Amyloid accumulation in Down syndrome measured with amyloid load

Matthew D. Zammit¹ | Charles M. Laymon² | Tobey J. Betthauser³ | Karly A. Cody³ | Dana L. Tudorascu⁴ | Davneet S. Minhas² | Marwan N. Sabbagh⁵ | Sterling C. Johnson³ | Shahid H. Zaman⁶ | Chester A. Mathis² | William E. Klunk⁷ | Benjamin L. Handen⁷ | Ann D. Cohen⁷ | Bradley T. Christian¹

¹University of Wisconsin-Madison, Waisman Center, Madison, Wisconsin
²Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania
³Alzheimer’s Disease Research Center, University of Wisconsin-Madison, Madison, Wisconsin
⁴Department of Internal Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania
⁵Cleveland Clinic Nevada, Las Vegas, Nevada
⁶Cambridge Intellectual Disability Research Group, University of Cambridge, Cambridge, UK
⁷Department of Psychiatry, University of Pittsburgh, Pittsburgh, Pennsylvania

Correspondence
Matthew D. Zammit, Waisman Brain Imaging Core, University of Wisconsin-Madison, 1500 Highland Avenue, Madison, WI 53705, USA. Email: mzammit@wisc.edu

Funding information
National Institute on Aging (NIA), Grant/Award Numbers: U01AG051406, R01AG031110; National Institute for Child Health and Human Development (NICHD), Grant/Award Number: U54HD090256

Abstract

Introduction: Individuals with Down syndrome (DS) show enhanced amyloid beta (Aβ) deposition in the brain. A new positron emission tomography (PET) index of amyloid load (AβL) was recently developed as an alternative to standardized uptake value ratios (SUVrs) to quantify Aβ burden with high sensitivity for detecting and tracking Aβ change.¹

Methods: AβL was calculated in a DS cohort (N = 169, mean age ± SD = 39.6 ± 8.7 years) using [C-11]Pittsburgh compound B (PiB) PET imaging. DS-specific PiB templates were created for Aβ carrying capacity (K) and non-specific binding (NS).

Results: The highest values of AβL carrying capacity were found in the striatum and precuneus. Longitudinal changes in AβL displayed less variability when compared to SUVrs.

Discussion: These results highlight the utility of AβL for characterizing Aβ deposition in DS. Rates of Aβ accumulation in DS were found to be similar to that observed in late-onset Alzheimer’s disease (AD; ≈3% to 4% per year), suggesting that AD progression in DS is of earlier onset but not accelerated.

KEYWORDS
Alzheimer’s disease, amyloid load, amyloid PET, Down syndrome, longitudinal, PiB

1 | INTRODUCTION

Amyloid β (Aβ) plaques are a pathological feature of Alzheimer’s disease (AD) and have been shown to precede symptoms of dementia by two decades.² Adults with Down syndrome (DS) are at increased risk for developing AD compared to the general population, with a sharp increase in prevalence after 50 years of age.³ An early presence of brain Aβ is evident in DS beginning as early as in adolescence with severe cortical prominence by age 40,⁴,⁵ which is several decades earlier than reported in late-onset AD.⁶ This stems from the triplication of chromosome 21, containing the gene encoding the production of the amyloid precursor protein and, the resulting increase in Aβ production.⁷,⁸ Similar to autosomal dominant AD (ADAD), the mechanism for AD pathophysiology in DS is likely more heavily influenced by Aβ overproduction than the failure of Aβ clearance mechanisms postulated for late-onset AD.⁹,¹⁰ Although the biological mechanisms

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2020 The Authors. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring published by Wiley Periodicals, Inc. on behalf of the Alzheimer’s Association.
underlying the disease differ, the structure of Aβ plaques between DS and late-onset AD are indistinguishable.11,12

Use of positron emission tomography (PET) with Aβ-targeting radioligands provides an in vivo assay of the spatial extent of Aβ deposition and can monitor Aβ progression during the course of AD.13 An early study using [C-11]Pittsburgh compound B (PiB) PET in non-demented DS demonstrated the feasibility of conducting scans in this population and reported elevated PiB retention as early as age 38, with earliest retention in the striatum.14 This striatum-first pattern of Aβ deposition was previously observed in presenilin-1 mutation carriers.15 Cross-sectional PET studies in DS with increased sample sizes revealed that positivity for Aβ was detectable as early as the late 30s, with cortical Aβ deposition showing consistency with the spatial pattern displayed in late-onset AD.16–27 In addition, a majority of DS individuals who were Aβ+ detected striatal Aβ retention,16,22 highlighting the striatum as a target region for early detection in this population.28 Longitudinal studies in non-demented DS revealed that participants converting from Aβ− to Aβ+ showed Aβ signal increases of ≈3% to 4% per year, with the striatum showing the earliest and most prominent change.29–31

