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MANUSCRIPT TITLE

Comparing COVID-19 Vaccination Coverage, Adverse Reactions, and Impact of Social Determinants of Health on Vaccine Hesitancy in ADRD/MCI and Non-ADRD/MCI Populations: Protocol for a Retrospective Cross-Sectional Study

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Keywords. Alzheimer's disease, Alzheimer's disease related dementias (ADRD), mild cognitive impairment, COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.

Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Abstract

Introduction. COVID-19 vaccination is crucial for vulnerable people with underlying chronic conditions such as Alzheimer's disease and related dementias (ADRD) and mild cognitive impairment (MCI). These individuals face unique challenges, including higher risk of COVID-19, difficulties in adopting preventive behaviors, and vaccine hesitancy due to concerns about adverse reactions. Therefore, efforts to promote vaccination, including boosters tailored to the currently circulating virus, are essential for people with ADRD/MCI.

Objective. The primary purpose of this study is to conduct a comprehensive analysis of COVID-19 vaccination coverage and adverse reactions among individuals with ADRD/MCI in comparison to those without ADRD/MCI. Additionally, the study aims to investigate the impact of social determinants of health on COVID vaccination and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Analysis. A retrospective cross-sectional study will be conducted utilizing data from the *All of Us* Researcher Workbench. Relevant data fields are extracted from sources including demographic information, COVID-19 Vaccine Survey, Basic Survey, Health Access & Utilization, Social Determinants of Health, Personal and Family Health History, COVID-19 Participant Experience, and EHR conditions data. Data on vaccination, adverse reactions and vaccine hesitancy will be collected through COVID-19 Survey Questionnaires. Generalized linear regression and multilevel logistic regression will be applied to assess the vaccination rates and vaccine hesitancy, while controlling for demographic characteristics and social determinants of health factors.

Ethics and Dissemination. This study received approval from the Institutional Review Board at Florida State University (STUDY00004571). Results will be disseminated through publication in peer-reviewed journals and presented at conferences.

(Word Count: 250)

Article Summary

Strengths and Limitations

This study has significant potential in advancing our understanding of COVID-19 vaccination behaviors and outcomes among individuals with ADRD/MCI and the impact of behavioral and social determinants of health.

This study will demonstrate whether individuals with ADRD/MCI are more hesitant to receive booster shots and underlying factors contributing to this hesitancy.

The study findings can inform more equitable and effective vaccination efforts for this vulnerable population by identifying the factors contributing to hesitancy towards booster shots and exploring the influence of behavioral and social determinants of health. Addressing these factors can help ensure that individuals with ADRD/MCI receive the necessary protection against COVID-19, especially as booster shots become increasingly critical in maintaining immunity.

One limitation of this study is missing data or EHR record may influence the sample size and power of analysis.

Background

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), which quickly spread and caused a significant medical, public health, and economic crisis worldwide.[1] COVID-19 vaccines are pivotal in preventing the disease and reducing the morbidity and mortality associated with COVID-19.[2,3] As of May 2023, at least 270,227,181 individuals, constituting 81% of the U.S. population, have received at least one COVID-19 vaccine dose. Furthermore, 230,637,348 people, equivalent to 70% of the population, have achieved full vaccination status.[4] This high rate is considered a highly positive development against the COVID-19 pandemic, due to the vulnerability of older adults with underlying chronic diseases who are at a great risk of severe complications.[5]

Previous studies have demonstrated the significant association between Alzheimer's disease (AD) and increased risk of COVID-19 infection and mortality.[6,7] Individuals with dementia and mild cognitive impairment (MCI) are particularly vulnerable, facing a 2 to 3-fold greater risk of COVID infection compared to the general older adult population and they exhibit poor outcomes.[7] Additionally, individuals with Alzheimer's disease and related dementias (ADRD) encounter challenges in adopting protective behaviors to mitigate infection risks.[8,9] Social isolation can further strain their relationships with their communities and healthcare providers.[10,11]

Increasing vaccination rates play a pivotal role in fostering herd immunity against COVID, which serves to curb virus transmission and safeguard those who are more susceptible to COVID adverse consequences.[12] Following the introduction of COVID-19 vaccines, a noticeable reduction in pandemic-related excess deaths was observed among individuals with ADRD.[8] Despite progress, COVID cases have been on the rise since July 2023, emphasizing the importance of accessible booster shots, especially for vulnerable populations such as the elderly and vulnerable individuals with underlying health conditions.[13,14] As of October 2022, 111,367,843 people, equivalent to 34% of the U.S. population, have received booster shots.[4] While ADRD patients and their caregivers exhibit willingness to facilitate vaccination, but a substantial portion express concerns about potential adverse events.[15-17] Understanding the impact of social determinants on vaccination intent and hesitancy among individuals with ADRD/MCI still requires further exploration.[18,19]

This study aims to provide a comprehensive comparison of vaccination coverage, including first doses, second doses, and booster doses, along with adverse reactions between ADRD/MCI individuals and those without ADRD/MCI. Additionally, this study seeks to examine the impact of social determinants of health on COVID-19 vaccination rates and vaccine hesitancy among individuals with ADRD/MCI. By gaining a better understanding of these factors, we can develop targeted strategies to improve vaccination rates and address concerns among this vulnerable population.

Study Objective

Research Aim 1: To determine the difference in COVID-19 vaccination rates (first dose, second dose and boosters) between ADRD/MCI individuals and those without ADRD/MCI.

Research Aim 2: To assess the variation in adverse reactions such as swelling, tiredness, muscle pain, chills, fever, following the COVID-19 vaccination in individuals with ADRD/MCI compared to those without ADRD/MCI.

Research Aim 3: To investigate the influence of social determinants of health (including age, race/ethnicity, sex, gender, language speaking, living status, income, healthcare facility accessibility, supportive relationships with neighborhood and healthcare providers, etc.) on COVID-19 vaccination rates and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Data Analysis

Data Source: *All of Us (AoU)* Researcher Workbench

The data source for this study will be the *All of Us (AoU)* Researcher Workbench, which is a secure and comprehensive source of biomedical datasets enrolled with a broad, diverse group of United States(U.S.)

populations.[20,21] These datasets consists of diverse range of U.S. population, ensuring inclusively and representation. The *AoU* Research Workbench seeks to engage individuals from underrepresented demographic groups, promoting diversity in research.[22] The *AoU* Research Program encompasses various data elements, including participants' basic demographic information, responses to health surveys, physical measurements, biospecimen collection (including blood, urine, and saliva samples stored in the secure *AoU* biobank), structured electronic health records (EHRs), and Fitbit tracker data collected from one million participants across the U.S.[23] Each participant has completed informed consent for sharing their EHR data with the data and research center, and they provide survey responses covering various domains on an ongoing basis.[23,24] Specifically, we will extract relevant data fields from sources such as the Demographics, Basic Survey, COVID-19 Vaccine Survey, Health Access & Utilization, Social Determinants of Health, Personal and Family History, COVID-19 Participant Experience and EHR conditions data. Enrollment for the *AoU* program commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research initiative successfully extended invitations to one million individuals nationwide.[25] The diverse population and data integration from multiple sources within the *AoU* Research Workbench allow for a comparative analysis of vaccination rates, adverse reactions, and the influence of social determinants of health on vaccine hesitancy between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The deidentified data are accessible through the *AoU* researcher workbench (https://workbench.researchallofus.org) under institutional data use agreements.[26] All analyses will be conducted within a secure platform provided by *AoU* Researcher Workbench. The study protocol and *AoU* materials have received approval from the Institutional Review Board at Florida State University Office of Research.

Workspace on the *AoU* Researcher Workbench Secure Platform: ADRD/MCI and COVID-19 Vaccination

We have established a workspace named "ADRD/MCI and COVID-19 Vaccination" within the *AoU* Researcher Workbench. This cloud-based platform grants authorized researchers access to and the ability to analyze data from the *AoU*. The platform offers two levels of data access available: the registered tier and the controlled tier. We have been granted access to the controlled data tier. Within this controlled tier, we have constructed two distinct cohorts: one consisting of individuals with ADRD/MCI and another consisting of those without ADRD/MCI. Cohort formation was based on participants' electronic health records (EHRs), including International Classification of Diseases (ICD) codes related to ADRD/MCI, as well as their responses to the Personal and Family History Survey questionnaire concerning ADRD/MCI history. We applied appropriate logical operators, such as "AND" and "OR" to combine the key inclusion and exclusion criteria. To facilitate our research, we utilized the dataset builder tool to construct the datasets. Subsequently, we exported the acquired data to Jupyter Notebooks for analysis, leveraging the R programming language (R Foundation for Statistical Computing) and Python version 3.0 (Python Software Foundation).

1) ADRD/MCI Cohort

The ADRD/MCI cohort is formed by gathering information from both EHR and Personal and Family History survey questionnaires. Through EHR, individuals are identified for inclusion in the ADRD/MCI cohort if they have been diagnosed with any of the following ICD-9/10 conditions: "mild cognitive impairment" or "Alzheimer's disease" or "dementia" or "dementia with or without behavioral and psychological symptoms" or "vascular dementia" or "Lewy body dementia" or "frontotemporal dementia" (**Table 1**).

To identify individuals within the ADRD/MCI cohort using the Personal and Family History Survey data, the inclusion criteria involve providing affirmative responses to the following questions: a) "Have you or anyone in your family ever been diagnosed with the following brain and nervous system conditions? – Dementia (includes Alzheimer's, vascular, etc.)" or b) "Including yourself, who in your family has had dementia (includes Alzheimer's, vascular, etc.)? – Self" or c) "Are you still seeing a doctor or health care provider for dementia (includes Alzheimer's, vascular, etc.)? – Yes" or d)"About how old were you when you were first told you had dementia (includes Alzheimer's, vascular, etc.)? – Adolescent, – Adult, – Older adult, – Elderly" or e) "Are you currently prescribed medications and/or receiving treatment for dementia (includes Alzheimer's, vascular, etc.)? – Yes". Individuals who satisfy at least one of the previously mentioned inclusion criteria, either through EHR conditions or valid responses to the Personal and Family History Survey, will be included in ADRD/MCI cohort. Deceased people are excluded from the study.

2) Non-ADRD/MCI Cohort

Individuals who have been diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease and related dementias (ADRD), as defined in the ADRD/MCI cohort, are not included. Additionally, deceased people are excluded from this cohort.

Table 1. ICD-9/10 diagnosis codes for ADRD/MCI conditions

	Code	Definition
Mild Cognitive Impairment		
ICD9	331.83	Mild cognitive impairment, so stated
	294.9	Unspecified persistent mental disorders due to conditions classified elsewhere
ICD10	G31.84	Mild cognitive impairment, so stated
	F09	Unspecified mental disorder due to known physiological condition
ADRD		
Alzheimer's disease		
ICD9	331.0	Alzheimer's disease
ICD10	G30	Alzheimer's disease
	G30.0	Alzheimer's disease with early onset
	G30.1	Alzheimer's disease with late onset
	G30.8	Other Alzheimer's disease
	G30.9	Alzheimer's disease, unspecified
Vascular dementia		
ICD9	290.4	Vascular dementia
	290.40	Vascular dementia, uncomplicated
	290.41	Vascular dementia, with delirium
	290.42	Vascular dementia, with delusions
	290.43	Vascular dementia, with depressed mood
ICD10	F01	Vascular dementia
	F01.5	Vascular dementia
	F01.50	Vascular dementia without behavioral disturbance
	F01.51	Vascular dementia with behavioral disturbance
Lewy Body Dementia		
ICD9	331.82	Dementia with Lewy bodies
ICD10	G31.83	Dementia with Lewy bodies
Frontotemporal Dementia		
ICD9	331.1	Frontotemporal Dementia
	331.11	Pick's disease
	331.19	Other frontotemporal dementia
ICD10	G31.0	Frontotemporal Dementia
	G31.01	Pick's disease
	G31.09	Other frontotemporal dementia

Variables

Outcome Variables

COVID-19 vaccination rates, adverse reactions and vaccine hesitancy will be assessed through COVID-19 Survey Questionnaires administered between the summer of 2021 and 2022. These questionnaires contain inquiries about receiving the first dose/second dose/boosters of COVID-19 vaccination, adverse reactions after vaccination, and how likely people are to get vaccinated and reasons that make people hesitate to get the

vaccine. The respondents will indicate how likely or unlikely they would be vaccinated on a 5-point Likert scale, ranging from “very likely” to “very unlikely”.

