Published in final edited form as:
Alzheimers Dement. 2011 March ; 7(2): 133–141. doi:10.1016/j.jalz.2010.08.230.

Transforming CSF Aβ42 measures into calculated Pittsburgh Compound B (PIBcalc) units of brain Aβ amyloid

Stephen D. Weigand, M.S.[1a], **Prashanthi Vemuri, Ph.D.**[1b], **Heather J. Wiste, B.A.**[1a], **Matthew L. Senjem, M.S.**[1b], **Vernon S. Pankratz, Ph.D.**[1a], **Paul S. Aisen, M.D.**[2], **Michael W. Weiner, M.D.**[3], **Ronald C. Petersen, M.D., Ph.D.**[1c], **Leslie M. Shaw, Ph.D.**[4], **John Q. Trojanowski, M.D., Ph.D.**[4], **David S. Knopman, M.D.**[1c], **Clifford R. Jack Jr., M.D.**[1b], and **Alzheimer's Disease Neuroimaging Initiative***

[1a]Division of Biomedical Statistics and Informatics, Mayo Clinic and Foundation, Rochester, MN

[1b]Department of Radiology, Mayo Clinic and Foundation, Rochester, MN

[1c]Department of Neurology, Mayo Clinic and Foundation, Rochester, MN

[2]Department of Neurosciences, University of California-San Diego, La Jolla, CA, USA

[3]Veterans Affairs and University of California, San Francisco, CA, USA

[4]Department of Pathology and Laboratory Medicine, and Institute on Aging, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Abstract

Background—PIB PET and CSF Aβ42 demonstrate a highly significant inverse correlation. Both are presumed to measure brain Aβ amyloid load. Our objectives were to develop a method to transform CSF Aβ42 measures into calculated PIB measures (PIBcalc) of Aβ amyloid load, and to partially validate the method in an independent sample of subjects.

Methods—Forty-one ADNI subjects underwent PIB PET imaging and lumbar puncture (LP) at the same time. This sample, referred to as the "training" sample (9 cognitively normal (CN), 22 MCI, and 10 AD), was used to develop a regression model by which CSF Aβ42 (with APOE ε4 genotype as a covariate) was transformed into units of PIB PET (PIBcalc). An independent "supporting" sample of 362 (105 CN, 164 MCI, 93AD) ADNI subjects who underwent LP but not PIB PET imaging had their CSF Aβ42 values converted to PIBcalc. These values were compared to the overall PIB PET distribution found in the ADNI subjects (n = 102).

Results—A linear regression model demonstrates good prediction of actual PIB PET from CSF Aβ42 measures obtained in the training sample (R^2 = 0.77, P<0.001). PIBcalc data (derived from CSF Aβ42) in the supporting sample of 362 ADNI subjects who underwent LP but not PIB PET imaging demonstrates group-wise distributions that are highly consistent with the larger ADNI PIB PET distribution and with published PIB PET imaging studies.

Conclusion—Although the precise parameters of this model are specific for the ADNI sample, we conclude that CSF Aβ42 can be transformed into calculated PIB (PIBcalc) measures of Aβ

Corresponding author: Clifford R. Jack, Jr., M.D., Department of Radiology, Mayo Clinic and Foundation, Rochester, MN, 55905, USA. Jack.Clifford@mayo.edu.
ADNI investigators include (complete listing available at (www.loni.ucla.edu\ADNI\Collaboration\ADNI_Manuscript_Citations.pdf).

amyloid load. Brain Aβ amyloid load can be ascertained at baseline in therapeutic or observational studies by either CSF or amyloid PET imaging and the data can be pooled using well-established multiple imputation techniques that account for the uncertainty in a CSF-based calculated PIB value.

Keywords

Alzheimer's disease; Pittsburgh Compound B; amyloid imaging; Aβ amyloid; cerebrospinal fluid; Alzheimer's disease biomarkers

1. Introduction

CSF Aβ42 and amyloid PET imaging with Pittsburgh Compound B (PIB) demonstrate a highly significant inverse correlation which has been faithfully replicated in each independent sample in which this correlation has been assessed [1-7]. Both techniques are presumed to measure brain Aβ amyloid load [8-14] (referred to from here on as Aβ load) which is an important disease feature that must be ascertained in individual subjects for many therapeutic and observational studies. However, in some circumstances it may not be possible to measure Aβ load in all subjects in a study by a single method. Our objective was to develop a method to transform CSF Aβ42 measures into calculated PIB measures (PIBcalc) of Aβ load, to partially validate the method in an independent sample of subjects, and illustrate how PIB PET and PIBcalc measures could be pooled in a statistical analysis.

2. Methods

2.1 Subjects

Criteria and methods to characterize ADNI subjects into diagnostic groups can be found in Petersen et al [15]. A total of 102 Alzheimer's Disease Neuroimaging Initiative (ADNI) subjects had usable PIB PET imaging data, and a subset of 41 of these subjects underwent both PIB PET and lumbar puncture (LP) at their 12-month visit. This subset, referred to as the “training” sample, consisted of individuals with the following clinical diagnoses: 9 cognitively normal (CN), 22 Mild Cognitive Impairment (MCI), and 10 Alzheimer's disease (AD). PIB PET and CSF Aβ42 data from these subjects was used to develop a linear regression model by which CSF Aβ42 (with APOE ε4 genotype as a covariate) was transformed into a unitless ratio customarily used in PIB PET imaging (referred to as PIBcalc). Although more ADNI subjects were available who underwent both PIB PET and LP at some time in the study, we included only the 41 subjects with LP and usable PIB PET studies obtained at the 12-month visit in the training sample.