Understanding the trajectory of Aβ accumulation in DS is a critical step toward characterizing the similarities and differences with the trajectory in late-onset AD. Accurate assessment for detecting these subtle changes in Aβ burden requires a quantitative metric that is representative of the concentration of Aβ protein. A common outcome measure for PET imaging of Aβ is the standardized uptake value ratio (SUVr), calculated as the quotient of the PET-measured signal from a target region and off-target region (eg, precuneus/cerebellum). For [C-11]PiB, SUVr has been validated as an accurate proxy for a more precise metric of distribution volume ratio (DVR).32 Both global and regional PiB SUVrs have been used to distinguish Aβ-positivity in preclinical AD,33 and demonstrated to detect increases in Aβ signal over time in DS.29,30 Although SUVr is used routinely to track changes in Aβ burden for longitudinal studies, it can be prone to high variability during assessment of longitudinal Aβ change,34,35 resulting in lower power to detect biological significance from the data.1

The metric of amyloid load (AβL) was developed as a global (ie, whole brain) outcome measure to reduce variability by utilizing template-based images of Aβ-specific and non-specific radioligand uptake.3 Proper voxel-based weighting of these images can then be used to provide a global estimate of AβL. Using model inputs of SUVr and canonical images of indexes for radioligand-specific (K) and non-specific (NS) binding,36 the AβL index shows reduced longitudinal variability by measuring only the SUVr signal corresponding to specific Aβ binding. A benefit to this method is that it can be fully implemented as a template-based approach. This allows for PET data processing without the need for magnetic resonance imaging (MRI) for spatial normalization,37–39 which is advantageous for populations prone to significant motion artifacts that negatively affect segmentation and registration.

The Alzheimer’s Biomarker Consortium—Down Syndrome (ABC-DS) is an ongoing study to characterize the natural history of AD-related biomarkers in individuals with DS. Aβ PET scans, using [C-11]PiB, have been acquired on participants from this study and reported in the literature using longitudinal data from legacy studies.39–31 The overall aim of this work is to assess and compare longitudinal Aβ change using AβL and SUVr in a large DS population. The algorithm for generating AβL was implemented as a template-based approach and modified for use in DS through inclusion of striatal Aβ deposition in DS by the University of Wisconsin-Madison Waisman

---

### RESEARCH IN CONTEXT

1. **Systematic review**: Longitudinal positron emission tomography (PET) studies in adults with Down syndrome (DS) have revealed elevated levels of brain amyloid beta (Aβ) at younger ages compared to the general population. The amyloid load index (AβL) serves as a metric for quantifying and tracking changes in Aβ with high sensitivity. However, AβL was evaluated in research studies of late-onset Alzheimer’s disease (AD) and has not been characterized in other populations.

2. **Interpretation**: Our findings in DS confirm the high sensitivity of AβL to detect Aβ change reported from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) data. The longitudinal rates of AβL change between late-onset AD and DS were similar, suggesting that AβL can be a standardized marker for drawing direct comparisons across populations.

3. **Future directions**: Future research should characterize AβL across different Aβ PET radioligands and populations. A direct comparison between AβL and other standardized methods of quantification (eg, Centiloids) should be explored to evaluate which metric is most sensitive to detect Aβ change.

---

### 2 | METHODS

#### 2.1 | Participants

The cohort of participants with DS (N = 169; 39.6 ± 8.7 years) was initially recruited through a project studying the natural history of Aβ deposition in DS by the University of Wisconsin-Madison Waisman
The first step in calculating the Aβ\(_L\) was determined from each subject’s SUVr image in MNI152 space utilizing published methods.\(^1\) Aβ\(_L\) is calculated from the SUVr image, the population-derived PIB template images of non-specific binding (NS) and carrying capacity (K), using the functional equation:

\[
SUV_{ri} = nsNS_{ri} + Aβ_{rL}K_{ri},
\]

where ns is the coefficient of non-specific binding used to weight the component of non-specific PIB signal (via the NS image) in the SUVr image. In its current form, Equation 2 represents an overdetermined system of linear equations, where Aβ\(_L\) and ns can be solved simultaneously using the linear least-squares method on the SUVr, NS, and K matrices. A single Aβ\(_L\) and ns are estimated for each subject across all of the voxels (i) in the images. These parameters can then be used to generate an SUVr\(_{fit}\) image for comparison with the measured SUVr. The residual difference between the SUVr and the SUVr\(_{fit}\) was calculated to evaluate how well the model estimated the SUVr based on the input parameters.