Independent Variables: Social determinants of health at Individual, Interpersonal and Community Level Factors

The study encompasses social determinants of health at three levels: individual, interpersonal, and community. Individual level factors include Individual demographics, medical history and medications in conditions data Interpersonal level factors consist of sociocultural environment & social support, relationship with neighborhood and healthcare providers. Community level factors include healthcare facility accessibility and utilization are included. **(Table 2)**

Table 2. Measurement Matrix

	Study Variables	**Measure**	**Data Source**
Outcomes	Vaccination rates	Did you receive the first dose, second dose and boosters of the COVID-19 vaccination: Yes; No; Not sure; Skip.	*AoU* COVID-19 Vaccine Survey
	Adverse reactions	Adverse reactions include swelling, fever, Guillain-Barre syndrome, headache, tiredness, muscle pain, chills, nausea, severe allergic reaction (anaphylaxis).	*AoU* COVID-19 Vaccine Survey
	Vaccine hesitancy and reasons	When a COVID-19 vaccine is available, how likely are you to get vaccinated: Very likely; Likely; I do not know yet; Unlikely; Very unlikely; Skip. Factors might make you less likely to get the vaccine: I will not get sick; I do not trust the vaccine; It depends on the risks/adverse events; I need more information first; etc.	*AoU* COVID-19 Vaccine Survey
Cohorts	ADRD/MCI and non-ADRD/MCI	ICD-9/10 diagnosed conditions such as “mild cognitive impairment” or “Alzheimer’s disease” or “dementia”, or positive responses related to ADRD/MCI diagnosis in the Personal and Family History Survey data.	*AoU* EHR Conditions Data and Personal and Family History Survey
Individual level factors	Demographics	Age, sex, gender, race, ethnicity, marital status, education level, employment status, insurance status, income.	*AoU* Basic Survey
	Medical history and medications	Medical history & comorbid conditions, medications	*AoU* Personal and Family Health History
Interpersonal level factors	Sociocultural environment and social support	Living status, type of residence, household and neighborhood environment, number of people living at residency.	*AoU* COVID-19 Participant Experience (COPE) Survey
	Relationship with neighborhood and healthcare providers	Supportive relationship with neighborhood, healthcare providers and others, interpersonal discrimination, cultural, religion and linguistic diversity.	*AoU* Social Determinants of Health Survey
Community level factors	Healthcare facility accessibility and Utilization	Healthcare coverage accepted by doctors, place for healthcare services, count of general doctors, nurse practitioners, physician assistants, obstetricians / gynecologists, midwives, and reasons for delayed medical care.	*AoU* Health Access & Utilization Survey

Samples

We have established study cohorts and preliminary datasets within the *AoU* researcher workbench to assess the availability of variables essential for this study. After conducting an initial screening within the *AoU* Researcher Workbench, we have determined a sample size of 30,132 individuals diagnosed with ADRD/MCI, of which 15,596 have provided responses regarding vaccine doses. Our study incorporates underrepresented racial and ethnic groups such as Blacks or African Americans, Hispanic or Latinos. Moreover, we are also considering underrepresented social determinants of health (SDoH) that both ADRD/MCI individuals and their communities experience. These determinants include factors like age, gender, language speaking, living status, income, healthcare facility accessibility, supportive relationship with neighborhood and healthcare providers, etc. **(Table 3).** Table 3 summarizes the demographic distribution of individuals with ADRD/MCI and non-ADRD/MCI patients who received vaccinations. Among the 15,596 ADRD/MCI patients, 24% were aged 18-44 (n=3,717), 33% were aged 45-64 (n=5,150), and 43% were aged over 65 (n=6,729). Approximately 32% were male (n=4,923), 64% were female (n=10,017), and 2% fell into other categories (Non-binary, Transgender, Additional options, Prefer not to answer; n=264). White individuals had the highest vaccination frequency (78%, n=12,226), followed by African Americans (7%, n=1,047), Asians (2%, n=294), and Hispanics (8%, n=1,246). In the case of the 71,664 non-ADRD/MCI patients, 20% were aged 18-44 (n=14,355), 33% were aged 45-64 (n=23,490), and 47% were over 65 years old (n=33,819). About 34% were male (n=24,578), 63% were female (n=45,032), and less than 1% were categorized differently (Non-binary, Transgender, Additional options, Prefer not to answer; n=581). The vaccination frequency among non-ADRD/MCI patients was highest among White individuals (71%, n=50,821), followed by African Americans (11%, n=7,652), Asians (2%, n=1,633), Hispanics (12%, n=8,624), and others (13%, n=9,617).

Table 3. Demographics of ADRD/MCI population of people with COVID-19 Vaccination in All of Us data

Demographics	ADRD/MCI Cohort (N=15,596)	Non-ADRD/MCI Cohort (N=71,664)
Age, N (%)		
18-44	3,717 (24)	14,355 (20)
45-64	5,150 (33)	23,490 (33)
>65	6,729 (43)	33,819 (47)
Gender, N (%)		
Male	4,923 (32)	24,578 (34)
Female	10,017 (64)	45,032 (63)
Other (Non-binary, Transgender, Additional options, Prefer not to answer)	264 (2)	581 (<1)
Skip	392 (3)	1,473 (2)
Sex at Birth, N (%)		
Male	4,996 (32)	24,702 (34)
Female	10,174 (65)	45,310 (63)
Other (None, Unknown, Prefer not to answer)	338 (2)	1,149 (2)
Skip	88 (<1)	503 (<1)
Race, N (%)		
White	12,226 (78)	50,821 (71)
Black or African American	1,047 (7)	7,652 (11)
Asian	294 (2)	1,633 (2)
Other (Native Hawaiian or Other Pacific Islander, Middle Eastern or North African, Multiple-racial, None indicated, Prefer not to answer)	1,425 (9)	9,617 (13)
Skip	604 (4)	1,941 (3)
Ethnicity, N (%)		
Hispanic or Latino	1,246 (8)	8,624 (12)
Non-Hispanic or Latino	13,578 (87)	60,250 (84)
Other (None of these, Prefer not to answer)	168 (1)	849 (1)
Skip	604 (4)	1,941 (3)

Sample Size and Power Calculation

A two-group retrospective study is used in this study. The sample size calculation is powered by the outcomes. The changes in vaccination rate and vaccination hesitancy will be compared between the ADRD/MCI groups and individuals without ADRD/MCI. Hence, there will be a total of two statistical tests conducted. We will follow the methodology proposed by Kelley and Maxell to estimate the sample size for survey questions.[27] Based on the study parameters, a sample size of 2,000 was determined sufficient to achieve a conjunctive power of 0.8 or higher at a significance level 0.05.[17]

Statistical Analysis Plan

Demographic variables will be summarized using descriptive statistics (e.g., Mean ± *SD* or median with interquartile range), as appropriate for continuous variables, and frequency and percentage for categorical variables. Data quality will be checked, including steps like outlier detection.[28] The distribution of all variables will be examined to check the validity of distribution assumptions before subsequent analyses, using univariate/multivariate Shapiro-Wilk test and a visual inspection of histograms and quantile-quantile plots. If the normal assumption of continuous variables is not met, appropriate data transformations or alternative data analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and figures, with reporting the corresponding *p*-values from independent samples t-test (or Kruskal-Wallis test when appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 sets as threshold. Variables that differ will be treated as covariates in all final models to maximize power. In our analysis of vaccination rates between ADRD/MCI individuals and those without ADRD/MCI, we will employ generalized linear regression to quantify the relationship between the outcome variable (vaccination rates for first dose, second dose and boosters) and the selected covariates. These covariates include the ADRD/MCI cohort or non-ADRD/MCI cohort, as well as age, race/ethnicity, sex, gender, language speaking, living status, income, healthcare facility accessibility, supportive relationships with neighborhood and healthcare providers, etc. Vaccine hesitancy will be computed and compared across cohorts using Chi-Squared tests. To analyze the association of vaccine hesitancy (i.e., individuals reported how likely to get vaccinated) with covariates, we will employ a multilevel logistic regression with vaccine hesitancy as the outcome, and covariates as controlled variables. This approach will enable us to compute the adjusted odds ratios (AOR) to determine the likelihood of vaccine hesitancy.[29] An AOR greater than 1 indicates higher odds for vaccine hesitancy, meaning individuals who are less likely to take the vaccination have high vaccine hesitancy.[29] 95% confidence intervals for each coefficient's adjusted odds ratios will be calculated. Python will be used to perform data processing and statistical analyses where appropriate.

Data Management and Safety

All datasets will be stored on *All of Us* Research Benchwork. Data filtering will be performed on the *AoU* Research platform. Data will be analyzed using R or Python. Our research team has experience using Python programming language and has pilot cohorts developed in the *AoU* Research platform and used for analysis. We will adhere to *AoU* Research Benchwork data protection regulations and data use guidelines.

Significance

The proposed study will contribute to scientific knowledge in several ways: Firstly. it will conduct a comprehensive analysis of vaccination coverage for individuals with ADRD/MCI by examining the first, second, and booster shots. This in-depth examination will shed light on any significant differences in vaccination behavior and adverse reactions between individuals with ADRD/MCI and those without. Such comparisons can provide insights into the unique challenges faced by individuals with ADRD/MCI. This is particularly important where booster shots have become a critical component of maintaining immunity. Additionally, this comprehensive study can provide insights into long-term vaccination behaviors and trends. Secondly, The study will assess adverse reactions to COVID vaccines among individuals with ADRD/MCI and those without. This information can offer valuable data on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then make more informed decisions about vaccine administration and monitoring. Thirdly, the study will integrate social

determinants of health into its analysis. recognizing the potential influence of social determinants of health on vaccination rates is crucial. Equitable vaccination plays an important role in mitigating health-related disparities among minority groups. This study goes beyond the clinical aspect and delves into the broader factors affecting healthcare access and decision-making. Lastly, the research findings will directly inform public health strategies and interventions. The research findings can directly inform public health strategies and interventions. If it is found that individuals with ADRD/MCI are more hesitant to receive booster shots, public health strategies can be tailored to address their specific concerns and needs. Policymakers and healthcare providers can use the study's results to make evidence-based decisions regarding vaccine distribution, outreach, and support for individuals with ADRD/MCI.

Overall, the proposed study will contribute to scientific knowledge by providing a comprehensive analysis of vaccination coverage, adverse reactions, and social determinants of health among individuals with ADRD/MCI. The insights gained from this study can inform public health strategies and interventions, improve vaccine administration and monitoring in vulnerable populations, and help address healthcare disparities.

Abbreviations

ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Ethics and Dissemination

This study has obtained the approval from the Institutional Review Board at Florida State University Office of Research (STUDY00004571). This secondary research utilized deidentified pre-existing data. Findings will be published in peer-reviewed journals and disseminated at conferences and through social media.

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Author contributions

YJY wrote the first draft of the protocol and JW and HJP led the editing and review. All authors reviewed the study, read, and approved the protocol.

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Data statement

The findings of the present study were supported by data accessible through the All of Us Research Workbench, which is available to registered researchers with an institutional Data Use and Registration Agreement (DURA).

Conflict of Interest

The authors declare that they have no competing interests.

Patient and public involvement

Patients and/or the public are not involved in the design, conduct, reporting, or dissemination plans.

Consent for publication

Not applicable.

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Comparing COVID-19 Vaccination Coverage, Adverse Reactions, and Impact of Social Determinants of Health on Vaccine Hesitancy in ADRD/MCI and Non-ADRD/MCI Population: Protocol for a Retrospective Cross-Sectional Study

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Comparing COVID-19 Vaccination Coverage, Adverse Reactions, and Impact of Social Determinants of Health on Vaccine Hesitancy in ADRD/MCI and Non-ADRD/MCI Population：Protocol for a Retrospective Cross-Sectional Study

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Keywords. Alzheimer's disease, Alzheimer's disease related dementias (ADRD), mild cognitive impairment, COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.

Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Abstract

Introduction. COVID-19 vaccination is crucial for vulnerable people with underlying chronic conditions such as Alzheimer's disease and related dementias (ADRD) and mild cognitive impairment (MCI). These individuals face unique challenges, including higher risk of COVID-19, difficulties in adopting preventive behaviors, and vaccine hesitancy due to concerns about adverse reactions. Therefore, efforts to promote vaccination, including boosters tailored to the currently circulating virus, are essential for people with ADRD/MCI.

Objective. The primary purpose of this study protocol is to conduct a comprehensive analysis of COVID-19 vaccination coverage and adverse reactions among individuals with ADRD/MCI in comparison to those without ADRD/MCI. Additionally, the proposed study aims to investigate the impact of social determinants of health on COVID-19 vaccination and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Analysis. A retrospective cross-sectional study will be conducted utilizing data from the *All of Us (AoU)* Researcher Workbench. Relevant data fields are extracted from sources including demographic information, COVID-19 Vaccine Survey, Basic Survey, Health Access & Utilization, Social Determinants of Health, and Electronic Health Record (EHR) data. Data on vaccination, adverse reactions and vaccine hesitancy will be collected through COVID-19 vaccine survey questionnaires. Propensity score matching and binary logistic regression will be applied to assess the vaccination rates and vaccine hesitancy, while controlling for demographic characteristics and social determinants of health factors.

