Comparison of Alzheimer's Disease research themes before and after lecanemab approval using text analysis of scientific literature

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Abstract (232 words)

Every year thousands of scientific articles are published concerning the chronic neurodegenerative disorder and leading cause of dementia, Alzheimer's disease (AD). Systematic reviews for AD research are labour intensive and limit the timely dissemination of information. *In silico* machine learning methods for text analysis are unbiased and have previously been used to comprehensively describe the AD research landscape. Currently there are no treatments that cure AD, however, the second anti-amyloid disease-modifying immunotherapy, lecanemab, was granted accelerated approval by the US Food and Drug Administration (FDA) on 06-01-2023. To determine whether the accelerated approval of lecanemab represented a major paradigm shift in AD research, we conducted n-gram frequency analysis and latent Dirichet allocation (LDA) topic modelling of full abstract text from PubMed and preprint databases. We analysed text data from 3,468 abstracts from the year preceding, and 3,276 abstracts from the year following the approval of lecanemab. The number of publications concerning lecanemab increased in 2023; however, the language use remained similar, with neurodegenerative diseases being commonly discussed alongside AD. Comparing two ten-topic LDA models, research themes surrounding lecanemab's approval concerned "*study terminology*" and "*treatments*", and the per-topic-per-word probabilities for "*tau*" and "*placebo*" increased in the latter LDA model. A longer follow up period will be necessary to investigate whether AD research themes are shifting towards new therapeutic targets and advances in later phase clinical trials using text analysis techniques.

Introduction

Alzheimer's Disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease affecting over 55 million people worldwide, and is the most common cause of dementia (1). The predominant symptoms of AD usually manifest after the age of 65 and include cognitive impairment, physical and emotional difficulties (2). The mechanisms determining the progression of AD are not fully understood, but many agree on the amyloid or tau hypotheses, originating from the presence of amyloid-beta (Aβ) plaques and neurofibrillary tau tangles frequently found in the brains of patients with AD (3,4). These abnormal proteins lead to disruptions in neuronal signalling pathways and mediate cell death (5,6). Degeneration of the hippocampus, which is a region vital for memory, and cortical atrophy can lead to cognitive decline seen in AD (7,8).

AD diagnosis requires the presence of both amyloid and tau pathologies, and signs of neuroinflammation, neuronal death and brain atrophy (9). Biomarkers of neuroinflammation can be found in cerebrospinal fluid (CSF) and blood plasma (10) or using brain imaging such as positron emission tomography (PET) (11). Brain atrophy can be measured with techniques such as magnetic resonance imaging (MRI) (12). Abnormal protein deposits manifest in the brain before the onset of symptoms, therefore early detection is required to prevent the spread of AD pathologies and identify the right stage to administer treatments.

AD also has multiple risk factors suggesting age, epigenetic modifiers, infectious agents, and diet all contribute to the development of AD (13,14). An epidemiological comparison of people aged 65 years and older from two different decades, suggested that the prevalence of AD is decreasing due to an improvement in other lifestyle factors (15). Observational studies are useful to identify other factors that are important in the search to find treatments to target the key AD pathologies.

Treatments for AD

There are currently no therapies or interventions that can cure AD, but several approved treatments exist to manage cognitive impairment, to alleviate symptoms, and enhance the overall quality of life for patients. Acetylcholinesterase inhibitors (AchE) aim to increase the levels of the neurotransmitter acetylcholine which are attenuated during the pathologies of AD, and associated with the loss of cholinergic neurons (16). Whilst AchEs provide many benefits to treat the symptoms of AD, they do not delay or stop the progression of the disease and the effects may only last for 12-24 months (17). Memantine is a NMDA receptor antagonist which inhibits glutamate mediated neurotoxicity caused by neuronal cell death during AD progression (18). Memantine has been approved for moderate severe to severe AD; however, the drug has not been shown to slow the progression, or prove effective in mild-to-moderate stages of the disease (19,20).

Two anti-amyloid human monoclonal immunotherapies, aducanumab and lecanemab, have recently

been granted approval by the United States Food and Drug Administration (US FDA) and aim to reduce the Aβ plaques in the AD brain (21,22). Aducanumab approval was rejected by the European Medicines Agency (EMA) due to the conflicting phase III clinical trial evidence and concerns over patient safety (23,24), whereas lecanumab is currently under review by the EMA for approval (25). Aducanemab targets the soluble Aβ oligomers and insoluble fibrils whereas lecanumab targets the soluble Aβ protofibrils, but both led to the development of severe adverse events including amyloid-related imaging abnormalities (ARIA) (26,27). These results suggest further research is needed to understand the full molecular causes of AD to help find safe yet effective treatments.

Recent comprehensive reviews have identified a shift in research, with more Phase I studies being conducted, and four more anti-amyloid monoclonal antibody treatments either completing or currently undergoing Phase III clinical trials (28,29). These trials involved more patients with early onset AD and mild cognitive impairment (MCI) as global estimates for people positive for AD biomarkers without an AD diagnosis, or living with preclinical AD were 69 and 315 million, respectively (30). Increasing the research focus on these patient populations may help to slow the progression of the disease to develop preventative therapies before irreversible clinical symptoms manifest. These reviews have not been updated since the accelerated approval of lecanemab, therefore we aim to identify whether there is a transition in research topics with the emergence of these novel disease-modifying treatments to target the underlying pathologies of AD rather than treating the symptoms.

Text Mining and Topic Modelling in AD Research

Thousands of articles are released every year concerning AD and the Alzheimer's Association publishes an annual report to describe the public health impact of AD for caregivers and society (2). Systematic reviews and meta-analyses, however, are time consuming and labour intensive, and pose a significant challenge to updating the current understandings in the research literature (31). Topic modelling, an unsupervised machine learning technique, can find patterns and relationships within natural language data, and could provide an automated and unbiased overview of research text. The most common topic modelling method is Latent Dirichlet Allocation (LDA) which assumes, for unstructured text data like research publications, that each document is made up of a number of topics and that each topic is made up of a collection of words (32). The gamma and beta values provide information about the proportion of each document composed of words from a topic, and the probability of a word being associated with a topic, respectively.

In silico topic modelling has been used for various applications relating to AD, including identifying novel biomarkers (33), and drug repurposing (34). LDA has also been used to describe trends in the research landscape, however, this has only been achieved until 01-01-2022 (35,36). Guan *et al* (36) identified fourteen clusters from abstract text from 95,876 papers published between 2007 and 2016 with the entry term 'Alzheimer's Disease'. Topics included the burden of AD such as 'cost' and 'health' as well as

protein terminology such as ‘APP’ which related to the amyloid-precursor protein which is cleaved into amyloid-beta via the amyloidogenic pathway (37). Martinelli (35) produced a nine-topic LDA model and identified five mechanistic themes, one topic relating to AD diagnosis and three concerning treatments. Whilst both descriptive analyses using LDA topic modelling have identified key topics in AD research, further research was suggested to validate their findings.

