI or dementia at 4.5 years (HR 0.9). This suggests that in a preclinical AD trial time frame of 3 to 4 years, therapeutic benefit may be better assessed in CN with <50 CL of Aβ by change in disease biomarkers rather than by slowing of cognitive decline.

In this study, we examined several measures known to be predictive of clinical progression in older CN adults. Low score on the baseline CVLT-II LDFR posed a moderate risk for clinical progression, though this may be a partly circular argument as low cognitive scores are a key component of a clinical diagnosis of MCI. As expected, APOE e4 carriage was associated with a 3-fold increase in risk of clinical progression. The effect of e4 may be indirect, as APOE e4 is associated with greater prevalence of AD and earlier disease onset so that at a given age, e4 carriers have more advanced disease and higher Aβ levels. We found no effect of sex on progression risk. Other studies suggest that AD is more prevalent in women and females have a greater risk of clinical progression from MCI to AD dementia. More research is needed on the effect of sex differences in the preclinical phase of the development of AD. HA predicts clinical progression to dementia and can discriminate patients with MCI from controls. In this study, the individuals with HA also had greater risk for progression. High and very high Aβ level had the

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largest HRs for progression of any of the factors examined, reaching 8.1 in the very high group and 11.4 in the full data set. The very high Aβ group had the highest prevalence of HA and APOE e4, both of which are consistent with longer disease duration and a more advanced preclinical stage of AD at the time of initial assessment.

We did not examine for interaction with other factors that may alter risk of disease progression in preclinical AD. This includes comparison to the ATN (Aβ, tau, neurodegeneration) classification scheme as tau measures were not available at baseline in this cohort. Previous analysis of longitudinal data from AIBL reported that rate of decline on cognitive test scores in CN with positive Aβ PET was greater in those who were APOE ε4 carriers but this was not found in ADNI or BioFINDER.

Extrapolation of our findings to an individual should be approached with caution. Aβ PET imaging of asymptomatic individuals other than for clinical trial screening is not recommended by the Society of Nuclear Medicine/Alzheimer’s Association Amyloid Imaging Task Force. Although we have demonstrated that risk of clinically significant decline in CN older individuals is strongly related to the degree of Aβ burden, the value of this prognostic information remains unclear in the absence of effective treatment. Although the CL method provides a standardized measure of brain Aβ burden, the results can differ slightly between laboratories due to factors such as PET camera make and model and local modifications to the standard CL method, some of which show tracer-dependent variance. Provided appropriate corrections have been made for modified methods, any residual variation between laboratories should not affect the conclusions of this study as they are based on groups with a broad range of CL. A limitation of all longitudinal studies is the withdrawal of participants over time. At 4.5 years, 15% of the stable cohort had withdrawn or not reached this time point. Their baseline demographics matched the entire cohort so this is unlikely to affect the study findings. The participant retention rate in this study compares well to other longitudinal studies.

The level of Aβ deposition is important for the prediction of progression to MCI or dementia. This study provides evidence that the currently used binary classification of positive or negative for the reporting of an Aβ scan is suboptimal for determination of prognosis in CN older individuals. Aβ level stratified by CL-defined groupings provides greater individual prognostic information and should assist design of therapeutic trials in preclinical AD.

Acknowledgment
The authors thank the participants who took part in the study as well as their families.

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Disclosure
L. van der Kall and T. Truong report no disclosures. S.C. Burnham reports a patent, “Method for detection of a neurologic disease,” issued to CSIRO. V. Doré, R.S. Mulligan, S. Bozinovski, and F. Lamb report no disclosures. P. Bourgeat reports a patent, “Method for detection of a neurologic disease,” issued to CSIRO. S. Schultz, Y.Y. Lim, S.M. Laws, D. Ames, C. Fowler, S.R. Rainey-Smith, and R.N. Martins report no disclosures. O. Salvador reports a patent, “Method for detection of a neurologic disease,” issued to CSIRO. J. Robertson reports no disclosures. P. Maruff is an employee of Cogstate Pty Ltd. C.L. Masters is a shareholder in Prana Biotechnology Ltd. V.L. Villemagne is supported by an NHMRC Senior Research Fellowship. C. Rowe is supported by an NHMRC Practitioner Fellowship (1140853) and has received research support from GE Healthcare, Avid Radiopharmaceuticals, and the National Health and Medical Research Council of Australia (1152623, 1132604, 1074130, 1011689). Go to Neurology.org/N for full disclosures.

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Appendix

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<tr>
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<th>Location</th>
<th>Contributions</th>
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</thead>
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<td>Designed and conceptualized study, analysed the data, drafted the manuscript</td>
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<tr>
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## References


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