A second sample of 362 (105 CN, 164 MCI, 93 AD) ADNI subjects underwent LP but not PIB PET imaging. We labeled these subjects the “supporting” data set. CSF Aβ42 in these subjects was transformed into PIBcalc units of brain Aβ load and evaluated for consistency with the PIB PET distribution found in ADNI subjects who had usable PIB PET imaging (n = 102). Figure 1 shows a flow chart summarizing the subjects whose data were included in this analysis.

2.2 Amyloid imaging methods

ADNI PIB PET studies were performed at 13 different sites. Production of PIB and radio labeling with ^{11}C was performed as outlined in Mathis et al [16]. The ADNI PIB PET images undergo several quality control and standardization steps. The PIB PET images used in our study were the “maximally pre processed files” available for download.

All PIB PET quantitative image analysis was performed at the Mayo Clinic using a fully automated image processing pipeline described in Senjem et al [17] and Jack et al [18]. The method includes partial volume correction and region of interest (ROI) sharpening of PIB PET images using each subject's spatially registered MRI. Statistics on image voxel values were extracted from automatically labeled cortical ROI's using an in-house modification of the automated anatomic labeling (AAL) atlas [19]. A global cortical PIB retention summary measure was formed by combining the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus ROI values for each subject, using a weighted average of these ROI values where larger ROIs were given greater weight. PIB PET ratio images were calculated by dividing the median value among all voxels in each target cortical ROI by the median value among all voxels in the cerebellar grey matter ROI of the atlas.

2.3 CSF methods

CSF was collected at each site, transferred into polypropylene transfer tubes followed by freezing on dry ice within 1 hr after collection and shipped overnight to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center (UPMC) on dry ice. A standardized protocol was implemented to quantify biomarker concentrations in each of the CSF ADNI baseline aliquots using a multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3, Ghent, Belgium; for research use only reagents) immunoassay kit-based reagents which was validated in Vanderstichele et al [20] and Shaw et al [21]. Quality control values obtained during the analyses of ADNI baseline CSF aliquots were: inter-day reproducibilities (%CV) for an AD CSF pool and a routine clinic patient CSF pool of 3.3% and 6.9% for $A\beta_{1\text{-}42}$ and R^2 values for comparison of retested samples were 0.90 [20,21].

2.4 Method to transform CSF Aβ42 measures into PIBcalc units

The training sample of 41 ADNI subjects consisted of those who underwent PIB PET imaging and LP at 12 months. We used least squares regression to estimate the relationship between cortical-to-cerebellar PIB PET ratio (y) on the $\log_2$ scale and CSF Aβ42 (x) on the $\log_2$ scale. While the base of the logarithm does not affect our results, we chose the base 2 logarithm to aid interpretation since it mapped the median PIB PET value of approximately 2.1 to a value 1.1 on the $\log_2$ scale. A log transformation was applied to both CSF42 and PIB values in order to reduce skewness that exists in both the distributions. This also increases the linearity between PIB PET and CSF Aβ42 and gives us access to a regression methodology that enables us to formulate a simple linear equation with symmetric Gaussian errors to estimate a complex inverse relationship between PIB and CSF. We note that the resulting model is a “linearized” version of a non-linear model that is essentially of the form $y = a/x^b$. Such an inverse model is biologically sensible in that as less and less Aβ42 is found in CSF, more and more amyloid is presumed to be deposited in the brain.

We assessed the linearity of the regression relationship by modeling x as a restricted cubic spline with 3 knots (2 d.f.) We evaluated whether the model fit could be improved by considering age, sex, education, and APOE ε4 carrier status as covariates. We used leave-one-out cross-validation (LOOCV) and the bootstrap to assess model performance and evaluate the out-of-sample performance of the model.

We assessed agreement between PIB PET and PIBcalc using the Bland-Altman approach [22]. We describe in the Appendix how the conversion model can be used to pool PIB PET and CSF Aβ42 in a statistical analysis by using multiple imputation to impute a calculated PIB PET value based on a subject's CSF Aβ42 value [23,24].

We note that we considered the commonly used cerebellar-to-cortical PIB PET ratio, as described above, to be the gold standard estimate of brain Aβ load and CSF Aβ42 to be a surrogate measured with error. For this and other reasons described in the discussion, we chose to transform CSF Aβ42 into PIB PET units. However, performing the transformation in the reverse direction is equally valid.

3. Results

Table 1 summarizes the characteristics of the subjects in the training sample. Panel (a) in Figure 2 shows the relationship between PIB PET ratio on the *y*-axis vs. CSF Aβ42 on the *x*-axis in the training sample ($n = 41$). The data illustrate the expected non-linear inverse relationship which becomes approximately linear when plotted on the $\log_2$ scale (panel b). The covariates age ($P = 0.32$), gender ($P = 0.68$), and years of education ($P = 0.66$) did not account for a significant amount of variability in PIB PET on the $\log_2$ scale. On the other hand, APOE ε4 carrier status was highly significant ($P = 0.004$), increasing R^2 from 0.71 to 0.77, and reducing the residual standard error from 0.20 to 0.18. The interaction between $\log_2$(CSF Aβ42) and APOE ε4 carrier status was not significant ($P = 0.81$). Given APOE ε4 carrier status in the model, there was no evidence of nonlinearity in the CSF measure ($P = 0.54$ for a restricted cubic spline model vs. a linear model.) The final "conversion model" was therefore $y^* = \log_2(y) = 5.326 - 0.615 \log_2(x) + 0.184(z) + e$, where z is 0 if the subject carries no APOE ε4 alleles and 1 if the subject is an ε4 carrier and e is a random error term that is normally distributed with mean 0 and SD 0.180, the residual standard error/RMSE from the fit.