Ethics and Dissemination. This study protocol received approval from the Institutional Review Board at Florida State University (STUDY00004571). Results will be disseminated through publication in peer-reviewed journals and presented at scientific conferences.

(Word Count: 250)

Article Summary

Strengths and Limitations

A comprehensive study of COVID-19 vaccination rates and hesitancy based on the diverse population and integrated data from EHR and COVID-19 panel survey within the *AoU* Research Workbench.

Over 75% of *AoU* participants are underrepresented populations from all 50 states in the U.S., which addresses the barriers and vaccine disparities.

The propensity score matching enables comparable COVID-19 vaccination rates and hesitancy between ADRD/MCI and non-ADRD/MCI cohort by controlling socio-demographic factors, chronic conditions, and mental health status.

One limitation of this proposed study is the limited availability of records pertaining to COVID-19 vaccination boosters, particularly the 4th dose and beyond, in the *AoU* vaccine survey conducted during 2021 and early 2022.

Background

Coronavirus disease 2019 (COVID-19) vaccines are pivotal in preventing the severe acute respiratory syndrome and long-term symptoms, and reducing mortality associated with COVID-19.[1-5] Previous studies have demonstrated the significant association between Alzheimer's disease (AD) and increased risk of COVID-19 infection and mortality.[6,7] Individuals with dementia are particularly vulnerable, facing a 2 to 3-fold greater risk of COVID-19 infection partly due to increased levels of angiotensin-converting enzyme 2 (ACE2) compared to the general older adults.[7,8] Additionally, individuals with Alzheimer's disease and related dementias (ADRD) encounter challenges in adopting protective behaviors to mitigate infection risks.[9,10]

As COVID -19 vaccine become available, studies on understanding vaccination rates in targeted population has gained significance. Previous studies had compared vaccination rates against COVID-19 between different socio-demographic population and chronic conditions. A study focused on community vulnerability found that socioeconomic vulnerability, housing type and composition, and epidemiological factors were associated with at least a 1.0 percentage point decline in county-level vaccination among the U.S. population.[11] Another study in the UK also found that ethnic minorities groups had lower age-standardized rates of vaccination compared with the white British population.[12] Mazereel et al. found that vaccine uptake among people with psychiatric disorders were high and comparable to the general population. However, there still lacks sufficient evidence of comparing vaccination rates among ADRD/MCI people.

Increasing vaccination rates play a pivotal role in fostering herd immunity against COVID-19, which serves to curb virus transmission and safeguard those who are more susceptible to COVID-19 adverse consequences.[13] Following the introduction of COVID-19 vaccines, a noticeable reduction in pandemic-related excess deaths was observed among individuals with ADRD.[9] Despite progress, patients with dementia are at a higher risk of breakthrough infections compared to patients without dementia,[14,15] emphasizing the importance of accessible booster shots, especially for vulnerable populations with underlying health conditions and comorbidities.[16,17] As of October 2022, 111,367,843 people, equivalent to 34% of the U.S. population, have received booster shots.[18] While ADRD patients and their caregivers exhibit willingness to facilitate vaccination, a substantial portion of them express concerns about potential adverse events.[19-21] In the example of influenza vaccine, vaccination barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and ethnicity, income, culture beliefs, dementia related symptoms), inter-personal level influences (relationships with caregivers, informal caregiver distress), and extra-personal level influences (media impact, religiosity, living accommodations).[22] Understanding the impact of individual, interpersonal, and community level social determinants on COVID-19 vaccination intent and hesitancy among individuals with ADRD/MCI still requires further exploration.[23,24]

This study aims to provide a comprehensive comparison of vaccination coverage, including at least one dose, two doses, and boosters or three full doses, along with adverse reactions between ADRD/MCI individuals and those without ADRD/MCI. Additionally, this study seeks to examine the impact of social determinants of health on COVID-19 vaccination rates and vaccine hesitancy among individuals with ADRD/MCI. By gaining a better understanding of these factors, we can develop targeted strategies to improve vaccination rates and address concerns among this vulnerable population.

Objective of Study Protocol

Research Aim 1: To determine the difference in COVID-19 vaccination rates (at least one dose, two doses, and boosters or three full doses) between ADRD/MCI individuals and those without ADRD/MCI.

Research Aim 2: To assess the variation in adverse reactions such as swelling, tiredness, muscle pain, chills, fever, following the COVID-19 vaccination in individuals with ADRD/MCI compared to those without ADRD/MCI.

Research Aim 3: To investigate the influence of social determinants of health on COVID-19 vaccination rates and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Data Analysis

Data Source: *All of Us (AoU)* Researcher Workbench

The data source for this study protocol will be the *All of Us (AoU)* Researcher Workbench, which is a secure and comprehensive source of biomedical datasets enrolled with a broad, diverse group of United States(U.S.) populations.[25,26] These datasets consists of diverse range of U.S. population, ensuring inclusively and representation. The *AoU* Research Workbench seeks to engage individuals from underrepresented demographic groups, promoting diversity in research.[27] The *AoU* Research Program encompasses various data elements, including participants' basic demographic information, responses to health surveys, physical measurements, biospecimen collection (including blood, urine, and saliva samples stored in the secure *AoU* biobank), structured electronic health records (EHRs), and Fitbit tracker data collected from one million participants across the U.S.[28] The EHR data is available since *AoU* participants enrolled in the program in 2018. Each participant has completed informed consent for sharing their EHR data with the data and research center, and they provide survey responses covering various domains on an ongoing basis.[28,29] Specifically, we will extract relevant data fields from sources such as the Demographics, Basic Survey, COVID-19 Vaccine Survey, Health Access & Utilization, Social Determinants of Health, and EHR conditions data. Enrollment for the *AoU* program commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research initiative successfully extended invitations to one million individuals nationwide.[30] The diverse population and data integration from multiple sources within the *AoU* Research Workbench allow for a comparative analysis of vaccination rates, adverse reactions, and the influence of social determinants of health on vaccine hesitancy between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The deidentified data are accessible through the *AoU* researcher workbench (https://workbench.researchallofus.org), under institutional data use agreements.[31] All analyses will be conducted within a secure platform provided by *AoU* Researcher Workbench. The study protocol and *AoU* materials have received approval from the Institutional Review Board at Florida State University Office of Research.

Workspace on the *AoU* Researcher Workbench Secure Platform: ADRD/MCI and COVID-19 Vaccination

We have established a workspace named "ADRD/MCI and COVID-19 Vaccination" within the *AoU* Researcher Workbench. This cloud-based platform grants authorized researchers access to and the ability to analyze data from the *AoU*. The platform offers two levels of data access: the registered tier and the controlled tier. We have been granted access to the controlled data tier. Within this controlled tier, we have constructed two distinct cohorts: one consists of individuals with ADRD/MCI and the other consists of those without ADRD/MCI. Cohort formation was based on participants' electronic health records (EHRs), including International Classification of Diseases (ICD) codes related to ADRD/MCI as original source concepts, as well as standard concepts grouped based on the ICD coding and classification. We applied appropriate logical operators such as "AND" and "OR" to combine the key inclusion and exclusion criteria. To facilitate our research, we utilized the dataset builder tool to construct the datasets. Subsequently, we exported the acquired data to Jupyter Notebooks for analysis, leveraging the R programming language version 4.3 (R Foundation for Statistical Computing) and Python version 3.12 (Python Software Foundation).

1) ADRD/MCI Cohort

The ADRD/MCI cohort is formed by gathering information from EHR .Through EHR, individuals are identified for inclusion in the ADRD/MCI cohort if they have been diagnosed with any of the following ICD-9/10 conditions: "mild cognitive impairment" or "Alzheimer's disease" or "dementia" or "dementia with or without behavioral and psychological symptoms" or "vascular dementia" or "Lewy body dementia" or "frontotemporal dementia". Deceased people are excluded. (**Supplementary Table 1**)

2) Non-ADRD/MCI Cohort

Individuals who have been diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease and related dementias (ADRD) are excluded. Additionally, deceased people are excluded from this cohort.

Outcome Variables

COVID-19 vaccination rates, adverse reactions and vaccine hesitancy will be assessed through EHR drug exposures and COVID-19 Vaccine Survey Questionnaires administered throughout the summer, fall, winter of 2021 and new year 2022. The vaccine survey questionnaires contain inquiries about receiving the first dose/second dose/boosters of COVID-19 vaccination, adverse reactions after vaccination (e.g., swelling, fever, headache, muscle pain, etc.), and how likely people are to get vaccinated and reasons that make people hesitate to get the vaccine. The respondents will indicate how likely or unlikely they would be vaccinated on a 5-point Likert scale, ranging from "very likely" to "very unlikely". **(Table 1)**

Independent Variables Social determinants of health at Individual, Interpersonal and Community Level Factors **(Table 1)**

The study protocol encompasses social determinants of health at three levels: individual, interpersonal, and community. Individual level factors include Individual demographics, chronic conditions, and mental health status. Chronic conditions related to ADRD/MCI and COVID-19 vaccination rates include[32,33]: hypertension, cerebrovascular disease, cerebral infarction, overweight and obesity, diabetes, coronary artery disease, heart failure, myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cancer, and mental health disorders.

Interpersonal level factors for ADRD/MCI patients consist of sociocultural environment and social support, as assessed in the *AoU* Basic Survey and *AoU* Social Determinants of Health Survey, with affirmative responses to the following questions: a) "Do you own or rent the place where you live?" b) "Where are you currently living?" c) "How many years have you lived at your current address?" d)"What is the main type of housing in your neighborhood?" e) "Not including yourself, how many other people live at home with you?" f) "how much you agree or disagree that people around here are willing to help their neighbor?" and g) "how much you agree or disagree that people in your neighborhood generally get along with each other?".

Community level factors include healthcare facility accessibility and utilization, as assessed in the *AoU* Health Access & Utilization Survey, with affirmative responses to the following questions: a) "During the past 12 months, were you told by a health care provider or doctor's office that they did not accept your health care coverage?" b) "What kind of place that you usually go to when you are sick or need advice about your health?" c) "Have you seen any of the following doctors or health care providers about your own health in the last 12 months?" – a general doctor; a nurse practitioner; a doctor specialized in women's health; a mental health professional; an optometrist; a podiatrist; a chiropractor; a physical therapist; a dentist; a medical doctor; traditional healers; d)"Have you delayed getting care for any of the following reasons in the past 12 months?" – didn't have transportation; live in the rural area where distance to health care provider is too far; nervous about seeing a health care provider; couldn't get time off work; couldn't get child care; couldn't get elderly care; couldn't afford the co-pay; couldn't afford the deductible; had to pay out of pocket for some or all of the procedure.

