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Title: Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study: Study Design

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Data Availability Statement: Access to pooled C4R data is regulated by the C4R publications and presentations (P&P) policy, which is available on the C4R website. Data is made available for analyses on the C4R Analysis Commons for investigators with manuscript proposals approved by the C4R publications and cohort coordinating committees as well as by each cohort included in a given proposal. Once harmonization and related quality control is completed, C4R common data

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elements will be transferred as a limited dataset for public access on BioData Catalyst in accord with cohort-specific consents and commitments.

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Running Head: C4R Study Design

Key words: COVID-19, cohort study, epidemiology

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Abbreviations

ARIC	Atherosclerosis Risk in Communities
BCL	Biorepository and Central Laboratory
C4R	Collaborative Cohort of Cohorts for COVID-19 Research
CARDIA	Coronary Artery Risk Development in Young Adults
CONNECTS	Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies

COPDGene	Genetic Epidemiology of COPD
COVID-19	Coronavirus Disease 2019
DBS	Dried Blood Spot
FHS	Framingham Heart Study
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
JHS	Jackson Heart Study
MASALA	Mediators of Atherosclerosis in South Asians Living in America
MESA	Multi-Ethnic Study of Atherosclerosis
NOMAS	Northern Manhattan Study
PASC	Post-Acute Sequelae of SARS-CoV-2 Infection
PrePF	Prevent Pulmonary Fibrosis
REGARDS	REasons for Geographic and Racial Differences in Stroke
SARP	Severe Asthma Research Program
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SPIROMICS	Subpopulations and Intermediate Outcome Measures in COPD Study
SHS	Strong Heart Study
W1Q	Wave 1 Questionnaire
W2Q	Wave 2 Questionnaire

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Abstract

The Collaborative Cohort of Cohorts for COVID-19 Research (C4R) is a national prospective study of adults comprising 14 established United States (US) prospective cohort studies.

Starting as early as 1971, C4R cohorts have collected data on clinical and subclinical diseases and their risk factors, including behavior, cognition, biomarkers, and social determinants of health. C4R links this pre-COVID phenotyping to information on SARS-CoV-2 infection and acute and post-acute COVID-related illness. C4R is largely population-based, has an age range of 18-108 years, and reflects the racial, ethnic, socioeconomic, and geographic diversity of the US. C4R ascertains SARS-CoV-2 infection and COVID-19 illness using standardized questionnaires, ascertainment of COVID-related hospitalizations and deaths, and a SARS-CoV-2 serosurvey via dried blood spots. Master protocols leverage existing robust retention rates for telephone and in-person examinations, and high-quality events surveillance. Extensive pre-pandemic data minimize referral, survival, and recall bias. Data are harmonized with research-quality phenotyping unmatched by clinical and survey-based studies; these will be pooled and shared widely to expedite collaboration and scientific findings. This resource will allow evaluation of risk and resilience factors for COVID-19 severity and outcomes, including post-acute sequelae, and assessment of the social and behavioral impact of the pandemic on long-term trajectories of health.

Keywords: COVID-19, cohort study, epidemiology

Adverse effects of the coronavirus disease 2019 (COVID-19) pandemic on United States (US) health, economy, and society are widespread (1). Eighteen months following the initial US outbreak in winter 2020, there have already been over 44 million cases and over 700,000 deaths, making COVID-19 the third-leading cause of death in the United States in 2020 and the

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second-leading cause of death in those over 85 years of age (2, 3). Prolonged symptoms and clinical abnormalities are observed in some COVID-19 survivors, raising concerns that post-acute sequelae of SARS-CoV-2 infection (PASC) could pose an additional long-term health burden (4).

C4R includes fourteen US prospective cohort studies that, collectively, constitute a large, well-characterized, population-based sample that ranges in age from young adults to centenarians, and reflects the racial, ethnic, socioeconomic, and geographic diversity of the US. C4R uses standardized protocols and active surveillance in an attempt to fully ascertain SARS-CoV-2 infection and COVID-19 illness across all cohorts.

C4R offers the additional major advantages of each component cohort's longstanding practices of standardized data collection, including robust retention rates and high-quality clinical events surveillance dating back as far as 1971 in some studies. For decades, the C4R cohorts have collected extensive longitudinal data on clinical and subclinical disease, behaviors, cognition, biomarkers, and social determinants of health. C4R links this "pre-COVID" phenotyping to information on SARS-CoV-2 infection and acute and post-acute COVID-related illness. The integration of antecedent and illness-related data will not only define the consequences of COVID-19 infection reliably, but also provide a unique opportunity to understand mechanisms and modifiers of risk and resilience for SARS-CoV-2 infection and adverse COVID-19 outcomes. C4R also supports comparisons of longitudinal changes in health measures over the course of the pandemic in persons with varying degrees of COVID-19 severity. Furthermore, the availability of

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well-characterized participants unaffected by COVID-19 allows assessment and differentiation of the effects of infection, illness, and pandemic-related social, economic, and behavioral changes.

Overall, C4R aims to provide a scientific resource to (1) evaluate risk and resilience factors for adverse COVID-19 outcomes, including severe illness and long-term complications, (2) assess the social and behavioral impact of the COVID-19 pandemic on long-term outcomes and trajectories of health, and (3) examine disparities in COVID-19 risk and outcomes according to race, ethnicity, geography, and other social determinants of health. This report summarizes the C4R study design and its progress in data collection in the first year of funding (October 1, 2020–September 30, 2021).

METHODS

Cohort of cohorts

Fourteen prospective cohorts are collaborating in C4R (**Table 1**). Eight of the cohorts were designed to study cardiovascular disease epidemiology: Atherosclerosis Risk in Communities (ARIC) Study (5), Coronary Artery Risk Development in Young Adults (CARDIA) Study (6), Framingham Heart Study (FHS) (7), Hispanic Community Health Study/Study of Latinos (HCHS/SOL) (8-10), Jackson Heart Study (JHS) (11-13), Mediators of Atherosclerosis in South Asians Living in America (MASALA) Study (14, 15), Multi-Ethnic Study of Atherosclerosis (MESA)

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(16), and the Strong Heart Study (SHS) (17, 18). These cohorts generally recruited population-based samples, although only three (ARIC, CARDIA, FHS, HCHS/SOL) used representational sampling techniques at some or all sites. Four of the cardiovascular studies (ARIC, CARDIA, FHS, MESA) recruited multi-racial participants, and four were designed to study primarily specific race or ethnic groups (Hispanic/Latino participants in HCHS/SOL, Black participants in JHS, South Asian participants in MASALA, American Indian participants in SHS). Four multi-ethnic cohorts were established to study respiratory epidemiology: the Genetic Epidemiology of COPD (COPDGene) Study (19) and the SubPopulations and InteRmediate Outcome Measures in COPD Study (SPIROMICS) (20) were established as longitudinal case-control studies of cigarette smokers with and without COPD; Prevent Pulmonary Fibrosis (PrePF) is a study of early and established interstitial lung disease; and, the Severe Asthma Research Program (SARP) is a study of the entire range of mild to severe asthma, enriched for severe disease (21). Two studies – the Northern Manhattan Study (NOMAS) and the REasons for Geographic and Racial Differences in Stroke (REGARDS) – were established to study primarily neurological outcomes, including stroke and cognition. NOMAS is a multi-ethnic community study (22) and REGARDS is a biracial (non-Hispanic Black, White) national sample of the continental US that oversampled Black people and those residing in the southeast (23).

These cohorts have collected detailed data on participants' health and behavior for as long as fifty years (**Figures 1, 2**). C4R cohorts have performed extensive longitudinal (repeated) phenotyping of subclinical and clinical disease as well as assessments of laboratory biomarkers, 'Omics, imaging, diet, behavior, and social determinants of health, and have extensive

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biorepositories of stored specimens (**Web Table 1**). Twelve cohorts have geocoding available, supporting participant-level assessment of neighborhood socioeconomic status, exposures to systemic racism, and environmental exposures such as air pollution. All cohorts use similar or identical adjudication protocols to ascertain all-cause mortality. Ten cohorts ascertain cardiovascular events including myocardial infarction, stroke, and heart failure. Eight cohorts ascertain respiratory events such as COPD and asthma exacerbations. Seven cohorts ascertain incident cognitive impairment and/or dementia.

Collaboration and governance

Most C4R cohorts have a history of collaboration in the genomics-oriented Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (24), the NHLBI Pooled Cohorts Study focusing on respiratory epidemiology (25), the Cross-Cohort Collaboration (CCC) for cardiovascular epidemiology (26), the Blood Pressure and Cognition (BP COG) Study (27), and the genetic sequencing and multi-omics-focused Trans-Omics for Precision Medicine (TOPMed) Project (28). C4R builds and expands upon these successes to advance COVID-19 research.