Figure 2c shows the relationship between observed $\log_2$(PIB PET) on the *x*-axis and the corresponding predicted values (also on the $\log_2$ scale) on the *y*-axis. For 8 subjects we show error bars representing 95% prediction intervals of PIBcalc from CSF Aβ42. These error bars represent the uncertainty in individual point estimates of PIBcalc from CSF Aβ42. While Figure 2c shows good agreement between observed and predicted values on the $\log_2$ scale, it also reinforces the idea that there is uncertainty in an individual subject's predicted PIB PET value when using CSF.

To obtain the PIBcalc value for a subject given their CSF Aβ42 and APOE genotype, one calculates the predicted value y^* and then anti-logs the result to obtain PIBcalc = 2^{y^*}. The Bland-Altman plot in Figure 2d summarizes the agreement between PIB PET and PIBcalc for subjects in the training sample and provides an estimate of how different an imaging-based Aβ load value will be from a CSF based value. With an average difference near zero, there appears to be no bias in the CSF-based PIBcalc estimate over the range of PIB PET values. The Bland-Altman limits of agreement were ± 0.48.

The R^2 value for the conversion model was found to be 0.77, indicating that approximately 77% of the variability in $\log_2$ (PIB PET) values in the training sample can be explained by $\log_2$ (CSF Aβ42) and APOE ε4 status. The adjusted R^2 which adjusts for the number of parameters being estimated was 0.76. The residual standard error/root mean squared error (RMSE) for the conversion model was estimated to be 0.180. Based on leave-one-out cross-validation, the residual standard error estimate was 0.185, suggesting little bias in the model's error estimates. The bootstrap method with 1000 replicates suggested there was very little, if any, bias in the conversion model's coefficient estimates and that model-based standard errors were not too small. Based on the percentile bootstrap, the estimate (95% CI) for the residual standard error was 0.187 (0.138 to 0.206).

A PIB PET ratio value of 1.5 is commonly used as the cutoff to separate positive from negative PIB PET studies [8,11,25-27]. Figure 3a shows group-wise box plots comparing

the ADNI distribution of PIB PET (n = 102, consisting of the 41 subject training sample plus an additional 61 ADNI subjects who had PIB PET (Table 2) vs. CSF-based PIBcalc values in the supporting sample of 362 ADNI subjects who underwent LP but not PIB PET imaging (Table 3). The median PIB PET values by clinical group (CN, MCI and AD) in the PIB PET ADNI sample (n = 102) were nearly identical to the PIBcalc values in the ADNI CSF supporting sample (n = 362). The median CN PIBcalc value is < 1.5 while the median AD PIBcalc value is > 2. The median MCI PIBcalc value lies between CN and AD. Based on a cutoff of 1.5 which equals 0.58 on the $\log_2$ scale in Figure 3a, 45% of CN were abnormal, 80% of MCI, and 94% of AD were abnormal for PIBcalc. This compares to percentages of 45%, 66%, and 89% in the ADNI PIB PET distribution. The area under the receiver operating characteristic (AUROC) curve for distinguishing CN from AD subjects was 0.85 (95% CI 0.79 to 0.90) for PIBcalc in the supporting sample and 0.84 (0.73, 0.96) for PIB PET in the ADNI PIB PET sample.

Figure 3b shows kernel density estimates of the ADNI PIB PET vs. the PIBcalc distribution. These can be thought of as smoothed histograms which estimate the underlying probability distribution of the data. In this figure the similarity of the PIB PET and PIBcalc distributions is evident with both distributions showing the bimodality resulting from the particular composition of the ADNI sample. The AUROC for comparing the two distributions was 0.52 ($P = 0.49$), suggesting that there are no systematic differences between the distributions.

4. Discussion

Brain Aβ load can be measured either by CSF Aβ42 or PET amyloid imaging. It is increasingly evident that obtaining estimates of brain Aβ load is necessary for many types of research studies in aging and dementia. Some would argue, for example, that brain Aβ load must be established in all subjects for inclusion in anti-amyloid therapeutic trials. In addition, establishing the presence of Aβ amyloid will likely be an important feature of future revised criteria for AD at all clinical stages. However, in some circumstances it may not be possible to measure Aβ load in all subjects in a study by a single method. This could be due to non-availability of amyloid PET imaging or the expense associated with performing amyloid PET imaging in large numbers of subjects. Some subjects may be unwilling to undergo an LP or may have contraindications to LP, such as use of anticoagulants. In these circumstances we believe that pooling CSF Aβ42 and amyloid PET imaging measures is preferable to the alternative which is to exclude subjects in whom one or the other method of ascertaining brain Aβ load is not available. Transforming CSF Aβ into PIBcalc units enables pooling measures across subjects who have brain Aβ load measured by either CSF or PET imaging.

Justification for our approach is the consistently observed tight inverse correlation between PIB PET and CSF Aβ42 measures [1-5,7]. Although both CSF Aβ42 and PIB PET measures change over time, both do so slowly [7,28-32]. Therefore at a fixed point in time, for any given subject CSF Aβ42 should mirror PIB PET and vice versa.

We chose to transform CSF Aβ42 into unitless PIB PET ratio values (rather than the reverse) for several reasons. PET amyloid imaging provides an image of the pathology in the brain and may therefore have slightly greater “face validity” as a gold standard measure of brain Aβ load compared to CSF Aβ42. PET amyloid imaging can also more easily be standardized across different centers by the common practice of referencing cortical retention to a subject specific standard (cerebellar retention). This is not the case with CSF Aβ42 where absolute units are a function of the specific assay used. Finally, we recognize that PIB PET has regional information and region specific transformations of PIB PET into

CSF Aβ42 units might provide useful information. However, most of the PIB PET literature to date has focused on global summary measures of PIB retention [8,11,18,26]. The value of regional information available from PIB PET seems to be less for example than regional information in other modalities such as MRI or FDG PET. If desired, however, the methods described here can be used to create a region-specific conversion model. With the reverse transform in mind however we did explore the feasibility of converting PIB PET to a CSF-based Aβ load measure informally and this appeared to also work well. A more formal comparison of the advantages and disadvantages of transforming in one direction or the other would require a larger independent sample of subjects with PIB PET and LP.