Table 1. Measurement Matrix

	Study Variables	Measure	Data Source
Outcomes	Vaccination rates	Did you receive the first dose, second dose and boosters of the COVID-19 vaccination: Yes; No; Not sure; Skip. EHR drug exposure with SARS-COV-2 (COVID-19) vaccination records.	*AoU* COVID-19 Vaccine Survey *& AoU* EHR Drug exposures
	Adverse reactions	Adverse reactions include swelling, fever, Guillain-Barre syndrome, headache, tiredness, muscle pain, chills, nausea, severe allergic reaction (anaphylaxis).	*AoU* COVID-19 Vaccine Survey
	Vaccine hesitancy	When a COVID-19 vaccine is available, how likely are you to get vaccinated: Very likely; Likely; I do not know yet; Unlikely; Very unlikely; Skip.	*AoU* COVID-19 Vaccine Survey
Cohorts	ADRD/MCI and non-ADRD/MCI	ICD-9/10 diagnosed conditions such as “mild cognitive impairment” or “Alzheimer’s disease” or “dementia”, or positive responses related to ADRD/MCI diagnosis in the EHR data.	*AoU* EHR Conditions
Individual level factors	Demographics	Age, sex at birth, gender, race, ethnicity.	*AoU* Basic Survey
	Chronic Conditions	Chronic conditions related with ADRD/MCI and mental health status: hypertension, cerebrovascular disease, cerebral infarction, overweight and obesity, diabetes, coronary artery disease, heart failure, myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cancer, anxiety, major depressive disorder, bipolar disorder, psychotic disorder, sleep disorder	*AoU* EHR Conditions
Interpersonal level factors	Sociocultural environment and social support	Living status, type of residence, household and neighborhood environment, years of living at residency.	*AoU* Social Determinants of Health Survey *& AoU* Basic Survey
Community level factors	Healthcare accessibility and Utilization	Healthcare insurance coverage accepted by health care providers, place for healthcare services, number of visits for general doctors, nurse practitioners, physician assistants, obstetricians/gynecologists, midwives, and reasons for delayed medical care.	*AoU* Health Access & Utilization Survey

Samples

We have set up study cohorts and preliminary datasets within the *AoU* researcher workbench to assess the availability of essential variables for this study protocol. After conducting an initial screening within the *AoU* Researcher Workbench, we have identified a sample size of 157,281 individuals with COVID-19 vaccination information in either EHR drug exposures domain or the COVID-19 vaccine survey. Among these individuals, 9,718 (6%) were diagnosed with ADRD/MCI conditions, and the remaining 110,355 without ADRD/MCI conditions; 37,208 individuals without EHR data are excluded. Through 1:1 propensity score matching, 9,718 individuals without ADRD/MCI are paired with 9,718 individuals with ADRD/MCI via balancing the demographics, chronic diseases, and mental health status. **(Figure 1 & Table 2)**

Table 2. Demographic Characteristics, Chronic Diseases and Mental Health Status of ADRD/MCI and non-ADRD/MCI cohorts Before 1:1 Propensity Score Matching, All of Us Research Workbench

Demographics	ADRD/MCI Cohort (N=9,718)	Non-ADRD/MCI Cohort (N=110,355)
Age, N (%)		
18-44	771 (8)	25,410 (23)
45-64	2,712 (28)	36,463 (33)
>65	6,235 (64)	48,482 (44)
Gender, N (%)		
Male	3,663 (38)	38,457 (35)
Female	5,745 (59)	68,807 (62)
Other (Non-binary, Transgender, Additional options, Prefer not to answer)	90 (1)	920 (1)
Skip or Uknown	220 (2)	2,171 (2)
Sex at Birth, N (%)		
Male	3,680 (38)	38,679 (35)
Female	5,773 (59)	69,254 (63)
Other (None, Intersex, Prefer not to answer)	7 (<1)	84 (<1)
Skip or Unknown	258 (3)	2,338 (2)
Race, N (%)		
White	6,632 (68)	72,830 (66)
Black or African American	1,180 (12)	14,290 (13)
Asian	143 (2)	2,909 (3)
Middle Eastern or North African	49 (<1)	548 (<1)
Native Hawaiian or Other Pacific Islander	4 (<1)	65 (<1)
Multiple-racial	156 (2)	1,811 (2)
Other (None indicated, Prefer not to answer)	1,235 (13)	15,036 (14)
Skip	319 (3)	2,866 (3)
Ethnicity, N (%)		
Hispanic or Latino	1,166 (12)	15,849 (14)
Non-Hispanic or Latino	8,034 (83)	90,266 (82)
Other (None of these, Prefer not to answer)	199 (2)	1,374 (1)
Skip	319 (3)	2,866 (3)
Chronic Conditions, N (%)		
Hypertension	7,033 (72)	49,455 (45)
Coronary artery disease	2,741 (28)	13,464 (12)
Cerebrovascular diseases	3,086 (32)	7,162 (6)
Heart failure	1,962 (20)	8,596 (8)
Myocardial infarction	1,172 (12)	4,998 (5)
Cerebral infarction	1,181 (12)	3,010 (3)
Overweight/Obesity	4,784 (49)	34,230 (31)
Diabetes	3,498 (36)	21,586 (20)
Chronic obstructive pulmonary disease	1,859 (19)	8,318 (8)
Chronic kidney diseases	2,010 (21)	9,871 (9)
Chronic liver diseases	1,198 (12)	6,030 (5)
Cancer	3,613 (37)	23,945 (22)
Mental Health Status		
Anxiety	5,913 (61)	32,843 (30)
Major depressive disorders	6,012 (62)	30,200 (27)
Bipolar disorders	1,126 (12)	4,381 (4)
Psychotic disorders	902 (9)	2,676 (2)
Sleep disorders	6,306 (65)	33,012 (30)

Sample Size and Power Calculation

A two-group retrospective cohort design is used in this study protocol. The sample size calculation is powered by the outcomes. The changes in vaccination rate and vaccination hesitancy will be compared between the ADRD/MCI groups and individuals without ADRD/MCI. Hence, there will be a total of two statistical tests conducted. We will follow the methodology proposed by Kelley and Maxell to estimate the sample size for survey questions.[34] Based on the study parameters, a sample size of 2,000 was determined sufficient to achieve a conjunctive power of 0.8 or higher at a significance level 0.05.[21]

Statistical Analysis Plan

Demographic variables will be summarized using descriptive statistics (e.g., Mean ± *SD* or median with interquartile range) as appropriate for continuous variables. Frequency and percentage will be summarized for categorical variables. Data quality will be checked, including steps like outlier detection.[35] The distribution of all variables will be examined to check the validity of distribution assumptions before subsequent analyses, using univariate/multivariate Shapiro-Wilk test and a visual inspection of histograms and quantile-quantile plots. If the normal assumption of continuous variables is not met, appropriate data transformations or alternative data analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and figures, with reporting the corresponding *p*-values from independent samples t-test (or Kruskal-Wallis test when appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 sets as threshold.

In our planned analysis of vaccination rates between ADRD/MCI individuals and those without ADRD/MCI, we utilize propensity score matching to evaluate the vaccination rate difference between the two cohorts while controlling the selected covariates. Propensity score matching is a statistical matching technique used with observational data which attempts to construct a balanced intervention and control group by matching each intervention unit with a controlled unit of similar characteristics.[36] The propensity score is a balancing score, the distribution of baseline covariates will be similar between cohorts.[37] In this retrospective observational study, the cohorts of ADRD/MCI and non-ADRD/MCI individuals are not randomly selected, leading to an imbalance sample sizes and uncontrolled baseline characteristics. This imbalance may cause confounding effects on the vaccination rates. To control the confounding effects, we generate propensity scores using logistic regression to identify the effects of confounding covariates, with the nearest available Mahalanobis metric matching applied to obtain 1:1 matched pair between ADRD/MCI and non-ADRD/MCI cohorts. The balanced covariates in the propensity score matching include age, gender, sex at birth, race, ethnicity, chronic diseases, and mental health status. The goal of propensity score matching is to achieve a balanced distribution of covariates between the ADRD/MCI and non-ADRD/MCI groups. We assess the effectiveness of matching by comparing the effective size of each included covariate before and after matching, with a decrease in effective size indicating balanced pairs. The results of propensity logit will be presented in the histogram, and standardized mean differences across covariates before and after matching are reported. The study utilizes the 'psmpy 0.3.13' propensity score matching package for propensity logits and graphical representations of matching outcomes, as well as matched pairs and standardized mean differences across covariates.[38]

Vaccine hesitancy will be computed and compared across cohorts using Chi-Squared tests. To analyze the association of vaccine hesitancy (i.e., individuals reported how likely to get vaccinated) with covariates, we will employ a binary logistic regression with vaccine hesitancy as the outcome (5-point Likert scale recategorized to binary outcome: likely or unlikely), and covariates as controlled variables. This approach will enable us to compute the adjusted odds ratios (AOR) to determine the likelihood of vaccine hesitancy.[39] An AOR greater than 1 indicates higher odds for vaccine hesitancy, meaning individuals who are unlikely to take the vaccination have high vaccine hesitancy.[39] 95% confidence intervals for each coefficient's adjusted odds ratios will be calculated. The statistical analysis is performed on Jupyter Notebooks, leveraging the R programming language version 4.3 (R Foundation for Statistical Computing) and Python version 3.12 (Python Software Foundation).

Data Management and Safety

All datasets will be stored on *All of Us* Research Benchwork. Data filtering will be performed on the *AoU* Research platform. Data will be analyzed using R or Python. Our research team has experience using Python programming language and has pilot cohorts developed in the *AoU* Research platform and used for analysis. We will adhere to *AoU* Research Benchwork data protection regulations and data use guidelines.

Discussion

As of May 2023, at least 270,227,181 individuals, constituting 81% of the U.S. population, have received at least one COVID-19 vaccine dose. Furthermore, 230,637,348 people, equivalent to 70% of the population, have achieved full vaccination status.[18] This high rate is considered a highly positive development against the COVID-19 pandemic, due to the vulnerability of older adults with underlying chronic diseases who are at a great risk of severe complications.[40]

Individuals with ADRD/MCI had a higher age compared with those without ADRD/MCI. Among the 9,718 ADRD/MCI patients, 8% were aged 18-44 (n=771), 28% were aged 45-64 (n=2,712), and 64% were aged over 65 (n=6,235). In the case of the 110,355 non-ADRD/MCI patients, 23% were aged 18-44 (n=25,410), 33% were aged 45-64 (n=36,463), and 44% were over 65 years old (n=48,482). Individuals with ADRD/MCI had higher rates of chronic conditions and mental health disorders. In comparison to the non-ADRD/MCI cohort, patients with ADRD/MCI had higher prevalence of hypertension, heart diseases, cerebrovascular diseases, overweight/obesity, diabetes, chronic pulmonary diseases, chronic kidney and liver diseases, and cancer. These findings align with reports from the Alzheimer's Association and other previous research.[32,41] Additionally, studies indicate that obesity has become the top risk factor for dementia in the US.[42] Individuals with ADRD/MCI also displayed a higher prevalence of mental health disorders compared to those without ADRD/MCI.

The proposed study will contribute to scientific knowledge in several ways: First, it will be a comprehensive analysis of vaccination coverage for individuals with ADRD/MCI by examining the first, second, and booster shots. This in-depth examination will shed light on any significant differences in vaccination behavior and adverse reactions between individuals with ADRD/MCI and those without. Such comparisons can provide insights into the unique challenges faced by individuals with ADRD/MCI. This is particularly important where booster shots have become a critical component of maintaining immunity, this comprehensive study can provide insights into long-term vaccination behaviors and trends. Second, this proposed study will assess adverse reactions to COVID-19 vaccines among individuals with ADRD/MCI and those without. This information can offer valuable data on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then make more informed decisions about vaccine administration and monitoring. Third, the proposed study will integrate social determinants of health into its analysis. recognizing the potential influence of social determinants of health on vaccination rates is crucial. Equitable vaccination plays an important role in mitigating health-related disparities among minority groups. This proposed study goes beyond the clinical aspect and delves into the broader factors affecting healthcare access and decision-making. Lastly, the research findings will directly inform public health strategies and interventions. The research findings can directly inform public health strategies and interventions. If it is found that individuals with ADRD/MCI are more hesitant to receive booster shots, public health strategies can be tailored to address their specific concerns and needs. Policymakers and healthcare providers can use the study's results to make evidence-based decisions regarding vaccine distribution, outreach, and support for individuals with ADRD/MCI.

A limitation of this proposed study is the availability of records pertaining to COVID-19 vaccination boosters, particularly the 4th dose and beyond, are limited in the *AoU* vaccine survey conducted during 2021 and early 2022. Additionally, missing data on EHR records may influence the sample size and power of the analysis, serving as another limitation.

Overall, the proposed study will contribute to scientific knowledge by providing a comprehensive analysis of vaccination coverage, adverse reactions, and social determinants of health among individuals with ADRD/MCI. The insights gained from this study can inform public health strategies and interventions, improve vaccine administration and monitoring in vulnerable populations, and help address healthcare disparities.

Abbreviations

ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Ethics and Dissemination

This study protocol has obtained the approval from the Institutional Review Board at Florida State University Office of Research (STUDY00004571). This secondary research utilized deidentified pre-existing data. Findings will be published in peer-reviewed journals and disseminated at conferences and through social media.

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Author contributions

YJY conceived the idea for the study. YJY, JW, HJP, CDL and DS drafted, participated in manuscript editing and study design. YJY, CDL and DS performed the acquisition and interpretation of data for the work. All authors reviewed the study critically, accountable for all aspects of the work, and approved the study protocol.

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Data statement

The findings of the proposed study were supported by data accessible through the All of Us Research Workbench, which is available to registered researchers with an institutional Data Use and Registration Agreement (DURA).

Conflict of Interest

The authors declare that they have no competing interests.

Patient and public involvement

Patients and/or the public are not involved in the design, conduct, reporting, or dissemination plans.