Planning for C4R began in March 2020, when the need for a coordinated, cross-cohort response to the knowledge gaps posed by the COVID-19 pandemic was self-evident and urgent. Cohort investigators initiated discussions regarding approaches to ascertain SARS-CoV-2 infections and COVID-related illnesses within the context of unprecedented cohort operational challenges

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associated with the outbreak. The National Heart, Lung, and Blood Institute (NHLBI) funded C4R via an Other Transactional Authority (OTA) mechanism in October 2020. Additional funding for inclusion of the neurology-focused cohorts was provided via the OTA by the National Institutes of Neurological Disorders and Stroke (NINDS) and the National Institute of Aging (NIA).

The collaborative governance structure for C4R is summarized in **Figure 3**. The administrative coordinating center (ACC) is the NHBLI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) program, which reviews C4R operational milestones biweekly. Central C4R functions are overseen by an observational studies monitoring board (OSMB) convened by CONNECTS.

Leadership for C4R is provided by an organizing committee that includes leading – and often, founding – principal investigators (PIs) from all C4R cohorts, PIs from the C4R Data Coordination and Harmonization Center (DCHC) at Columbia University Irving Medical Center, PIs from the C4R Biorepository and Central Laboratory (BCL) at the University of Vermont, and program officers from the NHLBI, NINDS, and NIA. Master C4R protocols for COVID-19 data collection were drafted, piloted, and refined using a consensus-driven approach by dedicated sub-committees that included content-area experts from each cohort. Draft protocols were reviewed, refined, and approved by the organizing committee. Protocols were designed to provide flexibility for multi-modal data collection, including remote options that could be accomplished by both on-site and off-site study personnel, and are available at the study website (c4r-nih.org).

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Consistent with an ancillary studies model, each cohort is directly responsible for accomplishing its own data collection in accordance with the master protocols and under the supervision of its respective OSMB, Steering Committee, and any other applicable regulatory authorities. To maintain full participation, cohorts were permitted to adapt protocols to cohort-specific needs.

The BCL is responsible for establishing a C4R biorepository of dried blood spots (DBS), plus other biospecimens that may be collected in the future, and for performing and/or coordinating performance of centralized clinical and biomarker assays and serology assays.

Data collection is coordinated centrally at the DCHC. Electronic data collection forms are programmed into REDCap for use or adaptation by the cohort data coordinating centers (DCCs). Metadata on completion of questionnaires, events ascertainment, and DBS are reported to the DCHC bi-weekly. The DCHC maintains the C4R website, which includes a password-protected investigator section with regular status updates and study materials.

To promote and sustain this broad collaborative effort, C4R PIs invited additional investigators and cohort personnel to participate in sub-committees and working groups. In this manner, C4R has engaged over 180 investigators to date.

Participants

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Cohort participants previously consented for in-person, telephone, and/or email contact and for abstraction of medical records. Additional consent for ascertainment of COVID-19 data, including the serosurvey, is obtained according to cohort-specific procedures, including verbal, remote, and traditional written informed consent.

All cohort participants who were alive on March 1st, 2020 and had not withdrawn consent for cohort participation were considered eligible for enrollment into C4R. Of 72,358 participants who were believed to meet these inclusion criteria, the C4R PIs estimated that 53,143 participants, hereafter described as the C4R target population, were readily available for recruitment into C4R based on recent participation in cohort follow-up calls. The socio-demographic characteristics of participants eligible for C4R (**Web Table 2**) are similar to those of the C4R target population (**Table 2**). Fifty-eight percent of participants in the target population are 65 years or older, and thus at high risk for severe COVID-19. The anticipated sample is racially and ethnically diverse, based on self-report (29), with approximately 6% American Indian participants, 2% Asian participants, 26% Black participants, and 20% Hispanic/Latino participants.

All forty-eight continental states are represented among C4R participants, including rural, suburban, and urban communities (**Figure 4**). C4R is being conducted across forty field/clinical centers, many of which are associated with more than one C4R cohort; one cohort with extensive geographic reach, the REGARDS, operates via telephone and in-home exams only (23).

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COVID-19 questionnaires

Each cohort was funded to deploy COVID-19 questionnaires twice within 18 months following the initial outbreak in March 2020 via telephone, mail-in, online, email, or smartphone apps. Both the first questionnaire administration, called Wave 1, and the second questionnaire administration, called Wave 2, are attempted across the entire target population.

Various COVID-19 questionnaires were developed as early as March 2020 in certain cohorts (30) and administered in spring and summer 2020. Although these efforts pre-dated funding of C4R, early informal cross-cohort collaborations ensured that many cohorts used identical questionnaires, and all of them generated common data elements regarding infection, testing, hospitalization, and recovery. Following funding, the C4R questionnaire was developed to include domains on COVID-19 infection, testing, hospitalization, symptoms, recovery, re-infection, contacts, vaccination, behavioral changes, sleep, memory loss, depression, anxiety, fatigue, and resilience. This C4R questionnaire includes validated and PhenX toolkit instruments (31-40) in order to optimize comparability with pre-pandemic assessments and across C4R and other cohorts. The C4R questionnaire, including translations into Spanish and Mandarin, is available on PhenX and the C4R website; Research Electronic Data Capture (REDCap (41, 42)) programming is available on request. The C4R questionnaire was used by three cohorts in Wave

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1 and was adapted for use by all 14 cohorts in Wave 2. Comparisons of cohort-specific instruments are provided in **Web Tables 3 and 4**.

As of September 30, 2021, Wave 1 was completed by 13 of the 14 cohorts and wave 2 was initiated in all cohorts (**Web Figure 1**). Characteristics of participants completing the Wave 1 Questionnaires as of this date are similar to the target population (**Table 2**).

COVID-related events

C4R ascertains COVID-related hospitalizations and deaths that are identified via the C4R questionnaire or other surveillance methods available to the cohorts, including EHR linkages, where available. Each cohort uses its own established infrastructure for ascertainment of medical records and death certificates, including the National Death Index, the Centers for Medicare & Medicaid Services, International Classification of Diseases codes (43), and linkage to records from local departments of health. Cohorts review events locally at their Field/Coordinating Centers or transfer records for central review by C4R. The C4R events review assesses severity and major complications of COVID-19 illness, including pneumonia, myocardial infarction, stroke, thromboembolism, and acute renal failure. The protocols use, or are modeled after, longstanding cohort protocols to classify and validate cardiovascular, respiratory (44), and thromboembolic (45) events. Protocols for ascertainment, review, and classification are available on the study website. As of one year after C4R funding, over 1,000 COVID-related hospitalizations or deaths had been ascertained across the consortium.

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DBS collection

DBS Collection kits are produced by the BCL and shipped to the cohorts (either to the individual field centers or the cohort coordinating center, based on cohort preference). DBS cards are labeled with a biospecimen identifier, which is linked to C4R identifiers that are maintained centrally and not shared with the BCL, through the use of a "linking key." Cohort field centers receive DBS collection kits from the BCL and are responsible for recruitment, consent, and distribution to participants. Updated details regarding vaccination status are obtained at the time of DBS consent and immediately prior to mailing the DBS kit to the participant. Participant instructions, including a video, are provided by the cohort and via the C4R website and/or cohort-specific websites. Participants mail the completed kits directly to the BCL or to the cohort field or coordinating center as an intermediary step. In cohorts with upcoming in-person exams, the DBS may be collected in-person by research staff. DBS deployment was initiated in February 2021 (**Web Figure 1**) and is ongoing, with over 10,000 DBS completed as of September 30, 2021.

Serology

After pre-processing of completed DBS cards by the BCL, serology assays are performed by the New York State Wadsworth Center's Bloodborne Viruses Laboratory (BVL) under CLIA and New

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York State certification. The BVL performs a SARS-CoV-2 IgG Microsphere Immunoassay using Luminex bead technology for qualitative detection of human IgG antibodies to SARS-CoV-2 nucleocapsid (N) and spike subunit 1 (S1) antigens. Based on testing 730 pre-COVID DBS and >1100 DBS from individuals with laboratory-confirmed infection, specificity is 99.5% for both N and S1 and sensitivity ranged from 90 to 96% for symptomatic individuals and 77 to 91% for asymptomatic individuals. Sensitivity increased for both groups with time from positive PCR test, accounting for the range. This assay was used successfully to test over 57,000 DBS for statewide serosurveys from April-June 2020 as part of New York State's public health response. Serology results are reported by the BVL to the BCL, and then to the cohort DCCs, which are responsible for a) recombining the results with the proper participants based on the "linking key", and b) reporting results to participants according to usual cohort practices. Serological results are not known to have clinical relevance, and the CDC does not currently recommend modifications to individual behavior or clinical care based on antibody status alone (46); hence, no protocols for "alert" findings were established, and participants may opt out of results return. Protocols for the serosurvey are available on the study website.

