Alzheimer disease (AD) is a neurodegenerative disorder that is the leading cause of dementia in people aged 65 years or older. At present, there is no cure and there are no survivors; all AD cases end in death. More than 5 million Americans have AD, and it recently passed diabetes mellitus to become the sixth leading cause of death in the United States.1 These demographic trends will result in a significant increase in the prevalence of AD. Indeed, the cost of AD now rivals that of cancer and heart disease, but the growing epidemic of AD means that these costs will race ahead of the costs of other diseases in the coming years.2 Thus, by 2050, we predict that 16 million Americans will have AD, resulting in $1 trillion per year in expenses to Medicare and Medicaid alone.3 This outcome will be catastrophic to patients and their families as well as to public health spending and policy. Moreover, US trends are mirrored in both the industrialized and developing world, meaning that the current epidemic of AD is global and will extend far into the future.

Consequently, there is enormous interest in research aiming to improve the diagnosis, treatment, and management of AD. In the United States, most funding for AD research comes from the federal government through the National Institute on Aging (NIA) of the National Institutes of Health (NIH).4 One
major facet of the NIA’s efforts has been the creation of AD centers (ADCs) in major medical schools throughout the country.\(^5\) The first 5 ADCs were created in 1984, and the program has grown to include 27 active centers across the United States. The initial ADCs were NIH-funded P50 AD research centers (ADRCs), and they include mandated administrative, clinical, and neuropathology cores. Subsequently, education and information transfer cores were added to all ADCs. In addition, these ADRCs included support for multiyear RO1-like research projects as well as a minimum of 2 nonrenewable pilot grants each year to stimulate new AD research initiatives. In 1990, the NIA introduced a second type of ADC with a different concept, and these are designated AD core centers. Like ADRCs, these centers provide core facilities and support for 3 RO1-like research projects. In addition, they provide essential research infrastructure for independently funded research projects, such as NIH ROIs, P50s, and POIs, or projects funded by foundation grants. Currently, AD core centers and ADRCs are referred to collectively as ADCs. Moreover, renewal of each ADC for another 5-year funding cycle requires submission of a competing renewal application that undergoes peer review, and each competitive renewal application cycle for ADC slots is announced by the NIA. Because all qualified institutions can respond to these periodic announcements with an application for an ADC slot, regardless of whether they have an existing ADC, there is turnover among the ADCs, with the best competing successfully for renewal each cycle.\(^4,5\) Additionally, the Alzheimer’s Disease Cooperative Study program was launched in 1991 to design, test, and implement AD clinical trial evaluation methods and conduct clinical studies of new treatments for AD, including the effects of new therapies on the diverse cognitive and behavioral impairments associated with AD. The Alzheimer’s Disease Cooperative Study program continues to be supported by the NIA, and most ADCs participate.\(^4,5\)

A principal aim of these centers is to establish the expertise and infrastructure to support independent research initiatives and catalyze collaborative efforts that transcend university boundaries. Much of this work has been devoted to generating common resources, including collections of tissue samples, patient populations, and electronic databases.\(^4,5\) A major accomplishment was the establishment of the National Alzheimer’s Coordinating Center database, a standardized repository for data collected during clinical studies of AD.\(^6\) Subsequently, the need for uniform protocols and data collection motivated the creation of a uniform data set to standardize clinical observations of patients with AD.\(^7,8\)

Moreover, collective efforts through ADCs have been made to identify genes and other risk factors associated with AD.\(^4\) The Alzheimer’s Disease Genetics Consortium (http://aloids.med.upenn.edu/adgc/) was formalized in 2009 to conduct genome-wide association studies to identify genes associated with an increased risk of developing late-onset AD. Other goals were to develop, standardize, and validate imaging tools and chemical biomarkers to be used in clinical trials of AD treatments as well as elucidate the mechanism of AD onset and progression through the establishment of the Alzheimer’s Disease Neuroimaging Initiative in 2004.\(^9,10\)

From an administrative standpoint, the goal of the ADC program is to foster collaboration between different universities and ultimately facilitate large-scale, high-impact research that is beyond the reach of any single investigator or institution. Indeed, the creation of the Alzheimer’s Disease Cooperative Study, National Alzheimer’s Coordinating Center, Alzheimer’s Disease Genetics Consortium, and Alzheimer’s Disease Neuroimaging Initiative would not have been possible without the existing ADC network that created a highly collaborative group of investigators open to data sharing. Anecdotal evidence suggests that ADCs have contributed to the successful completion of such projects, and many of the most influential AD researchers are members of ADCs.\(^11\) Nevertheless, the extent to which ADCs directly foster high-impact, multi-university collaborations has never been systematically evaluated.

