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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 Populations: Protocol for a Retrospective Cross-Sectional Study

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5 6 7	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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33 34	Keywords. Alzheimer's disease, Alzheimer's disease related dementias (ADRD), mild cognitive impairment,
35 36	COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.
37 38	
39 40	Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Milde
41 42 43	cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome
44 45	coronavirus 2; AoU: All of Us; EHR: Electronic health records; ICD: International Classification of Diseases;
46 47 48 49 50 51 52 53 54 55	SDoH: Social determinants of health; AOR: Adjusted odds ratios.
56 57	
58 59 60	1 For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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 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.
 Provide the concerns about adverse reactions among individuals with ADRD/MCI in comparison to those without ADRD/MCI.

 Objective. The primary purpose of this study is to conduct a comprehensive analysis of COVID-19 vaccination and vaccine hesitancy in individuals with ADRD/MCI in comparison to those without ADRD/MCI.
 Provide the concerns about adverse reactions among individuals with ADRD/MCI in comparison to those without ADRD/MCI.

 Methods and Analysis. A retrospective cross-sectional study will be conducted utilizing data from the All of Use the oracination adverse reactions and multilevel logistic regression will be applied to assess the vaccination released and vaccine hesitancy, while controlling for demographic characteristics and social determinants of health presonal adverse.

 Ethics and Dissemination. This study received approval from the Institutional Review Board at Florida Statements and vaccine hesitancy.
 Provide demographic characteristics and social determinants of health provide the conferences.

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 Article Summary

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Article Summary

Strengths and Limitations

This study has significant potential in advancing our understanding of COVID-19 vaccination behaviors and training 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 a identifying the factors contributing to besite out towards because shatter 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. <u>b</u>ol

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 communication of the second state of the seco 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 and safeguard those without the introduction of COVID-19 vaccines, a noticeable reduction in particular among individuals with ADRD.⁸ Despite progress, COVID cases have been on the 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, end 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 to further exploration.^{18,19} Increasing vaccination rates play a pivotal role in fostering herd immunity against COVID, which serves to curb

doses, and booster doses, along with adverse reactions between ADRD/MCI individuals and those without 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 encolled with a broad, diverse group of United States(U.S.) ADRD/MCI. Additionally, this study seeks to examine the impact of social determinants of health on COVID-19

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populations.^{20,21} These datasets consists of diverse range of U.S. population, ensuring inclusively and 1 representation. The AoU Research Workbench seeks to engage individuals from underrepresented 2 demographic groups, promoting diversity in research.²² The AoU Research Program encompasses various data 3 elements, including participants' basic demographic information, responses to health surveys, physical 4 measurements, biospecimen collection (including blood, urine, and saliva samples stored in the secure AoU 5 biobank), structured electronic health records (EHRs), and Fitbit tracker data collected from one million 6 participants across the U.S.²³ Each participant has completed informed consent for sharing their EHR data with 7 the data and research center, and they provide survey responses covering various domains on an ongoing 8 basis.^{23,24} Specifically, we will extract relevant data fields from sources such as the Demographics, Basic Survey, 9 COVID-19 Vaccine Survey, Health Access & Utilization, Social Determinants of Health, Personal and Family 10 History, COVID-19 Participant Experience and EHR conditions data. Enrollment for the AoU program 11 commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research initiative? 12 successfully extended invitations to one million individuals nationwide.²⁵ The diverse population and data 13 integration from multiple sources within the AoU Research Workbench allow for a comparative analysis of 14 15 vaccination rates, adverse reactions, and the influence of social determinants of health on vaccine hesitancy? 16 between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The 17 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 18 19 20 Review Board at Florida State University Office of Research. guipr 21

22 Workspace on the AoU Researcher Workbench Secure Platform: ADRD/MCI and COVID-19 Vaccination 23

July We have established a workspace named "ADRD/MCI and COVID-19 Vaccination" within the AoU Researcher 24 25 Workbench. This cloud-based platform grants authorized researchers access to and the ability to analyze data 2024. Downloaded eignement Superieu 26 from the AoU. The platform offers two levels of data access available: the registered tier and the controlled tier. 27 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 28 29 30 Classification of Diseases (ICD) codes related to ADRD/MCI, as well as their responses to the Personal and 31 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 32 33 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 34 35 Python version 3.0 (Python Software Foundation). 36 ≥ 37

1) <u>ADRD/MCI Cohort</u> The ADRD/MCI cohort is formed by gathering information from both EHR and Personal and Family History 39 40 survey questionnaires. Through EHR, individuals are identified for inclusion in the ADRD/MCI cohort if they have≌ 41 been diagnosed with any of the following ICD-9/10 conditions: "mild cognitive impairment" or "Alzheimer's 42 43 disease" or "dementia" or "dementia with or without behavioral and psychological symptoms" or "vasculara dementia" or "Lewy body dementia" or "frontotemporal dementia" (**Table 1**). 44 45

To identify individuals within the ADRD/MCI cohort using the Personal and Family History Survey data, the 46 inclusion criteria involve providing affirmative responses to the following questions: a) "Have you or anyone in 47 your family ever been diagnosed with the following brain and nervous system conditions? - Dementia (includes 48 Alzheimer's, vascular, etc.)" or b) "Including yourself, who in your family has had dementia (includes Alzheimer's, 49 50 vascular, etc.)? - Self" or c) "Are you still seeing a doctor or health care provider for dementia (includes 51 Alzheimer's, vascular, etc.)? - Yes" or d)"About how old were you when you were first told you had dementia 52 (includes Alzheimer's, vascular, etc.)? - Adolescent, - Adult, - Older adult, - Elderly" or e) "Are you currently 53 prescribed medications and/or receiving treatment for dementia (includes Alzheimer's, vascular, etc.)? - Yes". 54 Individuals who satisfy at least one of the previously mentioned inclusion criteria, either through EHR conditions 55 or valid responses to the Personal and Family History Survey, will be included in ADRD/MCI cohort. Deceased 56 people are excluded from the study. 57

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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
		Unspecified persistent mental disorders due to conditions
	294.9	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
1020	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

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Table 2. Measurement Matrix

he study enco	mpasses social de	terminants of health at <u>Individual, Interpersonal and Commu</u> eterminants of health at three levels: individual, interpersona ndividual demographics, medical history and medications i	I, and community.
nterpersonal le	vel factors consist providers. Comm	t of sociocultural environment & social support, relationship v nunity level factors include healthcare facility accessibility a	vith neighborhood and utilization are
	urement Matrix		Data Source
	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
	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 AoU COVID-19
	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.	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
	Medical history and medications	Medical history & comorbid conditions, medications	Survey 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.	Health History 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 AoU Health Access &
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			

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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 8 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). uding

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 Coho (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

9 Statistical Analysis Plan 10

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Demographic variables will be summarized using descriptive statistics (e.g., Mean ± SD or median with 11 12 interguartile range), as appropriate for continuous variables, and frequency and percentage for categorical 13 variables. Data quality will be checked, including steps like outlier detection.²⁸ The distribution of all variables will 14 be examined to check the validity of distribution assumptions before subsequent analyses, using 15 univariate/multivariate Shapiro-Wilk test and a visual inspection of histograms and quantile-quantile plots. If the 16 normal assumption of continuous variables is not met, appropriate data transformations or alternative data 17 analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and 18 survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and 19 20 figures, with reporting the corresponding p-values from independent samples t-test (or Kruskal-Wallis test when 21 appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 22 sets as threshold. Variables that differ will be treated as covariates in all final models to maximize power. In our 23 analysis of vaccination rates between ADRD/MCI individuals and those without ADRD/MCI, we will employ 24 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 25 26 cohort or non-ADRD/MCI cohort, as well as age, race/ethnicity, sex, gender, language speaking, living status, 27 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 28 29 association of vaccine hesitancy (i.e., individuals reported how likely to get vaccinated) with covariates, we will 30 employ a multilevel logistic regression with vaccine hesitancy as the outcome, and covariates as controlled 31 variables. This approach will enable us to compute the adjusted odds ratios (AOR) to determine the likelihood of $\frac{2}{3}$ 32 vaccine hesitancy.²⁹ An AOR greater than 1 indicates higher odds for vaccine hesitancy, meaning individuals and the vaccine hesitancy and the vaccine hesitancy. vaccine hesitancy.²⁹ An AOR greater than 1 indicates higher odds for vaccine nesitancy, meaning information who are less likely to take the vaccination have high vaccine hesitancy.²⁹ 95% confidence intervals for each 33 34 35 analyses where appropriate. 36 ≥ 37

38 Data Management and Safety 39

trainin All datasets will be stored on All of Us Research Benchwork. Data filtering will be performed on the AoU Research 40 platform. Data will be analyzed using R or Python. Our research team has experience using Python programming 41 42 language and has pilot cohorts developed in the AoU Research platform and used for analysis. We will adhere 43 3 to AoU Research Benchwork data protection regulations and data use guidelines. 44

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Significance The proposed study will contribute to scientific knowledge in several ways: Firstly. it will conduct a comprehensive 47 48 analysis of vaccination coverage for individuals with ADRD/MCI by examining the first, second, and booster 49 shots. This in-depth examination will shed light on any significant differences in vaccination behavior and adverse. 50 reactions between individuals with ADRD/MCI and those without. Such comparisons can provide insights into 51 the unique challenges faced by individuals with ADRD/MCI. This is particularly important where booster shots 52 have become a critical component of maintaining immunity. Additionally, this comprehensive study can provide 53 insights into long-term vaccination behaviors and trends. Secondly, The study will assess adverse reactions to 54 COVID vaccines among individuals with ADRD/MCI and those without. This information can offer valuable data 55 on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then make 56 more informed decisions about vaccine administration and monitoring. Thirdly, the study will integrate social 57

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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 2 among minority groups. This study goes beyond the clinical aspect and delves into the broader factors affecting 3 healthcare access and decision-making. Lastly, the research findings will directly inform public health strategies 4 and interventions. The research findings can directly inform public health strategies and interventions. If it is 5 found that individuals with ADRD/MCI are more hesitant to receive booster shots, public health strategies can 6 be tailored to address their specific concerns and needs. Policymakers and healthcare providers can use the 7 study's results to make evidence-based decisions regarding vaccine distribution, outreach, and support for 8 individuals with ADRD/MCI.