To the best of our knowledge, no studies have described the AD research landscape since these studies were conducted, and explored whether the emergence of newly approved immunotherapy treatments have affected research themes. We therefore aimed to comprehensively characterise AD research through the period that the AD drug, lecanemab, underwent accelerated approval for early AD on 06-01-2023 . We hypothesised that new treatments targeting the pathophysiological changes in patients with AD represent a major paradigm shift in AD research. We proposed that LDA topic models could summarise the latest research and help identify distinct thematic changes in the literature. Furthermore, this method could help understand the complexities of AD and aid in the assimilation of new research.

Methods

A full summary of the methodology is provided in Figure 1. All data analysis and visualisations were done in R version 4.3.2 using *tidyverse* packages (38) unless otherwise stated.

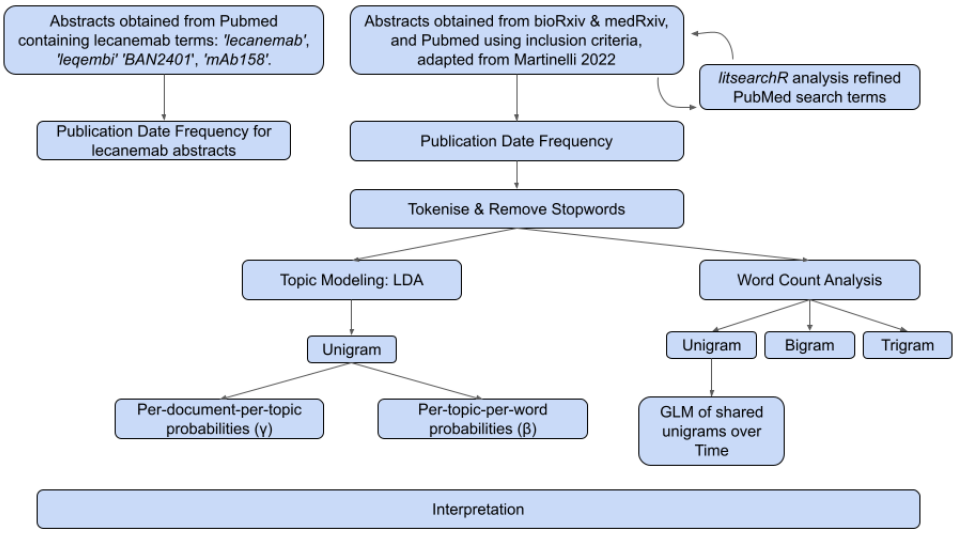


Figure 1: **Summary of methods.** Abstracts gathered from PubMed then updated with *litsearchr* results, or from preprint databases were read into R. Metadata analysis was performed then text was tidied and tokenised, then allocated to two corpuses relative to the accelerated approval date of lecanemab. LDA topic modelling and n-gram analysis were performed then results were interpreted.

Data Acquisition

Due to accessing constraints, abstracts represent the only document content for this study. Titles, full abstract text, and publication date were obtained from the National Center for Biotechnology Information (NCBI) database, PubMed, using the inclusion criteria described in Table 1, and accessed through *Rismed* (39) on 18-02-2024. Results from PubMed were combined with publications from the preprint data sources, bioRxiv and medXriv, using *medrxiv* (40). Entries were assigned Medical Subject Headings (MeSH) which identified health-related terms within each document, therefore classifying articles according to their subject nature. An additional dataset was generated for abstracts containing the associated terminology for the AD drug lecanemab: '*lecanemab*', '*leqembi*' '*BAN2401*', and '*mAb158*'.

Table 1: **Inclusion criteria used to query and identify all relevant terms concerning AD in the PubMed database.** Adapted from Martinelli (35). MeS, Medical Subject Headings.

Criteria	Filter Applied
MeSH Term	'Alzheimer's Disease'
Title and/or Abstract Text	'Alzheimer's Disease'
	'AD'
Article Type	"Books"
	"Case Reports"
	"Clinical Study"
	"Clinical Trial"
	"Controlled Clinical Trial"
	"Meta-analysis"
	"Randomised Controlled Trial"
	"Review"
	"Systematic Review"
Publication Date	1st January 2022 to 1st January 2024 inclusive
Language	English

litsearchR

To reassure us that the PubMed search query encapsulated all literature, we used *litsearchr* to automate identifying search terms and reduce bias in the initial keyword selection by using co-occurrence networks (41). Citations from the PubMed results, using the previous search criteria in Table 1, were read into R. The combined unique keyword and titles, as not all articles had keywords, for each result were collected. To ensure only the most relevant terms were searched, stop words were removed as these contained very frequent terms that provided no significant information, such as '*the*', '*and*' or '*a*'. The minimum frequency of words for keywords and title was then set to n = 50 and n = 75, respectively. A document-

frequency matrix of each search term in each article was created and computed into a co-occurrence network using *create_network* (42). The potential search terms were ranked using *strength* (43), and the change point method calculated the optimal cutoff positions where the strength of the next strongest term was greater than the previous one.

Data Preprocessing

Abstracts and their metadata were categorised into two corpuses: 'Pre-Lecanemab Accelerated Approval', and 'Post-Lecanemab Accelerated Approval', based on their publication date relative to the date of lecanemab's accelerated early approval, 06-01-2023 (22). Full abstract text was tokenised into one-, two- and three-word tokens using *tidytext* (44) (Figure 2a). Stop words, combined with the words frequent to the unigram analysis, "*alzheimer's*" and "*ad*", were then removed (Figure 2b). To prevent the different spellings of the same phrase from being counted multiple times, similar bigrams and trigrams were mapped to the same variable. For example, '*amyloid β*', '*beta amyloid*', and '*amyloid aβ*' were all mapped to '*amyloid beta*', and '*mild cognitive impairments*' and '*cognitive impairment mci*' were mapped to '*mild cognitive impairment*'. Additionally, for bigrams originating from trigrams, mapping to the first two terms was used or mapping to an acronym, for example '*central nervous*' and '*system cns*' were mapped to '*cns*'.