2.5 | Definition of Aβ\(_L\) cutoff for Aβ(+) 

Using sparse k-means clustering with resampling, regional and global cutoffs for Aβ(+) were established for PIB SUVr data in a control population and applied to DS data.\(^30,33\) The Aβ(+) cutoff for Aβ\(_L\) was determined by performing a linear regression between global PIB SUVr and Aβ\(_L\). The resulting fit was used to convert the global SUVr cutoff into a value of Aβ\(_L\).
2.6 Comparison of longitudinal $A\beta_L$ and SUVr change

For participants with longitudinal data ($n=68$), the percent change per year between imaging cycles for $A\beta_L$ was calculated. Similarly, percent change in global PiB SUVr per year was calculated for all participants using a DS-specific atlas. Mean rates of change were calculated and compared across $A\beta(-)$ and $A\beta(\pm)$ groups.

3 RESULTS

3.1 Parametric imaging of NS and K

The fit of the logistic growth model (Equation 1) to population-level global SUVr yielded fixed global values for $r$ ($\approx 0.21$ years$^{-1}$) and $T_{50}$ ($\approx 14.8$ years) as shown in Figure 1. When the growth model was applied to just striatal SUVr, the resulting parameters for $r$ and $T_{50}$ were identical to the global estimates. With these parameters for $r$ and $T_{50}$, the logistic growth model was applied at the voxel level for all participants, yielding theparametric images for NS and K (Figure 2). The highest values for carrying capacity were found in the striatum and precuneus (2.21 and 2.29 SUVr units, respectively). The image of NS was consistent with the known non-specific binding of PiB to white matter.

3.2 Quantification of $A\beta_L$

$A\beta_L$ showed a positive linear correlation (Pearson’s $r=0.97$; P value: .00001) with global PiB SUVr (Figure 3). There was no observable dependence of $ns$ (non-specific binding coefficient) on SUVr (Pearson’s $r=-0.01$; P value: .86). The quality of fit for SUVr$_{ns}$ was evaluated by assessing the percentage of voxels in the brain which satisfied $|SUVr—SUVr_{fit}| >0.3$, as described previously. Across 301 images, the mean percentage of voxels in the brain exceeding this threshold was $5.8\% \pm 4.2\%$, suggesting that the SUVr was well modeled by the algorithm. Of the poorly modeled voxels, $31.5\% \pm 6.95\%$ resided in high K regions, $30.0\% \pm 6.48\%$ resided in high NS regions (subcortical/cerebellar white matter), and $38.5\% \pm 9.20\%$ resided in low K/NS regions (low PiB-binding regions, cerebrospinal fluid [CSF] spaces). No correlation was observed between $A\beta_L$ and poorly modeled voxels in high K regions (Pearson’s $r=0.018$; P value: .76). However, a slight negative correlation was observed between $A\beta_L$ and poorly modeled voxels in high K regions (Pearson’s $r=0.018$; P value: .76). However, a slight negative correlation was observed between $A\beta_L$ and poorly modeled voxels in high K regions (Pearson’s $r=-0.026$; P value: .00001) and a slight positive correlation between $A\beta_L$ and low K/NS regions (Pearson’s $r=0.17$; P value: .01). When compared with age at the time of imaging, $A\beta_L$ showed cross-sectional increases with age at baseline as well as longitudinal increases over time within individuals that underwent multiple cycles of data collection (Figure 4).