9 Overall, the proposed study will contribute to scientific knowledge by providing a comprehensive analysis of $_{\mathbf{u}}$ 10 Abbreviations 11 12 13

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ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; 19 COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; AoU: All 20 21 of Us; EHR: Electronic health records; ICD: International Classification of Diseases; SDoH: Social determinants 22 of health; AOR: Adjusted odds ratios. for uses 23

24 **Ethics and Dissemination** 25

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 q published in peer-reviewed journals and disseminated at conferences and through social media. text

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Author contributions

ita mining, 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. training, and similar technologies

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48 Data statement

50 The findings of the present study were supported by data accessible through the All of Us Research Workbench, 51 which is available to registered researchers with an institutional Data Use and Registration Agreement (DURA). 52

Conflict of Interest

The authors declare that they have no competing interests.

and

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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	Reference 1. Cascella M. Rainik M. Aleem A. Dulebohn SC. Di Napoli R. Features, evaluation, and treatment of
1	1. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of
2	coronavirus (COVID-19). 2020; 2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine.
3	
4 5	New England journal of medicine. 2021;384(5):403-416.
6	 New England journal of medicine. 2021;384(5):403-416. 3. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. New England journal of medicine. 2020;383(27):2603-2615. 4. USAFacts. US coronavirus vaccine tracker. Accessed September 9, 2023. https://usafacts.org/visualizations/covid-vaccine-tracker-states/
7	New England journal of medicine. 2020;383(27):2603-2615.
, 8	4. USAFacts. US coronavirus vaccine tracker. Accessed September 9, 2023.
9	https://usafacts.org/visualizations/covid-vaccine-tracker-states/
10	5. Su Z, McDonnell D, Li Y. Why is COVID-19 more deadly to nursing home residents? QJM: An - 8
11	International Journal of Medicine. 2021;114(8):543-547.
12	International Journal of Medicine. 2021;114(8):543-547. 6. Hardan L, Filtchev D, Kassem R, et al. COVID-19 and Alzheimer's disease: a literature review. <i>Medicina</i> . 2021;57(11):1159. 7. Rolland Y, Baziard M, De Mauleon A, Dubus E, Saidlitz P, Soto ME. Coronavirus Disease-2019 in Olders People with Cognitive Impairment. <i>Clinics in Geriatric Medicine</i> . 2022;38(3):501-517. 8. Chen R, Charpignon M-L, Raguib RV, et al. Excess Mortality With Alzheimer Disease and Relateds
13	2021;57(11):1159.
14	7. Rolland Y, Baziard M, De Mauleon A, Dubus E, Saidlitz P, Soto ME. Coronavirus Disease-2019 in Older 😨 🚆
15	People with Cognitive Impairment. Clinics in Geriatric Medicine. 2022;38(3):501-517. 응 흥
16	8. Chen R, Charpignon M-L, Raquib RV, et al. Excess Mortality With Alzheimer Disease and Related S
17	Dementias as an Underlying or Contributing Cause During the COVID-19 Pandemic in the US. JAMA neurology.
18	Dementias as an Underlying or Contributing Cause During the COVID-19 Pandemic in the US. <i>JAMA neurology</i> . 2023;80(9):919-928. 9. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. <i>The Lancet</i> . 2020;396(10248):413-446.
19	9. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of 👌 👸
20	the Lancet Commission. The Lancet. 2020;396(10248):413-446.
21	10. Hwang T-J, Rabheru K, Peisah C, Reichman W, Ikeda M. Loneliness and social isolation during the
22	COVID-19 pandemic. International psychogeriatrics. 2020;32(10):1217-1220. 한 근
23 24	11. Ahmed MZ, Ahmed O, Aibao Z, Hanbin S, Siyu L, Ahmad A. Epidemic of COVID-19 in China and 🖕 🗝 🤅
24 25	associated psychological problems. Asian journal of psychiatry. 2020;51:102092.
26	12. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination
27	setting. New England Journal of Medicine. 2021;384(15):1412-1423.
28	13. Ali A. COVID numbers are rising again, but Fauci not predicting another 'tsunami of hospitalizations and ដ្ឋ ថ្មី 🎖
29	deaths'. https://abcnews.go.com/Politics/covid-numbers-rising-fauci-predicting-tsunami-hospitalizations-
30	deaths/story?id=103056079
31	14. Garrity K. Fauci: We 'need to be prepared' for likely Covid uptick this winter. Accessed September 10th,
32	2023. https://www.politico.com/news/2023/09/10/fauci-prepared-covid-uptick-winter-00114906
33	15. Yang Y, Nie J, Sun F, et al. The SARS-CoV-2 vaccination rate and hesitation in Shanghai older adults
34	with dementia. Frontiers in Public Health. 2023;11
35	16. Custodio N, Malaga D, Chambergo-Michilot D, et al. IMPACT OF THE COVID-19 PANDEMIC IN ADRD
36 37	PATIENTS AND CAREGIVERS IN A LATIN - AMERICAN COUNTRY. Alzheimer's & Dementia.
38	 2022;18:e066200. 17. Kreps S, Prasad S, Brownstein JS, Hswen Y, Garibaldi BT, Zhang B, Kriner DL. Factors associated within US adults' likelihood of accepting COVID-19 vaccination. <i>JAMA network open</i>. 2020;3(10):e2025594-e2025594. 18. Wang Y, Li M, Kazis LE, Xia W. Clinical outcomes of COVID-19 infection among patients with Alzheimer's disease or mild cognitive impairment. <i>Alzheimer's & Dementia</i>. 2022;18(5):911-923. 19. Malik AA, McFadden SM, Elharake J, Omer SB. Determinants of COVID-19 vaccine acceptance in the similar to the covid of the covi
39	17. Kreps S, Prasad S, Brownstein JS, Hswen Y, Garibaldi BT, Zhang B, Kriner DL. Factors associated with
40	US adults' likelihood of accepting COVID-19 vaccination. JAMA network open. 2020;3(10):e2025594-e2025594.
41	18. Wang Y, Li M, Kazis LE, Xia W. Clinical outcomes of COVID-19 infection among patients with Alzheimer's
42	disease or mild cognitive impairment. <i>Alzheimer's & Dementia</i> . 2022;18(5):911-923.
43	19. Malik AA, McFadden SM, Elharake J, Omer SB. Determinants of COVID-19 vaccine acceptance in the
44	US. EClinical Medicine. 2020;26
45	20. Zhang J, Yang X, Weissman S, Li X, Olatosi B. Protocol for developing a personalised prediction model for viral suppression among under-represented populations in the context of the COVID-19 pandemic. <i>BMJ open</i> .
46	
47	2023, 13(3).e070809. 21. NIH. About All of Us. Accessed October 5th, 2023. https://allofus.nih.gov/about
48	21. NIH. About All of Us. Accessed October 5th, 2023. https://allofus.nih.gov/about 22. Investigators AoURP. The "All of Us" research program. New England Journal of Medicine. mttps://gramma.science.com
49	2019;381(7):668-676.
50	23. NIH. The All of Us Consent Process. Accessed Oct 5th, 2023. https://allofus.nih.gov/about/protocol/all-
51 52	us-consent-process
52 53	24. NIH. Consent to Join the All of Us Research Program (June 20, 2018) at F1–8—F1–9.
53 54	25. NIH. All of Us Research Program FAQ. Accessed December 8th, 2023.
55	https://allofus.nih.gov/about/fag#:~:text=The%20All%20of%20Us%20Research%20Program%20is%20part%2
56	0of%20an,health%20data%20over%20many%20years.
57	<u></u>
58	 2023, 13(3).e070809. 21. NIH. About All of Us. Accessed October 5th, 2023. https://allofus.nih.gov/about 22. Investigators AoURP. The "All of Us" research program. New England Journal of Medicine.g 2019;381(7):668-676. 23. NIH. The All of Us Consent Process. Accessed Oct 5th, 2023. https://allofus.nih.gov/about/protocol/all-us-consent-process 24. NIH. Consent to Join the All of Us Research Program (June 20, 2018) at F1–8—F1–9. 25. NIH. All of Us Research Program FAQ. Accessed December 8th, 2023. https://allofus.nih.gov/about/faq#:~:text=The%20All%20of%20Us%20Research%20Program%20is%20part%2 26. Oof%20an,health%20data%20over%20many%20years.
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NIH. Registered Institutions. Accessed Oct 5th, 2023. https://www.researchallofus.org/institutional-26. agreements/ 27. Kelley K. Maxwell SE. Sample size for multiple regression: obtaining regression coefficients that are accurate, not simply significant. Psychological methods. 2003;8(3):305. Smiti A. A critical overview of outlier detection methods. Comput. Sci. Rev. 38, 100306. 2020. 28. Khubchandani J, Sharma S, Price JH, Wiblishauser MJ, Sharma M, Webb FJ. COVID-19 vaccination 29. hesitancy in the United States: a rapid national assessment. Journal of community health. 2021;46:270-277. Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies to beet telien only For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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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**

Protected by copyright, including for uses related Yijiong Yang, Ph.D.¹; Hye Jin Park, Ph.D.¹; Chengdong Li, Ph.D.¹; Dan Song, Ph.D.¹; Jing Wang, Ph.D., MPH RN. FAAN¹

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 Keywords. Alzheimer's disease, Alzheimer's disease related dementias (ADRD), mild cognitive impairment,
 g, Altraining, and similar

 COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.
 COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.

 Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild
 Mild

cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome nologies 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-192 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 logistica regression will be applied to assess the vaccination rates and vaccine hesitancy, while controlling ford 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) Ethics and Dissemination. This study protocol received approval from the Institutional Review Board at Florida

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 3. 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.

