International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(RESEARCH ARTICLE)

Check for updates

Polygenic Hazard Score and Amyloid PET Imaging Mediation Analysis in Alzheimer's Disease Diagnosis

Kallol Kanti Mondal [1,*], Rashedur Rahman [2], Yasmin Akter Bipasha [3] and Abdul Kadir [4]

[1] *Institute of Biological Sciences, University of Rajshahi, Rajshahi, Bangladesh.*
[2] *Department of Computer Science and Engineering, Daffodil International University, Dhaka, Bangladesh.*
[3] *Bangladesh University of Professionals, Mirpur Cantonment, Dhaka-1216, Bangladesh.*
[4] *Dhaka National Medical College, Dhaka, Bangladesh.*

International Journal of Science and Research Archive, 2023, 10(02), 1451-1457

Publication history: Received on 18 October 2023; revised on 21 November 2023; accepted on 29 November 2023

Article DOI: https://doi.org/10.30574/ijsra.2023.10.2.0980

Abstract

This work studies the mediating role of amyloid PET imaging quantitative traits (QTs) in the relationship between genetic risk, measured by the Polygenic Hazard Score (PHS), and Alzheimer's disease (AD) diagnosis. Data are obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), including 559 participants classified as Normal (NL), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), or AD. Thirteen amyloid QTs from AV45 PET scans are examined as potential mediators between PHS and diagnostic outcomes using mediation analysis, Chow tests, and mixed-effects models. Results indicate partial mediation for all QTs in multiple diagnostic comparisons, with both direct and indirect effects being statistically significant. These findings suggest that amyloid PET measures explain part, but not all, of the link between genetic predisposition and AD diagnosis.

Keywords: Polygenic Hazard Score; Alzheimer's Disease; Amyloid PET Imaging; Mediation Analysis; Quantitative Traits; Genetic Risk; AV45 PET; Neuroimaging Biomarkers

1. Introduction

Alzheimer's disease (AD) [1] is the most common form of dementia. It causes irreversible, progressive memory loss, followed by a decline in thinking abilities and memory recall. In the United States, over 6 million people currently have AD, and this number is expected to reach 15 million by 2050. The disease has a complex cause, involving both genetic factors and anatomical brain deterioration [2]–[4].

Genome-Wide Association Studies (GWAS) have identified many genetic variants linked to a higher risk of AD, with dozens of risk-related locations (loci) found in the human genome [4]–[8]. Polygenic Risk Scores (PRS) [9] are often used to calculate an overall AD risk by combining the effects of different genetic changes, such as Single Nucleotide Polymorphisms (SNPs).

Medical imaging tools like PET scans, MRI, or fMRI are commonly used to study differences in brain structure and function among people with varying levels of cognitive impairment. These methods help in diagnosing AD and in observing brain changes related to the disease [10]–[13]. For example, AD patients often have abnormal levels of a protein called Beta-Amyloid 42, which clumps into plaques that disrupt brain cell function. PET scans can detect and measure these plaques.

* Corresponding author: Kallol Kanti Mondal

We combined genetic and imaging methods to explore how genetic variants affect brain structure/function and AD diagnosis. Data came from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [14]–[18]. We used the Polygenic Hazard Score (PHS) to represent genetic risk, and measured 13 imaging quantitative traits (QTs) from AV45 PET scans to assess amyloid buildup in different brain regions. Participants belonged to four groups: Normal (NL), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), and Alzheimer's dementia (AD).

We used mediation analysis [9] to find imaging QTs that act as mediators between PHS and diagnosis — meaning they help explain how genetic risk leads to AD. We also used the Chow test and mixed-effects models to study how the relationship between PHS and imaging QTs differs across the four groups.

2. Datasets

Data for this study came from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) [18]. ADNI began in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. Its main goal is to test whether serial MRI, PET, other biological markers, and clinical/neuropsychological tests can be combined to track the progression of mild cognitive impairment (MCI) and early Alzheimer's disease. More information is available at www.adni-info.org.