3.3 Classification of $A\beta(\pm)$ based on $A\beta_L$

The $A\beta_L$ cutoff for $A\beta(\pm)$ determined through the linear regression of $A\beta_L$ and global PiB SUVr was calculated as 20.0%. Participants were classified as $A\beta(\pm)$ if their $A\beta_L$ exceeded this threshold. 27 participants were classified as $A\beta(\pm)$ at baseline while seven converted to $A\beta(\pm)$ during the study duration compared to 35 at baseline and 15 converting using a previously established regional ROI-based threshold (Table 2). Of our participants, 25% converted to $A\beta(\pm)$ between ages 35 and 49, 47% between ages 50 and 59, and 100% above age 60, which is consistent with the reported clinical disease conversion rates of 23%, 55%, and 75%-100% in DS for these respective age ranges. For the ROI-based threshold, the striatum was the first region to surpass the $A\beta(\pm)$ threshold for all but one participant.
3.4 | Assessment of longitudinal Aβ change in DS

Across all cycles of longitudinal data, the distribution of rates of change for $A\beta_L$ and global SUVr are shown in Figure 5. The mean rate of $A\beta_L$ change per year (with 95% confidence intervals [CIs]) was 0.60% [0.40, 0.80] in the $A\beta(-)$ group and 3.32% [2.72, 3.91] in the $A\beta(+)\text{ group}$. The mean rate of global SUVr change was 1.24% [0.80, 1.68] in the $A\beta(-)$ group and 3.23% [2.33, 4.14] in the $A\beta(+)\text{ group}$. These results show that the longitudinal variability is lower for $A\beta_L$ change compared to SUVr in the $A\beta(-)$ group. In addition, $A\beta_L$ shows similar increase to SUVr in the $A\beta(+)\text{ group}$. The results presented above illustrate the utility of the $A\beta_L$ index for tracking $A\beta$ burden in the DS population. Given inputs of typically measured SUVr and the canonical images of non-specific binding and carrying capacity, a global $A\beta_L$ was calculated that shows close agreement with global PiB SUVr determined from a subset of brain regions. The canonical images also revealed the precuneus and striatum to have the highest capacity to carry $A\beta$ in the DS brain (2.29 and 2.21 SUVr units, respectively), consistent with the pattern of $A\beta$ deposition observed in ADAD. The $A\beta_L$ model has not yet been evaluated in cases of ADAD, but would be insightful to compare the spread of $A\beta$ in forms of AD influenced by $A\beta$ overproduction. A direct comparison of carrying capacities between DS and ADAD with APP mutations may be useful to further classify the extent of $A\beta$ deposition in these regions. High $A\beta$ carrying capacities were observed in the parietal cortex (1.81) and anterior cingulate (1.68), while the frontal (1.35) and temporal cortices (1.02) had moderate carrying capacities. When the $A\beta_L$ index was characterized for the Alzheimer’s Disease Neuroimaging Initiative (ADNI) population, the regions with the highest $A\beta$ carrying capacities were the anterior cingulate and precuneus. The parietal cortex also displayed high carrying capacities, whereas the striatum, frontal, and temporal cortices displayed moderate carrying capacities. Compared to the ADNI data, our findings reveal that the spatial distribution of $A\beta$
and carrying capacities are very similar between DS and late-onset AD, with the exception of the striatum. This finding further highlights this region as a potential target of interest in the monitoring of the presence of early AD pathology in DS.

Estimating the trajectory of Aβ accumulation in DS at the population level using the logistic growth model yielded an uninhibited growth rate (r) of 0.21 years⁻¹ and a time point of half-maximal Aβ accumulation (T₅₀) of 14.8 years based on the global PiB SUVr images. As derived from the ADNI dataset, global values of r and T₅₀ were estimated as 0.20 years⁻¹ and 14.9 years, respectively. These findings indicate that even though the underlying mechanisms driving the production of Aβ and age at onset of PET-detectable deposition may differ, the rates of Aβ accumulation are indistinguishable between these populations. Furthermore, the findings from the ADNI data revealed no spatial heterogeneity in r and T₅₀ across brain regions, suggesting that an estimate of these parameters from a global composite ROI would be representative of the rate of Aβ accumulation in each of the individual regions. Based on these findings, we chose to estimate r and T₅₀ from a global composite ROI in the DS data rather than from each ROI individually. However, because early striatal Aβ accumulation is unique to DS, we applied the logistic growth model to the striatal SUVr from all DS participants to evaluate whether striatal r and T₅₀ differed from the global estimates. The estimated striatal values of r and T₅₀ were found to be identical to the global values, indicating that the only difference observed in the striatum is its higher carrying capacity, which leads to earlier detection by PET. One limitation to the estimate of the DS-specific Aβ growth curve was that individuals in the late stages of Aβ progression were underrepresented, mainly because participants were enrolled in the study as non-demented. As a result, there is higher uncertainty in the upper limit of the growth curve when estimated from the available population data (seen in Figure 1). To account for this, a sensitivity analysis was performed by varying the value of r within two standard deviations (SD) of the original estimate to encompass different limits of global Aβ carrying capacity, and then calculating values of AβL using these new parameters. We found that changing these limits had minimal influence (<2%) on the value of AβL, and when applied to the longitudinal data there was no change in variance between baseline and follow-up scans, affirming that our original estimates of these parameters were suitable for use in DS. In addition, the lower and upper limits of the Aβ growth curve from our original estimate were similar to those observed when evaluated in a late-onset AD study using [C-11]PiB.