Since all current vaccines in use in the U.S. generate an immune response to the Spike protein, antibody responses to vaccination versus viral infection may be distinguished by the anti-nucleocapsid assay results (47).

Quality control

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Cohorts use established protocols for checking data completeness and accuracy at the field center and coordinating center levels. Dual data entry for C4R is encouraged but not required since it is not feasible in all settings due to local impediments and COVID-related exigencies. Ten percent of event reviews are randomly selected for re-review. Reviewers not meeting standards receive regular feedback with recommendations for retraining and/or protocol modifications, as appropriate. Serological assays are repeated on a random 5% sub-sample of blind duplicates.

COVID-19 outcomes

C4R data defines a spectrum of COVID-19 outcomes, including those listed in **Web Table 5**. Ascertainment of COVID-related hospitalizations and deaths characterizes, classifies, and validates moderate-to-severe COVID-19 illnesses. Questionnaires obtain self-reported information on the nature, severity, and duration of symptoms in the acute and post-acute setting, supporting classification of symptomatic and asymptomatic infections and cases of prolonged recovery or PASC. Data on behaviors, attitudes, psychosocial impacts, and vaccinations are also collected. Seropositive individuals without self-reported infection may be reclassified as infected, whereas seronegative individuals with prior positive testing may be classified as sero-reverted.

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Harmonization

Harmonization of COVID-19 and pre-pandemic data are performed centrally by the DCHC on the C4R Analysis Commons to define COVID-19 outcomes and to align pre-pandemic data for large-scale, longitudinal analyses. This effort leverages prior harmonization efforts across C4R cohorts in the TOPMed Project, the NHLBI Pooled Cohorts Study, the BP COG Study, and the CHARGE Working Groups (24, 25, 27, 48-54). Core measures that have already been harmonized across the majority of C4R cohorts are available on the study website; additional variable harmonization is guided by scientific priority and data needs of approved manuscript proposals. As in prior published efforts (25, 55), major steps in data harmonization include identification of variables of interest, review of available data in consultation with cohort-specific investigators and analysts at cohort DCCs, and qualitative assessments of data collection instruments and data dictionaries. Variables are aligned to determine differences in measurement and classification. Next, candidate variables for harmonization are transferred to the C4R Analysis Commons for quantitative assessment, relabeling, and recoding according to a common C4R standard. Quantitative comparisons are made within and between individuals and cohorts to identify outliers and missing data. Data quality issues are investigated and corrected in collaboration with cohort DCCs. Harmonized and derived variables, plus codes used to generate them, are shared with the source cohorts.

Due to their significance to COVID-19 epidemiology, particular emphasis is being placed on harmonizing pre-pandemic physiologic (25), neurocognitive (27, 56-61), and imaging-based (62-

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69) phenotyping collected within the decade prior to the outbreak (**Table 3**). Harmonization of lung computed tomography is being accomplished using deep learning (70-73) and other methods, which will be published in separate reports.

Data management

The C4R Commons Agreement, modeled on the CHARGE Analysis Commons Consortium Agreement (74), is expediting cross-cohort data harmonization and sharing, as allowed (75). Following review and approval, cohort-specific agreements permit COVID-19 and pre-pandemic data to be uploaded to the C4R Analysis Commons, which is located on the NHLBI cloud computing platform, BioData Catalyst powered by Seven Bridges. This platform has enterprise-grade compliance and security certification and is HIPAA-compliant and compliant with dbGaP and CLIA security best practices. Nonetheless, no Protected Health Information (PHI) is retained on the C4R Analysis Commons. Participants are assigned a C4R study identifier by the cohort-specific DCC that is distinct from the original cohort participant identifier. Time-to-assessment and time-to-event are calculated as latencies with a random offset.

Access to pooled C4R data is regulated by the C4R publications and presentations (P&P) policy, which is available on the C4R website. Data is made available for analyses on the C4R Analysis Commons for investigators with manuscript proposals approved by the C4R publications and cohort coordinating committees as well as by each cohort included in a given proposal. Investigators are not permitted to access or analyze data for which there are relevant consent

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restrictions. Data downloads by investigators from the C4R Analysis Commons are prohibited. Recommendations to address common data issues anticipated for C4R analyses, such as missing data, are developed by the C4R Statistical Sub-Committee and related programming is shareable on the C4R Analysis Commons. Once harmonization and related quality control is completed, C4R common data elements will be transferred as a limited dataset for public access on BioData Catalyst in accord with cohort-specific consents and commitments.

DISCUSSION

C4R leverages existing American cohort studies to develop a large, multi-ethnic, pooled cohort of participants with incident COVID-19 and COVID-unaffected participants. C4R includes a diverse population of US adults, including older and socially disadvantaged populations that have especially high risk of adverse COVID-19 outcomes. C4R is distinguished from other large studies of COVID-19 by its wealth of pre-pandemic phenotyping, providing unique opportunities to evaluate a range of risk and resilience factors for SARS-CoV-2 infection and adverse COVID-19 outcomes, including severe COVID-19 illness, PASC, and other long-term effects of the pandemic response. Unlike case registries and EHR-based studies, C4R's repeated exams and cognitive assessments before and after COVID-19 also provide important opportunities to estimate the social and behavioral impact of the COVID-19-related pandemic response on changes in long-term mental and physical health across multiple domains.

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C4R constitutes a historic initiative to standardize and expedite data collection by US cohort studies despite major operational and societal challenges. Commitment from cohort PIs with experience in cross-cohort collaboration was critical to expediting study design, protocol development, approval, and deployment. The large scale of data collection was made possible not only by a culture shift toward multi-study collaborative efforts occasioned by experience in CHARGE and TOPMed, but also by the established cohort infrastructure, including sophisticated DCCs that were prepared to implement new protocols rapidly, and experienced and professional clinical staff with longstanding relationships with cohort participants. Differences in data collected by cohort are being reconciled by harmonization, where possible, or else they will be accounted for in analysis plans, in which cohorts without a necessary data element may be excluded. A similar approach is being used with respect to pre-COVID data heterogeneity; fortunately, many cohorts used similar or identical protocols for data collection in the pre-COVID era, due often to overlapping investigative groups, facilitating harmonization efforts. The challenges of data sharing across fourteen cohorts are well documented (76) and have been surmounted in recent decades by several strategies, including meta-analysis of results generated by cohort-specific DCCs and analyses of pooled cohort data assembled at a single center or on an NHLBI repository. To enhance accessibility, increase security, and expedite high priority analyses, C4R adapted and extended prior data management models by building a cloud-based enclave for assembly, harmonization, and analysis of pooled data.

C4R has certain limitations. Although it includes a diverse, nationwide sample, it was not sampled to be representative of the US population; to some extent, this may be addressed

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analytically by weighting approaches. Participation in C4R is voluntary, which may lead to selection biases. Nonetheless, we do not observe major differences in the socio-demographic characteristics of eligible participants compared to participants completing the wave 1 questionnaire, and the preponderance of women in the sample may be explained to some extent by the advanced age of contributing cohorts. Data on acute COVID-19 is sparse in C4R compared to certain EHR resources, but, conversely, data on pre-COVID biomarkers, multi-omics, physiology, organ structure, and symptomatology may be richer in C4R and less subject to diagnostic or referral biases. Due to antibody waning, only a subset of self-reported COVID-19 in C4R will be validated by C4R serology, and negative serology will not be suitable to rule out infection. Nonetheless, serology provides opportunities to reclassify some participants with subclinical infection and to examine antibody responses to vaccination and the impact on subsequent "breakthrough" infection risk. Events adjudication is primarily validating more severe illness, although many cohorts are ascertaining positive test results among non-hospitalized participants to confirm history of infection.

C4R provides opportunities for future studies using a range of epidemiologic study designs (Figure 5). For example, nested within C4R, longitudinal cohort studies of COVID-affected and unaffected participants could repeat measures (e.g., echocardiography, lung imaging, neuro-cognitive assessment) to define reliably the consequences of COVID-19 infection. Ongoing high-quality events follow-up allows assessment of long-term clinical outcomes following COVID-19 and the pandemic period. Extensive biobanks maintained by the cohorts could support measurement of prior viral infections, immune-phenotypes, metabo-types, 'Omics, and other

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pre-COVID characteristics that may be risk determinants or modifiers for COVID-19 susceptibility and vaccine effectiveness. The fact that the cohorts continue to follow their participants provides a dynamic resource to study emerging questions in COVID-19 epidemiology, including but not limited to viral variants and vaccination. And, C4R provides a model for cross-cohort collaboration and active data sharing that will promote consortium-based epidemiologic work on biological, social, and epidemiologic questions beyond the COVID-19 pandemic, in alignment with recommendations for strategic transformation of population studies (77).