Consent for publication

Not applicable. Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

Figure Legend

Figure 1. Study Flowchart of Participants in ADRD/MCI and non-ADRD/MCI Cohorts

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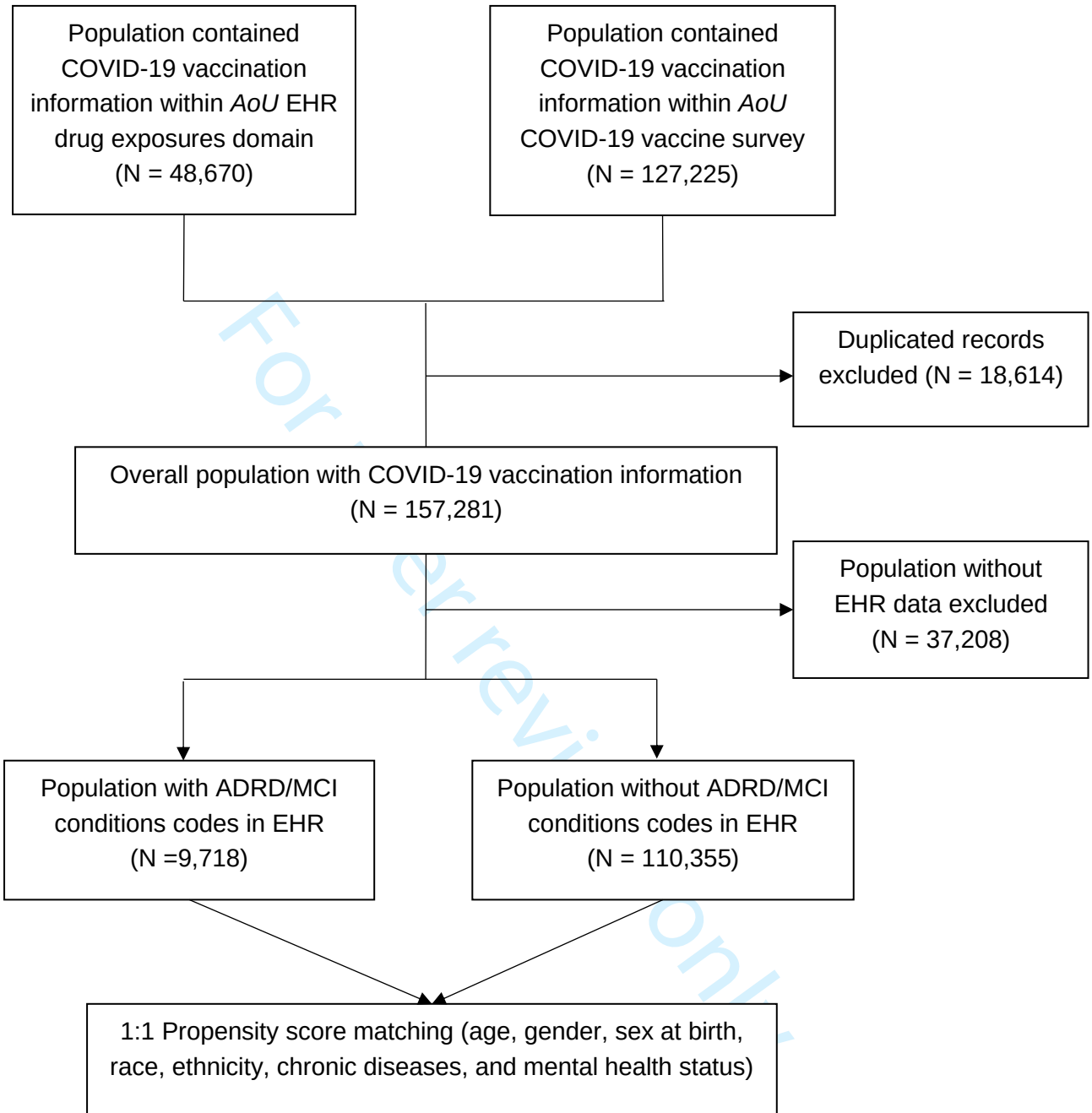
Figure 1. Study Flowchart of Participants in ADRD/MCI and non-ADRD/MCI Cohorts



Supplementary Table 1. ICD-9 and ICD-10 diagnosis codes for Alzheimer's disease and related dementias (ADRD) / mild cognitive impairment (MCI) and chronic conditions[41,43]

Medical Conditions	Code	Definition
Mild Cognitive Impairment		
ICD9	331.83	Mild cognitive impairment, so stated
ICD10	G31.84	Mild cognitive impairment, so stated
Alzheimer's disease and related dementias		
Alzheimer's disease		
ICD9	331.0	Alzheimer's disease
ICD10	G30	Alzheimer's disease
	G30.0	Alzheimer's disease with early onset
	G30.1	Alzheimer's disease with late onset
	G30.8	Other Alzheimer's disease
	G30.9	Alzheimer's disease, unspecified
Vascular dementia		
ICD9	290.4	Vascular dementia
	290.40	Vascular dementia, uncomplicated
	290.41	Vascular dementia, with delirium
	290.42	Vascular dementia, with delusions
	290.43	Vascular dementia, with depressed mood
ICD10	F01	Vascular dementia
	F01.5	Vascular dementia
	F01.50	Vascular dementia without behavioral disturbance
	F01.51	Vascular dementia with behavioral disturbance
Lewy Body Dementia		
ICD9	331.82	Dementia with Lewy bodies
ICD10	G31.83	Dementia with Lewy bodies
Frontotemporal Dementia		
ICD9	331.1	Frontotemporal Dementia
	331.11	Pick's disease
	331.19	Other frontotemporal dementia
ICD10	G31.0	Frontotemporal Dementia
	G31.01	Pick's disease
	G31.09	Other frontotemporal dementia
Mental Health Disorders		
Anxiety		
ICD9	300.0	Anxiety states
	300.00	Anxiety state, unspecified
	300.02	Generalized anxiety disorder
ICD10	F41	Other Anxiety disorders
	F41.0	Panic disorder [episodic paroxysmal anxiety]
	F41.1	Generalized anxiety disorder
	F41.8	Other specified anxiety disorders
	F41.9	Anxiety disorder, unspecified
Major Depressive Disorder		
ICD9	296.2	Major depressive disorder, single episode
	296.3	Major depressive disorder, recurrent
ICD10	F32.0-F32.9	Major depressive disorder
	F32.A	Depression, unspecified
	F33.0-F33.9	Major depressive disorder, recurrent
Bipolar Disorder		

ICD9	296.0-296.9	Bipolar disorders
ICD10	F31.0-F31.9	Bipolar disorders
Psychotic Disorder		
ICD9	295.0-295.9	Schizophrenic disorders
	297.0-297.9	Delusional disorders
ICD10	F20.0-F20.9	Schizophrenia
	F22	Delusional disorders
	F23	Brief psychotic disorder
	F24	Shared psychotic disorder
	F25.0, F25.1, F25.8, F25.9	Schizoaffective disorders
	F28	Other psychotic disorder not due to a substance or known physiological condition
	F29	Unspecified psychosis not due to a substance or known physiological condition
Sleep Disorder		
ICD9	307.4	Specific disorder of sleep of nonorganic origin
	327.0-327.8	Organic sleep disorders
	780.5	Sleep disturbances
ICD10	G47.0-G47.9	Sleep disorder
Chronic Conditions		
Hypertension		
ICD9	401.0, 401.1, 401.9	Essential hypertension
	405.0, 405.1, 405.9	Secondary hypertension
ICD10	I10	Essential (primary) hypertension
	I15	Secondary hypertension
	I1A	Other hypertension
Cerebrovascular Disease		
ICD9	436	Acute, but ill-defined, cerebrovascular disease
	437.0-437.9	Other and ill-defined cerebrovascular disease
	438.0-438.9	Late effects of cerebrovascular disease
ICD10	I67.0-I67.9	Other cerebrovascular diseases
	I68.0, I68.2, I68.8	Cerebrovascular disorders in diseases classified elsewhere
	I69.8, I69.9	Sequelae of cerebrovascular disease
Cerebral infarction		
ICD9	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
	433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
	434.01	Cerebral thrombosis with cerebral infarction
	434.11	Cerebral embolism with cerebral infarction
	434.91	Cerebral artery occlusion, unspecified with cerebral infarction
ICD10	I63.0-I63.9	Cerebral infarction
Overweight and Obesity		
ICD9	278.0	Overweight and obesity

	278.00	Obesity, unspecified
	278.01	Morbid obesity
	278.02	Overweight
	278.03	Obesity hypoventilation syndrome
ICD10	E66.0-E66.9	Overweight and obesity
Diabetes		
ICD9	250.0-250.9	Diabetes mellitus (Type 1 & 2)
ICD10	E10.1-E10.9	Type 1 diabetes mellitus
	E11.1-E11.9	Type 2 diabetes mellitus
Coronary artery disease		
ICD9	414.0	Coronary atherosclerosis
	414.2	Chronic total occlusion of coronary artery
	414.3	Coronary atherosclerosis due to lipid rich plaque
	414.4	Coronary atherosclerosis due to calcified coronary lesion
	414.8	Other specified forms of chronic ischemic heart disease
	414.9	Chronic ischemic heart disease, unspecified
ICD10	I25.1	Atherosclerotic heart disease of native coronary artery
	I25.8	Other forms of chronic ischemic heart disease
	I25.9	Chronic ischemic heart disease, unspecified
Heart failure		
ICD9	428.0	Congestive heart failure
	428.1	Left heart failure
	428.2	Systolic heart failure
	428.3	Diastolic heart failure
	428.4	Combined systolic and diastolic heart failure
	428.9	Heart failure, unspecified
ICD10	I50.1	Left ventricular failure, unspecified
	I50.2	Systolic (congestive) heart failure
	I50.3	Diastolic (congestive) heart failure
	I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure
	I50.8	Other heart failure
	I50.9	Heart failure, unspecified
Myocardial infarction		
ICD9	410.0-410.9	Acute myocardial infarction
ICD10	I21.0-I21.9	Acute myocardial infarction
	I21.A	Other type of myocardial infarction
	I21.B	Myocardial infarction with coronary microvascular dysfunction
Chronic obstructive pulmonary disease		
	493.20	Chronic obstructive asthma, unspecified
	493.21	Chronic obstructive asthma with status asthmaticus
	493.22	Chronic obstructive asthma with (acute) exacerbation
	496	Chronic airway obstruction, not elsewhere classified
ICD10	J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
	J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
	J44.8	Other specified chronic obstructive pulmonary disease
	J44.9	Chronic obstructive pulmonary disease, unspecified
Chronic kidney disease		
ICD9	585.1-585.5	Chronic kidney disease, Stage I-Stage V
	585.6	End stage renal disease
	585.9	Chronic kidney disease, unspecified
ICD10	N18.1-N18.5	Chronic kidney disease, stage 1-Stage 5

	N18.6	End stage renal disease
	N18.9	Chronic kidney disease, unspecified
Chronic liver disease		
ICD9	571.0-571.9	Chronic liver disease and cirrhosis
ICD10	K73.0-K73.9	Chronic hepatitis, not elsewhere classified
Cancer		
ICD9	140-239	Neoplasms
ICD10	C00-C96	Neoplasms
	D00-D49	Neoplasms

Sources:

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BMJ Open

Comparing COVID-19 Vaccination Coverage, Adverse Reactions, and Impact of Social Determinants of Health on Vaccine Hesitancy in ADRD/MCI and Non-ADRD/MCI Population: Protocol for a Retrospective Cross-Sectional Study

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Comparing COVID-19 Vaccination Coverage, Adverse Reactions, and Impact of Social Determinants of Health on Vaccine Hesitancy in ADRD/MCI and Non-ADRD/MCI Population：Protocol for a Retrospective Cross-Sectional Study

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Keywords. Alzheimer's disease, Alzheimer's disease related dementias (ADRD), mild cognitive impairment, COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.

Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Abstract

Introduction. COVID-19 vaccination is crucial for vulnerable people with underlying chronic conditions such as Alzheimer's disease and related dementias (ADRD) and mild cognitive impairment (MCI). These individuals face unique challenges, including higher risk of COVID-19, difficulties in adopting preventive behaviors, and vaccine hesitancy due to concerns about adverse reactions. Therefore, efforts to promote vaccination, including boosters tailored to the currently circulating virus, are essential for people with ADRD/MCI.

Objective. The primary purpose of this study protocol is to conduct a comprehensive analysis of COVID-19 vaccination coverage and adverse reactions among individuals with ADRD/MCI in comparison to those without ADRD/MCI. Additionally, the proposed study aims to investigate the impact of social determinants of health on COVID-19 vaccination and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Analysis. A retrospective cross-sectional study will be conducted utilizing data from the *All of Us (AoU)* Researcher Workbench. Relevant data fields are extracted from sources including demographic information, COVID-19 Vaccine Survey, Basic Survey, Health Access & Utilization, Social Determinants of Health, and Electronic Health Record (EHR) data. Data on vaccination, adverse reactions and vaccine hesitancy will be collected through COVID-19 vaccine survey questionnaires. Propensity score matching and binary logistic regression will be applied to assess the vaccination rates and vaccine hesitancy, while controlling for demographic characteristics and social determinants of health factors.