This work has demonstrated that AβL can be derived from static PET images acquired from short scanning periods and can be implemented as a template-based approach without the need for an anatomical
CONCLUSION

Preclinical AD studies have implemented use of a wide variety of Aβ PET radioligands, each with different binding characteristics and variability in quantification methods, making direct comparisons between studies challenging. Thus, there is motivation to standardize the methods of Aβ quantification from PET imaging to allow for a more practical interpretation of results in the clinical setting. One current method of standardizing Aβ PET quantification is implementation of the Centiloid scale, in which PET signal (units of SUVr) is linearly scaled to anchors determined in young controls (−0 Centiloids) and “typical” AD patients (~100 Centiloids). The Centiloid methodology allows for a direct comparison between imaging studies regardless of the radioligand used, since uptake values of every radioligand can be converted to the same scale. Similar to the Centiloid scale, AβL would allow for direct comparisons between radioligands because the PET signal is scaled dependent on the Aβ burden relative to the total theoretical Aβ carrying capacity. The total Aβ carrying capacity can be derived for a population using any Aβ-specific radioligand, thus a conversion factor between AβL for different PET radioligands would not be necessary. Because the Centiloid values are derived directly from SUVr data without any additional processing to remove the non-specific signal, this method of quantification would suffer from the same longitudinal variability as observed with SUVr. Compared to Centiloids, AβL provides the advantage of being a standardized measure of Aβ burden that is less susceptible to non-specific binding signal in the images, so quantification is indicative of only Aβ-specific signal. Studies using multiple Aβ PET radioligands will be required to evaluate the differences in these two outcome measures.

5 | CONCLUSION

Using a fully template-based approach, AβL has been effectively modeled in DS from static [C-11]PiB PET scans. Furthermore, this template-based approach can make image acquisition and analysis in DS more feasible. At the cross-sectional level, AβL showed consistency with SUVr in evaluating global Aβ burden. However, given its global nature, AβL was not as sensitive to classify Aβ(+) cases compared to a ROI-based SUVr approach. In the longitudinal analysis, AβL showed reduced variability between scans compared to SUVr while displaying high sensitivity to detect Aβ change, suggesting AβL as a promising PET outcome measure for Aβ analysis.

**TABLE 2**  Number of participants converting to Aβ(+) at each imaging cycle classified with AβL and SUVr metrics

| AβL(+) Classification | Cycle 1 n = 169 | Cycle 2 n = 68 | Cycle 3 n = 50 | Cycle 4 n = 14 |
|-----------------------|----------------|----------------|----------------|----------------|
| AβL                  | 27             | 0              | 6              | 1              |
| ROI SUVr              | 35             | 6              | 7              | 2              |

For the ROI-based threshold, all but one participant converted to Aβ(+) in the striatum first.

MRI, allowing feasibility of use in DS. Compared to conventional SUVr analysis, AβL results were similar to SUVr when evaluated at the cross-sectional level but showed lower variability when evaluating longitudinal change in Aβ. However, for the purposes of determining Aβ(−) or Aβ(+) status, our results suggest that AβL is not as sensitive at classifying Aβ(+) cases compared to an ROI-based SUVr threshold in DS. Because the AβL index is derived from all Aβ-carrying voxels in the brain, it will have reduced sensitivity for detecting smaller focal increases in Aβ accumulation, such as those seen in the striatum. As the striatum contains fewer voxels than the cortical regions, the AβL will be more heavily influenced by the lower intensity cortical voxel values during the early stages of Aβ progression. If the objective is to identify the earliest evidence of regional Aβ accumulation, it may be more advantageous to focus on striatal SUVr, since this region was the first to show significant increase for all but one individual from our DS cohort. It is not fully understood why the striatum is the first to show elevated PiB binding in DS, but it is speculated that the signal observed is a result of large amounts of diffuse Aβ plaques in this region. However, further histopathological investigation is needed to better understand this phenomenon. For the outlying case, Aβ(+) was reached globally with the highest signal in the precuneus and very low signal in the striatum that did not increase across longitudinal scans.