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11 Background 2

Coronavirus disease 2019 (COVID-19) vaccines are pivotal in preventing the severe acute respiratory syndrome 32 43 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 54 65 infection and mortality.^{6,7} Individuals with dementia are particularly vulnerable, facing a 2 to 3-fold greater risk of 76 COVID-19 infection partly due to increased levels of angiotensin-converting enzyme 2 (ACE2) compared to the 87 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.139 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 observed among individuals with ADRD.⁹ Despite progress, patients with dementia are at a higher risk of set 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} Asg of October 2022, 111,367,843 people, equivalent to 34% of the U.S. population, have received booster shots.¹⁸ of While ADRD patients and their caregivers exhibit willingness to facilitate vaccination, a substantial portion of strengthere 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 a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and a barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and e barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and e barriers and hesitancy among patients with expression demonstrates events) inter personal level influences (e.g., age, race and e barriers) inter personal level influences (e.g., age, race and e barriers) inter personal level influences (e.g., age, ra ethnicity, income, culture beliefs, dementia related symptoms), inter-personal level influences (relationships with a caregivers informal caregiver distress), and extra-personal level influences (media impact, religiosity, living a final caregivers). 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 a on COVID-19 vaccination rates and vaccine hesitancy among individuals with ADRD/MCI. By gaining a bettera understanding of these factors, we can develop targeted strategies to improve vaccination rates and address concerns among this vulnerable population. lar

Objective of Study Protocol Research Aim 1: To determine the difference in COVID-19 vaccination rates (at least one dose, two doses, and besters or three full doses) between ADRD/MCL individuals and these without ADRD/MCL 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

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

554556556556 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, 59 and they provide survey responses covering various domains on an ongoing basis.^{28,29} Specifically, we will 60 64 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 AoUS 62 program commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research 63 64 initiative successfully extended invitations to one million individuals nationwide.³⁰ The diverse population and 65 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 60 69 between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The 887722 22 22233558 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. relatec

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 a consistence of those without a consistence of those without a consistence of the constant of the cohorts: one consists of individuals with ADRD/MCI and the other consists of those without ADRD/MCI. Cohort 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). and

1) ADRD/MCI Cohort

43 The ADRD/MCI cohort is formed by gathering information from EHR . Through EHR, individuals are identified for 86 inclusion in the ADRD/MCI cohort if they have been diagnosed with any of the following ICD-9/10 conditions: 878 "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**) 88 89 Deceased people are excluded. (Supplementary Table 1) 918 ies 49

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 954

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95 COVID-19 vaccination rates, adverse reactions and vaccine hesitancy will be assessed through EHR drug 96 97 98 999 100 101 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)

, 102 103 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 11 104 105 community. Individual level factors include Individual demographics, chronic conditions, and mental health 106 status. Chronic conditions related to ADRD/MCI and COVID-19 vaccination rates include^{32,33}: hypertension, g cerebrovascular disease, cerebral infarction, overweight and obesity, diabetes, coronary artery disease, hearts 107 failure, myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver 108 109 disease, cancer, and mental health disorders. 18

Interpersonal level factors for ADRD/MCI patients consist of sociocultural environment and social support, as 110 120 assessed in the AoU Basic Survey and AoU Social Determinants of Health Survey, with affirmative responses 17**2** to the following questions: a) "Do you own or rent the place where you live?" b) "Where are you currently living?" a 173 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_{D}^{2} 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; a 12;4; d)"Have you delayed getting care for any of the following reasons in the past 12 months?" – didn't have and the past 12 months?" 12,5 transportation; live in the rural area where distance to health care provider is too far; nervous about seeing a² health care provider; couldn't get time off work; couldn't get child care; couldn't get elderly care; couldn't afford≥ 126 128 the co-pay; couldn't afford the deductible; had to pay out of pocket for some or all of the procedure. raining,

Table 1. Measurement Matrix 137 1

	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 Dru 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 Surve
	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	<i>AoU</i> 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 Surve
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.	<i>AoU</i> Health Access & Utilization Surve

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<u>Samples</u> 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, 14,55 chronic diseases, and mental health status. (Figure 1 & Table 2) 146

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Table 2. Demographic Characteristics, Chronic Diseases and Mental Health Status of ADRD/MCI and 147 148 2 non-ADRD/MCI cohorts Before 1:1 Propensity Score Matching, All of Us Research Workbench 3 4 **ADRD/MCI** Cohort **Demographics** Non-ADRD/MCI Cohort (N=9,718) (N=110,355) 5 Age, N (%) 6 18-44 771 (8) 25,410 (23) 7 2,712 (28) 45-64 36,463 (33) 8 >65 6,235 (64) 48,482 (44) 9 Gender, N (%) 10 11 3,663 (38) 38,457 (35) Male 12 Female 5,745 (59) 68,807 (62) 13 Other (Non-binary, Transgender, Additional 920 (1) 90(1) 14 options, Prefer not to answer) 15 Skip or Uknown 220 (2) 2,171 (2) 16 Sex at Birth, N (%) 17 3,680 (38) 38,679 (35) Male 18 Female 5,773 (59) 69,254 (63) 19 84 (<1) Other (None, Intersex, Prefer not to answer) 7 (<1) 20 Skip or Unknown 258 (3) 2,338 (2) 21 Race, N (%) 22 23 6,632 (68) White 72,830 (66) 24 Black or African American 1,180 (12) 14,290 (13) 25 143 (2) 2.909 (3) Asian 26 Middle Eastern or North African 49 (<1) 548 (<1) 27 4 (<1) 65 (<1) Native Hawaiian or Other Pacific Islander 28 Multiple-racial 156 (2) 1,811 (2) 29 Other (None indicated, Prefer not to answer) 1,235 (13) 15,036 (14) 30 2,866 (3) Skip 319 (3) 31 Ethnicity, N (%) 32 Hispanic or Latino 1,166 (12) 15,849 (14) 33 34 Non-Hispanic or Latino 8,034 (83) 90,266 (82) 35 Other (None of these, Prefer not to answer) 199 (2) 1,374 (1) 36 319 (3) 2,866 (3) Skip 37 Chronic Conditions, N (%) 38 Hypertension 49,455 (45) 7,033 (72) 39 Coronary artery disease 2,741 (28) 13,464 (12) 40 Cerebrovascular diseases 3,086 (32) 7,162 (6) 41 Heart failure 1,962 (20) 8,596 (8) 42 Myocardial infarction 1,172 (12) 4,998 (5) 43 Cerebral infarction 1,181 (12) 3,010 (3) 44 Overweight/Obesity 4,784 (49) 34,230 (31) 45 46 Diabetes 3,498 (36) 21,586 (20) 47 Chronic obstructive pulmonary disease 1,859 (19) 8,318 (8) 48 Chronic kidney diseases 2,010 (21) 9,871 (9) 49 Chronic liver diseases 1,198 (12) 6,030 (5) 50 Cancer 3,613 (37) 23,945 (22) 51 **Mental Health Status** 52 Anxiety 5,913 (61) 32,843 (30) 53 30,200 (27) Major depressive disorders 6,012 (62) 54 **Bipolar disorders** 1,126 (12) 4,381 (4) 55 **Psychotic disorders** 902 (9) 2,676 (2) 56 57 Sleep disorders 6,306 (65) 33,012 (30) 58 5

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149 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

156 Statistical Analysis Plan

Demographic variables will be summarized using descriptive statistics (e.g., Mean ± SD or median withe 11 157 158 interguartile 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 159 variables will be examined to check the validity of distribution assumptions before subsequent analyses, using 160 166 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 162 analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and 163 survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and 164 169 figures, with reporting the corresponding p-values from independent samples t-test (or Kruskal-Wallis test when 166 appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 167 23 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 1737 identify the effects of confounding covariates, with the nearest available Mahalanobis metric matching applied to a 1738 obtain 1:1 matched pair between ADRD/MCI and non-ADRD/MCI cohorts. The balanced covariates in the 17398 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[≥] 180 188 ADRD/MCI and non-ADRD/MCI groups. We assess the effectiveness of matching by comparing the effective 182 size of each included covariate before and after matching, with a decrease in effective size indicating balanced 1819 pairs. The results of propensity logit will be presented in the histogram, and standardized mean differences 1844 across covariates before and after matching are reported. The study utilizes the 'psmpy 0.3.13' propensity score 183 matching package for propensity logits and graphical representations of matching outcomes, as well as matched 186 pairs and standardized mean differences across covariates.³⁸ 44

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).

197 Data Management and Safety

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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.

2052 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

13 208 Individuals with ADRD/MCI had a higher age compared with those without ADRD/MCI. Among the 9,718g 209 ADRD/MCI patients, 8% were aged 18-44 (n=771), 28% were aged 45-64 (n=2,712), and 64% were aged overg 210 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 211 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 212 219 with ADRD/MCI had higher prevalence of hypertension, heart diseases, cerebrovascular diseases, 21244 overweight/obesity, diabetes, chronic pulmonary diseases, chronic kidney and liver diseases, and cancer. These 2¥5 findings align with reports from the Alzheimer's Association and other previous research.^{32,41} Additionally, studies 216 indicate that obesity has become the top risk factor for dementia in the US.42 Individuals with ADRD/MCI also 277 displayed a higher prevalence of mental health disorders compared to those without ADRD/MCI. 2<u>78</u>

279 220 221 222 223 223 223 223 223 225 The proposed study will contribute to scientific knowledge in several ways: First, it will be a comprehensive a 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 22365 COVID-19 vaccines among individuals with ADRD/MCI and those without. This information can offer valuable 22374 data on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then makea 2238 more informed decisions about vaccine administration and monitoring. Third, the proposed study will integrate 229 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 230 238 disparities among minority groups. This proposed study goes beyond the clinical aspect and delves into the 232 broader factors affecting healthcare access and decision-making. Lastly, the research findings will directly inform 2**3**9 public health strategies and interventions. The research findings can directly inform public health strategies and 234 interventions. If it is found that individuals with ADRD/MCI are more hesitant to receive booster shots, public 235 236 236 237 237 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.

248 Abbreviations

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249 ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild cognitive impairment; 250 251 252 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.