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A full list of participating REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/

References

1. Kissler SM, Tedijanto C, Goldstein E, Grad YH, Lipsitch M. Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. Science. 2020.
2. Woolf SH, Chapman DA, Lee JH. COVID-19 as the Leading Cause of Death in the United States. JAMA. 2021;325(2):123-4.
3. Andrasfay T, Goldman N. Reductions in 2020 US life expectancy due to COVID-19 and the disproportionate impact on the Black and Latino populations. Proc Natl Acad Sci U S A. 2021;118(5).
4. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021;397(10270):220-32.
5. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol. 1989;129(4):687-702.
6. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs DR, Jr., et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. J Clin Epidemiol. 1988;41(11):1105-16.
7. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. Int J Epidemiol. 2015;44(6):1800-13.
8. Daviglus ML, Talavera GA, Aviles-Santa ML, Allison M, Cai J, Criqui MH, et al. Prevalence of major cardiovascular risk factors and cardiovascular diseases among Hispanic/Latino individuals of diverse backgrounds in the United States. JAMA. 2012;308(17):1775-84.
9. Lavange LM, Kalsbeek WD, Sorlie PD, Aviles-Santa LM, Kaplan RC, Barnhart J, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol. 2010;20(8):642-9.
10. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. Ann Epidemiol. 2010;20(8):629-41.
11. Carpenter MA, Crow R, Steffes M, Rock W, Heilbraun J, Evans G, et al. Laboratory, reading center, and coordinating center data management methods in the Jackson Heart Study. Am J Med Sci. 2004;328(3):131-44.

ORIGINAL UNEDITED MANUSCRIPT

12. Keku E, Rosamond W, Taylor HA, Jr., Garrison R, Wyatt SB, Richard M, et al. Cardiovascular disease event classification in the Jackson Heart Study: methods and procedures. Ethn Dis. 2005;15(4 Suppl 6):S6-62-70.
13. Taylor HA, Jr., Wilson JG, Jones DW, Sarpong DF, Srinivasan A, Garrison RJ, et al. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. Ethn Dis. 2005;15(4 Suppl 6):S6-4-17.
14. Kanaya AM, Chang A, Schembri M, Puri-Taneja A, Srivastava S, Dave SS, et al. Recruitment and retention of US South Asians for an epidemiologic cohort: Experience from the MASALA study. J Clin Transl Sci. 2019;3(2-3):97-104.
15. Kanaya AM, Kandula N, Herrington D, Budoff MJ, Hulley S, Vittinghoff E, et al. Mediators of Atherosclerosis in South Asians Living in America (MASALA) study: objectives, methods, and cohort description. Clin Cardiol. 2013;36(12):713-20.
16. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. Am J Epidemiol. 2002;156(9):871-81.
17. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le NA, Oopik AJ, et al. The Strong Heart Study. A study of cardiovascular disease in American Indians: design and methods. Am J Epidemiol. 1990;132(6):1141-55.
18. North KE, Howard BV, Welty TK, Best LG, Lee ET, Yeh JL, et al. Genetic and environmental contributions to cardiovascular disease risk in American Indians: the strong heart family study. Am J Epidemiol. 2003;157(4):303-14.
19. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, et al. Genetic epidemiology of COPD (COPDGene) study design. COPD. 2010;7(1):32-43.
20. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, et al. Design of the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). Thorax. 2014;69(5):491-4.
21. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline Features of the Severe Asthma Research Program (SARP III) Cohort: Differences with Age. J Allergy Clin Immunol Pract. 2018;6(2):545-54 e4.
22. Sacco RL, Boden-Albala B, Gan R, Chen X, Kargman DE, Shea S, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol. 1998;147(3):259-68.
23. Howard VJ, Cushman M, Pulley L, Gomez CR, Go RC, Prineas RJ, et al. The reasons for geographic and racial differences in stroke study: objectives and design. Neuroepidemiology. 2005;25(3):135-43.
24. Psaty BM, O'Donnell CJ, Gudnason V, Lunetta KL, Folsom AR, Rotter JI, et al. Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium: Design of prospective meta-analyses of genome-wide association studies from 5 cohorts. Circ Cardiovasc Genet. 2009;2(1):73-80.
25. Oelsner EC, Balte PP, Cassano PA, Couper D, Enright PL, Folsom AR, et al. Harmonization of Respiratory Data From 9 US Population-Based Cohorts: The NHLBI Pooled Cohorts Study. Am J Epidemiol. 2018;187(11):2265-78.
26. Cross Cohort Collaboration [updated May 10, 2021. Available from: https://chs-nhlbi.org/node/6539.

ORIGINAL UNEDITED MANUSCRIPT

27. Levine DA, Gross AL, Briceno EM, Tilton N, Kabeto MU, Hingtgen SM, et al. Association Between Blood Pressure and Later-Life Cognition Among Black and White Individuals. JAMA Neurol. 2020;77(7):810-9.
28. Taliun D, Harris DN, Kessler MD, Carlson J, Szpiech ZA, Torres R, et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature. 2021;590(7845):290-9.
29. Flanagin A, Frey T, Christiansen SL, Bauchner H. The Reporting of Race and Ethnicity in Medical and Science Journals: Comments Invited. JAMA. 2021.
30. Multi-Ethnic Study of Atherosclerosis. Oelsner MESA COVID-19 Questionnaire 2020. https://www.phenxtoolkit.org/toolkit_content/PDF/MESA_Questionnaire_Annotated.pdf. Accessed October 13, 2021.
31. Behavioral Risk Factor Surveillance System. Questionnaire 2019. https://www.cdc.gov/brfss/questionnaires/. Updated August 26, 2021. Accessed October 13, 2021.
32. Health and Retirement Survey. HRS Biennial Interview Questionnaires 2020. https://hrs.isr.umich.edu/documentation/questionnaires. Accessed October 13, 2021.
33. MACS-WIHS Combined Cohort Study. BASELINE COVID-19 ABBREVIATED QUESTIONNAIRE (BLCOVID) 2020. https://www.nlm.nih.gov/dr2/MACS-WIHS_questionnaire_BLCOVID-040620.pdf. Updates April 6, 2020. Accessed October 13, 2021.
34. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). Am J Prev Med. 1994;10(2):77-84.
35. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
36. Levine DW, Kripke DF, Kaplan RM, Lewis MA, Naughton MJ, Bowen DJ, et al. Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. Psychol Assess. 2003;15(2):137-48.
37. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, et al. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment. 2011;18(3):263-83.
38. RAND Corporation. Social Support Survey Instrument. https://www.rand.org/health-care/surveys_tools/mos/social-support/survey-instrument.html. Accessed October 13, 2021.
39. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. J Pers Assess. 1996;66(1):20-40.
40. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med. 2008;15(3):194-200.
41. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
42. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81.
43. Centers for Disease Control and Prevention. ICD-10-CM Official Coding and Reporting Guidelines April 1, 2020 through September 30, 2020. Accessed October 13, 2021.