Data Analysis

Frequency Analysis

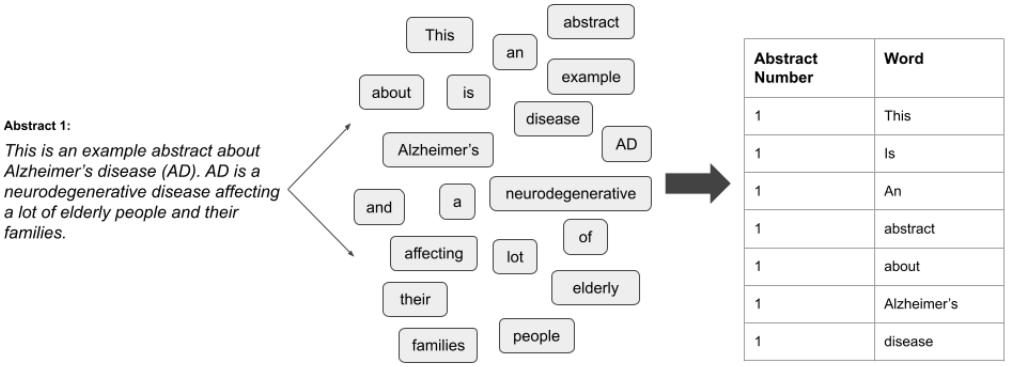
The frequency of all eligible abstracts published per month as well as the frequency of publications containing the associated terminology for the AD drug lecanemab were visualised.

After tokenisation, the top 15 most frequent unigrams were determined for each dataset. The top 15 most frequent bigrams and trigrams were also determined due to many unigrams being associated with pairs or triplets of words. For example, "*mild cognitive impairment*" relates to a neurological condition, whereas the words "*mild*", "*cognitive*" and "*impairment*" have ambiguous connotations individually. A generalised linear model (GLM) was used to determine whether there was a significant change in word usage per month for the most frequent unigrams shared by both corpuses.

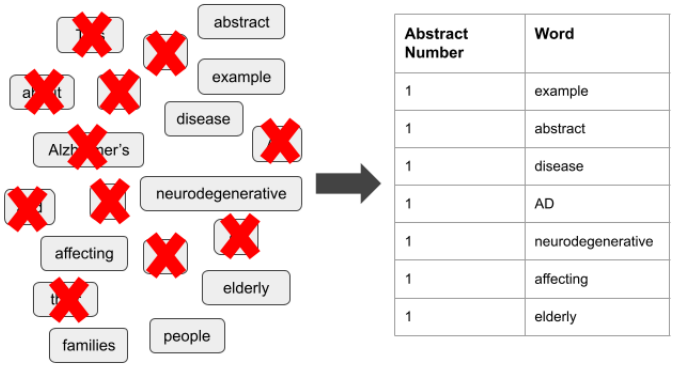
Topic Modelling

A document term matrix (dtm) was constructed for each dataset, indicating each word's term frequency (tf), which is a measure of how often a word appears in each abstract. To determine if a statistical model could distinguish between the text corpuses surrounding the accelerated approval date of lecanemab, a

two-topic Latent Dirich Allocation (LDA) model was applied to the dtm using *topicmodels* (32,45). A two-way ANOVA was applied to determine whether there was an association between a topic and either pre- or post-accelerated approval of lecanemab in the average proportion of an abstract comprising words from its assigned topic (γ). If AD research themes differed, we would expect one topic to be associated with pre-accelerated approval abstracts and the other to post-accelerated approval abstracts.



(a) *Unigram Tokenisation*



(b) *Removal of Stop Words*

Figure 2: **Abstract preprocessing into unigrams.** Schematic of an abstract being (a) tokenised into single-word tokens followed by (b) removal of stop words and, '*alzheimers*' and '*AD*', which were frequent to the unigram analysis. Tokenisation and data cleaning of bigrams and trigrams followed the same methods, not shown.

Two ten-topic LDA models were also created, one for each text corpus, to determine the most prevalent topics. Ten topics were chosen during exploratory analyses to maximise the number of themes without

losing interpretability or introducing topic repetition. In each model, the abstracts were considered mixtures of topics and each topic was considered a mixture of words. The per-topic-per-word probabilities (β) were extracted, and the top 10 terms most common words found in each topic were visualised. Topic titles were manually created and validated by a neuroscience expert.

Results and Discussion

The final dataset contained 6744 abstracts that were published between 01-01-2022 and 30-12-2023 (Figure 3).

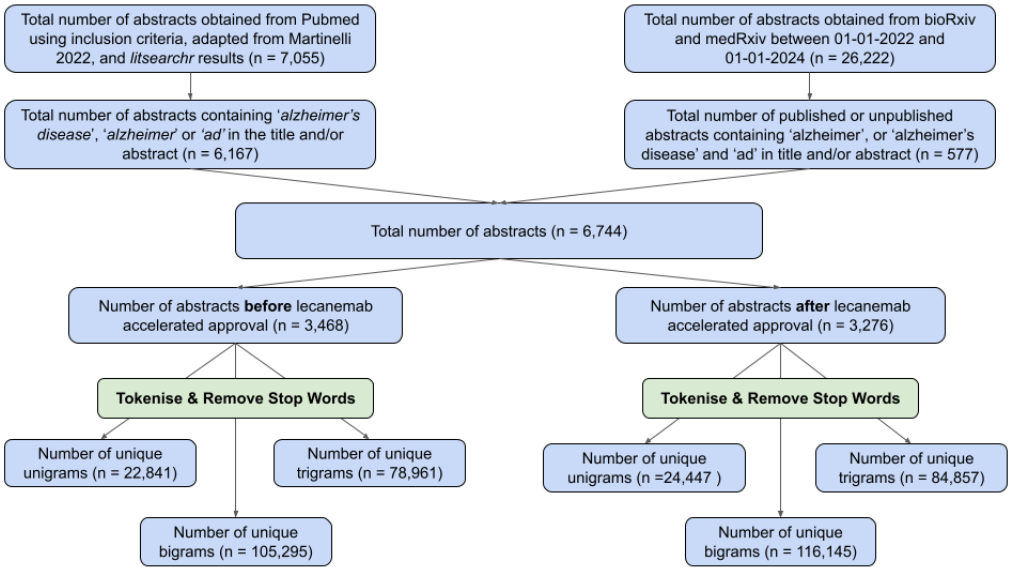


Figure 3: **Summary of abstracts and n-grams used for analysis**. Counts for abstracts obtained from PubMed and preprint databases were allocated to two corpuses based on their publication date relative to the accelerated approval date of lecanemab, 06-01-2023. Frequencies for unique n-grams after tokenisation and stop-word removal were calculated.

Search query refinement identified the term '*alzheimer*'

Our initial search query was refined using *litsearchr* (41) to determine the most important terms to the articles ranked by their strength (Figure 4). We disregarded '*alzheimer's disease*' as this MeSH term was included in the original search query, but we updated the PubMed search query with '*alzheimer*' (Table 1). We omitted the unigram '*disease*' as this term was too broad and may have encapsulated articles concerning other irrelevant neurodegenerative diseases into our query. We included English articles only, which are estimated to be about 75% of the scientific literature (46).