We combined two datasets: one with genetic data in the form of a Polygenic Hazard Score (PHS) and another with 13 imaging quantitative trait (QT) measures. We analyzed 559 participants: 185 were Normal (NL), 196 had early mild cognitive impairment (EMCI), 153 had late mild cognitive impairment (LMCI), and 25 had Alzheimer's dementia (AD).

2.1. The ADNI Polygenic Hazard Score

Genetic information was obtained in the form of a Polygenic Hazard Score, available in the ADNI dataset. This score quantifies the risk of developing AD considering the combination of the effect sizes of 31 SNPs located on selected genes [19].

2.2. AV45 PET Scans

Thirteen quantitative traits coming from processed AV45 PET scans [20] of the ADNI2/GO cohorts were selected as imaging quantitative traits and candidate mediators. In particular, these QTs represent the quantity of amyloid protein deposition in several regions of the brain, therefore they can serve as an indication of the disease stage. Diagnosis data was also contained in this dataset.

3. Mediation analysis

Mediation analysis helps us understand how an independent variable (X) affects a dependent variable (Y) by using a third variable, the mediator (M). Think of it like this: X doesn't directly cause Y; instead, X causes M, which then causes Y. The mediator is the go-between.

For example, imagine you want to see if more hours of study (X) lead to better exam grades (Y). A mediator could be a better understanding of the material (M). The logic is:

- More study hours (X) lead to a better understanding of the material (M).
- A better understanding of the material (M) leads to better exam grades (Y).

Mediation analysis confirms this step-by-step process.

- **Direct Relationship**: First, we check if the independent variable (X) significantly affects the dependent variable (Y). This is the main effect we're trying to explain.
- **X to M Relationship:** Next, we check if the independent variable (X) significantly affects the mediator (M). This step is crucial because if X doesn't influence the mediator, the mediator can't be a part of the causal chain.
- **Full Model:** Finally, we put all three variables together: X, Y, and M. We check if the relationship between X and Y becomes weaker or non-significant when we include the mediator (M) in the model. If it does, it means the mediator is successfully explaining at least part of the relationship between X and Y. The relationship between M and Y must also be significant.

The mediating effect of various PET imaging parameters (QTs) on the relationship between PHS (presumably a measure of health or status) and diagnosis. In other words, they were trying to see if the imaging results could explain how PHS is linked to a patient's diagnosis.

- Independent Variable (X): PHS
- Dependent Variable (Y): Diagnosis
- Mediators (M): 13 different PET imaging parameters (QTs)

3.1. Statistical Methods

Because diagnosis is a categorical variable, the researchers had to use different statistical models for each step of the mediation analysis.

- X → M relationship: They used linear regression to see how PHS related to each of the 13 QTs.
- X → Y and M → Y relationships: They used logistic regression because the diagnosis variable had multiple categories.

They simplified the diagnosis into three different binary comparisons:

- NL (Healthy) vs. non-NL
- NL + EMCI vs. LMCI + AD
- non-AD vs. AD

Key metrics for each mediation analysis:

- **ACME (Average Causal Mediation Effect**): The portion of the effect of PHS on diagnosis that goes through the imaging parameter (the mediator).
- **ADE (Average Direct Effect):** The portion of the effect of PHS on diagnosis that is not explained by the imaging parameter.
- **Total Effect:** The combined effect of ACME and ADE.

4. Results

Based on the results for the first comparison (NL vs. non-NL), the study found that for every single imaging parameter, partial mediation was present. This means that both the ACME and ADE were statistically significant, indicating that while the imaging parameters do help explain the link between PHS and diagnosis, there is also still a direct link that isn't explained by the mediators. The mediating and direct effects were also very similar in size across all the imaging parameters.