ORIGINAL UNEDITED MANUSCRIPT

44. Oelsner EC, Loehr LR, Henderson AG, Donohue KM, Enright PL, Kalhan R, et al. Classifying Chronic Lower Respiratory Disease Events in Epidemiologic Cohort Studies. Ann Am Thorac Soc. 2016;13(7):1057-66.
45. Zakai NA, McClure LA, Judd SE, Safford MM, Folsom AR, Lutsey PL, et al. Racial and regional differences in venous thromboembolism in the United States in 3 cohorts. Circulation. 2014;129(14):1502-9.
46. Centers for Disease Control and Prevention. Interim Guidelines for COVID-19 Antibody Testing. https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html#anchor_1590264293982. Accessed October 13, 2021.
47. Laing ED, Sterling SL, Richard SA, Epsi NJ, Coggins S, Samuels EC, et al. Antigen-based multiplex strategies to discriminate SARS-CoV-2 natural and vaccine induced immunity from seasonal human coronavirus humoral responses. medRxiv. 2021.
48. Balte PP, Chaves PHM, Couper DJ, Enright P, Jacobs DR, Jr., Kalhan R, et al. Association of Nonobstructive Chronic Bronchitis With Respiratory Health Outcomes in Adults. JAMA Intern Med. 2020.
49. Bhatt SP, Balte PP, Schwartz JE, Cassano PA, Couper D, Jacobs DR, Jr., et al. Discriminative Accuracy of FEV1:FVC Thresholds for COPD-Related Hospitalization and Mortality. JAMA. 2019;321(24):2438-47.
50. Bhatt SP, Schwartz JE, Oelsner EC. FEV1:FVC Thresholds for Defining Chronic Obstructive Pulmonary Disease-Reply. JAMA. 2019;322(16):1611-2.
51. Cornelius T BP, Bhatt SP, Cassano PA, Currow D, Jacobs DR, Johnson M, Kalhan R, Kronmal R, Loehr LR, O'Connor GT, Schwartz JE, Smith BM, White WB, Yende S, Oelsner EC. . A dyadic growth modeling approach to weight gain and lung function loss: The NHLBI Pooled Cohorts Study. . Am J Epidemiol. 2020 (Accepted).
52. Oelsner EC, Balte PP, Bhatt SP, Cassano PA, Couper D, Folsom AR, et al. Lung function decline in former smokers and low-intensity current smokers: a secondary data analysis of the NHLBI Pooled Cohorts Study. Lancet Respir Med. 2020;8(1):34-44.
53. Zhang Y, Vittinghoff E, Pletcher MJ, Allen NB, Zeki Al Hazzouri A, Yaffe K, et al. Associations of Blood Pressure and Cholesterol Levels During Young Adulthood With Later Cardiovascular Events. J Am Coll Cardiol. 2019;74(3):330-41.
54. Oelsner EC, Balte PP, Grams ME, Cassano PA, Jacobs DR, Barr RG, et al. Albuminuria, Lung Function Decline, and Risk of Incident Chronic Obstructive Pulmonary Disease. The NHLBI Pooled Cohorts Study. Am J Respir Crit Care Med. 2019;199(3):321-32.
55. Stilp AM, Emery LS, Broome JG, Buth EJ, Khan AT, Laurie CA, et al. A System for Phenotype Harmonization in the NHLBI Trans-Omics for Precision Medicine (TOPMed) Program. Am J Epidemiol. 2021.
56. Griffith L, van den Heuvel E, Fortier I, Hofer S, Raina P, Sohel N, Payette H, Wolfson C, Belleville S. Harmonization of Cognitive Measures in Individual Participant Data and Aggregate Data Meta-Analysis. Methods Research Report. (Prepared by the McMaster University Evidence-based Practice Center under Contract No. 290-2007-10060-I.) AHRQ Publication No.13-EHC040-EF. Rockville, MD: Agency for Healthcare Research and Quality; March 2013. www.effectivehealthcare.ahrq.gov/reports/final.cfm. .

ORIGINAL UNEDITED MANUSCRIPT

57. Griffith LE, van den Heuvel E, Fortier I, Sohel N, Hofer SM, Payette H, et al. Statistical approaches to harmonize data on cognitive measures in systematic reviews are rarely reported. J Clin Epidemiol. 2015;68(2):154-62.
58. Gross AL, Jones RN, Fong TG, Tommet D, Inouye SK. Calibration and validation of an innovative approach for estimating general cognitive performance. Neuroepidemiology. 2014;42(3):144-53.
59. Gross AL, Sherva R, Mukherjee S, Newhouse S, Kauwe JS, Munsie LM, et al. Calibrating longitudinal cognition in Alzheimer's disease across diverse test batteries and datasets. Neuroepidemiology. 2014;43(3-4):194-205.
60. Gross AL, Mungas DM, Crane PK, Gibbons LE, MacKay-Brandt A, Manly JJ, et al. Effects of education and race on cognitive decline: An integrative study of generalizability versus study-specific results. Psychol Aging. 2015;30(4):863-80.
61. Langa KM, Ryan LH, McCammon RJ, Jones RN, Manly JJ, Levine DA, et al. The Health and Retirement Study Harmonized Cognitive Assessment Protocol Project: Study Design and Methods. Neuroepidemiology. 2020;54(1):64-74.
62. Oelsner EC, Ortega VE, Smith BM, Nguyen JN, Manichaikul AW, Hoffman EA, et al. A Genetic Risk Score Associated with Chronic Obstructive Pulmonary Disease Susceptibility and Lung Structure on Computed Tomography. Am J Respir Crit Care Med. 2019;200(6):721-31.
63. Smith BM, Kirby M, Hoffman EA, Kronmal RA, Aaron SD, Allen NB, et al. Association of Dysanapsis With Chronic Obstructive Pulmonary Disease Among Older Adults. JAMA. 2020;323(22):2268-80.
64. Smith BM, Hoffman EA, Rabinowitz D, Bleecker E, Christenson S, Couper D, et al. Comparison of spatially matched airways reveals thinner airway walls in COPD. The Multi-Ethnic Study of Atherosclerosis (MESA) COPD Study and the Subpopulations and Intermediate Outcomes in COPD Study (SPIROMICS). Thorax. 2014;69(11):987-96.
65. Hame Y, Angelini E, Hoffman E, Barr G, Laine A. Adaptive quantification and longitudinal analysis of pulmonary emphysema with a hidden Markov measure field model. IEEE Transactions on Medical Imaging. 2014;33(7):1527-40.
66. Wang M, Aaron CP, Madrigano J, Hoffman EA, Angelini E, Yang J, et al. Association Between Long-term Exposure to Ambient Air Pollution and Change in Quantitatively Assessed Emphysema and Lung Function. JAMA. 2019;322(6):546-56.
67. Yang J, Angelini E, Smith BM, Balte P, Hoffman E, Barr RG, et al. Unsupervised Discovery of Spatially- Informed Lung Texture Patterns for Pulmonary Emphysema: The MESA COPD Study. International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI)2017. p. 116-24.
68. Yang J, Angelini ED, Balte PP, Hoffman EA, Wu CO, Venkatesh BA, et al. Emphysema quantification on cardiac CT scans using hidden Markov measure field model: The MESA Lung Study. International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI); Athenes, Greece: Springer; 2016. p. 624-31.
69. Yang J, Vetterli T, Balte PP, Barr RG, Laine AF, Angelini ED. Unsupervised Domain Adaption With Adversarial Learning (UDAA) for Emphysema Subtyping on Cardiac CT Scans: The Mesa Study. IEEE International Symposium on Biomedical Imaging (ISBI)2019. p. 289-93.
70. Ravi D, Wong C, Deligianni F, Berthelot M, Andreu-Perez J, Lo B, et al. Deep Learning for Health Informatics. IEEE J Biomed Health Inform. 2017;21(1):4-21.

ORIGINAL UNEDITED MANUSCRIPT

71. Pham T TT, Phung D and Venkatesh S. . Deepcare: A deep dynamic memory model for predictive medicine. Paper presented at: Pacific-Asia Conference on Knowledge Discovery and Data Mining; 2016.
72. Miotto R, Li L, Kidd BA, Dudley JT. Deep Patient: An Unsupervised Representation to Predict the Future of Patients from the Electronic Health Records. Sci Rep. 2016;6:26094.
73. He K, ZHang X, Ren S, Sun J. (2015-12-10). "Deep Residual Learning for Image Recognition". arXiv:1512.03385.
74. Brody JA, Morrison AC, Bis JC, O'Connell JR, Brown MR, Huffman JE, et al. Analysis commons, a team approach to discovery in a big-data environment for genetic epidemiology. Nat Genet. 2017;49(11):1560-3.
75. Health NIo. NIH Tribal Consultation Report: NIH Draft Policy for Data Management and Sharing. 2020.
76. Psaty BM, Rich SS, Boerwinkle E. Innovation in Genomic Data Sharing at the NIH. N Engl J Med. 2019;380(23):2192-5.
77. Roger VL, Boerwinkle E, Crapo JD, Douglas PS, Epstein JA, Granger CB, et al. Strategic transformation of population studies: recommendations of the working group on epidemiology and population sciences from the National Heart, Lung, and Blood Advisory Council and Board of External Experts. Am J Epidemiol. 2015;181(6):363-8.

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Table 1. Characteristics of participants in C4R cohorts, United States, March 1, 2020.

Cohort	N	Current age range, years	Sex, % Female	Race/ethnicity, % NHW	B	H/L	As	Am Ind	Other	Original research focus
ARIC	6,690	75-97	63	77	23	0[a]	0	0	0	Cardiovascular
CARDIA	4,590	53-66	56	50	50	0	0	0	0	Cardiovascular
COPDGene	7,731	50-90	48	65	35	0	0	0	0	Pulmonary
FHS	7,339	26-108	56	86	3	4	0	0	7	Cardiovascular
HCHS/SOL	13,142	30-87	60	0	0	100	0	0	0	Cardiovascular
JHS	2,444	38-102	63	0	100	0	0	0	0	Cardiovascular
MASALA	1,132	50-94	47	0	0	0	100	0	0	Cardiovascular
MESA	4,683	65-103	56	38	27	24	12	0	0	Cardiovascular
NOMAS	1,256	62-106	65	12	14	72	0	1	0	Neurologic
PrePF	5,000	40-80	55	92	3	3	0	0	0	Pulmonary
REGARDS	12,766	57-105	58	62	38	0	0	0	0	Neurologic
SARP	397	18-80	65	75	25	0	0	0	0	Pulmonary
SPIROMICS	2,273	47-87	48	82	4	4	0	0	0	Pulmonary
SHS	2,915	31-105	62	0	0	0	0	100	0	Cardiovascular

Am Ind = American Indian; As = Asian American; B = Black; H/L = Hispanic/Latinx; NHW = Non-Hispanic White.