Due to our search strategy, a lot of papers containing the MeSH term '*Alzheimer's disease*' may have been mentioned as a collective with other neurodegenerative diseases. MeSH terms are added manually to articles in PubMed, therefore, there could be an interpretive bias when authors add these to their

publications. We tried to avoid this by filtering the titles and abstracts of PubMed articles to also contain the term '*alzheimer's disease*', '*ad*' or '*alzheimer*' (Figure 3). Similarly, when MeSH terms were not available for the bioRxiv and medRxv databases, we used a similar search strategy to filter titles and abstract text to contain the term '*alzheimer's disease*' or '*alzheimer*', or '*ad*' and '*alzheimer's disease*'. This filtering may have underestimated our dataset, as abstracts not containing these search terms were omitted, despite the full article text potentially concerning AD. Abstract text has previously successfully been used to identify themes in AD literature (36); however, we would suggest that further studies use full article text to help validate our findings.

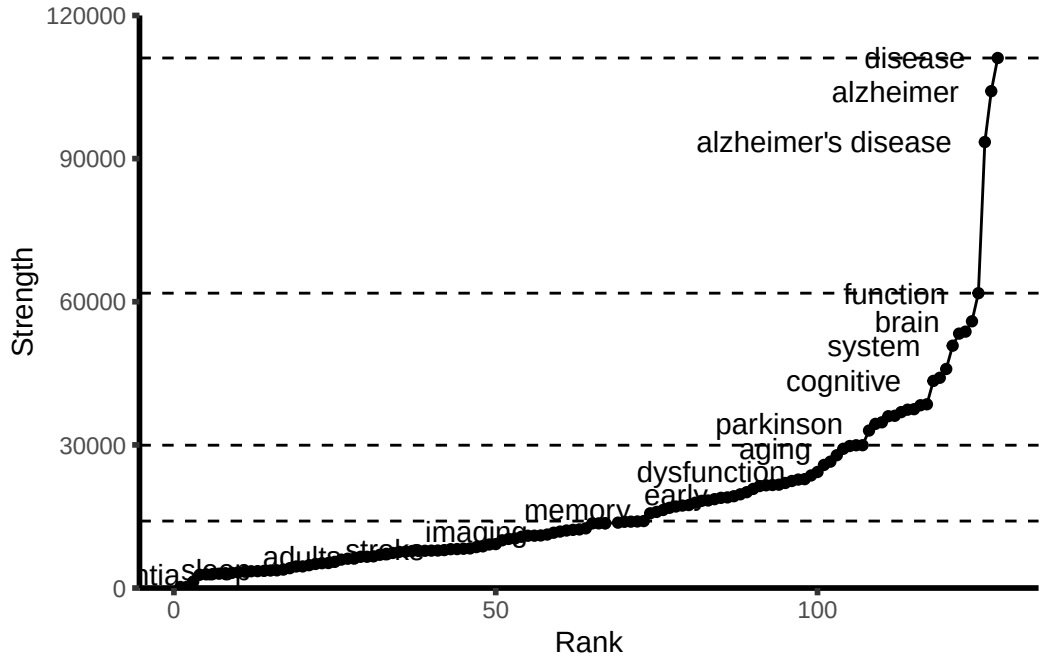
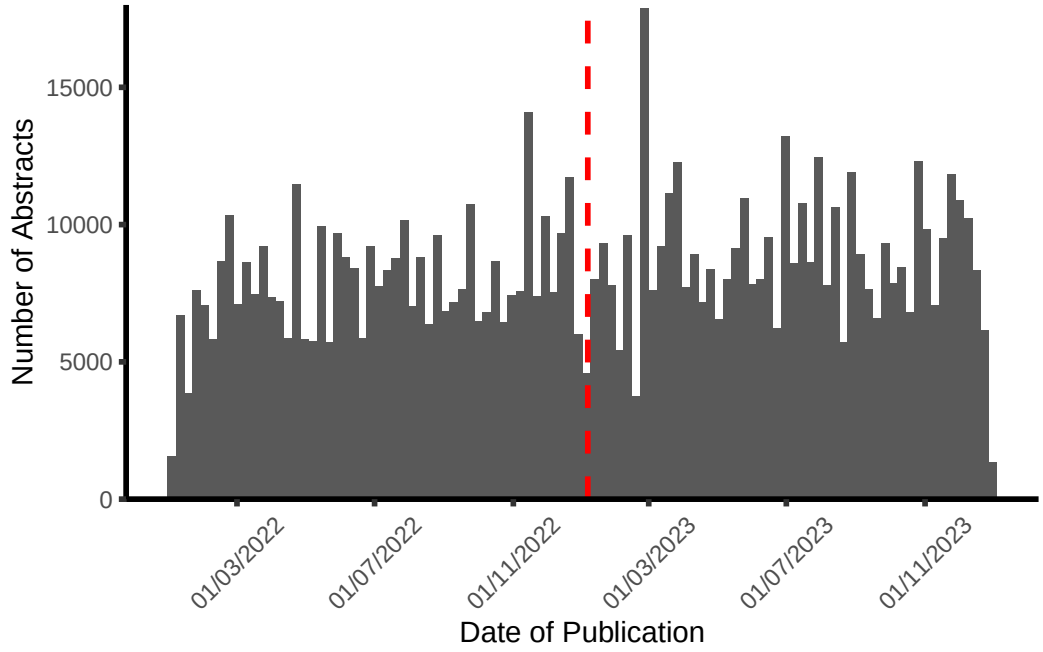


Figure 4: **Search query refinement using *litsearchr* identified '*alzheimer*'.** A matrix of each word in each article was created and the potential search terms were ranked with *create_network* and *strength* (42) from the *igraph* package (43). The dashed lines mark the optimal cutoff positions where the strength of the next strongest term was greater than the previous one. The top keywords and words from the titles of AD papers, with minimum frequencies of n = 50 and n = 75, respectively, were ranked by their importance to article content then the top terms were considered to refine the original search query, adapted from Martinelli (35).