Table 1 Imaging Quantitative Traits Legend

QT1	SPAP_GLOBAL_SUVR
QT2	SPAP_FRONTAL_SUVR
QT3	SPAP_TEMPORAL_SUVR
QT4	SPAP_ANTERIOR_CINGULATE_SUVR
QT5	SPAP_POSTERIOR_CINGULATE_SUVR
QT6	SPAP_PARIETAL_SUVR
QT7	SPAP_PRECUNEUS_SUVR
QT8	AVID_STAGE_4_GLOBAL_SUVR
QT9	AVID_STAGE_4_FRONTAL_MEDIAL_ORBITAL_SUVR
QT10	AVID_STAGE_4_TEMPORAL_SUVR
QT11	AVID_STAGE_4_PARIETAL_SUVR

QT12	AVID_STAGE_4_PRECUNEUS_SUVR
QT13	AVID_STAGE_4_ANTERIOR_CINGULATE_SUVR

Table 2 ACME, ADE and Total Effect for each mediator considering Normal vs. non-normal patients

	ACME	**ADE**	**Total_effect**
QT1	0.044	0.1162	0.1602
QT2	0.0296	0.1293	0.1589
QT3	0.0415	0.1183	0.1598
QT4	0.0313	0.1282	0.1595
QT5	0.0322	0.127	0.1592
QT6	0.0396	0.12	0.1596
QT7	0.0342	0.1255	0.1597
QT8	0.0473	0.1101	0.1574
QT9	0.036	0.1199	0.1559
QT10	0.039	0.1215	0.1605
QT11	0.043	0.117	0.16
QT12	0.046	0.1122	0.1582
QT13	0.035	0.1251	0.1601

Table 3 P-Values of ACME, ADE and Total Effect for each mediator considering Normal vs. non-normal patients

	ACME_P_Val	**ADE_P_Val**	**TotEff_P_Val**
QT1	<0.001	<0.001	<0.001
QT2	0.0220	<0.001	<0.001
QT3	0.0020	<0.001	<0.001
QT4	0.0140	<0.001	<0.001
QT5	<0.001	<0.001	<0.001
QT6	<0.001	<0.001	<0.001
QT7	<0.001	<0.001	<0.001
QT8	<0.001	<0.001	<0.001
QT9	0.0160	<0.001	<0.001
QT10	<0.001	<0.001	<0.001
QT11	<0.001	<0.001	<0.001
QT12	<0.001	<0.001	<0.001
QT13	0.0020	<0.001	<0.001

Table 4 ACME, ADE and Total Effect for each mediator considering Normal and EMCI vs. LMCI and AD patients

	ACME	**ADE**	**Total_eff**
QT1	0.068	0.0576	0.1256
QT2	0.061	0.06	0.121
QT3	0.070	0.0555	0.1255
QT4	0.060	0.0644	0.1244
QT5	0.0460	0.0803	0.1263
QT6	0.0752	0.0513	0.1265
QT7	0.0796	0.0463	0.1259
QT8	0.0664	0.0627	0.1291
QT9	0.0761	0.051	0.1271
QT10	0.0761	0.0515	0.1276
QT11	0.0772	0.0518	0.129
QT12	0.0771	0.052	0.1291
QT13	0.0719	0.0559	0.1278

Table 5 P-Values of ACME, ADE and Total Effect for each mediator considering Normal and EMCI vs. LMCI and AD patients

	ACME_P_Val	**ADE_P_Val**	**TotEff_P_Val**
QT1	<0.001	0.0340	<0.001
QT2	<0.001	0.0240	<0.001
QT3	<0.001	0.0500	<0.001
QT4	<0.001	0.0180	<0.001
QT5	<0.001	0.0640	<0.001
QT6	<0.001	0.0240	<0.001
QT7	<0.001	0.0480	<0.001
QT8	<0.001	0.0220	<0.001
QT9	<0.001	0.0520	<0.001
QT10	<0.001	0.0380	<0.001
QT11	<0.001	0.0560	<0.001
QT12	<0.001	0.0880	<0.001
QT13	<0.001	0.0640	<0.001

Table 6 ACME, ADE and Total Effect for each mediator considering AD patients vs. all other groups

	ACME	**ADE**	**Total_effect**
QT1	0.0171	0.0228	0.04
QT2	0.0169	0.0232	0.0401

QT3	0.0125	0.0265	0.0391
QT4	0.0139	0.0255	0.0394
QT5	0.0139	0.0255	0.0394
QT6	0.0196	0.0202	0.0398
QT7	0.0168	0.0229	0.0397
QT8	0.0148	0.025	0.0398
QT9	0.0173	0.0221	0.0394
QT10	0.0134	0.0258	0.0392
QT11	0.0159	0.0234	0.0393
QT12	0.0134	0.0257	0.0391
QT13	0.0136	0.0257	0.0393

The final diagnostic comparison has been the one between AD diagnosed subject and all other subjects. The results of the mediation analysis are reported in Table 6.