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ARIC = Atherosclerosis Risk in Communities Study; C4R = Collaborative Cohort of Cohorts for COVID-19 Research; CARDIA = Coronary Artery Risk Development in Young Adults; COPDGene= Genetic Epidemiology of COPD; FHS = Framingham Heart Study; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; JHS = Jackson Heart Study; MASALA = Mediators of Atherosclerosis in South Asians Living in America; MESA = Multi-Ethnic Study of Atherosclerosis; NOMAS = Northern Manhattan Study; PrePF = Prevent Pulmonary Fibrosis; REGARDS = REasons for Geographic and Racial Differences in Stroke; SARP = Severe Asthma Research Program; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; SHS = Strong Heart Study

[a] ARIC did not inquire regarding Hispanic/Latino ethnicity, hence White participants cannot be definitely defined as non-Hispanic.

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Table 2. Characteristics of the C4R target population compared to participants completing the C4R Wave 1 Questionnaire, March 1, 2020 – September 30, 2021.

	Target population (n=53,143)		Participants completing C4R wave 1 questionnaires through September 30, 2021 (n=45,262)	
Cohort	N	%	N	%
Sex				
Female	30,557	57.50	26,814	59.24
Male	22,586	42.50	18,448	40.76
Race				
Asian	1,238	2.33	1,044	2.31
American Indian and Alaska Native	2,971	5.59	1,923	4.25
Black	13,722	25.82	9,860	21.78
Native Hawaiian or Pacific Islander	32	0.06	34	0.08
White	28,655	53.92	25,070	55.39
Other	3,109	5.85	4,544	10.04
Multiple	2,003	3.77	1,954	4.32
Unknown	1,413	2.66	833	1.84
Ethnicity				
Hispanic	10,698	20.13	12,677	28.01
Non-Hispanic	34,362	64.66	25,549	56.45
Unknown	8,083	15.21	7,036	15.55
Age group				
18-29	654	1.23	388	0.86
30-64	21,581	40.61	15,697	34.68
65+	30,908	58.16	29,177	64.46

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Cohort				
ARIC	5,046	9.50	5,466	12.08
CARDIA	4,221	7.94	2,530	5.59
COPDGene	4,000	7.53	3,764	8.32
FHS	7,339	13.81	3,173	7.01
HCHS/SOL	8,400	15.81	11,152	26.64
JHS	2,317	4.36	1,697	3.75
MASALA	500	0.94	460	1.02
MESA	4,683	8.81	3,450	7.62
NOMAS	1,256	2.36	887	1.96
PrePF	2,500	4.70	614	1.36
REGARDS	8,000	15.05	8,750	19.33
SARP	380	0.72	326	0.72
SPIROMICS	1,800	3.39	1,483	3.28
SHS	2,701	5.08	1,510	3.34

C4R = Collaborative Cohort of Cohorts for COVID-19 Research. ARIC = Atherosclerosis Risk in Communities Study; C4R = Collaborative Cohort of Cohorts for COVID-19 Research; CARDIA = Coronary Artery Risk Development in Young Adults; COPDGene= Genetic Epidemiology of COPD; FHS = Framingham Heart Study; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; JHS = Jackson Heart Study; MASALA = Mediators of Atherosclerosis in South Asians Living in America; MESA = Multi-Ethnic Study of Atherosclerosis; NOMAS = Northern Manhattan Study; PrePF = Prevent Pulmonary Fibrosis; REGARDS = REasons for Geographic and Racial Differences in Stroke; SARP = Severe Asthma Research Program; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; SHS = Strong Heart Study

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Table 3. Estimated number of participants with recent pre-pandemic deep phenotyping for harmonization in C4R, by cohort, United States, 2010-2020.[a]

Measures	ARIC	CARDIA	COPDGene	FHS	HCHS/SOL	JHS	MASALA	MESA	NOMAS	PrePF	REGARDS	SARP	SPIROMICS	SHS	C4R
Physical function															
Timed walk	3,140		3,879	2,257				2,473					1,064		12,813
Hand-grip	3,140		1,342	6,232					628				1,160		12,502
Spirometry	3,612	3,119	4,000	5,914	8,400	2,317		3,502		1,123		380	1,149	94	33,610
DLCO	457		3,075	5,914						1,123					10,569
Resting O2	11		4,000		8,400			3,973					1,069		17,453
CT															
CT Lung			3,775	2,799				3,459		1,059		229	1,138		12,459
Cardiac CT	2,267	3,068		2,799		2,317	500	2,801							13,752
Dual energy CT								731					330		1,061
Any CT	2,267	3,068	3,775	2,799		2,317	500	3,549		1,059		229	1,138		20,701
Cardiac															
Cardiac MRI						1,421		2,556					67		4,044
Echocardiogram	2,973	3,115			6,427	2,317		2,920	502				82	1,901	20,237
ECG	2,409			7,258	8,400	2,317	500	3,802	502		7,778			1,910	34,876
Brain															
Brain MRI	771	653		3,543	1,245			1,113	803						8,128
Neurocog-long	3,589	3,354		2,477	8,400			1,487	600		528			817	21,252
Neurocog-short			1,360	3,934	8,400			3,788	1,260		8,000			817	27,559
Neurocog-any	3,589	3,354	1,360	3,800	8,400			3,857	1,260		8,000			817	34,437
Sleep+Activity															
Polysomnography	11	835			8,400	913		1,779							11,938
Actimetry	513	1,397		4,100	8,400	852		1,828							17,090
ECG monitoring	2,257							1,510	300						4,067
Biomarkers															
Blood	5,046	4,221	4,000	7,258	8,400	2,317	500	4,683	1,267	2,500	8,000	380	1,800	2,701	53,073
Urine	5,046	4,221		7,258	8,400	2,317	500	3,900	1,267		8,000		1,800	2,701	45,410
GWAS	4,541	3,799	4,000	6,817	8,400	2,317		4,455		2,250		380	1,620		38,579
RNAseq (blood)			800	2,730				1,082		1,000		342	1,800		7,754
Metabolomics				3,025	8,000	2,317		812		100				2,701	16,955
Methylation		3,799	4,000	1,900	3,000	1,752		1,212		1,000				2,325	18,988
Proteomics				2,813		1,852		812		250					5,727
Sputum/bronch												380	1,000		1,380
Gut microbiome		607			8,000										8,607

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Bronch = bronchoscopy; CT = computed tomography; DLCO = diffusing capacity of the lung for carbon monoxide; ECG = electrocardiogram; GWAS = genome-wide association study; MRI = magnetic resonance imaging; neurocog = neurocognitive; O2 = oxygen;
ARIC = Atherosclerosis Risk in Communities Study; C4R = Collaborative Cohort of Cohorts for COVID-19 Research; CARDIA = Coronary Artery Risk Development in Young Adults; COPDGene= Genetic Epidemiology of COPD; FHS = Framingham Heart Study; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; JHS = Jackson Heart Study; MASALA = Mediators of Atherosclerosis in South Asians Living in America; MESA = Multi-Ethnic Study of Atherosclerosis; NOMAS = Northern Manhattan Study; PrePF = Prevent Pulmonary Fibrosis; REGARDS = REasons for Geographic and Racial Differences in Stroke; SARP = Severe Asthma Research Program; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; SHS = Strong Heart Study

[a] If the most recent exam was prior to 2010, data are not included.

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Figure Legends

Figure 1. Longitudinal pre-COVID follow-up and planned follow-up for cardiovascular cohorts collaborating in C4R, by cohort, United States, 1971-2025. Some visits were overlapping, which is not shown; instead, midpoints of the visits are indicated. COVID-era exams are shaded in blue. Solid lines indicate cohort follow up, which typically includes regular contact by telephone and mail and ongoing events ascertainment. ARIC = Atherosclerosis Risk in Communities Study; CARDIA = Coronary Artery Risk Development in Young Adults; FHS-Gen3 = Framingham Heart Study Third Generation; FHS-O = Framingham Offspring Study; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; JHS = Jackson Heart Study; MASALA = Mediators of Atherosclerosis in South Asians Living in America; MESA = Multi-Ethnic Study of Atherosclerosis; SHS = Strong Heart Study; Exam = examination. In ARIC, 424 gave restricted consent; JHS[i] 1,626 participants recruited from ARIC; CARDIA includes withdrawal of consent by one participant; MESA is MESA + 257 new recruits into the MESA Air Pollution Study.