Preclinical AD studies have implemented use of a wide variety of Aβ PET radioligands, each with different binding characteristics and variability in quantification methods, making direct comparisons between studies challenging. Thus, there is motivation to standardize the methods of Aβ quantification from PET imaging to allow for a more practical interpretation of results in the clinical setting. One current method of standardizing Aβ PET quantification is implementation of the Centiloid scale, in which PET signal (units of SUVr) is linearly scaled to anchors determined in young controls (~0 Centiloids) and “typical” AD patients (~100 Centiloids). The Centiloid methodology allows for a direct comparison between imaging studies regardless of the radioligand used, since uptake values of every radioligand can be converted to the same scale. Similar to the Centiloid scale, AβL would allow for direct comparisons between radioligands because the PET signal is scaled dependent on the Aβ burden relative to the total theoretical Aβ carrying capacity. The total Aβ carrying capacity can be derived for a population using any Aβ-specific radioligand, thus a conversion factor between AβL for different PET radioligands would not be necessary. Because the Centiloid values are derived directly from SUVr data without any additional processing to remove the non-specific signal, this method of quantification would suffer from the same longitudinal variability as observed with SUVr. Compared to Centiloids, AβL provides the advantage of being a standardized measure of Aβ burden that is less susceptible to non-specific binding signal in the images, so quantification is indicative of only Aβ-specific signal. Studies using multiple Aβ PET radioligands will be required to evaluate the differences in these two outcome measures.

**FIGURE 5** Distribution of longitudinal change in AβL and global PiB SUVr. Lower longitudinal variability is observed for AβL compared to SUVr for both Aβ(−) and Aβ(+) cases.
ACKNOWLEDGMENTS
ABC-DS: The Alzheimer’s Biomarkers Consortium—Down Syndrome (ABC-DS) project is a longitudinal study of cognition and blood-based, genetic and imaging biomarkers of Alzheimer’s disease. This study is funded by the National Institute on Aging (NIA) grants [U01AG051406, R01AG031110] and the National Institute for Child Health and Human Development (NICHD), grant [U54HD090256]. We thank the ABC-DS study participants and the ABC-DS research and support staff for their contributions to this study. We also thank Alex Whittington for insightful discussions on the implementation and use of the amyloid load index.

This manuscript has been reviewed by ABC-DS investigators for scientific content and consistency of data interpretation with previous ABC-DS study publications. We acknowledge the ABC-DS study participants and the ABC-DS research and support staff for their contributions to this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health (NIH).