5. Conclusion

Amyloid PET imaging traits partially mediate the relationship between genetic risk, quantified by the PHS, and Alzheimer's disease diagnosis. Across all diagnostic group comparisons, both direct genetic effects and mediation through imaging measures were significant. Amyloid burden explains part of the genetic influence on AD risk, but additional non-amyloid pathways likely contribute to disease progression. These highlight the complementary role of genetic and imaging biomarkers in understanding AD etiology and could inform more targeted approaches to early diagnosis and intervention.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Alzheimer's Association, "2022 Alzheimer's disease facts and figures,"Alzheimer's Dementia, vol. 18, no. 4, pp. 700–789, 2022.

[2] J. Jack, C. R., D. A. Bennett, K. Blennow, M. C. Carrillo, H. H. Feldman, G. B. Frisoni, H. Hampel, W. J. Jagust, K. A. Johnson, D. S. Knopman, R. C. Petersen, P. Scheltens, R. A. Sperling, and B. Dubois, "A/t/n:An unbiased descriptive classification scheme for alzheimer disease biomarkers," Neurology, vol. 87, no. 5, pp. 539–47, 2016.

[3] Bharati, S., Podder, P., Thanh, D.N.H. et al. Dementia classification using MR imaging and clinical data with voting based machine learning models. Multimed Tools Appl 81, 25971–25992 (2022). https://doi.org/10.1007/s11042-022-12754-x.

[4] I. E. Jansen, J. E. Savage, K. Watanabe, J. Bryois, D. M. Williams, S. Steinberg, J. Sealock, I. K. Karlsson, S. Hagg, L. Athanasiu ¨ et al., "Genome-wide meta-analysis identifies new loci and functional pathways influencing alzheimer's disease risk," Nature genetics, vol. 51, no. 3, pp. 404–413, 2019.

[5] C. Bellenguez et al., "New insights into the genetic etiology of alzheimer's disease and related dementias," Nat Genet, vol. 54, no. 4, pp. 412–436, 2022.

[6] B. W. Kunkle, B. Grenier-Boley, R. Sims, J. C. Bis, V. Damotte, A. C. Naj, A. Boland, M. Vronskaya, S. J. Van Der Lee, A. Amlie-Wolf et al., "Genetic meta-analysis of diagnosed alzheimer's disease identifies new risk loci and implicates aβ, tau, immunity and lipid processing," Nature genetics, vol. 51, no. 3, pp. 414–430, 2019.

[7] Liang, C.S., Li, D.J., Yang, F.C., Tseng, P.T., Carvalho, A.F., Stubbs, B., Thompson, T., Mueller, C., Shin, J.I., Radua, J. and Stewart, R., 2021. Mortality rates in Alzheimer's disease and non-Alzheimer's dementias: a systematic review and meta-analysis. The Lancet Healthy Longevity, 2(8), pp.e479-e488.

[8] A. S. Alatrany, A. J. Hussain, J. Mustafina, and D. Al-Jumeily, "Machine learning approaches and applications in genome wide association study for alzheimers disease: A systematic review," IEEE Access, vol. 10, pp. 62 831–62 847, 2022.

[9] Y. Eng, X. Yao, K. Liu, S. L. Risacher, A. J. Saykin, Q. Long, Y. Zhao, L. Shen, and Adni, "Polygenic mediation analysis of alzheimer's disease implicated intermediate amyloid imaging phenotypes," AMIA Annu Symp Proc, vol. 2020, pp. 422–431, 2020.