Figure 2. Longitudinal pre-COVID follow-up and planned follow-up for pulmonary and neurological cohorts in C4R, by cohort, United States, 1991-2025. Some visits were overlapping, which is not shown; instead, midpoints of the visits are indicated. COVID-era exams are shaded in blue. Solid lines indicate cohort follow up, which typically includes regular contact by telephone and mail and ongoing events ascertainment. COPDGene= Genetic Epidemiology of COPD; Exam = examination; NOMAS = Northern Manhattan Study; PrePF = Prevent Pulmonary Fibrosis; REGARDS = REasons for Geographic and Racial Differences in Stroke; SARP = Severe Asthma Research Program; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.

Figure 3. C4R organizational chart. CONNECTS = Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies. DSMB = data safety monitoring board. OSMB = observational studies monitoring board. ARIC = Atherosclerosis Risk in Communities Study; C4R = Collaborative Cohort of Cohorts for COVID-19 Research; CARDIA = Coronary Artery Risk Development in Young Adults; COPDGene= Genetic Epidemiology of COPD; FHS = Framingham Heart Study; HCHS/SOL = Hispanic Community Health Study/Study of Latinos; JHS = Jackson Heart Study; MASALA = Mediators of Atherosclerosis in South Asians Living in America; MESA = Multi-Ethnic Study of Atherosclerosis; NOMAS = Northern Manhattan Study; PrePF = Prevent Pulmonary Fibrosis; REGARDS = REasons for Geographic and Racial Differences in Stroke; SARP = Severe Asthma Research Program; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; SHS = Strong Heart Study

Figure 4. C4R participants, field/clinical centers, and coordinating centers. Blue circles indicate field/clinical centers, and the size is proportional to the number of participants at that field/clinical center. Participants in the REGARDS, which does not have field/clinical centers, are shown by additional blue shading according to their geocoded home addresses. Red squares indicate coordinating centers involved in the study. Yellow squares indicate C4R central resources: the data coordination and harmonization center, the biorepository and central laboratory, and the administrative coordinating center.

Figure 5. Lessons learned from the Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study.

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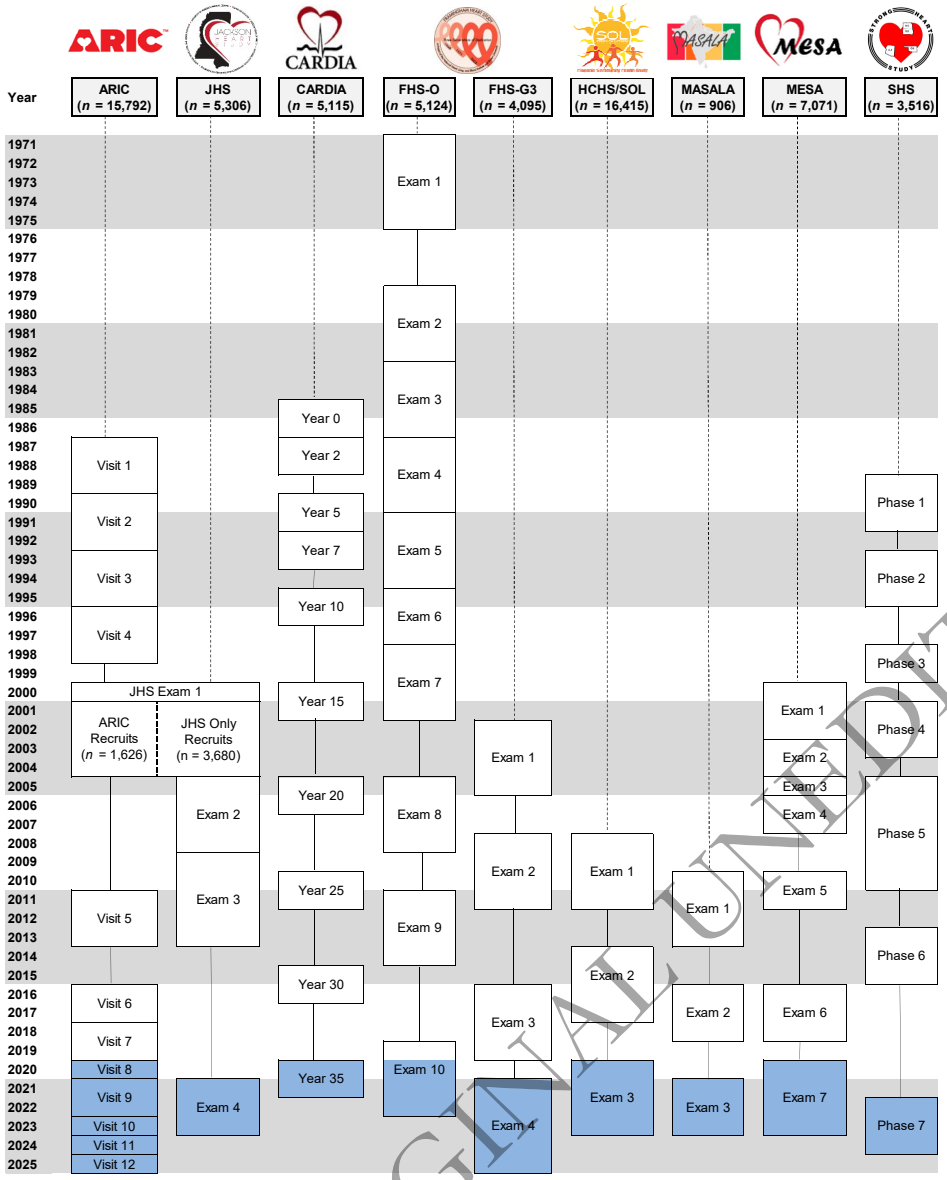

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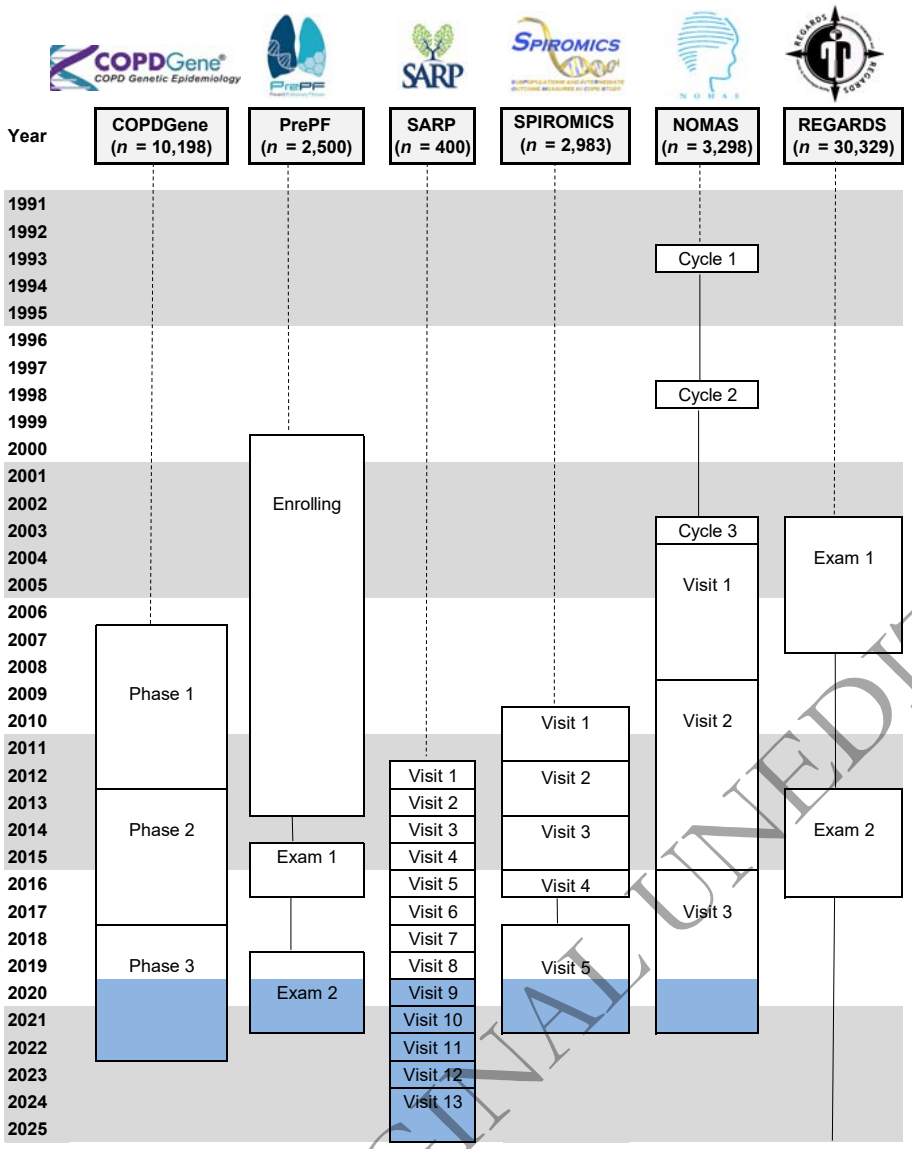