Ethics and Dissemination. This study protocol received approval from the Institutional Review Board at Florida State University (STUDY00004571). Results will be disseminated through publication in peer-reviewed journals and presented at scientific conferences.

(Word Count: 250)

Article Summary

Strengths and Limitations

A comprehensive study of COVID-19 vaccination rates and hesitancy based on the diverse population and integrated data from EHR and COVID-19 panel survey within the *AoU* Research Workbench.

Over 75% of *AoU* participants are underrepresented populations from all 50 states in the U.S., which addresses the barriers and vaccine disparities.

The propensity score matching enables comparable COVID-19 vaccination rates and hesitancy between ADRD/MCI and non-ADRD/MCI cohort by controlling socio-demographic factors, chronic conditions, and mental health status.

One limitation of this proposed study is the limited availability of records pertaining to COVID-19 vaccination boosters, particularly the 4th dose and beyond, in the *AoU* vaccine survey conducted during 2021 and early 2022.

Background

Coronavirus disease 2019 (COVID-19) vaccines are pivotal in preventing the severe acute respiratory syndrome and long-term symptoms, and reducing mortality associated with COVID-19.[1-5] Previous studies have demonstrated the significant association between Alzheimer's disease (AD) and increased risk of COVID-19 infection and mortality.[6,7] Individuals with dementia are particularly vulnerable, facing a 2 to 3-fold greater risk of COVID-19 infection partly due to increased levels of angiotensin-converting enzyme 2 (ACE2) compared to the general older adults.[7,8] Additionally, individuals with Alzheimer's disease and related dementias (ADRD) encounter challenges in adopting protective behaviors to mitigate infection risks.[9,10]

As COVID -19 vaccine become available, studies on understanding vaccination rates in targeted population has gained significance. Previous studies had compared vaccination rates against COVID-19 between different socio-demographic population and chronic conditions. A study focused on community vulnerability found that socioeconomic vulnerability, housing type and composition, and epidemiological factors were associated with at least a 1.0 percentage point decline in county-level vaccination among the U.S. population.[11] Another study in the UK also found that ethnic minorities groups had lower age-standardized rates of vaccination compared with the white British population.[12] Mazereel et al. found that vaccine uptake among people with psychiatric disorders were high and comparable to the general population. However, there still lacks sufficient evidence of comparing vaccination rates among ADRD/MCI people.

Increasing vaccination rates play a pivotal role in fostering herd immunity against COVID-19, which serves to curb virus transmission and safeguard those who are more susceptible to COVID-19 adverse consequences.[13] Following the introduction of COVID-19 vaccines, a noticeable reduction in pandemic-related excess deaths was observed among individuals with ADRD.[9] Despite progress, patients with dementia are at a higher risk of breakthrough infections compared to patients without dementia,[14,15] emphasizing the importance of accessible booster shots, especially for vulnerable populations with underlying health conditions and comorbidities.[16,17] As of October 2022, 111,367,843 people, equivalent to 34% of the U.S. population, have received booster shots.[18] While ADRD patients and their caregivers exhibit willingness to facilitate vaccination, a substantial portion of them express concerns about potential adverse events.[19-21] In the example of influenza vaccine, vaccination barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and ethnicity, income, culture beliefs, dementia related symptoms), inter-personal level influences (relationships with caregivers, informal caregiver distress), and extra-personal level influences (media impact, religiosity, living accommodations).[22] Understanding the impact of individual, interpersonal, and community level social determinants on COVID-19 vaccination intent and hesitancy among individuals with ADRD/MCI still requires further exploration.[23,24]

This study aims to provide a comprehensive comparison of vaccination coverage, including at least one dose, two doses, and boosters or three full doses, along with adverse reactions between ADRD/MCI individuals and those without ADRD/MCI. Additionally, this study seeks to examine the impact of social determinants of health on COVID-19 vaccination rates and vaccine hesitancy among individuals with ADRD/MCI. By gaining a better understanding of these factors, we can develop targeted strategies to improve vaccination rates and address concerns among this vulnerable population.

Objective of Study Protocol

Research Aim 1: To determine the difference in COVID-19 vaccination rates (at least one dose, two doses, and boosters or three full doses) between ADRD/MCI individuals and those without ADRD/MCI.

Research Aim 2: To assess the variation in adverse reactions such as swelling, tiredness, muscle pain, chills, fever, following the COVID-19 vaccination in individuals with ADRD/MCI compared to those without ADRD/MCI.

Research Aim 3: To investigate the influence of social determinants of health on COVID-19 vaccination rates and vaccine hesitancy in individuals with ADRD/MCI.

Methods and Data Analysis

Data Source: *All of Us (AoU)* Researcher Workbench

The data source for this study protocol will be the *All of Us (AoU)* Researcher Workbench, which is a secure and comprehensive source of biomedical datasets enrolled with a broad, diverse group of United States(U.S.) populations.[25,26] These datasets consists of diverse range of U.S. population, ensuring inclusively and representation. The *AoU* Research Workbench seeks to engage individuals from underrepresented demographic groups, promoting diversity in research.[27] The *AoU* Research Program encompasses various data elements, including participants' basic demographic information, responses to health surveys, physical measurements, biospecimen collection (including blood, urine, and saliva samples stored in the secure *AoU* biobank), structured electronic health records (EHRs), and Fitbit tracker data collected from one million participants across the U.S.[28] The EHR data is available since *AoU* participants enrolled in the program in 2018. Each participant has completed informed consent for sharing their EHR data with the data and research center, and they provide survey responses covering various domains on an ongoing basis.[28,29] Specifically, we will extract relevant data fields from sources such as the Demographics, Basic Survey, COVID-19 Vaccine Survey, Health Access & Utilization, Social Determinants of Health, and EHR conditions data. Enrollment for the *AoU* program commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research initiative successfully extended invitations to one million individuals nationwide.[30] The diverse population and data integration from multiple sources within the *AoU* Research Workbench allow for a comparative analysis of vaccination rates, adverse reactions, and the influence of social determinants of health on vaccine hesitancy between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The deidentified data are accessible through the *AoU* researcher workbench (https://workbench.researchallofus.org), under institutional data use agreements.[31] All analyses will be conducted within a secure platform provided by *AoU* Researcher Workbench. The study protocol and *AoU* materials have received approval from the Institutional Review Board at Florida State University Office of Research.

Workspace on the *AoU* Researcher Workbench Secure Platform: ADRD/MCI and COVID-19 Vaccination

We have established a workspace named "ADRD/MCI and COVID-19 Vaccination" within the *AoU* Researcher Workbench. This cloud-based platform grants authorized researchers access to and the ability to analyze data from the *AoU*. The platform offers two levels of data access: the registered tier and the controlled tier. We have been granted access to the controlled data tier. Within this controlled tier, we have constructed two distinct cohorts: one consists of individuals with ADRD/MCI and the other consists of those without ADRD/MCI. Cohort formation was based on participants' electronic health records (EHRs), including International Classification of Diseases (ICD) codes related to ADRD/MCI as original source concepts, as well as standard concepts grouped based on the ICD coding and classification. We applied appropriate logical operators such as "AND" and "OR" to combine the key inclusion and exclusion criteria. To facilitate our research, we utilized the dataset builder tool to construct the datasets. Subsequently, we exported the acquired data to Jupyter Notebooks for analysis, leveraging the R programming language version 4.3 (R Foundation for Statistical Computing) and Python version 3.12 (Python Software Foundation).

1) ADRD/MCI Cohort

The ADRD/MCI cohort is formed by gathering information from EHR .Through EHR, individuals are identified for inclusion in the ADRD/MCI cohort if they have been diagnosed with any of the following ICD-9/10 conditions: "mild cognitive impairment" or "Alzheimer's disease" or "dementia" or "dementia with or without behavioral and psychological symptoms" or "vascular dementia" or "Lewy body dementia" or "frontotemporal dementia". Deceased people are excluded. (**Supplementary Table 1**)

2) Non-ADRD/MCI Cohort

Individuals who have been diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease and related dementias (ADRD) are excluded. Additionally, deceased people are excluded from this cohort.

Patient and Public Involvement

There was no patient or public involvement in this research.

Outcome Variables

COVID-19 vaccination rates, adverse reactions and vaccine hesitancy will be assessed through EHR drug exposures and COVID-19 Vaccine Survey Questionnaires administered throughout the summer, fall, winter of 2021 and new year 2022. The vaccine survey questionnaires contain inquiries about receiving the first dose/second dose/boosters of COVID-19 vaccination, adverse reactions after vaccination (e.g., swelling, fever, headache, muscle pain, etc.), and how likely people are to get vaccinated and reasons that make people hesitate to get the vaccine. The respondents will indicate how likely or unlikely they would be vaccinated on a 5-point Likert scale, ranging from "very likely" to "very unlikely". **(Table 1)**

Independent Variables Social determinants of health at Individual, Interpersonal and Community Level Factors **(Table 1)**

The study protocol encompasses social determinants of health at three levels: individual, interpersonal, and community. Individual level factors include Individual demographics, chronic conditions, and mental health status. Chronic conditions related to ADRD/MCI and COVID-19 vaccination rates include[32,33]: hypertension, cerebrovascular disease, cerebral infarction, overweight and obesity, diabetes, coronary artery disease, heart failure, myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cancer, and mental health disorders.

Interpersonal level factors for ADRD/MCI patients consist of sociocultural environment and social support, as assessed in the *AoU* Basic Survey and *AoU* Social Determinants of Health Survey, with affirmative responses to the following questions: a) "Do you own or rent the place where you live?" b) "Where are you currently living?" c) "How many years have you lived at your current address?" d)"What is the main type of housing in your neighborhood?" e) "Not including yourself, how many other people live at home with you?" f) "how much you agree or disagree that people around here are willing to help their neighbor?" and g) "how much you agree or disagree that people in your neighborhood generally get along with each other?".

Community level factors include healthcare facility accessibility and utilization, as assessed in the *AoU* Health Access & Utilization Survey, with affirmative responses to the following questions: a) "During the past 12 months, were you told by a health care provider or doctor's office that they did not accept your health care coverage?" b) "What kind of place that you usually go to when you are sick or need advice about your health?" c) "Have you seen any of the following doctors or health care providers about your own health in the last 12 months?" – a general doctor; a nurse practitioner; a doctor specialized in women's health; a mental health professional; an optometrist; a podiatrist; a chiropractor; a physical therapist; a dentist; a medical doctor; traditional healers; d)"Have you delayed getting care for any of the following reasons in the past 12 months?" – didn't have transportation; live in the rural area where distance to health care provider is too far; nervous about seeing a health care provider; couldn't get time off work; couldn't get child care; couldn't get elderly care; couldn't afford the co-pay; couldn't afford the deductible; had to pay out of pocket for some or all of the procedure.