There are three aspects of generalizability issue that are relevant. First, there is technical generalizability. We recognize that the specific equation for our CSF Aβ42 to PIBcalc conversion model was derived from CSF samples processed on the Luminex platform [21] and the precise equation might differ for CSF analyzed with different platforms. A different equation might be obtained using a different PIB PET image analysis method and ^{18}F amyloid PET ligands may not produce the same conversion model that ^{11}C PIB PET does. Second is patient/subject generalizability. We emphasize that the method applies to ADNI and “ADNI-like” subjects and that for other populations a new conversion model would likely need to be developed. A third aspect is method generalizability. Our objective was not to exhaustively analyze the relationship between PIB PET and CSF Aβ42 under all possible circumstances but to develop an approach for combining these two measurement methods. The apparent success of this method given a relatively small training set suggests that these two measurement methods could be combined in future studies with different imaging or assay parameters with the need to calibrate the two measurements on a relatively small subset of the study population.

Establishing the correct temporal order in which AD biomarkers become abnormal as the disease progresses has been identified as an important research goal [33,34]. A key question is which biomarker of brain Aβ load becomes abnormal first, CSF Aβ42 or amyloid PET imaging? Our purpose here was not to detract from this important research question but rather to propose a practical solution to the situation where pooling measures of brain Aβ load ascertained by different methods is beneficial (or perhaps necessary) to accomplish the scientific aims of a study.

A CSF Aβ42 value of 192 pg/ml was initially derived from an autopsy verified sample as an appropriate cut point denoting an abnormal CSF Aβ42 level [21]. This 192 pg/ml has been used as the normal/abnormal CSF Aβ42 cut point in ADNI [21]. A commonly used analogous cut point in the PIB PET literature denoting positive from negative PIB PET studies is 1.5. With our transformation method a CSF Aβ42 value of 192 pg/ml corresponds closely to a PIBcalc value of 1.5. The equivalence in cut points using our method to transform CSF Aβ42 into units of PIBcalc supports the validity of this approach. The Bland-Altman plot (Figure 2c) illustrates that there are no systematic differences between the two measurement methods. While the limits of agreement of ± 0.48 are probably too wide for the two methods to be considered clinically interchangeable for a given patient, the two methods can be considered statistically equivalent at the study level.

The PIBcalc data (derived from CSF) in our supporting (n = 362) sample are consistent with those reported for PIB PET imaging studies [8,11,18,25-27,35-37]. The median CN retention ratio was < 1.5 while the median AD ratio was > 2. The MCI ratio lies between CN and AD. Taking a PIBcalc value of 1.5 as a cutoff denoting an abnormal PIB value, 87/93 (94%) AD subjects, 132/164 (80%) MCI subjects, and 47/105 (45%) CN subjects fall into the abnormal range. Perhaps the most compelling independent evidence of the data transformation method validation however comes from comparing group-wise values of

PIBcalc in the supporting sample (n = 362) with PIB PET values in the ADNI PIB PET cohort (n = 102). These 464 (102 + 362) subjects were all drawn from the same ADNI sample. As illustrated in Figure 3 both the group-wise Aβ load distributions and also the density plots were essentially identical when measured by PIB PET vs PIBcalc (CSF Aβ42). In addition, the AUROC curves for distinguishing CN from AD subjects were nearly identical for PIB PET in the ADNI PIB PET sample and for PIBcalc in the supporting sample. This equivalent diagnostic performance across two different sets of subjects drawn from the same sample lends validity to the measurement transformation method.

We acknowledge that our supporting sample ideally would have consisted of subjects who underwent both PIB PET and LP, and which was independent of the sample used to train the conversion algorithm. This would have permitted evaluating PIBcalc values (calculated from CSF) directly against actual PIB PET imaging values acquired at the same time in the supporting sample. Unfortunately, the number of subjects in ADNI who underwent LP and PIB PET at the same time was too small (n = 41) to permit splitting the group into independent training and test samples. While acknowledging that the training sample was small we would like to emphasize that the multiple imputation measurement error (MIME) method which we describe fully in the Appendix deals with the sample size in a principled manner by accounting for model-estimation uncertainty. With greater recruitment of subjects undergoing both LP and amyloid PET imaging into ADNI this will be possible in the future, and may be possible now in some non-ADNI samples [38,39].

When Aβ load in PIBcalc units is derived from CSF, a proper statistical analysis must take into account the uncertainty underlying the conversion process. This uncertainty can be considered as coming from two sources. First, there is uncertainty in the conversion model regression equation and residual standard error estimate since a different training sample would provide different, albeit similar, parameter estimates. Second, because of subject-level factors, intrinsic measurement error, and other sources of unexplained variation, there is uncertainty about how far from the regression line a subject's true PIB PET value would be. This uncertainty illustrated by the prediction interval error bars in Figure 2c. We explain in the Appendix how to propagate these sources of uncertainty through the analysis stage using the approach of measurement error multiple imputation (MIME) [23]. In the MIME framework, the unavailability of PIB PET in some subjects (i.e., those with CSF Aβ42 and no PIB PET scan) is treated as a missing data problem and the statistical technique of multiple imputation is used to first impute a set of plausible PIB PET values given the subject's CSF and APOE genotype and second to analyze the data in a manner that accounts for the imputation process. The essential idea is that standard errors of model estimates from an analysis that pools PIB PET and CSF Aβ42 need to be adjusted to reflect the uncertainty in the conversion model.