25z3 **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. **Author affiliations** ¹College of Nursing, Florida State University, Tallahassee, FL, 32306. **Author contributions**

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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 Researchers with an institution of the All o ≥ Agreement (DURA). training,

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	Elowohart of Portioinanto in ADPD/MCL and non ADDD/MCL Catanta
Figure 1. Study	Flowchart of Participants in ADRD/MCI and non-ADRD/MCI Cohorts
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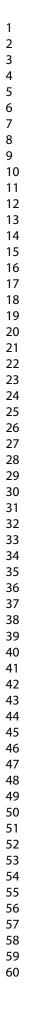
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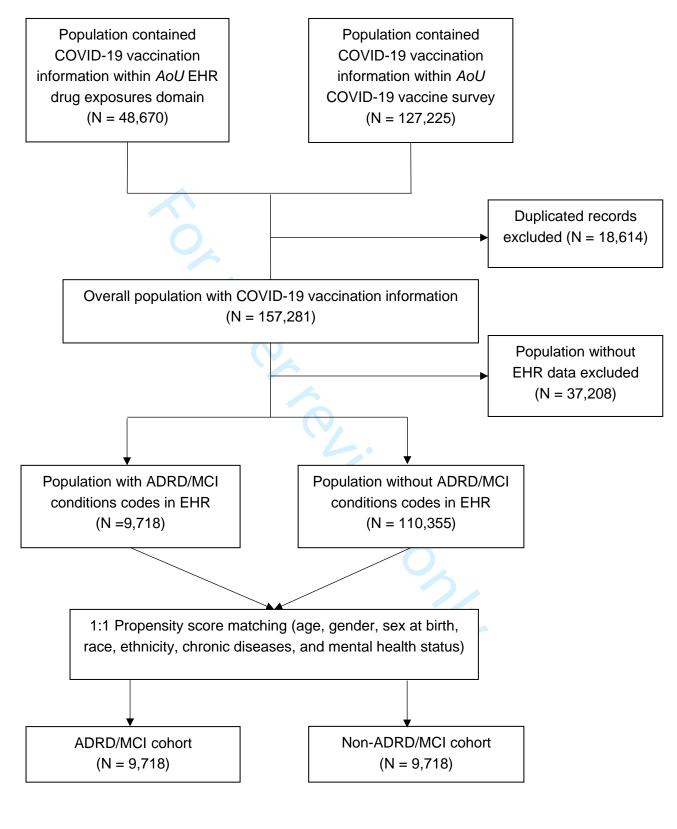
Reference Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. 1. New England journal of medicine. 2021;384(5):403-416. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. 2. New England journal of medicine. 2020;383(27):2603-2615. Taylor L. Covid-19: Vaccination reduces severity and duration of long covid. study finds, bmi. 3. 2023:380(4) 4. MacCallum-Bridges C, Hirschtick JL, Patel A, Orellana RC, Elliott MR, Fleischer NL. The impact of COVID-19 vaccination prior to SARS-CoV-2 infection on prevalence of long COVID among a population-based probability sample of Michiganders, 2020-2022. Annals of Epidemiology. 2024; Trinh NT, Jödicke AM, Català M, et al. Effectiveness of COVID-19 vaccines to prevent long COVID: 5. data from Norway. The Lancet Respiratory Medicine. 2024; Hardan L, Filtchev D, Kassem R, et al. COVID-19 and Alzheimer's disease: a literature review. 6. Medicina. 2021;57(11):1159. Rolland Y, Baziard M, De Mauleon A, Dubus E, Saidlitz P, Soto ME. Coronavirus Disease-2019 in 7. Older People with Cognitive Impairment. Clinics in Geriatric Medicine. 2022;38(3):501-517. Pszczołowska M, Walczak K, Misków W, Antosz K, Batko J, Karska J, Leszek J. Molecular cross-talk 8. between long COVID-19 and Alzheimer's disease. GeroScience. 2024:1-15. 9. Chen R, Charpignon M-L, Raguib RV, et al. Excess Mortality With Alzheimer Disease and Related Dementias as an Underlying or Contributing Cause During the COVID-19 Pandemic in the US. JAMA *Interplay* 2023;80(9):919-928. *Integration of the Lancet Commission. The Lancet.* 2020;396(10248):413-446. *Integration of the Lancet Commission. The Lancet.* 2021;39(31):4245-4249. *Gaughan CH, Razieh C, Khunti K, et al.* COVID-19 vaccination uptake amongst ethnic minority communities in England: a linked study exploring the drivers of differential vaccination rates. *Journal of Public Pealth.* 2023;45(1):e65-e74. *Dagan N, Barda N, Kepten E, et al.* BNT162b2 mRNA Covid-19 vaccination and norpitalizations anterion setting. *New England Journal of Medicine.* 2021;39(41(5):1412-1423. *Wang L, Davis PB, Kaelber DC, Xu R.* COVID-19 breakthrough infections and hospitalizations among older adults with dementia: a comparative cohort study. *Frontiers in Public Health.* 2023;1(2):421-432. *Radomyslsky Z, Kivity S, Lidar S, et al.* Association between December 2020 and August 2021. *Alzheimer's table adults vith dementia: a comparative cohort study. Frontiers in Public Health.* 2023;11:1281266. *Ali A.* COVID numbers are rising again, but Fauci not predicting stunami-hospitalizations. *death/story*71d=103056079 *Carrity K.* Fauci: We 'need to be prepared' for likely Covid uptick this winter. Accessed September 9, 2023. https://www.politic.com/news/2023/09/10/fauci-prepared-covid-uptick-winter-00114906 *USAF acts.* US coronavirus vaccine tracker. Accessed September 9, 2023. https://www.politic.com/news/2023/09/10/fauci-prep neurology. 2023;80(9):919-928. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report 10.

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1 2 3 4 5 6 7 8 9 10 1 12 13 14 5 6 7 18 9 20 1 22 3 22 22 22 22 22 30 3 1 22 33 33 35 6 7 8 9 10 1 12 13 14 5 6 7 18 9 20 1 22 3 24 5 26 7 8 9 30 1 32 33 34 5 36 7 8 9 40 1 22 3 44 5 6 7 8 9 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	 Serverstein Steiner Strassociation. Chronic Diseases and Dementia. Accessed May 6th, 2024. Materneel V, Vanbrabant T, Desplenter F, et al. COVID-19 vaccination rates in a cohort study of patients with mental illness in residential and community care. <i>Frontiers in psychiatry</i>. 2021;12:805528. Kelley K, Maxwell SE. Sample size for multiple regression: obtaining regression coefficients that are accurate, not simply significant. <i>Psychological methods</i>. 2003;8(3):305. Smith A. critical overview of outlier detection methods. Comput. Sci. Rev. 38, 100306. 2020. The World Bank. Propensity Score Matching. Accessed May 6th, 2024. https://dimewiki.worldbank.org/Propensity. Score Matching#:~itext=Propensity%20score%20matching%20(PS My%20sithe%20ing%20mks/2	Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar techr	BMJ Open: first published as 10.1136/bmjopen-2023-082988 on 16 July 2024. Downloaded from http://bmjopen.bmj.com/ on June 8, 2025 at Agence Bibliographique de I
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Medical Conditions	Code	Definition
Aild Cognitive Impair		
ICD9	331.83	Mild cognitive impairment, so stated
ICD10	G31.84	Mild cognitive impairment, so stated
Alzheimer's disease a	and related dement	ias
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
/ascular dementia		
ICD9	290.4	Vascular dementia
	290.40	Vascular dementia, uncomplicated
	290.41	Vascular dementia, with delirium
	290.42	V Vascular dementia, with delusions
	290.43	N 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
ewy Body Dementia		
ICD9	331.82	Dementia with Lewy bodies
ICD10	G31.83	Dementia with Lewy bodies
Frontotemporal Demo		
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
Ventel Lleelth Die and	G31.09	Other frontotemporal dementia
Mental Health Disord	ers	
Anxiety ICD9	300.0	Anxiety states
1009	300.00	
	300.00	Anxiety state, unspecified 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 Dis		אוואוסני מוסטימטו, מווסףכטווכט
ICD9	296.2	Major depressive disorder, single episode
	296.3	Major depressive disorder, single episode
ICD10	F32.0-F32.9	Major depressive disorder
	F32.0-F32.9 F32.A	Depression, unspecified
	F32.A F33.0-F33.9	Major depressive disorder, recurrent

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3 4	ICD9	296.0-296.9	Bipolar disorders
5	ICD10	F31.0-F31.9	Bipolar disorders
6	Psychotic Disorder	205 0 205 0	Cohizophronia diagradara
7	ICD9	295.0-295.9 297.0-297.9	Schizophrenic disorders Delusional disorders
8	ICD10	F20.0-F20.9	Schizophrenia
9	10010	F22	Delusional disorders
10 11		F23	Brief psychotic disorder
12		F24	Shared psychotic disorder
13		F25.0, F25.1, F25.8,	
14		F25.9	Schizoaffective disorders
15			Other psychotic disorder not due to a substance or known
16		F28	physiological condition
17		F 00	Unspecified psychosis not due to a substance or known
18 10	Clean Disender	F29	physiological condition
19 20	Sleep Disorder ICD9	307.4	Specific disorder of algon of poperganic origin
20	ICD9	307.4	Specific disorder of sleep of nonorganic origin Organic sleep disorders
22		780.5	Sleep disturbances
23	ICD10	G47.0-G47.9	Sleep disorder
24	Chronic Conditions		
25 26	Hypertension		
26 27	ICD9	401.0, 401.1, 401.9	Essential hypertension
28		405.0, 405.1, 405.9	Secondary hypertension
29	ICD10	110	Essential (primary) hypertension
30		115	Secondary hypertension
31		I1A	Other hypertension
32	Cerebrovascular Dise		
33	ICD9	436	Acute, but ill-defined, cerebrovascular disease
34 35		437.0-437.9	Other and ill-defined cerebrovascular disease
36	ICD10	438.0-438.9 167.0-167.9	Late effects of cerebrovascular disease Other cerebrovascular diseases
37		168.0, 168.2, 168.8	Cerebrovascular disorders in diseases classified elsewhere
38		169.8, 169.9	Sequelae of cerebrovascular disease
39	Cerebral infarction	100.0, 100.0	
40	ICD9		Occlusion and stenosis of basilar artery with cerebral
41		433.01	infarction
42 43			Occlusion and stenosis of carotid artery with cerebral
44		433.11	infarction
45			Occlusion and stenosis of vertebral artery with cerebral
46		433.21	infarction
47		400.04	Occlusion and stenosis of multiple and bilateral precerebral
48		433.31	arteries with cerebral infarction
49 50		433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
50 51		455.01	Occlusion and stenosis of unspecified precerebral artery
52		433.91	with cerebral infarction
53		434.01	Cerebral thrombosis with cerebral infarction
54		434.11	Cerebral embolism with cerebral infarction
55			Cerebral artery occlusion, unspecified with cerebral
56		434.91	infarction
57	ICD10	163.0-163.9	Cerebral infarction
58 59	Overweight and Obes	-	
60	ICD9	278.0	Overweight and obesity