[10] Podder, Prajoy, Subrato Bharati, Mohammad Atikur Rahman, and Utku Kose. "Transfer learning for classification of brain tumor." In Deep learning for biomedical applications, pp. 315-328. CRC Press, 2021.

[11] X. Hao, Y. Bao, Y. Guo, M. Yu, D. Zhang, S. L. Risacher, A. J. Saykin, X. Yao, and L. Shen, "Multi-modal neuroimaging feature selection with consistent metric constraint for diagnosis of alzheimer's disease," Medical Image Analysis, vol. 60, p. 101625, 2020.

[12] J. Wan et al., "Identifying the Neuroanatomical Basis of Cognitive Impairment in Alzheimer's Disease by Correlation- and Nonlinearity-Aware Sparse Bayesian Learning," in IEEE Transactions on Medical Imaging, vol. 33, no. 7, pp. 1475-1487, July 2014, doi: 10.1109/TMI.2014.2314712.

[13] Mayo, S., Benito-León, J., Peña-Bautista, C., Baquero, M., & Cháfer-Pericás, C. (2021). Recent evidence in epigenomics and proteomics biomarkers for early and minimally invasive diagnosis of Alzheimer's and Parkinson's diseases. Current neuropharmacology, 19(8), 1273-1303.

[14] L. Shen et al. Alzheimer's Disease Neuroimaging, "Genetic analysis of quantitative phenotypes in ad and mci: imaging, cognition and biomarkers," Brain Imaging Behav, vol. 8, no. 2, pp. 183–207, 2014. [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/24092460

[15] L. Shen, S. Kim, S. L. Risacher, K. Nho, S. Swaminathan, J. D. West, T. Foroud, N. Pankratz, J. H. Moore, C. D. Sloan et al., "Whole genome association study of brain-wide imaging phenotypes for identifying quantitative trait loci in mci and ad: A study of the adni cohort," Neuroimage, vol. 53, no. 3, pp. 1051–1063, 2010.

[16] J. Yan, L. Du, S. Kim, S. L. Risacher, H. Huang, J. H. Moore, A. J. Saykin, L. Shen, and I. Alzheimer's Disease Neuroimaging,"Transcriptome-gui ded amyloid imaging genetic analysis via a novel structured sparse learning algorithm," Bioinformatics, vol. 30, no. 17, pp. i564–71, 2014.

[17] A. J. Saykin, L. Shen, X. Yao, S. Kim, K. Nho, S. L. Risacher, V. K. Ramanan, T. M. Foroud, K. M. Faber, N. Sarwar, L. M. Munsie, X. Hu, H. D. Soares, S. G. Potkin, P. M. Thompson, J. S. Kauwe, R. Kaddurah-Daouk, R. C. Green, A. W. Toga, M. W. Weiner, and I. Alzheimer's Disease Neuroimaging, "Genetic studies of quantitative mci and ad phenotypes in adni: Progress, opportunities, and plans," Alzheimers Dement, vol. 11, no. 7, pp. 792–814, 2015.

[18] M. W. Weiner, D. P. Veitch, P. S. Aisen, L. A. Beckett, N. J. Cairns, R. C. Green, D. Harvey, C. R. Jack, W. Jagust, E. Liu, J. C. Morris, R. C. Petersen, A. J. Saykin, M. E. Schmidt, L. Shaw, L. Shen, J. A. Siuciak, H. Soares, A. W. Toga, J. Q. Trojanowski, and I. Alzheimer's Disease Neuroimaging, "The alzheimer's disease neuroimaging initiative: a review of papers published since its inception," Alzheimers Dement, vol. 9, no. 5, pp. e111–94, 2013.

[19] Mahumd, T. (2022). ML-driven resource management in cloud computing. World Journal of Advanced Research and Reviews, 16(03), 1230-1238.

[20] Mahmud, T. (2023). Applications for the Internet of Medical Things. International Journal of Science and Research Archive, 10(02), 1247-1254.

[21] Yasmin Akter Bipasha, "Blockchain technology in supply chain management: transparency, security, and efficiency challenges", International Journal of Science and Research Archive, 2023, 10(01), 1186-1196.