In summary, our data supports the conclusion that CSF Aβ42 can be successfully transformed into calculated PIB (PIBcalc) measures of Aβ load. We emphasize that the exact parameters of the conversion model are specific to the ADNI study sample and the CSF platform and amyloid PET imaging methods employed. The method however is generalzable in that the approach to calibrating CSF to PIB PET can be applied under a variety of study conditions and study populations provided a validation subsample of moderate size (i.e., a training sample) is available. Therapeutic or observational studies can be performed with brain Aβ load measured by either CSF Aβ42 or amyloid PET imaging at baseline and the data can be pooled across subjects using well-established multiple imputation techniques that account for the uncertainty in a CSF-based calculated PIB value. We advocate this approach in clinical trials *only* for baseline inclusion/exclusion and subject stratification purposes. Anti-amyloid treatment may affect the relationship between CSF Aβ42 and PIB PET in unknown ways and until this is established, we would not recommend

pooling CSF Aβ42 and PIB PET data for purposes of measuring therapeutic Aβ load reduction [40].

Acknowledgments

The Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation, U.S.A and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer's Disease Research Program of the Mayo Foundation, U.S.A. Denise Reyes and Samantha Wille, Manuscript preparation.

Funding

This work was supported by the National Institute on Aging (P50 AG16574, U01 AG06786, R01 AG11378, and AG024904) and National Institute of Health Construction Grant (NIH C06 RR018898)

Appendix

The multiple imputation measurement error (MIME) approach can be used to pool PIB PET and CSF Aβ42 by following these steps [23]. A) Randomly draw a value for the residual standard error/root mean square error from a scaled inverse chi-squared distribution [41]. This can be done by drawing a chi-squared random variate with 41-3 = 38 degrees of freedom. Denoting this variate by v, the simulated residual standard error value is $s^* = 0.180 \times (38/v)^{1/2}$ where 0.180 is the residual standard error from the conversion model. B) If we let V be the unscaled variance-covariance matrix of the conversion model, generate a set of 3 model coefficients from a multivariate normal distribution centered at the observed parameter estimates (5.326, − 0.615, 0.183) and having covariance matrix $s^* \times V$. In our conversion model, the rows of V were [7.518, − 1.004, − 0.3299], [−1.004, 0.1349, 0.0376], and [−0.3299, 0.0376, 0.1081]. C) For each subject calculate an estimated Aβ load value based on the subject's observed CSF Aβ42 value and the conversion model parameter estimates from step B. D) To each of the values obtained in step C, add the random error component e, where e is drawn from a normal distribution with mean zero and SD s^* from step A. These steps are repeated m times to obtain m multiple imputation data sets. Cole et al [23] recommends setting m upwards of 40. That the regression equation coefficients and the error term are drawn from a distribution of values is illustrated in the Appendix Figure.

For a simple example, assume the desired analysis using the pooled PIB PET and CSF Aβ42 values is a regression of performance on a cognitive test (y) versus Aβ load (x). The analyst would perform this regression for each imputation data set and obtains m slope coefficients and m SEs. Using the multiple imputation combining rules, the overall slope estimate is the mean of these m slope estimates. A confidence interval for this overall slope estimate requires an SE for this estimate which can be obtained using the fact that the variance for the overall slope estimate is $V_1 + (1 + 1/m) \times V_2$ where V_1 is the mean of the m estimated variances (i.e., squared SEs) and V_2 is the sample variance of the m slope coefficients [24].

References

1. Fagan AM, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol. 2006; 59(3):512–9. [PubMed: 16372280]
2. Fagan AM, et al. Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease. EMBO Mol Med. 2009; 1(8-9):371–80. [PubMed: 20049742]
3. Forsberg A, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging. 2008; 29(10):1456–65. [PubMed: 17499392]
4. Jagust WJ, et al. Relationships between biomarkers in aging and dementia. Neurology. 2009; 73(15):1193–9. [PubMed: 19822868]