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

REFERENCES
1. Whittington A, Gunn RN. Amyloid Load—a more sensitive biomarker for amyloid imaging. J Nucl Med. 2018;60(4):536-540.
2. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer’s disease: a prospective cohort study. Lancet Neurol. 2013;12(4):357-367.
3. Schupf N. Genetic and host factors for dementia in Down’s syndrome. Br J Psychiatry. 2002;180(5):405-410.
4. Mann DMA. Alzheimer’s disease and Down’s syndrome. Histopathology. 1988;13:125-137.
5. Wisniewski KE, Wisniewski HM, Wen GY. Occurrence of neuropathological changes and dementia of Alzheimer’s disease in Down’s syndrome. Ann Neurol. 1985;17:278-282.
6. Jack CR, Lowe VJ, Weigand SD, et al. PET Imaging of Tau Pathology and Relationship to Amyloid, Longitudinal MRI, and Cognitive Change in Down Syndrome: Results from the Down Syndrome Biomarker Initiative (DSBI) pilot: proof of concept for deep phenotyping of Alzheimer’s disease biomarkers in down syndrome. Front Behav Neurosci. 2015;9:239.
7. Cohen AD, McCabe E, Christian B, et al. Early striatal amyloid deposition distinguishes Down syndrome and autosomal dominant Alzheimer’s disease from late-onset amyloid deposition. Alzheimers Dement. 2015;11:994-1004.
8. Lao PJ, Handen BL, Betthauser TJ, et al. Imaging neurodegeneration in Down syndrome: brain templates for amyloid burden and tissue segmentation. Brain Imaging Behav. 2019;13(2):345-353.
9. Raffi M, Wishnek H, Brewer J, et al. The down syndrome biomarker initiative (DSBI) pilot: proof of concept for deep phenotyping of Alzheimer’s disease biomarkers in down syndrome. Front Behav Neurosci. 2009;13:1255-1365.
10. Oyama F, Cairns NJ, Shimada H, Oyama R, Titani K, Ihara Y. Down’s syndrome: Up-regulation of β-amyloid protein precursor and α mRNAs and their defective coordination. J Neurochem. 1994;62:1062-1066.
11. Rumble B, Retallack R, Hilbich C, et al. Amyloid A4 protein and its precursor in down’s syndrome and Alzheimer’s disease. N Engl J Med. 1989;320:1446-1452.
12. Tellier JK, Russo C, Debusk LM, et al. Presence of soluble amyloid β- peptide precedes amyloid plaque formation in Down’s syndrome. FEBS Lett. 1997:409:411-416.
13. Ellis WG, McCulloch JR, Corley CL. Presenile dementia in down’s syndrome: Ultrastructural identity with alzheimer’s disease. Neurology 1974;24:101-106.
14. Obara PT. Electron microscopical study of the brain in down’s syndrome. Brain. 1972:95:681-684.
15. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer’s disease with Pittsburgh Compound-B. Ann Neurol. 2004;55:306-319.
16. Handen BL, Cohen AD, Channamalappa U, et al. Imaging brain amyloid in nondonedated young adults with Down syndrome using Pittsburgh compound B. Alzheimers Dement. 2012;8:496-501.
17. Klunk WE, Price JC, Mathis CA, et al. Amyloid Deposition Begins In the Striatum of Presenilin-1 Mutation Carriers from Two Unrelated Pedigrees. J Neurosci. 2007;27:6174-6184.
18. Anns T, Wilson LR, Hong YT, et al. The pattern of amyloid accumulation in the brains of adults with Down syndrome. Alzheimers Dement. 2016;12:538-545.
19. Cole JH, Anns T, Wilson LR, et al. Brain-predicted age in Down syndrome is associated with beta amyloid deposition and cognitive decline. Neurobiol Aging. 2017;56:41-49.
20. Hartley SL, Handen BL, Devenny DA, et al. Cognitive functioning in relation to brain amyloid-β in healthy adults with Down syndrome. Brain 2014;137:2556-2563.
21. Jennings D, Seibyl J, Sabbagh M, et al. Age dependence of brain β-amyloid deposition in Down syndrome. Neurology 2015;84:500.
22. Landt J, O’Driscoll JC, Holland AJ, et al. Using Positron Emission Tomography and Carbon 11–Labeled Pittsburgh Compound B to Image Brain Fibrillar β-Amyloid in Adults With Down Syndrome: Safety, Acceptability, and Feasibility. Arch Neurol. 2011;68:890-896.
23. Lao PJ, Handen BL, Betthauser TJ, et al. Imaging neurodegeneration in Down syndrome: brain templates for amyloid burden and tissue segmentation. Brain Imaging Behav. 2019;13(2):345-353.
24. Lao PJ, Betthauser TJ, Hillmer AT, et al. The effects of normal aging on amyloid-β deposition in nondonedated adults with Down syndrome as imaged by carbon 11–labeled Pittsburgh compound B. Alzheimers Dement. 2016:12:380-390.
25. Mak E, Bickerton A, Padilla C, et al. Longitudinal trajectories of amyloid deposition, cortical thickness, and tau in Down syndrome: A deep-phenotyping case report. Alzheimers Dement Diagn Assess Dis Monit. 2019;11:654-658.