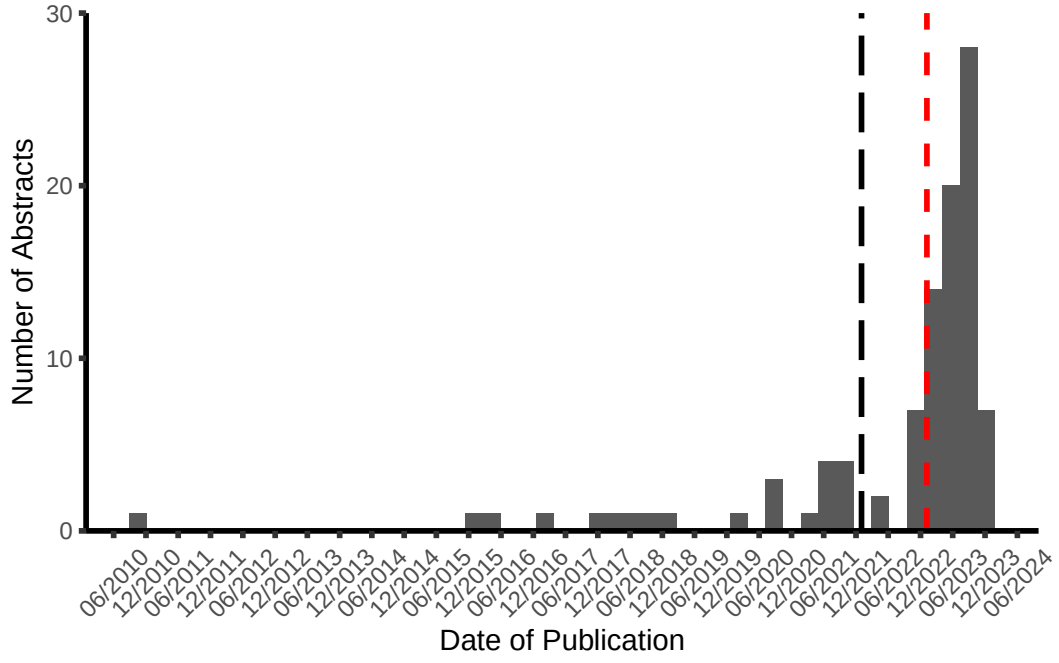
Similar language use around accelerated approval of lecanemab

Lecanemab received accelerated and traditional approval in 2023 (22,47); however, we did not find any variability in the overall frequency of literature published containing terms associated with the MeSH term '*Alzheimer's Disease*', with 3,468 abstracts published before and 3,276 abstracts published after the accelerated approval of lecanemab (Figure 3, Figure 5a). The number of publications containing the terms associated with the AD drug lecanemab exponentially increased in 2023 (Figure 5b). Whilst there was a statistically significant association between topics and corpus type in gamma, the magnitude of this effect was extremely small, explaining only 0.01% of the variance (Figure 6). This suggested that the

increase in abstracts concerning lecanemab may not have introduced new vocabulary, therefore the full dataset was unable to separate into two distinct topics reflecting the periods surrounding lecanemab's accelerated approval.



(a) Abstracts containing Alzheimer's Disease terms



(b) Abstracts containing lecanemab terms

Figure 5: **Increase in lecanemab publications does not change AD publication frequency.** Distribution of articles published over time containing (a) the terms associated with the MeSH term 'Alzheimer's Disease' in the title and/or abstract (n = 6744) or (b) terms associated with the AD drug lecanemab: '*lecanemab*', '*leqembi*', '*BAN2401*', and '*mAb158*' (n = 202). Black long-dashed line represents the start of our observation period. Red dashed-line represents date of lecanemab accelerated approval, 06-01-2023.

Previous studies have used a five-year or a ten-year time period to characterise topics in AD literature (35,36), however no studies have compared LDA topics in two time periods. A limitation of our two-year observation was that changes to research themes may take multiple years to manifest, so this period may have also been too short to account for changes in the research themes. We would recommend that further work should explore a larger time period after the accelerated approval of lecanemab to conclude whether a change in the research literature can be found using topic models.

The full abstract dataset may not significantly split into two distinct topics before and after the approval of lecanemab, because the language use was very similar between the two corpses. We explored the most common n-grams and found that fourteen of the fifteen most frequent unigrams were shared between the two corpuses (Figure 7a). There were no significant differences between the monthly frequencies of these unigrams; however general trends fluctuated similarly in the two-year period (Figure 7b). Fourteen of the fifteen most frequent bigrams and trigrams were shared between the two corpuses (Figure 7c, Figure 7d). This suggested that the word usage has remained consistent, and indicated that the introduction of another anti-amyloid disease-modifying immunotherapy may not have changed the research landscape.

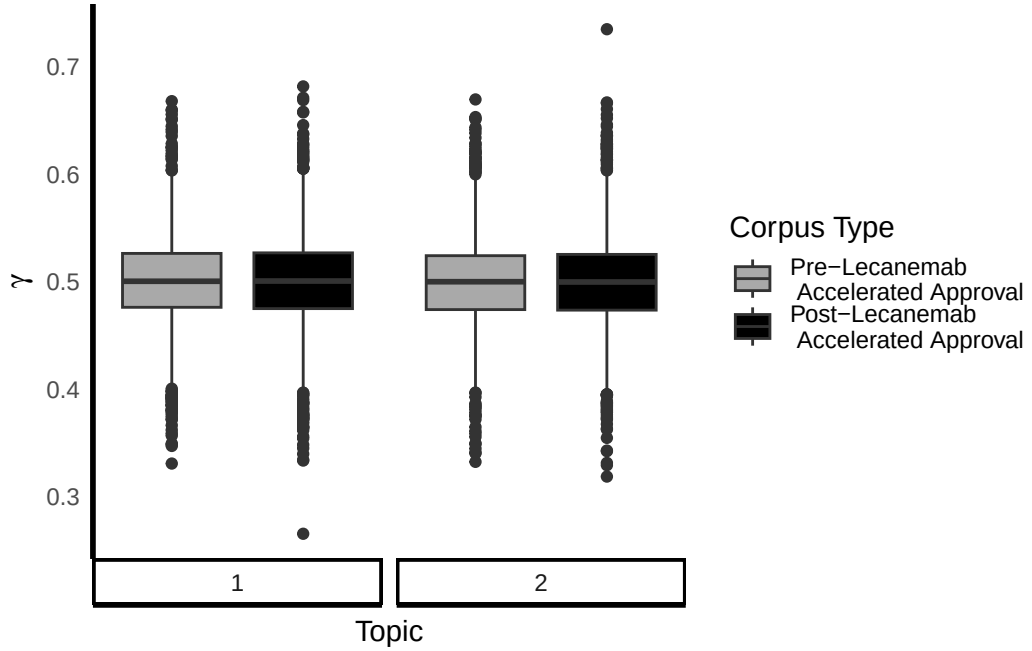


Figure 6: **Assigning two topics to AD abstracts surrounding accelerated approval of lecanemab using LDA topic models**. A document term matrix (dtm) was constructed for the unigram dataset and a two-topic LDA model was applied to the dtm using *topicmodels* (45). Boxplots show first and third quartiles, and median per-document-per-topic probabilities, γ. Corpus type was determined based on accelerated approval date for lecanemab, 06-01-2023. n = 6744. Statistical significance between all topics and corpus types, except when comparing pre-lecanemab accelerated approval in either topic. $p < 0.001$; Two-way ANOVA with Tukey's HSD post-hoc analysis.