5. Grimmer T, et al. Beta amyloid in Alzheimer's disease: increased deposition in brain is reflected in reduced concentration in cerebrospinal fluid. Biol Psychiatry. 2009; 65(11):927–34. [PubMed: 19268916]
6. Tolboom N, et al. Relationship of cerebrospinal fluid markers to 11C-PiB and 18F-FDDNP binding. J Nucl Med. 2009; 50(9):1464–70. [PubMed: 19690025]
7. Degerman Gunnarsson M, et al. Pittsburgh compound-B and Alzheimer's disease biomarkers in CSF, plasma and urine: An exploratory study. Dement Geriatr Cogn Disord. 2010; 29(3):204–12. [PubMed: 20332638]
8. Klunk WE, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol. 2004; 55(3):306–19. [PubMed: 14991808]
9. Ikonomovic MD, et al. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain. 2008; 131(Pt 6):1630–45. [PubMed: 18339640]
10. Leinonen V, et al. Assessment of beta-amyloid in a frontal cortical brain biopsy specimen and by positron emission tomography with carbon 11-labeled Pittsburgh Compound B. Arch Neurol. 2008; 65(10):1304–9. [PubMed: 18695050]
11. Rowe CC, et al. Imaging beta-amyloid burden in aging and dementia. Neurology. 2007; 68(20): 1718–25. [PubMed: 17502554]
12. Clark CM, et al. Cerebrospinal fluid tau and beta-amyloid: how well do these biomarkers reflect autopsy-confirmed dementia diagnoses? Arch Neurol. 2003; 60(12):1696–702. [PubMed: 14676043]
13. Strozyk D, et al. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. Neurology. 2003; 60(4):652–6. [PubMed: 12601108]
14. Tapiola T, et al. Cerebrospinal fluid {beta}-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. Arch Neurol. 2009; 66(3):382–9. [PubMed: 19273758]
15. Petersen RC, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology. 2010; 74(3):201–9. [PubMed: 20042704]
16. Mathis CA, et al. Synthesis and evaluation of 11C-labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. J Med Chem. 2003; 46(13):2740–54. [PubMed: 12801237]
17. Senjem, ML., et al. Automated ROI analysis of 11C Pittsburgh compound B images using structural magnetic resonance imaging atlases, Alzheimer's and Dementia. Alzheimer's Association International Conference on Alzheimer's Disease; 2008;
18. Jack CR Jr, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain. 2008; 131(Pt 3):665–80. [PubMed: 18263627]
19. Tzourio-Mazoyer N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002; 15(1):273–89. [PubMed: 11771995]
20. Vanderstichele, H.; DM, G.; Shapiro, F., et al. Biomarkers For Early Diagnosis Of Alzheimer's Disease. Hauppauge;NY: Nova Science Publishers; 2008.
21. Shaw LM, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol. 2009; 65(4):403–13. [PubMed: 19296504]
22. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986; 1(8476):307–10. [PubMed: 2868172]
23. Cole SR, Chu H, Greenland S. Multiple-imputation for measurement-error correction. Int J Epidemiol. 2006; 35(4):1074–81. [PubMed: 16709616]
24. Little, R.; Rubin, Donald. Statistcal Analysis with Missing Data. Second. Wiley-Interscience; 2002.
25. Aizenstein HJ, et al. Frequent amyloid deposition without significant cognitive impairment among the elderly. Arch Neurol. 2008; 65(11):1509–17. [PubMed: 19001171]
26. Edison P, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study. Neurology. 2007; 68(7):501–8. [PubMed: 17065593]

27. Pike KE, et al. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. Brain. 2007; 130(Pt 11):2837–44. [PubMed: 17928318]
28. Engler H, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006; 129(Pt 11):2856–66. [PubMed: 16854944]
29. Jack CR Jr, et al. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain. 2009; 132(Pt 5):1355–65. [PubMed: 19339253]
30. Scheinin NM, et al. Follow-up of [11C]PIB uptake and brain volume in patients with Alzheimer disease and controls. Neurology. 2009; 73(15):1186–92. [PubMed: 19726751]
31. Buchhave P, et al. Longitudinal study of CSF biomarkers in patients with Alzheimer's disease. PLoS One. 2009; 4(7):e6294. [PubMed: 19609443]
32. Vemuri P, et al. Serial MRI and CSF Biomarkers in Normal Aging, MCI and AD. Neurology. 2010 p. accepted for publication.
33. Cairns NJ, et al. Absence of Pittsburgh Compound B detection of cerebral amyloid beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer disease: a case report. Arch Neurol. 2009; 66(12):1557–62. [PubMed: 20008664]
34. Jack CR Jr, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010; 9(1):119–28. [PubMed: 20083042]
35. Kemppainen NM, et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology. 2007; 68(19):1603–6. [PubMed: 17485647]
36. Frisoni GB, et al. In vivo mapping of amyloid toxicity in Alzheimer disease. Neurology. 2009; 72(17):1504–11. [PubMed: 19398705]
37. Mormino EC, et al. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. Brain. 2009; 132(Pt 5):1310–23. [PubMed: 19042931]
38. Fagan AM, et al. Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. Ann Neurol. 2009; 65(2):176–83. [PubMed: 19260027]
39. Morris JC, et al. Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease. Arch Neurol. 2009; 66(12):1469–75. [PubMed: 20008650]
40. Rinne JO, et al. 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. Lancet Neurol. 2010; 9(4):363–72. [PubMed: 20189881]
41. Gelman Andrew, HJ. Data analysis using regression and multilevel/hierarchical models. Cambridge University Press; Cambridge; New York: 2007. p. 140-143.

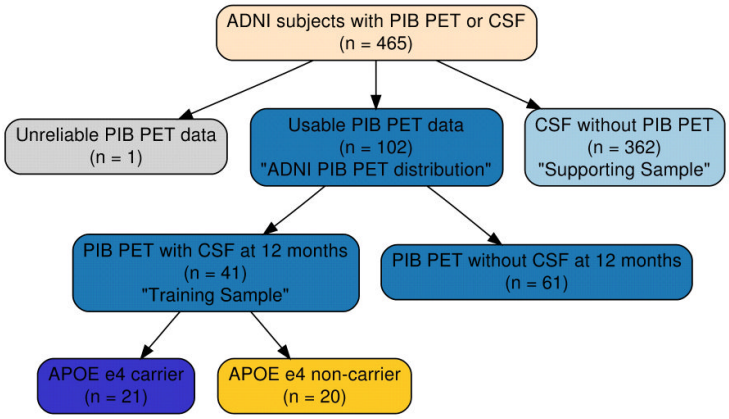


Figure 1. Flow chart of subjects

Subsets of subjects that contributed to the analysis. The royal blue and gold notes at the bottom represent the APOE ε4 carriers and non-carriers in the training set (*see* Figure 2). The light blue node represents the 362 subjects without PIB PET whose CSF-based PIBcalc values constitute the independent supporting sample. The distribution of PIBcalc values from the supporting sample are compared to the PIB PET distribution of the 102 subjects in ADNI who had usable PIB PET (*see* Figure 3).