Table 1. Measurement Matrix

	Study Variables	Measure	Data Source
Outcomes	Vaccination rates	Did you receive the first dose, second dose and boosters of the COVID-19 vaccination: Yes; No; Not sure; Skip. EHR drug exposure with SARS-COV-2 (COVID-19) vaccination records.	*AoU* COVID-19 Vaccine Survey *& AoU* EHR Drug exposures
	Adverse reactions	Adverse reactions include swelling, fever, Guillain-Barre syndrome, headache, tiredness, muscle pain, chills, nausea, severe allergic reaction (anaphylaxis).	*AoU* COVID-19 Vaccine Survey
	Vaccine hesitancy	When a COVID-19 vaccine is available, how likely are you to get vaccinated: Very likely; Likely; I do not know yet; Unlikely; Very unlikely; Skip.	*AoU* COVID-19 Vaccine Survey
Cohorts	ADRD/MCI and non-ADRD/MCI	ICD-9/10 diagnosed conditions such as “mild cognitive impairment” or “Alzheimer’s disease” or “dementia”, or positive responses related to ADRD/MCI diagnosis in the EHR data.	*AoU* EHR Conditions
Individual level factors	Demographics	Age, sex at birth, gender, race, ethnicity.	*AoU* Basic Survey
	Chronic Conditions	Chronic conditions related with ADRD/MCI and mental health status: hypertension, cerebrovascular disease, cerebral infarction, overweight and obesity, diabetes, coronary artery disease, heart failure, myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, cancer, anxiety, major depressive disorder, bipolar disorder, psychotic disorder, sleep disorder	*AoU* EHR Conditions
Interpersonal level factors	Sociocultural environment and social support	Living status, type of residence, household and neighborhood environment, years of living at residency.	*AoU* Social Determinants of Health Survey *& AoU* Basic Survey
Community level factors	Healthcare accessibility and Utilization	Healthcare insurance coverage accepted by health care providers, place for healthcare services, number of visits for general doctors, nurse practitioners, physician assistants, obstetricians/gynecologists, midwives, and reasons for delayed medical care.	*AoU* Health Access & Utilization Survey

Samples

We have set up study cohorts and preliminary datasets within the *AoU* researcher workbench to assess the availability of essential variables for this study protocol. After conducting an initial screening within the *AoU* Researcher Workbench, we have identified a sample size of 157,281 individuals with COVID-19 vaccination information in either EHR drug exposures domain or the COVID-19 vaccine survey. Among these individuals, 9,718 (6%) were diagnosed with ADRD/MCI conditions, and the remaining 110,355 without ADRD/MCI conditions; 37,208 individuals without EHR data are excluded. Through 1:1 propensity score matching, 9,718 individuals without ADRD/MCI are paired with 9,718 individuals with ADRD/MCI via balancing the demographics, chronic diseases, and mental health status. **(Figure 1 & Table 2)**

Table 2. Demographic Characteristics, Chronic Diseases and Mental Health Status of ADRD/MCI and non-ADRD/MCI cohorts Before 1:1 Propensity Score Matching, All of Us Research Workbench

Demographics	ADRD/MCI Cohort (N=9,718)	Non-ADRD/MCI Cohort (N=110,355)
Age, N (%)		
18-44	771 (8)	25,410 (23)
45-64	2,712 (28)	36,463 (33)
>65	6,235 (64)	48,482 (44)
Gender, N (%)		
Male	3,663 (38)	38,457 (35)
Female	5,745 (59)	68,807 (62)
Other (Non-binary, Transgender, Additional options, Prefer not to answer)	90 (1)	920 (1)
Skip or Uknown	220 (2)	2,171 (2)
Sex at Birth, N (%)		
Male	3,680 (38)	38,679 (35)
Female	5,773 (59)	69,254 (63)
Other (None, Intersex, Prefer not to answer)	7 (<1)	84 (<1)
Skip or Unknown	258 (3)	2,338 (2)
Race, N (%)		
White	6,632 (68)	72,830 (66)
Black or African American	1,180 (12)	14,290 (13)
Asian	143 (2)	2,909 (3)
Middle Eastern or North African	49 (<1)	548 (<1)
Native Hawaiian or Other Pacific Islander	4 (<1)	65 (<1)
Multiple-racial	156 (2)	1,811 (2)
Other (None indicated, Prefer not to answer)	1,235 (13)	15,036 (14)
Skip	319 (3)	2,866 (3)
Ethnicity, N (%)		
Hispanic or Latino	1,166 (12)	15,849 (14)
Non-Hispanic or Latino	8,034 (83)	90,266 (82)
Other (None of these, Prefer not to answer)	199 (2)	1,374 (1)
Skip	319 (3)	2,866 (3)
Chronic Conditions, N (%)		
Hypertension	7,033 (72)	49,455 (45)
Coronary artery disease	2,741 (28)	13,464 (12)
Cerebrovascular diseases	3,086 (32)	7,162 (6)
Heart failure	1,962 (20)	8,596 (8)
Myocardial infarction	1,172 (12)	4,998 (5)
Cerebral infarction	1,181 (12)	3,010 (3)
Overweight/Obesity	4,784 (49)	34,230 (31)
Diabetes	3,498 (36)	21,586 (20)
Chronic obstructive pulmonary disease	1,859 (19)	8,318 (8)
Chronic kidney diseases	2,010 (21)	9,871 (9)
Chronic liver diseases	1,198 (12)	6,030 (5)
Cancer	3,613 (37)	23,945 (22)
Mental Health Status		
Anxiety	5,913 (61)	32,843 (30)
Major depressive disorders	6,012 (62)	30,200 (27)
Bipolar disorders	1,126 (12)	4,381 (4)
Psychotic disorders	902 (9)	2,676 (2)
Sleep disorders	6,306 (65)	33,012 (30)

Sample Size and Power Calculation

A two-group retrospective cohort design is used in this study protocol. The sample size calculation is powered by the outcomes. The changes in vaccination rate and vaccination hesitancy will be compared between the ADRD/MCI groups and individuals without ADRD/MCI. Hence, there will be a total of two statistical tests conducted. We will follow the methodology proposed by Kelley and Maxell to estimate the sample size for survey questions.[34] Based on the study parameters, a sample size of 2,000 was determined sufficient to achieve a conjunctive power of 0.8 or higher at a significance level 0.05.[21]

Statistical Analysis Plan

Demographic variables will be summarized using descriptive statistics (e.g., Mean ± *SD* or median with interquartile range) as appropriate for continuous variables. Frequency and percentage will be summarized for categorical variables. Data quality will be checked, including steps like outlier detection.[35] The distribution of all variables will be examined to check the validity of distribution assumptions before subsequent analyses, using univariate/multivariate Shapiro-Wilk test and a visual inspection of histograms and quantile-quantile plots. If the normal assumption of continuous variables is not met, appropriate data transformations or alternative data analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and figures, with reporting the corresponding *p*-values from independent samples t-test (or Kruskal-Wallis test when appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 sets as threshold.

In our planned analysis of vaccination rates between ADRD/MCI individuals and those without ADRD/MCI, we utilize propensity score matching to evaluate the vaccination rate difference between the two cohorts while controlling the selected covariates. Propensity score matching is a statistical matching technique used with observational data which attempts to construct a balanced intervention and control group by matching each intervention unit with a controlled unit of similar characteristics.[36] The propensity score is a balancing score, the distribution of baseline covariates will be similar between cohorts.[37] In this retrospective observational study, the cohorts of ADRD/MCI and non-ADRD/MCI individuals are not randomly selected, leading to an imbalance sample sizes and uncontrolled baseline characteristics. This imbalance may cause confounding effects on the vaccination rates. To control the confounding effects, we generate propensity scores using logistic regression to identify the effects of confounding covariates, with the nearest available Mahalanobis metric matching applied to obtain 1:1 matched pair between ADRD/MCI and non-ADRD/MCI cohorts. The balanced covariates in the propensity score matching include age, gender, sex at birth, race, ethnicity, chronic diseases, and mental health status. The goal of propensity score matching is to achieve a balanced distribution of covariates between the ADRD/MCI and non-ADRD/MCI groups. We assess the effectiveness of matching by comparing the effective size of each included covariate before and after matching, with a decrease in effective size indicating balanced pairs. The results of propensity logit will be presented in the histogram, and standardized mean differences across covariates before and after matching are reported. The study utilizes the 'psmpy 0.3.13' propensity score matching package for propensity logits and graphical representations of matching outcomes, as well as matched pairs and standardized mean differences across covariates.[38]

Vaccine hesitancy will be computed and compared across cohorts using Chi-Squared tests. To analyze the association of vaccine hesitancy (i.e., individuals reported how likely to get vaccinated) with covariates, we will employ a binary logistic regression with vaccine hesitancy as the outcome (5-point Likert scale recategorized to binary outcome: likely or unlikely), and covariates as controlled variables. This approach will enable us to compute the adjusted odds ratios (AOR) to determine the likelihood of vaccine hesitancy.[39] An AOR greater than 1 indicates higher odds for vaccine hesitancy, meaning individuals who are unlikely to take the vaccination have high vaccine hesitancy.[39] 95% confidence intervals for each coefficient's adjusted odds ratios will be calculated. The statistical analysis is performed on Jupyter Notebooks, leveraging the R programming language version 4.3 (R Foundation for Statistical Computing) and Python version 3.12 (Python Software Foundation).

Data Management and Safety

All datasets will be stored on *All of Us* Research Benchwork. Data filtering will be performed on the *AoU* Research platform. Data will be analyzed using R or Python. Our research team has experience using Python programming language and has pilot cohorts developed in the *AoU* Research platform and used for analysis. We will adhere to *AoU* Research Benchwork data protection regulations and data use guidelines.

Discussion

As of May 2023, at least 270,227,181 individuals, constituting 81% of the U.S. population, have received at least one COVID-19 vaccine dose. Furthermore, 230,637,348 people, equivalent to 70% of the population, have achieved full vaccination status.[18] This high rate is considered a highly positive development against the COVID-19 pandemic, due to the vulnerability of older adults with underlying chronic diseases who are at a great risk of severe complications.[40]

The authors compared the cohort of diagnosed Alzheimer's and related dementias (ADRD) individuals in the *AoU* research dataset to the ADRD prevalence in the U.S. population from the CDC and the 2024 Alzheimer's Disease Facts and Figures Report. According to the 2024 Alzheimer's Association Facts and Figures Report, approximately 6.9 million older adults aged over 65 have been diagnosed with ADRD,[41] along with about 200,000 individuals under age 65 with younger-onset dementia,[42] totaling around 7.1 million diagnosed individuals. This represents approximately 2% of the total U.S. population of 333.3 million. Our findings align with these statistics: in the *AoU* research dataset, we identified 9,718 participants diagnosed with ADRD and COVID-19 vaccination records out of a total of 410,235 enrolled *AoU* participants, representing 2% of the overall population. The distribution of chronic conditions in the ADRD cohort in our study, such as hypertension, diabetes, and cardiovascular disease, closely aligns with the statistics presented in the Alzheimer's Association's chronic diseases and dementia factsheet.[32] These findings enhance the generalizability of our sample to the broader U.S. population with ADRD.

Individuals with ADRD/MCI had a higher age compared with those without ADRD/MCI. Among the 9,718 ADRD/MCI patients, 8% were aged 18-44 (n=771), 28% were aged 45-64 (n=2,712), and 64% were aged over 65 (n=6,235). In the case of the 110,355 non-ADRD/MCI patients, 23% were aged 18-44 (n=25,410), 33% were aged 45-64 (n=36,463), and 44% were over 65 years old (n=48,482). Individuals with ADRD/MCI had higher rates of chronic conditions and mental health disorders. In comparison to the non-ADRD/MCI cohort, patients with ADRD/MCI had higher prevalence of hypertension, heart diseases, cerebrovascular diseases, overweight/obesity, diabetes, chronic pulmonary diseases, chronic kidney and liver diseases, and cancer. These findings align with reports from the Alzheimer's Association and other previous research.[32,43] Additionally, studies indicate that obesity has become the top risk factor for dementia in the US.[44] Individuals with ADRD/MCI also displayed a higher prevalence of mental health disorders compared to those without ADRD/MCI.

The proposed study will contribute to scientific knowledge in several ways: First, it will be a comprehensive analysis of vaccination coverage for individuals with ADRD/MCI by examining the first, second, and booster shots. This in-depth examination will shed light on any significant differences in vaccination behavior and adverse reactions between individuals with ADRD/MCI and those without. Such comparisons can provide insights into the unique challenges faced by individuals with ADRD/MCI. This is particularly important where booster shots have become a critical component of maintaining immunity, this comprehensive study can provide insights into long-term vaccination behaviors and trends. Second, this proposed study will assess adverse reactions to COVID-19 vaccines among individuals with ADRD/MCI and those without. This information can offer valuable data on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then make more informed decisions about vaccine administration and monitoring. Third, the proposed study will integrate social determinants of health into its analysis. recognizing the potential influence of social determinants of health on vaccination rates is crucial. Equitable vaccination plays an important role in mitigating health-related disparities among minority groups. This proposed study goes beyond the clinical aspect and delves into the broader factors affecting healthcare access and decision-making. Lastly, the research findings will directly inform public health strategies and interventions. The research findings can directly inform public health strategies and interventions. If it is found that individuals with ADRD/MCI are more hesitant to receive booster shots, public health strategies can be tailored to address their specific concerns and needs. Policymakers and healthcare

providers can use the study's results to make evidence-based decisions regarding vaccine distribution, outreach, and support for individuals with ADRD/MCI.

A limitation of this proposed study is the availability of records pertaining to COVID-19 vaccination boosters, particularly the 4th dose and beyond, are limited in the repeated *AoU* vaccine surveys conducted during the summer, fall, winter of 2021 and new year 2022. Additionally, missing data on EHR records may influence the sample size and power of the analysis, serving as another limitation. To address potential recall bias of adverse reactions associated with COVID-19 vaccination, the four repeated standardized surveys conducted every three months allowed us to cross-validate reported adverse events at different time points and reduce the likelihood of recall bias. Additionally, we will verify participants' EHR condition codes for adverse events to ensure accuracy and completeness.

Overall, the proposed study will contribute to scientific knowledge by providing a comprehensive analysis of vaccination coverage, adverse reactions, and social determinants of health among individuals with ADRD/MCI. The insights gained from this study can inform public health strategies and interventions, improve vaccine administration and monitoring in vulnerable populations, and help address healthcare disparities.