2			
3		278.00	Obesity, unspecified
4		278.00	Morbid obesity
5		278.02	Overweight
6		278.02	•
7			Obesity hypoventilation syndrome
8	ICD10	E66.0-E66.9	Overweight and obesity
9	Diabetes	050 0 050 0	
10	ICD9	250.0-250.9	Diabetes mellitus (Type 1 & 2)
11	ICD10	E10.1-E10.9	Type 1 diabetes mellitus
12	-	E11.1-E11.9	Type 2 diabetes mellitus
13	Coronary artery disea		
14	ICD9	414.0	Coronary atherosclerosis
15		414.2	Chronic total occlusion of coronary artery
16		414.3	Coronary atherosclerosis due to lipid rich plaque
17		414.4	Coronary atherosclerosis due to calcified coronary lesion
18		414.8	Other specified forms of chronic ischemic heart disease
19		414.9	Chronic ischemic heart disease, unspecified
20	ICD10	125.1	Atherosclerotic heart disease of native coronary artery
21		125.8	Other forms of chronic ischemic heart disease
22		125.9	Chronic ischemic heart disease, unspecified
23	Heart failure		
24	ICD9	428.0	Congestive heart failure
25		428.1	Left heart failure
26 27		428.2	Systolic heart failure
27 28		428.3	Diastolic heart failure
28 29		428.4	Combined systolic and diastolic heart failure
29 30		428.9	Heart failure, unspecified
31	ICD10	150.1	Left ventricular failure, unspecified
32		150.2	Systolic (congestive) heart failure
33		150.3	Diastolic (congestive) heart failure
34			Combined systolic (congestive) and diastolic (congestive)
35		150.4	heart failure
36		150.8	Other heart failure
37		150.9	Heart failure, unspecified
38	Myocardial infarction		
39	ICD9	410.0-410.9	Acute myocardial infarction
40	ICD10	121.0-121.9	Acute myocardial infarction
41	10010	I21.A	Other type of myocardial infarction
42		121.7	Myocardial infarction with coronary microvascular
43		I21.B	dysfunction
44	Chronic obstructive p		dyblandion
45		493.20	Chronic obstructive asthma, unspecified
46		493.21	Chronic obstructive asthma with status asthmaticus
47		493.22	Chronic obstructive asthma with (acute) exacerbation
48		496	Chronic airway obstruction, not elsewhere classified
49	ICD10	490	Chronic obstructive pulmonary disease with (acute) lower
50	ICDIU	J44.0	respiratory infection
51		544.0	Chronic obstructive pulmonary disease with (acute)
52		J44.1	exacerbation
53			
54		J44.8 J44.9	Other specified chronic obstructive pulmonary disease
55	Chronic kidnov diacos		Chronic obstructive pulmonary disease, unspecified
56 57	Chronic kidney diseas		Chronic kidnov diacona Stars I Stars V
57 58	ICD9	585.1-585.5	Chronic kidney disease, Stage I-Stage V
58 59		585.6	End stage renal disease
60		585.9	Chronic kidney disease, unspecified
50	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 dise	ase	
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:

[41] Du, X. L., Song, L., Schulz, P. E., Xu, H., & Chan, W. (2022). Risk of Developing Alzheimer's Disease and Related Dementias in Association with Cardiovascular Disease, Stroke, Hypertension, and Diabetes in a Large Cohort of Women with Breast Cancer and with up to 26 Years of Follow-Up. Journal of Alzheimer's disease: JAD, 87(1), 415–432. https://doi.org/10.3233/JAD-215657

[43] Torrandell-Haro, G., Branigan, G. L., Brinton, R. D., & Rodgers, K. E. (2022). Association between specific type 2 diabetes therapies and risk of alzheimer's disease and related dementias in propensity-score matched type 2 diabetic patients. *Frontiers in Aging Neuroscience*, *14*, 878304.

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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:	COVID-19, PUBLIC HEALTH, Chronic Disease, GERIATRIC MEDICINE, Dementia < NEUROLOGY



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,
 g, Altraining, and similar

 COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.
 COVID-19 Vaccination, Vaccine Hesitancy, Social Determinants of Health.

 Abbreviations. ADRD: Alzheimer's disease and related dementias; AD: Alzheimer's disease; MCI: Mild
 Mild

cognitive impairment; COVID-19: Coronavirus disease 2019; SARS-CoV2: Severe acute respiratory syndrome nologies 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-192 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 logistica regression will be applied to assess the vaccination rates and vaccine hesitancy, while controlling ford 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) Ethics and Dissemination. This study protocol received approval from the Institutional Review Board at Florida

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 3. 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

2 Coronavirus disease 2019 (COVID-19) vaccines are pivotal in preventing the severe acute respiratory syndrome 3 and long-term symptoms, and reducing mortality associated with COVID-19.1-5 Previous studies have 4 5 demonstrated the significant association between Alzheimer's disease (AD) and increased risk of COVID-19 6 infection and mortality.^{6,7} Individuals with dementia are particularly vulnerable, facing a 2 to 3-fold greater risk of 7 COVID-19 infection partly due to increased levels of angiotensin-converting enzyme 2 (ACE2) compared to the 8 general older adults.^{7,8} Additionally, individuals with Alzheimer's disease and related dementias (ADRD) 9 encounter challenges in adopting protective behaviors to mitigate infection risks.^{9,10} 10

مة As COVID -19 vaccine become available, studies on understanding vaccination rates in targeted population has 11 12 gained significance. Previous studies had compared vaccination rates against COVID-19 between different 13 socio-demographic population and chronic conditions. A study focused on community vulnerability found that 14 socioeconomic vulnerability, housing type and composition, and epidemiological factors were associated with at 15 least a 1.0 percentage point decline in county-level vaccination among the U.S. population.¹¹ Another study in 16 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. 17 18 were high and comparable to the general population. However, there still lacks sufficient evidence of comparing 19 vaccination rates among ADRD/MCI people. 20

21 Increasing vaccination rates play a pivotal role in fostering herd immunity against COVID-19, which serves to 22 curb virus transmission and safeguard those who are more susceptible to COVID-19 adverse consequences.139 23 Following the introduction of COVID-19 vaccines, a noticeable reduction in pandemic-related excess deaths was 24 observed among individuals with ADRD.⁹ Despite progress, patients with dementia are at a higher risk of 25 observed among individuals with ADRD.⁹ Despite progress, patients with dementia are at a higher risk of set 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} Asg of October 2022, 111,367,843 people, equivalent to 34% of the U.S. population, have received booster shots.¹⁸ of While ADRD patients and their caregivers exhibit willingness to facilitate vaccination, a substantial portion of barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., age, race and barriers and hesitancy among patients with dementia include intra-personal level influences (relationships with dementia include intra-personal level influences (relationships with dementia include intra-personal level influences (e.g., age, race and definition of the set of 26 27 28 29 30 barriers and hesitancy among patients with dementia include intra-personal level influences (e.g., e.g., e.g., the ethnicity, income, culture beliefs, dementia related symptoms), inter-personal level influences (relationships with ethnicity, living ethnicity, income, culture beliefs, dementia related symptoms), inter-personal level influences (media impact. religiosity, living ethnicity) and ethnicity influences (media impact. religiosity, living ethnicity). 31 32 33 caregivers, informal caregiver distress), and extra-personal level influences (media impact, religiosity, living 34 accommodations).²² Understanding the impact of individual, interpersonal, and community level social 35 determinants on COVID-19 vaccination intent and hesitancy among individuals with ADRD/MCI still requires 36 further exploration.^{23,24} ≥ 37

This study aims to provide a comprehensive comparison of vaccination coverage, including at least one dose, 38 39 two doses, and boosters or three full doses, along with adverse reactions between ADRD/MCI individuals and 40 those without ADRD/MCI. Additionally, this study seeks to examine the impact of social determinants of health a 41 on COVID-19 vaccination rates and vaccine hesitancy among individuals with ADRD/MCI. By gaining a better 42 understanding of these factors, we can develop targeted strategies to improve vaccination rates and address 43 concerns among this vulnerable population. 44

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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 besters or three full doses) between ADRD/MCL individuals and these without ADRD/MCL 47 48 boosters or three full doses) between ADRD/MCI individuals and those without ADRD/MCI. 49

50 Research Aim 2: To assess the variation in adverse reactions such as swelling, tiredness, muscle pain, chills, 51 fever, following the COVID-19 vaccination in individuals with ADRD/MCI compared to those without ADRD/MCI. 52

53 Research Aim 3: To investigate the influence of social determinants of health on COVID-19 vaccination rates 54 and vaccine hesitancy in individuals with ADRD/MCI. 55

56 **Methods and Data Analysis** 57

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Data Source: All of Us (AoU) Researcher Workbench

2 The data source for this study protocol will be the All of Us (AoU) Researcher Workbench, which is a secure and 3 comprehensive source of biomedical datasets enrolled with a broad, diverse group of United States(U.S.) 4 populations.^{25,26} These datasets consists of diverse range of U.S. population, ensuring inclusively and 5 representation. The AoU Research Workbench seeks to engage individuals from underrepresented 6 demographic groups, promoting diversity in research.²⁷ The AoU Research Program encompasses various data 7 elements, including participants' basic demographic information, responses to health surveys, physical 8 measurements, biospecimen collection (including blood, urine, and saliva samples stored in the secure AoU 9 biobank), structured electronic health records (EHRs), and Fitbit tracker data collected from one million 10 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, 11 12 and they provide survey responses covering various domains on an ongoing basis.^{28,29} Specifically, we will 13 extract relevant data fields from sources such as the Demographics, Basic Survey, COVID-19 Vaccine Survey, 14 Health Access & Utilization, Social Determinants of Health, and EHR conditions data. Enrollment for the AoUS 15 program commenced in 2018 and is anticipated to continue for at least 10 years. By 2023, the AoU research 16 17 initiative successfully extended invitations to one million individuals nationwide.³⁰ The diverse population and 18 data integration from multiple sources within the AoU Research Workbench allow for a comparative analysis of 19 vaccination rates, adverse reactions, and the influence of social determinants of health on vaccine hesitancy 20 between populations with ADRD/MCI and Non-ADRD/MCI populations with a sequential follow-up. The 21 deidentified data are accessible through the AoU researcher workbench (https://workbench.researchallofus.org) 22 under institutional data use agreements.³¹ All analyses will be conducted within a secure platform provided by 23 AoU Researcher Workbench. The study protocol and AoU materials have received approval from the Institutional 24 Review Board at Florida State University Office of Research. 25 relatec