Alzheimer's disease is discussed with age-related neurodegenerative diseases

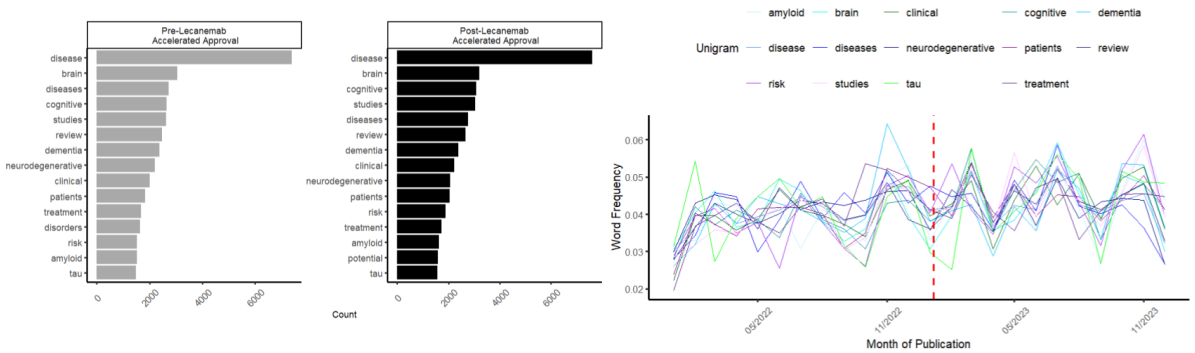
To understand whether the words were being used in similar contexts, we created two ten-topic LDA models to identify the distribution of unigrams in topics in each corpus. We found topics concerning: '*genetic risk*', '*study terminology*', '*cellular*' and '*molecular pathologies*', '*AD diagnosis*' and '*treatments*', in both LDA models before and after the accelerated approval of lecanemab (Figure 8). Unique topics within abstracts before lecanemab approval included, '*drug discovery*', '*neurodegeneration*', '*trial types*', and one topic containing words associated with the term '*cognitive*' (Figure 8a). In the latter corpus, novel topics included, '*epidemiology*', '*cognitive impairment*', and words commonly occurring in '*AD review articles*' (Figure 8b).

'*Disease*' was the most frequent unigram (Figure 7a) and a component of the bigrams and trigrams, '*neurodegenerative disease*', '*Parkinson's disease [pd],'* and '*Huntington's disease [hd]*', found in both corpuses (Figure 7c, Figure 7d). The neurodegenerative diseases, '*multiple sclerosis*', '*amyotrophic* lateral sclerosis' (ALS), and '*dementia*', were also common to abstracts before and after lecanemab's approval. We had refined our search query to ensure all published abstracts were predominantly concerning AD; however, research seems to cover many diseases which all have a progressive degenerative cause.

Whilst '*neurodegenerative*' and '*dementia*' occurred in the LDA models for both corpuses, '*parkinson's* [disease]' was the only non-dementia disease to occur in a topic, and only appeared in the earlier model (Figure 8). Parkinson's disease (PD) is another common neurodegenerative disease, caused by α-synuclein accumulation, and affects coordination and motor skills (48,49). Aggregates containing α-synuclein and Lewy bodies have also been found in patients with familial AD (50,51), therefore research into other age-related diseases may be influencing AD publication themes.

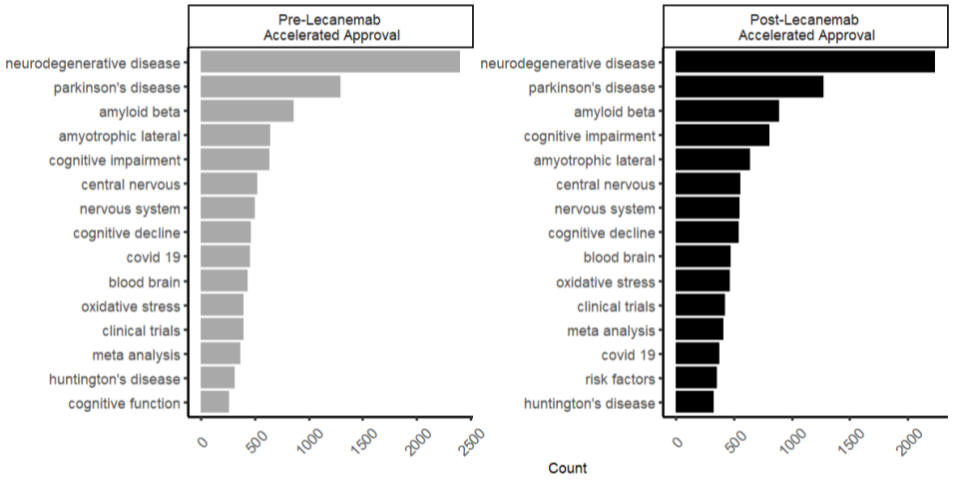
Amyloid hypothesis and inflammation in AD pathology

Abnormal protein aggregates are common to many of the age-related neurodegenerative diseases we have reported (52). The rare dominantly inherited AD (DIAD) is caused by the accumulation of Aβ from mutations in the amyloid precursor protein (*APP*) gene, and genes for presenilin 1 and presenilin 2 (*PSEN1/PSEN2*) (53). We only found '*amyloid precursor protein*' referenced in the n-gram analysis, however, the gene '*apoe*' occurred in LDA topics in both corpuses (Figure 7d, Figure 8). The apolipoprotein E (ApoE) allele is the most significant risk gene for late-onset AD and associated with age-related cognitive decline (54,55). This correlated with our observation of '*apoe*' occurring in a topic in the latter LDA model with '*risk*', '*association*', '*factors*', and '*cognitive*' (Figure 8b). Studies suggest ApoE may be enhancing APP expression leading to increased Aβ aggregations (56). '*Amyloid*', '*aβ*', '*beta*', and '*plaques*' were common to the '*molecular pathology*' topic in both LDA models, therefore, AD research around lecanemab's approval may be focusing on the importance of the amyloid hypothesis in AD pathology.