26. Matthews DC, Lukic AS, Andrews RD, et al. Dissociation of Down syndrome and Alzheimer’s disease effects with imaging. Alzheimers Dement Transl Res Clin Interv. 2016;2:69-81.
27. Raffi M, Wishnek H, Brewer J, et al. The down syndrome biomarker initiative (DSBI) pilot: proof of concept for deep phenotyping of Alzheimer’s disease biomarkers in down syndrome. Front Behav Neurosci. 2015;9:239.
28. Cohen AD, McCabe E, Christian B, et al. Early striatal amyloid deposition distinguishes Down syndrome and autosomal dominant Alzheimer’s disease from late-onset amyloid deposition. Alzheimers Dement. 2015;11:994-1004.
29. Lao PJ, Handen BL, Betthauser TJ, et al. Longitudinal changes in amyloid positron emission tomography and volumetric magnetic resonance imaging in the nondonedated Down syndrome population. Alzheimers Dement Diagn Assess Dis Monit. 2017;9:1-9.
30. Raffi M, Lukic AS, Andrews RD, et al. PET Imaging of Amyloid, Longitudinal MRI, and Cognitive Change in Down Syndrome: Results from the Down Syndrome Biomarker Initiative (DSBI). Alzheimers Dis. 2017;60:439-450.
31. Sabbagh MN, Chen K, Rogers J, et al. Florbetapir PET, FDG PET, and MRI in Down syndrome individuals with and without Alzheimer’s dementia. Alzheimers Dement. 2015;11:994-1004.
32. Cohen AD, McCade E, Christian B, et al. Early striatal amyloid deposition distinguishes Down syndrome and autosomal dominant Alzheimer’s disease from late-onset amyloid deposition. Alzheimers Dement. 2018;14:743-750.
33. Lopresti BJ, Klunk WE, Mathis CA, et al. Simplified Quantification of Pittsburgh Compound B Amyloid Imaging PET Studies: A Comparative Analysis. J Nucl Med. 2005;46:1959-1972.
33. Cohen AD, Mowrey W, Weissfeld LA, et al. Classification of amyloid-positivity in controls: Comparison of visual read and quantitative approaches. NeuroImage. 2013;71:207-215.
34. Landau SM, Fero A, Baker SL, et al. Measurement of Longitudinal \( \beta \)-Amyloid Change with 18F-Florbetapir PET and Standardized Uptake Value Ratios. J Nucl Med. 2015;56:567-574.
35. Trypouts V, DiBernardo A, Samtani M, et al. Optimizing Regions-of-Interest Composites for Capturing Treatment Effects on Brain Amyloid in Clinical Trials. J Alzheimer's Dis. 2015;43:809-821.
36. Whittington A, Sharp DJ, Gunn RN. Spatiotemporal Distribution of \( \beta \)-Amyloid in Alzheimer Disease Is the Result of Heterogeneous Regional Carrying Capacities. J Nucl Med. 2018;59:822-827.
37. Della Rosa PA, Cerami C, Gallivanone F, et al. A Standardized [18F]-FDG-PET Template for Spatial Normalization in Statistical Parametric Mapping of Dementia. Neuroinformatics. 2014;12:575-593.
38. Friston KJ, Ashburner J, Frith CD, Poline J-B, Heather JD, Frackowiak RSJ. Spatial registration and normalization of images. Hum Brain Mapp. 1995;3:165-189.
39. Meyer JH, Gunn RN, Myers R, Grasby PM. Assessment of Spatial Normalization of PET Ligand Images Using Ligand-Specific Templates. NeuroImage. 1999;9:545-553.
40. Jack CR, Wiste HJ, Lesnick TG, et al. Brain \( \beta \)-amyloid load approaches a plateau. Neurology. 2013;80:890-896.
41. Strydom A, Coppus A, Blesa R, et al. Alzheimer’s disease in Down syndrome: An overlooked population for prevention trials. Alzheimers Dement Transl Res Clin Interv. 2018;4:703-713.
42. Morris JC, Aisen PS, Bateman RJ, et al. Developing an international network for Alzheimer research: The Dominantly Inherited Alzheimer Network. Clin Investig. 2012;2:975-984.
43. Villemagne VL, Ataka S, Mizuno T, et al. High Striatal Amyloid \( \beta \)-Peptide Deposition Across Different Autosomal Alzheimer Disease Mutation Types. Arch Neurol. 2009;66(12):1537-1544.
44. Abrahamson EE, Head E, Lott IT, et al. Neuropathological correlates of amyloid PET imaging in Down syndrome. Dev Neurobiol. 2019;79:750-766.
45. Klink WE, Koepp RA, Price JC, et al. The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET. Alzheimers Dement. 2015;11:1-15.e4.
46. Su Y, Flores S, Hornbeck RC, et al. Utilizing the Centiloid scale in cross-sectional and longitudinal PIB PET studies. Neuroimage Clin. 2018;19:406-16.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Zammit MD, Laymon CM, Betthauser TJ, et al. Amyloid accumulation in Down syndrome measured with amyloid load. Alzheimer’s Dement. 2020;12:e12020.
https://doi.org/10.1002/dad2.12020