26 Workspace on the AoU Researcher Workbench Secure Platform: ADRD/MCI and COVID-19 Vaccination 27

28 We have established a workspace named "ADRD/MCI and COVID-19 Vaccination" within the AoU Researcher 29 Workbench. This cloud-based platform grants authorized researchers access to and the ability to analyze data 30 from the AoU. The platform offers two levels of data access: the registered tier and the controlled tier. We have 31 been granted access to the controlled data tier. Within this controlled tier, we have constructed two distinct 32 cohorts: one consists of individuals with ADRD/MCI and the other consists of mose without ADRD/MCI and the other conservation of a gradient and cohorts: one consists of individuals with ADRD/MCI and the other consists of those without ADRD/MCI. Cohort 33 34 35 based on the ICD coding and classification. We applied appropriate logical operators such as "AND" and "OR" 36 to combine the key inclusion and exclusion criteria. To facilitate our research, we utilized the dataset builder tool[▶] 37 38 to construct the datasets. Subsequently, we exported the acquired data to Jupyter Notebooks for analysis, 39 leveraging the R programming language version 4.3 (R Foundation for Statistical Computing) and Python version 40 3.12 (Python Software Foundation). and 41

1) ADRD/MCI Cohort

simi 43 The ADRD/MCI cohort is formed by gathering information from EHR . Through EHR, individuals are identified for 44 inclusion in the ADRD/MCI cohort is tormed by gamering information norm Envertnicegin Envertnicegin Envert "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) 45 46 47 48 lies 49

2) Non-ADRD/MCI Cohort

51 Individuals who have been diagnosed with mild cognitive impairment (MCI) or Alzheimer's disease and related 52 dementias (ADRD) are excluded. Additionally, deceased people are excluded from this cohort. 53 54

Patient and Public Involvement 55

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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)**

Likert scale, ranging from "very likely" to "very unlikely". **(Table 1)**Independent Variables Social determinants of health at Individual, Interpersonal and Community Level Factors **a**(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.

₫ 23 Interpersonal level factors for ADRD/MCI patients consist of sociocultural environment and social support, as2 24 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?" 25 26 c) "How many years have you lived at your current address?" d)"What is the main type of housing in your 27 neighborhood?" e) "Not including yourself, how many other people live at home with you?" f) "how much you" 28 agree or disagree that people around here are willing to help their neighbor?" and g) "how much you agree or 29 disagree that people in your neighborhood generally get along with each other?". 30

31 Community level factors include healthcare facility accessibility and utilization, as assessed in the AoU Health 32 Access & Utilization Survey, with affirmative responses to the following questions: a) "During the past 12 months, 33 were you told by a health care provider or doctor's office that they did not accept your health care coverage?" b_{\exists} 34 "What kind of place that you usually go to when you are sick or need advice about your health?" c) "Have you i 35 seen any of the following doctors or health care providers about your own health in the last 12 months?" – $a \vec{\varphi}$. 36 general doctor; a nurse practitioner; a doctor specialized in women's health; a mental health professional; an≥ 37 optometrist; a podiatrist; a chiropractor; a physical therapist; a dentist; a medical doctor; traditional healers; 38 d)"Have you delayed getting care for any of the following reasons in the past 12 months?" - didn't have 39 transportation; live in the rural area where distance to health care provider is too far; nervous about seeing a 40 health care provider; couldn't get time off work; couldn't get child care; couldn't get elderly care; couldn't afford 41 42 the co-pay; couldn't afford the deductible; had to pay out of pocket for some or all of the procedure. similar technologies 43

abla 1. Maacuramant 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.	<i>AoU</i> COVID-19 Vaccine Survey
Cohorts ADRD/MCI ICD-9/10 diagnosed conditions such as "mild cognitive and non- ADRD/MCI positive responses related to ADRD/MCI diagnosis in the EHR data.		AOU COVID-19 Vaccine Survey AOU COVID-19 Vaccine Survey 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
level factors environment neighborhood environment, years of living at residency. Deter and social Healt		AoU Social Determinants of Health Survey & AoU Basic Survey	
level factors accessibility provid and Utilization for g assist		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.	<i>AoU</i> Health Access & Utilization Survey

<u>Samples</u> 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 Cohor (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	90 (1)	920 (1)
options, Prefer not to answer)		
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	5 012 (61)	20 042 (20)
Anxiety Major doprosojvo dipordoro	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) 5	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

9 10 <u>Statistical Analysis Plan</u>

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Demographic variables will be summarized using descriptive statistics (e.g., Mean ± SD or median wither 11 12 interguartile range) as appropriate for continuous variables. Frequency and percentage will be summarized for 13 categorical variables. Data quality will be checked, including steps like outlier detection.³⁵ The distribution of all 14 variables will be examined to check the validity of distribution assumptions before subsequent analyses, using 15 univariate/multivariate Shapiro-Wilk test and a visual inspection of histograms and guantile-guantile plots. If the 16 normal assumption of continuous variables is not met, appropriate data transformations or alternative data 17 analysis procedures (e.g., nonparametric, bootstrapping) will be employed. The baseline demographics and 18 survey answers of the ADRD/MCI and without ADRD/MCI cohorts will be summarized in forms of tables and 19 20 figures, with reporting the corresponding p-values from independent samples t-test (or Kruskal-Wallis test when 21 appropriate) for continuous variables and Chi-squared test for categorical variables. Significance level at 0.05 22 sets as threshold. 23

24 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 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 a observational data which attempts to construct a balanced intervention and control group by matching each observation 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 details. 25 26 27 28 29 30 31 sample sizes and uncontrolled baseline characteristics. This imbalance may cause confounding effects on the 32 vaccination rates. To control the confounding effects, we generate propensity scores using logistic regression to a sidentify the effects of confounding energies with the personal available. Mehalenable matrix matching energies and the second state of the second sta vaccination rates. To control the confounding effects, we generate propensity source source source and the source and the source source source and the source source source and the source 33 34 35 propensity score matching include age, gender, sex at birth, race, ethnicity, chronic diseases, and mental health 36 status. The goal of propensity score matching is to achieve a balanced distribution of covariates between the[≥] 37 38 ADRD/MCI and non-ADRD/MCI groups. We assess the effectiveness of matching by comparing the effective 39 size of each included covariate before and after matching, with a decrease in effective size indicating balanced 40 pairs. The results of propensity logit will be presented in the histogram, and standardized mean differences 41 across covariates before and after matching are reported. The study utilizes the 'psmpy 0.3.13' propensity score 42 matching package for propensity logits and graphical representations of matching outcomes, as well as matched 43 pairs and standardized mean differences across covariates.³⁸ 44

45 Vaccine hesitancy will be computed and compared across cohorts using Chi-Squared tests. To analyze the 46 association of vaccine hesitancy (i.e., individuals reported how likely to get vaccinated) with covariates, we will 47 employ a binary logistic regression with vaccine hesitancy as the outcome (5-point Likert scale recategorized to 48 binary outcome: likely or unlikely), and covariates as controlled variables. This approach will enable us to 49 compute the adjusted odds ratios (AOR) to determine the likelihood of vaccine hesitancy.³⁹ An AOR greater than⁴ 50 1 indicates higher odds for vaccine hesitancy, meaning individuals who are unlikely to take the vaccination have 51 high vaccine hesitancy.³⁹ 95% confidence intervals for each coefficient's adjusted odds ratios will be calculated. 52 The statistical analysis is performed on Jupyter Notebooks, leveraging the R programming language version 4.3 53 (R Foundation for Statistical Computing) and Python version 3.12 (Python Software Foundation). 54

55 56 Data Management and Safety

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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

7 As of May 2023, at least 270,227,181 individuals, constituting 81% of the U.S. population, have received at least 8 one COVID-19 vaccine dose. Furthermore, 230,637,348 people, equivalent to 70% of the population, have 9 achieved full vaccination status.¹⁸ This high rate is considered a highly positive development against the COVIDachieved 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 10 11 12

The authors compared the cohort of diagnosed Alzheimer's and related dementias (ADRD) individuals in the 14 AoU research dataset to the ADRD prevalence in the U.S. population from the CDC and the 2024 Alzheimer's 15 Disease Facts and Figures Report. According to the 2024 Alzheimer's Association Facts and Figures Report. 16 17 approximately 6.9 million older adults aged over 65 have been diagnosed with ADRD.41 along with about 200,000 18 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: 19 20 in the AoU research dataset, we identified 9.718 participants diagnosed with ADRD and COVID-19 vaccination 21 records out of a total of 410,235 enrolled AoU participants, representing 2% of the overall population. The 22 distribution of chronic conditions in the ADRD cohort in our study, such as hypertension, diabetes, and 23 cardiovascular disease, closely aligns with the statistics presented in the Alzheimer's Association's chronics 24 diseases and dementia factsheet.³² These findings enhance the generalizability of our sample to the broader 25 26

U.S. population with ADRD. Individuals with ADRD/MCI had a higher age compared with those without ADRD/MCI. Among the 9,718 27 28 ADRD/MCI patients, 8% were aged 18-44 (n=771), 28% were aged 45-64 (n=2,712), and 64% were aged over 29 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 30 aged 45-64 (n=36,463), and 44% were over 65 years old (n=48,482). Individuals with ADRD/MCI had higher 31 rates of chronic conditions and mental health disorders. In comparison to the non-ADRD/MCI cohort, patients a s 32 with ADRD/MCI had higher prevalence of hypertension, heart diseases, cerebrovascular diseases, a s 33 34 overweight/obesity, diabetes, chronic pulmonary diseases, chronic kidney and liver diseases, and cancer. These 35 findings align with reports from the Alzheimer's Association and other previous research.^{32,43} Additionally, studies 36 indicate that obesity has become the top risk factor for dementia in the US.44 Individuals with ADRD/MCI also 37 displayed a higher prevalence of mental health disorders compared to those without ADRD/MCI. 38