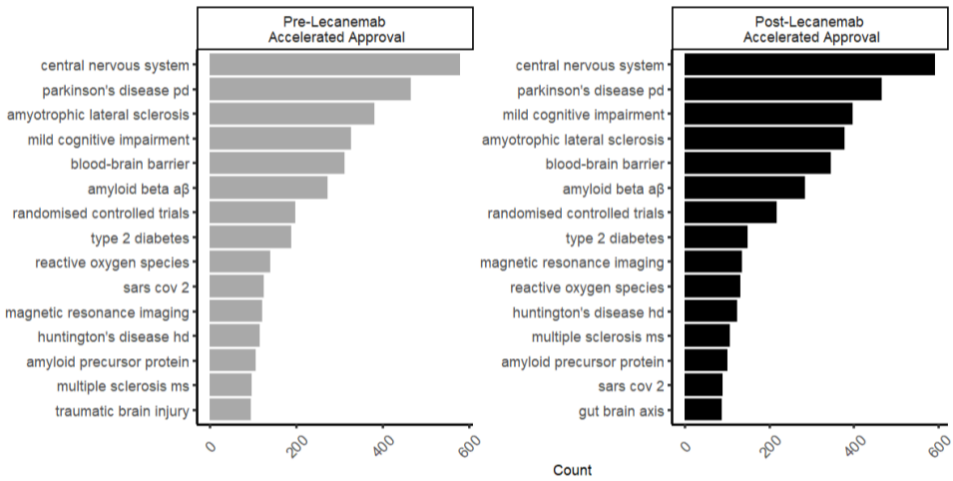


(a) *Unigram*

(b) *Frequency of Most Common Unigrams*



(c) *Bigram*



(d) *Trigram*

Figure 7: **Literature use before and after the accelerated approval of lecanemab.** Abstract text for 6744 abstracts was tokenised and stop words were removed. Corpus type was determined based on the accelerated approval date for lecanemab, 06-01-2023. Frequency analysis identified the (a) 15 most common unigrams, and (b) their distribution by month of the top 14 shared most frequent unigrams for both corpuses. Dashed-line represents the accelerated approval date of lecanemab, 06-01-2023. ns p >0.05, generalised linear model. The frequency of the 15 most common (c) bigrams and (d) trigrams after mapping was also reported, as many unigrams appeared in pairs or triplets of words.

As the cause of AD is not fully understood, topics concerning the '*cellular pathology*' occurred in both LDA models (Figure 8). Neuroinflammation is increased in AD due to the recruitment and activation of immune cells (57). We found '*microglia*' were the only immune cells specified in the text analysis, and only in the earlier LDA model (Figure 8a). The term '*mitochondrial*' occurred in both LDA models, and '*oxidative stress*' and '*reactive oxygen species*' appeared in both corpuses in the n-gram analysis (Figure 7c, Figure 7d). Mitochondria produce reactive oxygen species and initiate neuronal cell death in AD from the accumulation of Aβ plaques (58). Microglia are important as part of the innate immune response to remove Aβ; however, tau pathologies may induce an inflammatory state in microglia causing the phagocytosis of synapses and secretion of neurotoxic cytokines (59,60). This suggests current literature may be focusing on dysfunctional immune cell activation and protein aggregate clearance contributing to neurotoxicity in AD.

The condition, '*type 2 diabetes*', was one of the most common trigrams for both corpuses, and '*insulin*' emerged in the pre-accelerated approval LDA model (Figure 7d, Figure 8a). AD has been considered a form of type 3 diabetes due to the growing literature concerning brain insulin resistance, and experimental evidence has shown insulin sensitiser treatments may help attenuate learning deficits (61–64). Many epidemiological studies have suggested T2DM may be increasing the risk of AD, leading to the lower brain insulin levels resulting in decreased clearance of amyloid-beta (65,66). Despite this growing area of research, observations between non-demented participants and AD patients with T2DM have not been able to show a significant difference in amyloid accumulation (67), but research may still be ongoing for these findings to have appeared from our analyses.

We found the unigrams, '*covid*' and '*19*', were unique only to the earlier LDA model, despite '*covid 19*' and '*sars cov 2*' being among the most frequent bigrams and trigrams in both corpuses (Figure 8, Figure 7c, Figure 7d). This might be a consequence of the larger volume of COVID-19-related research published during the post-pandemic years. Research has shown higher immune cell CSF proinflammatory cytokines and reduced amyloid processing in patients with COVID-19 neurological disease (68), therefore research themes may be shifting to explore inflammatory causes of AD.

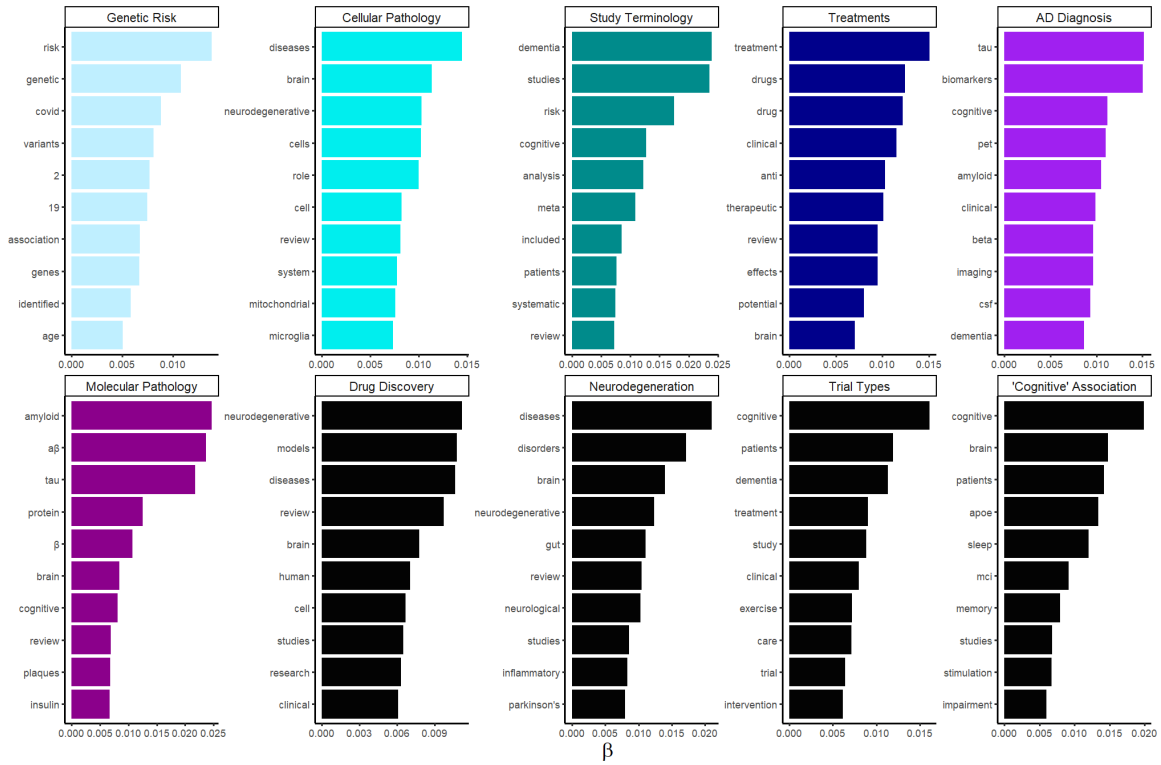
Focus on late phase clinical trials and treatments around accelerated approval of lecanemab