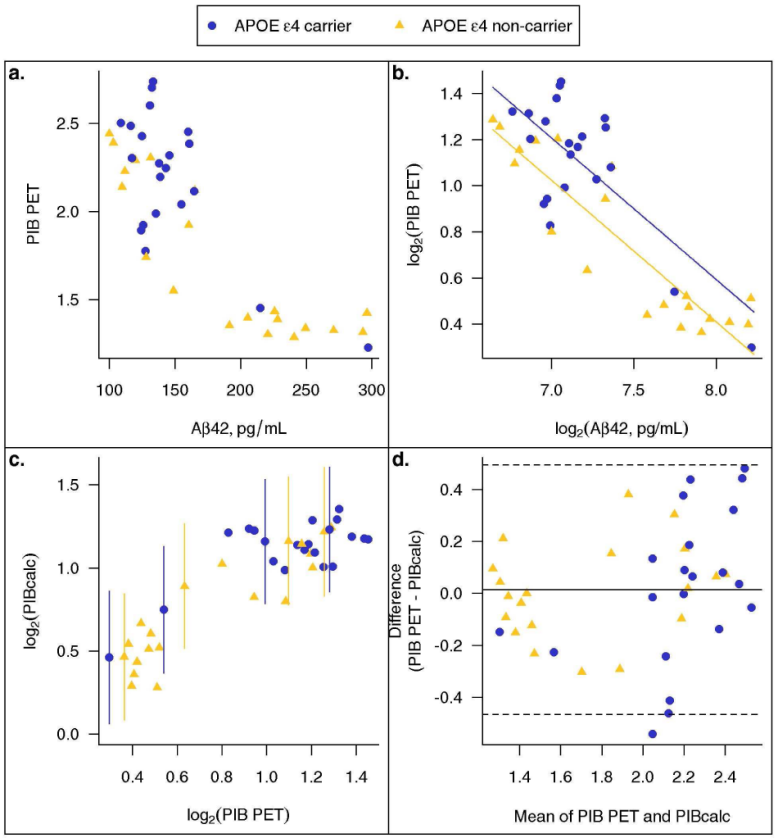


Figure 2. PIB PET and CSF Aβ42 in Training Data Set

Figure 2a: scatterplot of global cortical PIB ratio from PIB PET images on the *y*-axis vs. Aβ42 from CSF on the *x*-axis for the 41 subjects in the training data set. *Figure 2b*: same data as in *Figure 2a* but after a $\log_2$ transformation and shown with least squares regression lines representing the fitted conversion model. *Figure 2c*: Scatterplot of calculated global cortical PIB ratio (PIBcalc) derived from CSF Aβ42 vs. global cortical PIB ratio from actual PIB PET imaging on the $\log_2$ scale. The vertical lines indicate 95% prediction intervals illustrating the uncertainty in the estimated PIB values in 8 selected individuals. *Figure 2d*: Bland-Altman plot of the difference between PIBcalc vs. PIB PET over the range of PIB PET values. Solid line represents the mean difference while dotted lines represent Bland-Altman limits of agreement.

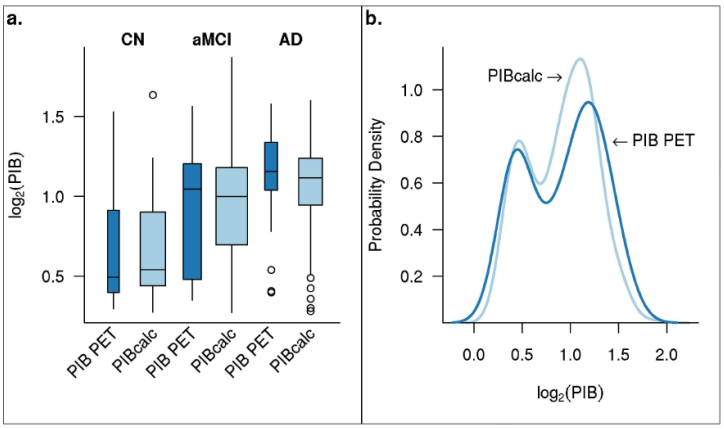
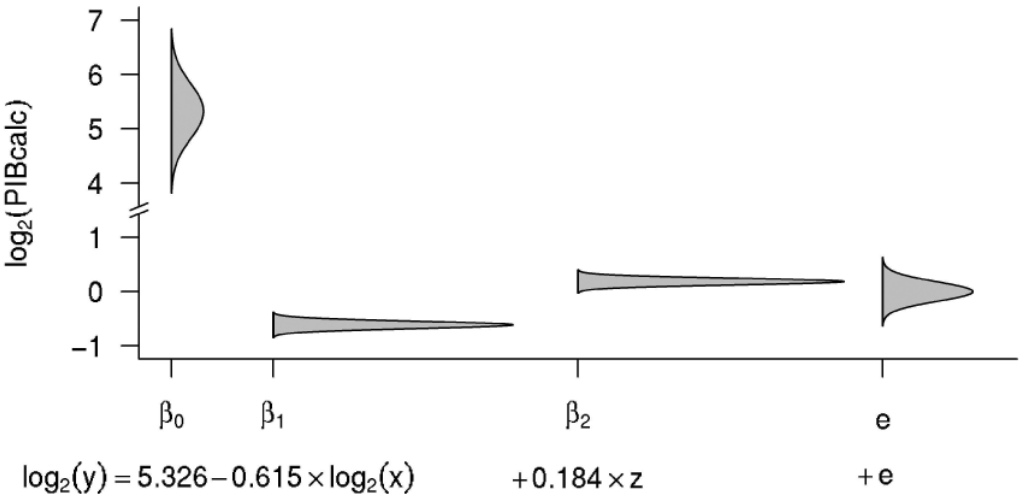


Figure 3. Comparing ADNI PIB PET distribution to PIBcalc distribution in the independent supporting sample

Figure 3a: Box plots by diagnosis comparing ADNI PIB PET distribution (n = 102) values to PIBcalc values based on 362 subjects in the supporting sample. *Figure 3b*: Kernel density estimates of the ADNI PIB PET distribution and PIBcalc distribution from the supporting sample. The two distributions were not found to be systematically different with an AUROC of 0.52 (P = 0.49).