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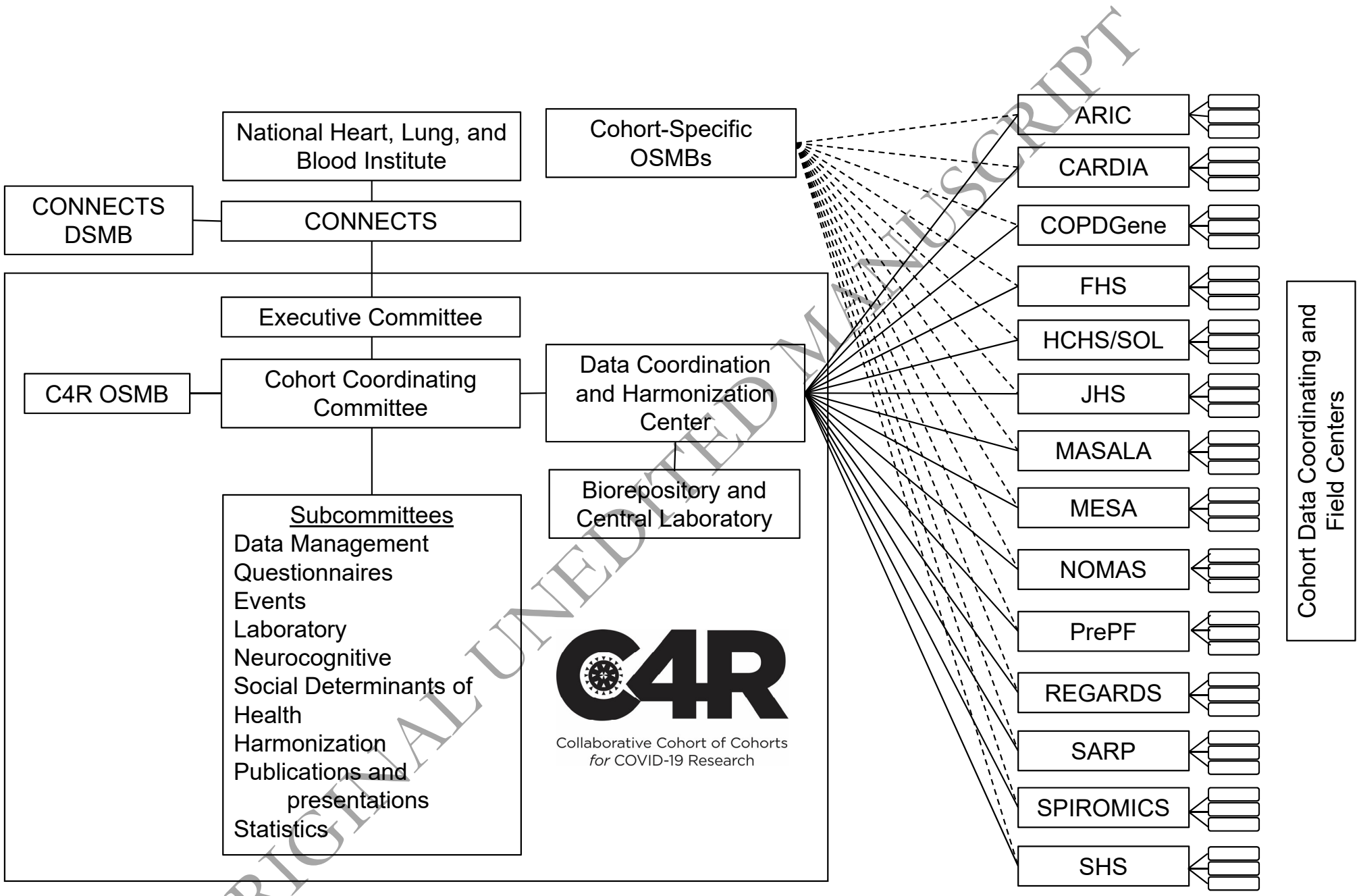

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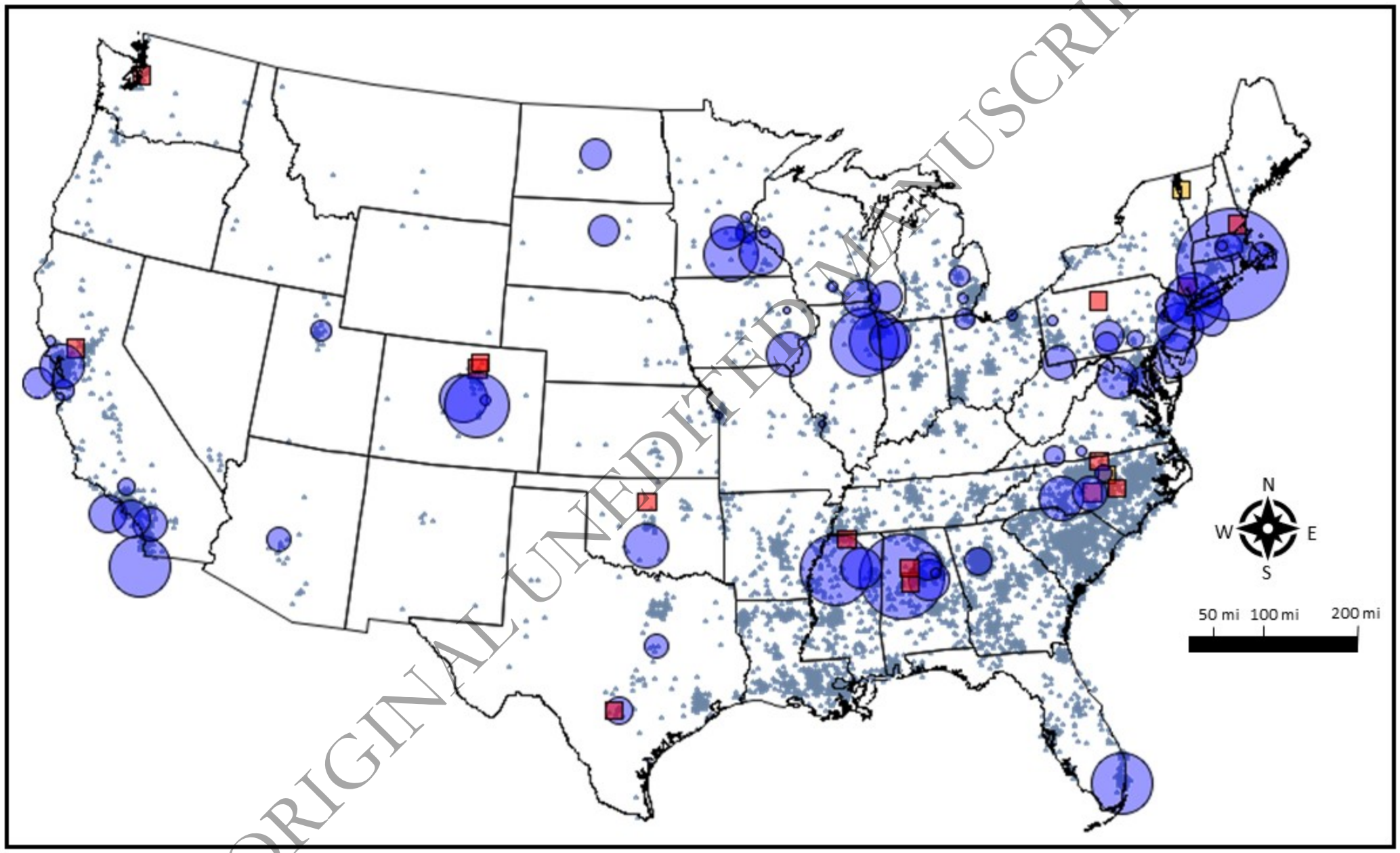

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Lessons Learned

- Unlike case registries and electronic health record-based studies, C4R's repeated examinations and cognitive assessments before and after COVID-19 provide important opportunities to estimate the biological, clinical, social, and behavioral impact of the COVID-19 pandemic on changes in long-term physical and mental health across multiple domains.
- Success of the C4R serosurvey suggests that blood collection by self-collected dried blood spots is feasible and acceptable for remote and, potentially, repeated biosampling and can be integrated into existing and new population-based cohort studies. Traditional cohort participant-contact methods and procedures work for in-home biosample collection and are critical to success.
- C4R provides a model for cross-cohort collaboration, harmonization, and active data sharing that will promote consortium-based epidemiologic work on biological, social, and epidemiologic questions beyond the COVID-19 pandemic, in alignment with recommendations for strategic transformation of population studies.

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