Topics containing '*study terminology*' were common to both LDA models; however, the unigram '*placebo*' was unique to the later model (Figure 8b). The trigram, '*randomised controlled trials',* was more frequent in the later corpus which could suggest an increase in the number of randomised clinical trials (RCT) after lecanemab received accelerated approval (Figure 7d). Placebos are required for the comparison of a study drug in later phase clinical trials when there are no FDA-approved therapies that can already be tolerated by patients. Since AD does not have a standard of care treatment, a placebo may be used for comparison in RCTs. Previous text mining analysis in AD research has identified clinical outcomes

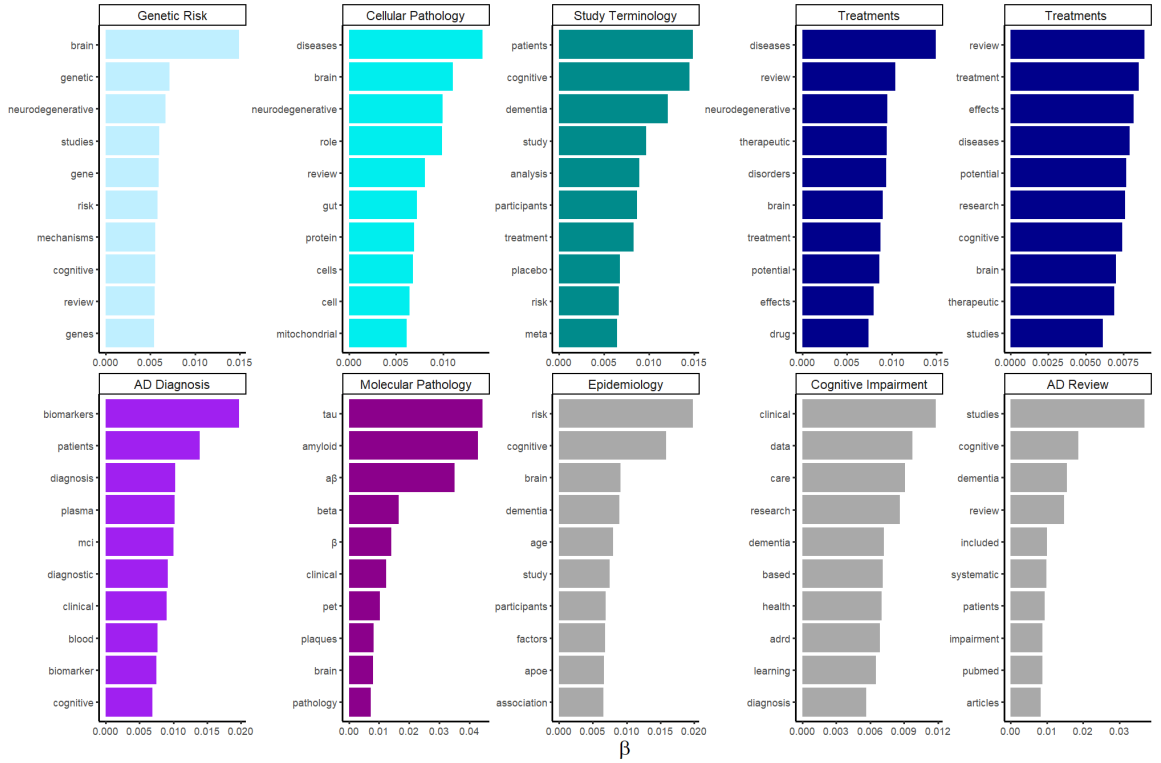
(35); however, literature concerning RCTs and placebo-controlled trials was unique to our analysis. Our findings were consistent with the trends observed in Huang *et al* (29), which showed an increase in Phase III clinical trials for anti-amyloid therapies in 2023, which included the traditional approval date of lecanemab by the FDA in July 2023 from the CLARITY AD clinical trial (47). Later phase trials in AD may, therefore, be increasing in the period after lecanemab approval, due to more therapies targeting the amyloid pathologies.

Topics discussing '*drug discovery*' and '*trial types'* were unique to the earlier LDA model, and encompassed unigrams from pre-clinical studies: '*cells*' and '*models*', and clinical studies: '*trial*', '*human*' (Figure 8a). In the LDA model after the accelerated approval of lecanemab, more topics related to '*treatments'* emerged, containing unigrams such as'*effects'*, *'therapeutic*', and '*drug*' (Figure 8b). We also observed an increase in beta for the terms '*tau*', '*amyloid*', and '*aβ',* in the topic concerning '*molecular pathology'* in the later LDA model. The number of clinical trials focusing on disease-modifying therapies targeting tau has been increasing, as evidenced by the 14 active trials at the beginning of 2023 (28). This trend suggests research may be shifting towards identifying drugs that target the tau hypothesis for AD, in addition to current anti-amyloid therapies including lecanemab. Language concerning many phases of drug discovery may imply research is continuing to find therapies that aim to cure AD.

In conclusion, we conducted text analysis to compare the AD research themes before and after the accelerated approval of lecanemab. We highlighted how many neurodegenerative diseases were frequently discussed alongside AD, suggesting potential commonalities in research. We showed that compared to previous *in silico* text analyses for AD literature, research may be shifting to include more clinical studies, and focusing on treatments targeting the key molecular pathologies underlying the amyloid and tau hypotheses about AD. We would suggest that our automated approach using LDA topic models could help provide an overview of major topics, and increase the efficiency of disseminating large quantities of text data in the AD literature.



(a) *Pre-Lecenamab Accelerated Approval: Top 10 unigrams in each LDA topic*



(b) *Post-Lecenamab Accelerated Approval: Top 10 unigrams in each LDA topic*

Figure 8: **AD research theme comparison for ten-topic LDA models surrounding accelerated approval of lecanemab.** Outputs from the ten-topic LDA model for abstracts published (a) before and (b) after the accelerated approval date of lecenamab, 06-01-2023. The top 10 unigrams per topic are ordered by their per-topic-per-word probability, β. Topic titles were manually created and validated with a neuroscience expert. Topic colours matched when the same topic was identified in (a) then (b).

Word Count: 3904

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