Appendix Figure. Conversion Model Illustration

Illustration of the idea that there is not one conversion model with fixed parameters but a distribution of models. In practice, when a CSF Aβ value is converted to PIBcalc, a number of PIBcalc values will be generated based on this distribution of models. Each distribution shown above is centered at the least squares estimates with a standard deviation approximately equal to the standard error from the least squares fit. The intercept which we denote by β_0 has a distribution centered at the least squares estimate of 5.326. Similarly, the CSF Aβ (β_1) and the APOE (β_2) coefficients will the centered at -0.615 and 0.184. The differences in the standard errors among the coefficients are reflected in the differences in the heights and widths of the distribution curves. The error term (e) will be centered at 0 with a standard deviation of approximately 0.180, the residual standard error from the least squares fit.

Table 1

Descriptive characteristics of training sample: 41 ADNI subjects with PIB PET and CSF Aβ42 data.

Characteristic	All (n = 41)	CN (n = 9)	aMCI (n = 22)	AD (n = 10)
Female gender, no. (%)	14 (34)	4 (44)	6 (27)	4 (40)
Age, years, median (IQR)	74 (71, 79)	72 (71, 79)	75 (73, 80)	72 (70, 76)
APOE ε4 positive, no. (%)	21 (51)	2 (22)	12 (55)	7 (70)
Education, years, median (IQR)	16 (12, 19)	16 (12, 18)	16 (14, 19)	15 (12, 19)
MMSE, median (IQR)	28 (25, 29)	29 (28, 29)	28 (26, 29)	22 (21, 24)
CDR-SB, median (IQR)	1.5 (0.9, 3.5)	0.0 (0.0, 0.5)	1.5 (1.0, 2.0)	5.0 (4.1, 6.0)
PIB PET, median (IQR)	2.1 (1.4, 2.3)	1.4 (1.3, 1.7)	2.3 (1.9, 2.4)	2.1 (1.8, 2.4)
PIB Positive (>1.5 by PIB PET), no. (%)	29 (71)	3 (33)	18 (82)	8 (80)
PIBcalc, median (IQR)	2.1 (1.6, 2.3)	1.4 (1.4, 2.0)	2.1 (1.8, 2.3)	2.2 (2.0, 2.3)
PIB Positive (by PIBcalc), no. (%)	32 (78)	4 (44)	19 (86)	9 (90)

Abbreviations: IQR, inter-quartile range; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating sum of boxes; PIB, Pittsburgh Compound B; PET, positron emission tomography; PIBcalc, calulated PIB PET based on CSF Aβ42.

Table 2

Descriptive characteristics of 102 ADNI subjects with PIB PET.

Characteristic	All (n = 102)	CN (n = 22)	aMCI (n = 53)	AD (n = 27)
Female gender, no. (%)	35 (34)	8 (36)	18 (34)	9 (33)
Age, years, median (IQR)	75 (71, 82)	78 (72, 82)	75 (73, 82)	75 (70, 81)
APOE ε4 positive, no. (%)	52 (51)	6 (27)	28 (53)	18 (67)
Education, years, median (IQR)	16 (13, 18)	16 (13, 18)	16 (14, 18)	16 (12, 18)
MMSE, median (IQR)	27 (25, 29)	29 (28, 30)	27 (26, 29)	23 (21, 25)
CDR-SB, median (IQR)	1.5 (0.5, 3.6)	0.0 (0.0, 0.5)	1.5 (1.0, 2.5)	5.0 (3.8, 6.0)
PIB PET, median (IQR)	2.0 (1.4, 2.3)	1.4 (1.3, 1.9)	2.1 (1.4, 2.3)	2.2 (2.1, 2.5)
PIB Positive (> 1.5 by PIB PET), no. (%)	69 (68)	10 (45)	35 (66)	24 (89)

Abbreviations: IQR, inter-quartile range; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating sum of boxes; PIB, Pittsburgh Compound B; PET, positron emission tomography; PIBcalc, calulated PIB PET based on CSF Aβ42.

Table 3

Descriptive characteristics of supporting sample: 362 ADNI subjects with CSF only.

Characteristic	All (n = 362)	CN (n = 105)	aMCI (n = 164)	AD (n = 93)
Female gender, no. (%)	148 (41)	51 (49)	57 (35)	40 (43)
Age, years, median (IQR)	76 (71, 80)	76 (72, 78)	75 (70, 80)	77 (71, 81)
APOE ε4 positive, no. (%)	174 (48)	23 (22)	86 (52)	65 (70)
Education, years, median (IQR)	16 (14, 18)	16 (14, 18)	16 (14, 18)	16 (13, 18)
MMSE, median (IQR)	27 (25, 29)	29 (29, 30)	27 (25, 28)	24 (22, 25)
CDR-SB, median (IQR)	1.5 (0.0, 3.0)	0.0 (0.0, 0.0)	1.5 (1.0, 2.0)	4.0 (3.5, 5.0)
PIBcalc, median (IQR)	1.9 (1.5, 2.3)	1.5 (1.4, 1.9)	2.0 (1.6, 2.3)	2.2 (1.9, 2.4)
PIB Positive (>1.5 by PIBcalc), no. (%)	266 (73)	47 (45)	132 (80)	87 (94)

Abbreviations: IQR, inter-quartile range; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR-SB, Clinical Dementia Rating sum of boxes; PIB, Pittsburgh Compound B; PET, positron emission tomography; PIBcalc, calulated PIB PET based on CSF Aβ42.