39 The proposed study will contribute to scientific knowledge in several ways: First, it will be a comprehensive 40 analysis of vaccination coverage for individuals with ADRD/MCI by examining the first, second, and booster 41 shots. This in-depth examination will shed light on any significant differences in vaccination behavior and adverse 42 reactions between individuals with ADRD/MCI and those without. Such comparisons can provide insights into 43 the unique challenges faced by individuals with ADRD/MCI. This is particularly important where booster shots 44 have become a critical component of maintaining immunity, this comprehensive study can provide insights into 45 long-term vaccination behaviors and trends. Second, this proposed study will assess adverse reactions to 46 COVID-19 vaccines among individuals with ADRD/MCI and those without. This information can offer valuable 47 data on the safety and tolerability of vaccines in vulnerable populations. Healthcare professionals can then make 48 more informed decisions about vaccine administration and monitoring. Third, the proposed study will integrate 49 social determinants of health into its analysis. recognizing the potential influence of social determinants of health 50 on vaccination rates is crucial. Equitable vaccination plays an important role in mitigating health-related 51 52 disparities among minority groups. This proposed study goes beyond the clinical aspect and delves into the 53 broader factors affecting healthcare access and decision-making. Lastly, the research findings will directly inform 54 public health strategies and interventions. The research findings can directly inform public health strategies and 55 interventions. If it is found that individuals with ADRD/MCI are more hesitant to receive booster shots, public 56 health strategies can be tailored to address their specific concerns and needs. Policymakers and healthcare 57

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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 reaction and requestion of recall bias. Additionally, we will verify participants' EHR condition codes for adverse events to ensure accuracy

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.g

 Abbreviations

 ADRD: Alzheimer's disease and related dementias: AD: Alzheimer's disease: MCI: Mild cognitive impairment; a

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.

Author affiliations

¹College of Nursing, Florida State University, Tallahassee, FL, 32306. **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 sure built of the study. College of Nursing, Florida State c.... Author contributions YJY conceived the idea for the study. YJY, JW, HJP, CDL and DS drafted, participated in manuscript con-study design. YJY, CDL and DS performed the acquisition and interpretation of data for the work. All authors are 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.

Funding

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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 disseminations plans of our research.

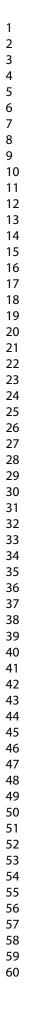
Figure Legend

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

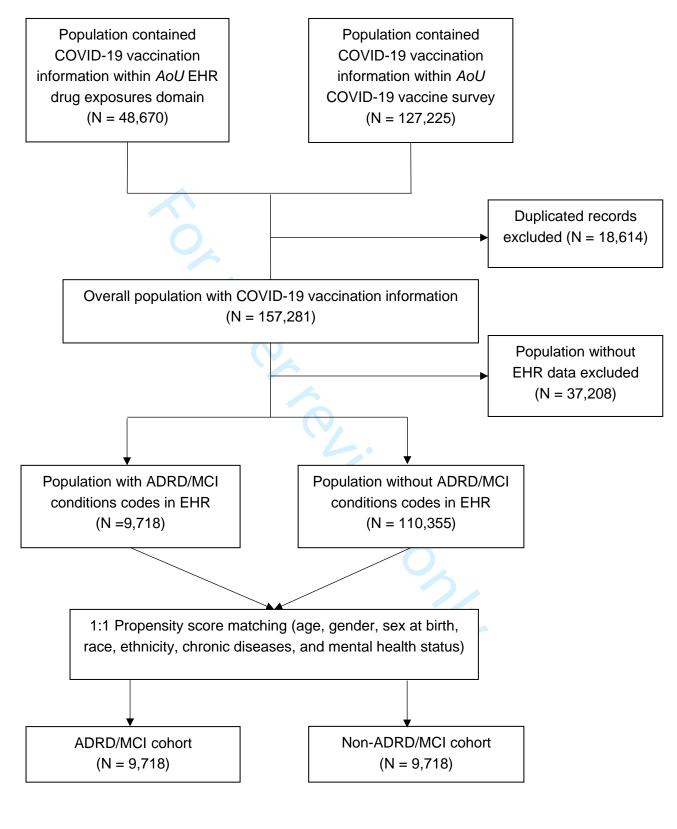
Reference

Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. 1. New England journal of medicine. 2021;384(5):403-416. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. 2. New England journal of medicine. 2020;383(27):2603-2615. Taylor L. Covid-19: Vaccination reduces severity and duration of long covid, study finds. bmj. 3. 2023:380(4) 4. MacCallum-Bridges C, Hirschtick JL, Patel A, Orellana RC, Elliott MR, Fleischer NL. The impact of COVID-19 vaccination prior to SARS-CoV-2 infection on prevalence of long COVID among a population-based probability sample of Michiganders, 2020-2022. Annals of Epidemiology. 2024; Protected by copyright, including Trinh NT, Jödicke AM, Català M, et al. Effectiveness of COVID-19 vaccines to prevent long COVID: 5. data from Norway. The Lancet Respiratory Medicine. 2024; Hardan L, Filtchev D, Kassem R, et al. COVID-19 and Alzheimer's disease: a literature review. 6. Medicina. 2021;57(11):1159. Rolland Y, Baziard M, De Mauleon A, Dubus E, Saidlitz P, Soto ME. Coronavirus Disease-2019 in 7. Older People with Cognitive Impairment. Clinics in Geriatric Medicine. 2022;38(3):501-517. Pszczołowska M, Walczak K, Misków W, et al. Molecular cross-talk between long COVID-19 and 8. Alzheimer's disease. GeroScience. 2024:1-15. 9. Chen R, Charpignon M-L, Raguib RV, et al. Excess Mortality With Alzheimer Disease and Related Dementias as an Underlying or Contributing Cause During the COVID-19 Pandemic in the US. JAMA Interprotogy. 2023;80(9):919-928.
 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet.* 2020;396(10248):413-446.
 Brown CC, Young SG, Pro GC. COVID-19 vaccination rates vary by community vulnerability: A courty-theel analysis. *Vaccine*. 2021;39(31):4245-4249.
 Gaughan CH, Razieh C, Khunti K, et al. COVID-19 vaccination uptake amongst ethnic minority communities in England: a linked study exploring the drivers of differential vaccination rates. *Journal of Public Health*. 2023;45(1):e65-e74.
 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *New England Journal of Medicine*. 2021;39(415):1412-1423.
 Wang L, Davis PB, Kaelber DC, Xu R. COVID-19 breakthrough infections and hospitalizations among vaccinate patients with dementia in the United States between December 2020 and August 2021. *Alzheimer*. 54 Dementia. 2023;19(2):421-432.
 Radomyslsky Z, Kivity S, Lidar S, et al. Association between COVID-19 vaccination and critical outcomes among older adults with dementia: a comparative cohort study. *Frontiers in Public Health*. 2023;11:1281266.
 Ali A. COVID numbers are rising again, but Fauci not predicting another 'tsunami of hospitalizations. deaths/story?id=103056079
 Garrity K, Fauci: We need to be prepared 'for likely Covid uptick this winter. Accessed September 9, 2023. https://usafcts.org/viaulzalions/codid-vaccine-tracker-states/
 Yang Y, Nie J, Sun F, et al. The SARS-CoV-2 vaccination rate and hesitation in Shanghai older adults with dementia. a literature review. *Aging Clinical and Experimental Research*. 2022;14:e066200.
 Yang Y, Nie J, Sun F, et al. The SARS-CoV-2 vaccination rate and hesitation in Shanghai older adults with dementia: a literature review. *Aging Clinical and Experimental Research*. 2022;14:e066200.
 <l neurology. 2023;80(9):919-928. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report ę 10. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1	24. Malik AA, McFadden SM, Elharake J, Omer SB. Determinants of COVID-19 vaccine acceptance in the
1	US. EClinicalMedicine. 2020;26
2 3	25. Zhang J, Yang X, Weissman S, Li X, Olatosi B. Protocol for developing a personalised prediction model
3 4	for viral suppression among under-represented populations in the context of the COVID-19 pandemic. BMJ
5	open. 2023;13(5):e070869.
6	26. NIH. About All of Us. Accessed October 5th, 2023. <u>https://allofus.nih.gov/about</u>
7	27. Investigators AoURP. The "All of Us" research program. New England Journal of Medicine.
8	2019;381(7):668-676.
9	28. NIH. The All of Us Consent Process. Accessed Oct 5th, 2023. <u>https://allofus.nih.gov/about/protocol/all-</u>
10	us-consent-process
11	29. NIH. Consent to Join the All of Us Research Program (June 20, 2018) at F1–8—F1–9.
12	30. NIH. All of Us Research Program FAQ. Accessed December 8th, 2023.
13	https://allofus.nih.gov/about/faq#:~:text=The%20All%20of%20Us%20Research%20Program%20is%20part%2
14	0of%20an,health%20data%20over%20many%20years.
15	31. NIH. Registered Institutions. Accessed Oct 5th, 2023. https://www.researchallofus.org/institutional-
16	 NIH. Registered Institutions. Accessed Oct 5th, 2023. <u>https://www.researchallofus.org/institutional-agreements/</u> Alzheimer's Association. Chronic Diseases and Dementia. Accessed May 6th, 2024
17	32. Alzheimer's Association. Chronic Diseases and Dementia. Accessed May 6th, 2024.
18	https://www.alz.org/professionals/public-health/public-health-topics/chronic-
19	diseases#:~:text=Almost%20all%20individuals%20with%20dementia,to%2C%20cognitive%20decline%20and
20	<u>%20dementia</u> .
21	33. Mazereel V, Vanbrabant T, Desplenter F, et al. COVID-19 vaccination rates in a cohort study of
22 23	patients with mental illness in residential and community care. Frontiers in psychiatry. 2021;12:805528. ਰ੍ਰੇ
25 24	34. Kelley K, Maxwell SE. Sample size for multiple regression: obtaining regression coefficients that are accurate, not simply significant. <i>Psychological methods</i> . 2003;8(3):305.
24 25	accurate, not simply significant. Psychological methods. 2003;8(3):305.
26	35. Smiti A. A critical overview of outlier detection methods. Comput. Sci. Rev. 38, 100306. 2020.
27	36. The World Bank. Propensity Score Matching. Accessed May 6th, 2024.
28	https://dimewiki.worldbank.org/Propensity_Score_Matching#:~:text=Propensity%20score%20matching%20(PS
29	M)%20is,the%20impact%20of%20an%20intervention.
30	37. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in
31	observational studies. Multivariate behavioral research. 2011;46(3):399-424.
32	38. Kline A, Luo Y. PsmPy: A package for retrospective cohort matching in Python. IEEE; 2022:1354-1357.
33	39. Khubchandani J, Sharma S, Price JH, Wiblishauser MJ, Sharma M, Webb FJ. COVID-19 vaccination
34	hesitancy in the United States: a rapid national assessment. Journal of community health. 2021;46:270-277.
35	hesitancy in the United States: a rapid national assessment. <i>Journal of community health</i> . 2021;46:270-277. 40. Su Z, McDonnell D, Li Y. Why is COVID-19 more deadly to nursing home residents? <i>QJM: An</i>
36	
37	-41 = 2024 Alzheimer's disease facts and figures. Alzheimers Dement May 2024:20(5):3708-3821
38	doi:10.1002/alz.13809
39 40	42. CDC Alzheimer's Disease and Healthy Aging. Minorities and Women Are at Greater Risk for
40 41	doi:10.1002/alz.13809 42. CDC Alzheimer's Disease and Healthy Aging. Minorities and Women Are at Greater Risk for Alzheimer's Disease. Accessed June 12th, 2024. <u>https://www.cdc.gov/aging/publications/features/Alz-Greater-</u> <u>Risk.htm</u>
42	
43	 43. Du XL, Song L, Schulz PE, Xu H, Chan W. Risk of developing Alzheimer's disease and related dementias in association with cardiovascular disease, stroke, hypertension, and diabetes in a large cohort of women with breast cancer and with up to 26 years of follow-up. <i>Journal of Alzheimer's Disease</i>. 2022;87(1):415-432. 44. Slomski A. Obesity is now the top modifiable dementia risk factor in the US. <i>Jama</i>. 2022;328(1):10-10.
44	dementias in association with cardiovascular disease, stroke, hypertension, and diabetes in a large cohort of
45	women with breast cancer and with up to 26 years of follow-up. <i>Journal of Alzheimer's Disease</i> .
46	2022;87(1):415-432.
47	44. Slomski A. Obesity is now the top modifiable dementia risk factor in the US. Jama. 2022;328(1):10-10.
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Medical Conditions	Code	Definition
Mild Cognitive Impair		
ICD9	331.83	Mild cognitive impairment, so stated
ICD10	G31.84	Mild cognitive impairment, so stated
Alzheimer's disease a Alzheimer's disease	and related dementias	S
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 Demo		
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
Man (al II al (h. D'a and	G31.09	Other frontotemporal dementia
Mental Health Disord Anxiety	ers	
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 Dis	order	
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