Abbreviations

ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants of health; AOR: Adjusted odds ratios.

Ethics and Dissemination

This study protocol has obtained the approval from the Institutional Review Board at Florida State University Office of Research (STUDY00004571). This secondary research utilized deidentified pre-existing data. Findings will be published in peer-reviewed journals and disseminated at conferences and through social media.

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Author contributions

YJY conceived the idea for the study. YJY, JW, HJP, CDL and DS drafted, participated in manuscript editing and study design. YJY, CDL and DS performed the acquisition and interpretation of data for the work. All authors reviewed the study critically, accountable for all aspects of the work, and approved the study protocol. YJY serves as the guarantor and accepts the responsibility for the overall content.

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Data statement

The findings of the proposed study were supported by data accessible through the All of Us Research Workbench, which is available to registered researchers with an institutional Data Use and Registration Agreement (DURA).

Conflict of Interest

The authors declare that they have no competing interests.

Patient and public involvement

Patients and/or the public are not involved in the design, conduct, reporting, or dissemination plans.

Consent for publication

Not applicable. Patients or the public WERE NOT involved in the design, conduct, reporting, or dissemination plans of our research.

Figure Legend

Figure 1. Study Flowchart of Participants in ADRD/MCI and non-ADRD/MCI Cohorts

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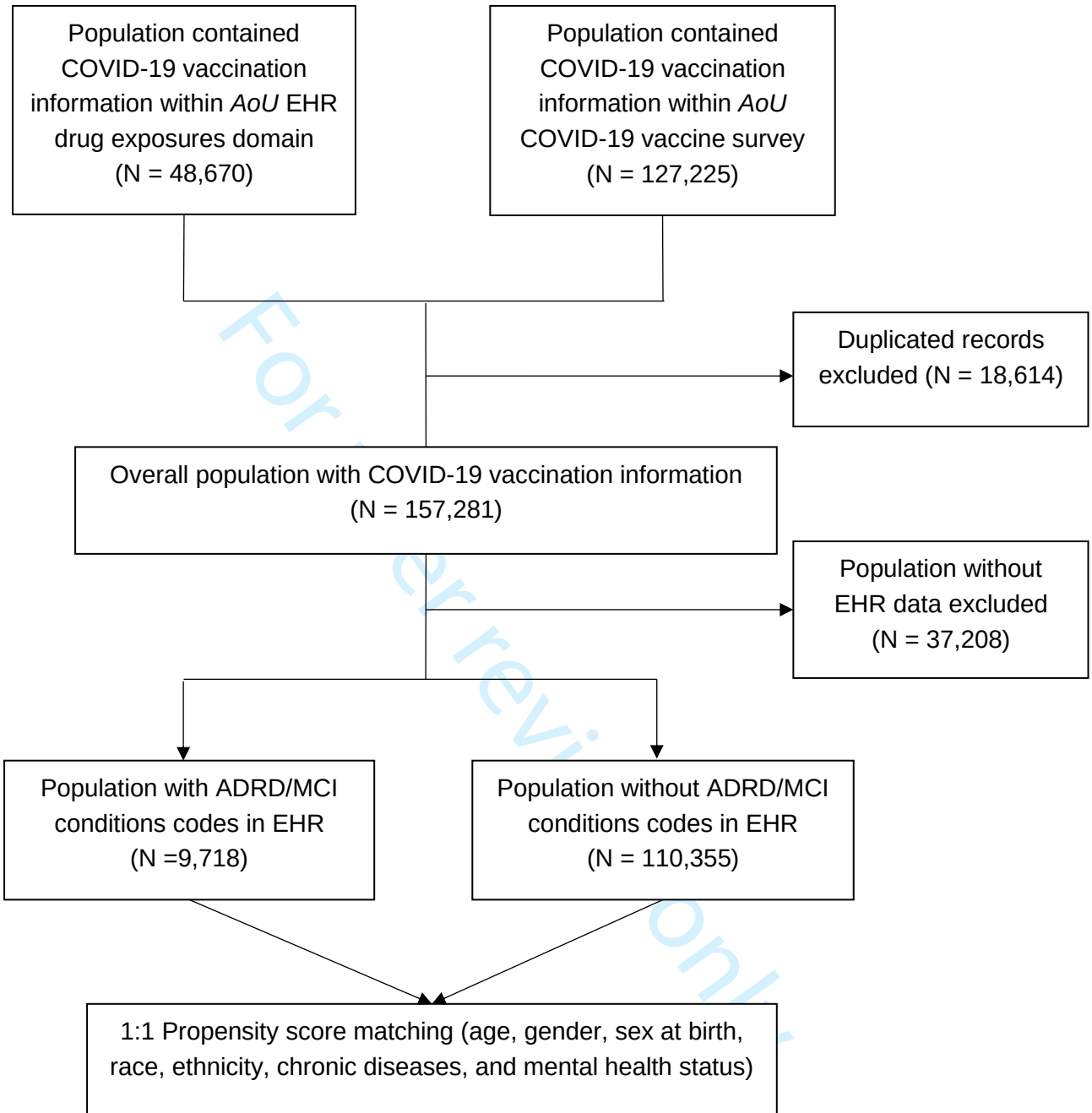
Figure 1. Study Flowchart of Participants in ADRD/MCI and non-ADRD/MCI Cohorts



Supplementary Table 1. ICD-9 and ICD-10 diagnosis codes for Alzheimer's disease and related dementias (ADRD) / mild cognitive impairment (MCI) and chronic conditions[43]

Medical Conditions	Code	Definition
Mild Cognitive Impairment		
ICD9	331.83	Mild cognitive impairment, so stated
ICD10	G31.84	Mild cognitive impairment, so stated
Alzheimer's disease and related dementias		
Alzheimer's disease		
ICD9	331.0	Alzheimer's disease
ICD10	G30	Alzheimer's disease
	G30.0	Alzheimer's disease with early onset
	G30.1	Alzheimer's disease with late onset
	G30.8	Other Alzheimer's disease
	G30.9	Alzheimer's disease, unspecified
Vascular dementia		
ICD9	290.4	Vascular dementia
	290.40	Vascular dementia, uncomplicated
	290.41	Vascular dementia, with delirium
	290.42	Vascular dementia, with delusions
	290.43	Vascular dementia, with depressed mood
ICD10	F01	Vascular dementia
	F01.5	Vascular dementia
	F01.50	Vascular dementia without behavioral disturbance
	F01.51	Vascular dementia with behavioral disturbance
Lewy Body Dementia		
ICD9	331.82	Dementia with Lewy bodies
ICD10	G31.83	Dementia with Lewy bodies
Frontotemporal Dementia		
ICD9	331.1	Frontotemporal Dementia
	331.11	Pick's disease
	331.19	Other frontotemporal dementia
ICD10	G31.0	Frontotemporal Dementia
	G31.01	Pick's disease
	G31.09	Other frontotemporal dementia
Mental Health Disorders		
Anxiety		
ICD9	300.0	Anxiety states
	300.00	Anxiety state, unspecified
	300.02	Generalized anxiety disorder
ICD10	F41	Other Anxiety disorders
	F41.0	Panic disorder [episodic paroxysmal anxiety]
	F41.1	Generalized anxiety disorder
	F41.8	Other specified anxiety disorders
	F41.9	Anxiety disorder, unspecified
Major Depressive Disorder		
ICD9	296.2	Major depressive disorder, single episode
	296.3	Major depressive disorder, recurrent
ICD10	F32.0-F32.9	Major depressive disorder
	F32.A	Depression, unspecified
	F33.0-F33.9	Major depressive disorder, recurrent
Bipolar Disorder		

ICD9	296.0-296.9	Bipolar disorders
ICD10	F31.0-F31.9	Bipolar disorders
Psychotic Disorder		
ICD9	295.0-295.9	Schizophrenic disorders
	297.0-297.9	Delusional disorders
ICD10	F20.0-F20.9	Schizophrenia
	F22	Delusional disorders
	F23	Brief psychotic disorder
	F24	Shared psychotic disorder
	F25.0, F25.1, F25.8, F25.9	Schizoaffective disorders
	F28	Other psychotic disorder not due to a substance or known physiological condition
	F29	Unspecified psychosis not due to a substance or known physiological condition
Sleep Disorder		
ICD9	307.4	Specific disorder of sleep of nonorganic origin
	327.0-327.8	Organic sleep disorders
	780.5	Sleep disturbances
ICD10	G47.0-G47.9	Sleep disorder
Chronic Conditions		
Hypertension		
ICD9	401.0, 401.1, 401.9	Essential hypertension
	405.0, 405.1, 405.9	Secondary hypertension
ICD10	I10	Essential (primary) hypertension
	I15	Secondary hypertension
	I1A	Other hypertension
Cerebrovascular Disease		
ICD9	436	Acute, but ill-defined, cerebrovascular disease
	437.0-437.9	Other and ill-defined cerebrovascular disease
	438.0-438.9	Late effects of cerebrovascular disease
ICD10	I67.0-I67.9	Other cerebrovascular diseases
	I68.0, I68.2, I68.8	Cerebrovascular disorders in diseases classified elsewhere
	I69.8, I69.9	Sequelae of cerebrovascular disease
Cerebral infarction		
ICD9	433.01	Occlusion and stenosis of basilar artery with cerebral infarction
	433.11	Occlusion and stenosis of carotid artery with cerebral infarction
	433.21	Occlusion and stenosis of vertebral artery with cerebral infarction
	433.31	Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
	433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
	433.91	Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
	434.01	Cerebral thrombosis with cerebral infarction
	434.11	Cerebral embolism with cerebral infarction
	434.91	Cerebral artery occlusion, unspecified with cerebral infarction
ICD10	I63.0-I63.9	Cerebral infarction
Overweight and Obesity		
ICD9	278.0	Overweight and obesity

	278.00	Obesity, unspecified
	278.01	Morbid obesity
	278.02	Overweight
	278.03	Obesity hypoventilation syndrome
ICD10	E66.0-E66.9	Overweight and obesity
Diabetes		
ICD9	250.0-250.9	Diabetes mellitus (Type 1 & 2)
ICD10	E10.1-E10.9	Type 1 diabetes mellitus
	E11.1-E11.9	Type 2 diabetes mellitus
Coronary artery disease		
ICD9	414.0	Coronary atherosclerosis
	414.2	Chronic total occlusion of coronary artery
	414.3	Coronary atherosclerosis due to lipid rich plaque
	414.4	Coronary atherosclerosis due to calcified coronary lesion
	414.8	Other specified forms of chronic ischemic heart disease
	414.9	Chronic ischemic heart disease, unspecified
ICD10	I25.1	Atherosclerotic heart disease of native coronary artery
	I25.8	Other forms of chronic ischemic heart disease
	I25.9	Chronic ischemic heart disease, unspecified
Heart failure		
ICD9	428.0	Congestive heart failure
	428.1	Left heart failure
	428.2	Systolic heart failure
	428.3	Diastolic heart failure
	428.4	Combined systolic and diastolic heart failure
	428.9	Heart failure, unspecified
ICD10	I50.1	Left ventricular failure, unspecified
	I50.2	Systolic (congestive) heart failure
	I50.3	Diastolic (congestive) heart failure
	I50.4	Combined systolic (congestive) and diastolic (congestive) heart failure
	I50.8	Other heart failure
	I50.9	Heart failure, unspecified
Myocardial infarction		
ICD9	410.0-410.9	Acute myocardial infarction
ICD10	I21.0-I21.9	Acute myocardial infarction
	I21.A	Other type of myocardial infarction
	I21.B	Myocardial infarction with coronary microvascular dysfunction
Chronic obstructive pulmonary disease		
	493.20	Chronic obstructive asthma, unspecified
	493.21	Chronic obstructive asthma with status asthmaticus
	493.22	Chronic obstructive asthma with (acute) exacerbation
	496	Chronic airway obstruction, not elsewhere classified
ICD10	J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory infection
	J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
	J44.8	Other specified chronic obstructive pulmonary disease
	J44.9	Chronic obstructive pulmonary disease, unspecified
Chronic kidney disease		
ICD9	585.1-585.5	Chronic kidney disease, Stage I-Stage V
	585.6	End stage renal disease
	585.9	Chronic kidney disease, unspecified
ICD10	N18.1-N18.5	Chronic kidney disease, stage 1-Stage 5

	N18.6	End stage renal disease
	N18.9	Chronic kidney disease, unspecified
Chronic liver disease		
ICD9	571.0-571.9	Chronic liver disease and cirrhosis
ICD10	K73.0-K73.9	Chronic hepatitis, not elsewhere classified
Cancer		
ICD9	140-239	Neoplasms
ICD10	C00-C96	Neoplasms
	D00-D49	Neoplasms

Sources:

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