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3 4	ICD9	296.0-296.9	Bipolar disorders
5	ICD10	F31.0-F31.9	Bipolar disorders
6	Psychotic Disorder	205 0 205 0	Cohizophronia diagradara
7	ICD9	295.0-295.9 297.0-297.9	Schizophrenic disorders Delusional disorders
8	ICD10	F20.0-F20.9	Schizophrenia
9	10010	F22	Delusional disorders
10 11		F23	Brief psychotic disorder
12		F24	Shared psychotic disorder
13		F25.0, F25.1, F25.8,	
14		F25.9	Schizoaffective disorders
15			Other psychotic disorder not due to a substance or known
16		F28	physiological condition
17		F 00	Unspecified psychosis not due to a substance or known
18 10	Clean Disender	F29	physiological condition
19 20	Sleep Disorder ICD9	307.4	Specific disorder of algon of poperganic origin
20	ICD9	307.4	Specific disorder of sleep of nonorganic origin Organic sleep disorders
22		780.5	Sleep disturbances
23	ICD10	G47.0-G47.9	Sleep disorder
24	Chronic Conditions		
25 26	Hypertension		
26 27	ICD9	401.0, 401.1, 401.9	Essential hypertension
28		405.0, 405.1, 405.9	Secondary hypertension
29	ICD10	110	Essential (primary) hypertension
30		115	Secondary hypertension
31		I1A	Other hypertension
32	Cerebrovascular Dise		
33	ICD9	436	Acute, but ill-defined, cerebrovascular disease
34 35		437.0-437.9	Other and ill-defined cerebrovascular disease
36	ICD10	438.0-438.9 167.0-167.9	Late effects of cerebrovascular disease Other cerebrovascular diseases
37		168.0, 168.2, 168.8	Cerebrovascular disorders in diseases classified elsewhere
38		169.8, 169.9	Sequelae of cerebrovascular disease
39	Cerebral infarction	100.0, 100.0	
40	ICD9		Occlusion and stenosis of basilar artery with cerebral
41		433.01	infarction
42 43			Occlusion and stenosis of carotid artery with cerebral
44		433.11	infarction
45			Occlusion and stenosis of vertebral artery with cerebral
46		433.21	infarction
47		400.04	Occlusion and stenosis of multiple and bilateral precerebral
48		433.31	arteries with cerebral infarction
49 50		433.81	Occlusion and stenosis of other specified precerebral artery with cerebral infarction
50 51		455.01	Occlusion and stenosis of unspecified precerebral artery
52		433.91	with cerebral infarction
53		434.01	Cerebral thrombosis with cerebral infarction
54		434.11	Cerebral embolism with cerebral infarction
55			Cerebral artery occlusion, unspecified with cerebral
56		434.91	infarction
57	ICD10	163.0-163.9	Cerebral infarction
58 59	Overweight and Obes	-	
60	ICD9	278.0	Overweight and obesity

2			
3		278.00	Obesity, unspecified
4		278.00	Morbid obesity
5		278.02	Overweight
6		278.02	•
7			Obesity hypoventilation syndrome
8	ICD10	E66.0-E66.9	Overweight and obesity
9	Diabetes	050 0 050 0	
10	ICD9	250.0-250.9	Diabetes mellitus (Type 1 & 2)
11	ICD10	E10.1-E10.9	Type 1 diabetes mellitus
12	-	E11.1-E11.9	Type 2 diabetes mellitus
13	Coronary artery disea		
14	ICD9	414.0	Coronary atherosclerosis
15		414.2	Chronic total occlusion of coronary artery
16		414.3	Coronary atherosclerosis due to lipid rich plaque
17		414.4	Coronary atherosclerosis due to calcified coronary lesion
18		414.8	Other specified forms of chronic ischemic heart disease
19		414.9	Chronic ischemic heart disease, unspecified
20	ICD10	125.1	Atherosclerotic heart disease of native coronary artery
21		125.8	Other forms of chronic ischemic heart disease
22		125.9	Chronic ischemic heart disease, unspecified
23	Heart failure		
24	ICD9	428.0	Congestive heart failure
25		428.1	Left heart failure
26 27		428.2	Systolic heart failure
27 28		428.3	Diastolic heart failure
28 29		428.4	Combined systolic and diastolic heart failure
30		428.9	Heart failure, unspecified
31	ICD10	150.1	Left ventricular failure, unspecified
32		150.2	Systolic (congestive) heart failure
33		150.3	Diastolic (congestive) heart failure
34			Combined systolic (congestive) and diastolic (congestive)
35		150.4	heart failure
36		150.8	Other heart failure
37		150.9	Heart failure, unspecified
38	Myocardial infarction		
39	ICD9	410.0-410.9	Acute myocardial infarction
40	ICD10	121.0-121.9	Acute myocardial infarction
41	10010	I21.A	Other type of myocardial infarction
42		121.7	Myocardial infarction with coronary microvascular
43		I21.B	dysfunction
44	Chronic obstructive p		ajoranolion
45		493.20	Chronic obstructive asthma, unspecified
46		493.21	Chronic obstructive asthma with status asthmaticus
47		493.22	Chronic obstructive asthma with (acute) exacerbation
48		496	Chronic airway obstruction, not elsewhere classified
49	ICD10	450	Chronic obstructive pulmonary disease with (acute) lower
50	ICDIO	J44.0	respiratory infection
51		344.0	Chronic obstructive pulmonary disease with (acute)
52		J44.1	exacerbation
53		J44.1 J44.8	
54 55		J44.8 J44.9	Other specified chronic obstructive pulmonary disease
55 56	Chronic kidnov dices		Chronic obstructive pulmonary disease, unspecified
50 57	Chronic kidney diseas		Chronic kidnov disoaso, Stago I Stago V
57 58	1009	585.1-585.5 585.6	Chronic kidney disease, Stage I-Stage V
58 59			End stage renal disease
60	ICD10	585.9 N18 1 N18 5	Chronic kidney disease, unspecified
		N18.1-N18.5	Chronic kidney disease, stage 1-Stage 5

2			
3		N18.6	End stage renal disease
4		N18.9	Chronic kidney disease, unspecified
	Chronic liver disease		
5	ICD9	571.0-571.9	Chronic liver disease and cirrhosis
/ 3	ICD10	K73.0-K73.9	Chronic hepatitis, not elsewhere classified
))	Cancer		
0	ICD9	140-239	Neoplasms
11	ICD10	C00-C96	Neoplasms
12 _		D00-D49	Neoplasms
13 \$	Sources:		

[43] Du, X. L., Song, L., Schulz, P. E., Xu, H., & Chan, W. (2022). Risk of Developing Alzheimer's Disease and Related Dementias in Association with Cardiovascular Disease, Stroke, Hypertension, and Diabetes in a Large Cohort of Women with Breast Cancer and with up to 26 Years of Follow-Up. Journal of Alzheimer's disease: JAD, 87(1), 415-432. https://doi.org/10.3233/JAD-215657