The most common methods for quantitatively measuring scientific productivity are largely based on counting publications and citations. For example, a journal’s impact factor and an investigator’s H-index\(^12\) are metrics built on the assumption that a given article’s influence (as measured by citation count) correlates with its importance and quality. Although these metrics are imperfect, they possess several valuable attributes, including being quantitative, impractical to manipulate, and focused on quality rather than quantity of output.\(^13\) These and similar efforts to objectively measure scientific productivity have been aided immeasurably by the growth and development of analytical tools to harvest and analyze publication records from online databases. Termed metaknowledge, this growing discipline aims to study the scientific enterprise, with a particular emphasis on the structural, sociologic, and technological innovations that underlie scientific discovery.\(^14\)

Such methodologies have shown that, during the past 50 years, the basic unit of scientific activity has shifted from single investigators toward larger and more complex teams.\(^15,16\) This trend is particularly relevant to the study of AD, which encompasses many different basic science disciplines, including neurosciences, biochemistry, molecular genetics, and physiology as well as a wide range of clinical disciplines extending from neurology, geriatrics, and psychiatry to radiology, neuropathology, biostatistics, epidemiology, and clinical trials. Most important, discoveries in the basic science of AD would be impotent without close collaborations with investigators in translational, clinical, and public health disciplines. Therefore, it is important that we understand what best fosters effective multidisciplinary team science.\(^17,18\) Particularly given the continued barriers to effective collaboration between different universities.\(^19\)

Social network analysis (SNA) is one approach to understanding scientific collaborations.\(^20,21\) Copublication of a research article can be visually represented as a link between 2 or more investigators. Expanding this abstraction to an entire scientific field thereby facilitates its analysis using the power of network statistics. This is an effective way to measure the scope and connectivity of a field,\(^20\) identify investigators with a knack for fostering collaboration,\(^21,22\) or develop network-level interventions to foster new
collaborations.\textsuperscript{23} We recently used this method to assess how effectively the University of Pennsylvania's Clinical and Translational Science Award has promoted collaborations over time.\textsuperscript{24} We reasoned that a similar approach with a particular emphasis on how collaborative networks change over time between institutions could dramatically increase our understanding of how ADCs have performed since their inception. Therefore, we built copublication networks of ADCs on a year-by-year basis and measured their growth, productivity, and impact. Based on these analyses, we present evidence supporting the conclusion that ADCs have been effective catalysts of productive collaborations in research on AD and related dementias between universities.

Given our aging population, AD represents a looming public health crisis. The development of novel therapeutics for AD requires the combined expertise and resources of many different research projects. Therefore, we believe that a close analysis of how well the ADC program has fostered collaborations will be a valuable contribution to the field, especially in an increasingly tight funding environment.

Methods

Data Collection and Validation

Year-by-year rosters for all active ADCs were manually reconstructed from archived personnel directories from 1989 through 2012. Custom-built Ruby scripts were written to systematically harvest ADC publications and their associated Medical Subject Headings (MeSH) terms from the National Center for Biotechnology Information's PubMed. Articles were required to be written in English, include an active ADC member as senior author, and have at least 2 ADC members from the same institution as authors. A key word filter was used post hoc to select publications dealing with AD, neurodegenerative disease, aging, or nervous system function. To assess the false-positive rate, 500 randomly selected articles meeting these criteria were manually examined. Based on these data, the false-positive rate (ie, the number of articles not directly supported by ADC mechanisms) was estimated to be less than 3%. False-negative rates are more difficult to estimate. Nevertheless, during this analysis, we manually examined ADC publications from more than 12 institutions spanning several hundred individual articles. False-negative articles fell into 2 categories: (1) articles by active ADC members that were unrelated to AD or brain function and (2) articles with atypical author lists, such as publications by consortiums. We considered the exclusion of the former case to be justifiable; exclusion of the latter case affected less than 1% of ADC publications. Citations were assessed during several days in January 2013. All scripts used in this study are freely available on demand.

Network Generation, Statistics, and Visualization

Copublication was defined as 2 or more active ADC members authoring the same publication. Individual pairs of copublishing authors were identified using custom Ruby scripts and weighted according to the number of publications in common. Networks were generated and visualized using Cytoscape version 3.0.0 beta 1 (http://www.cytoscape.org). Network statistics were calculated using Cytoscape and Excel (Microsoft Corp). Node degree over time (NDT) was calculated as previously described.\textsuperscript{24}

Results

A total of 12,170 unique ADC papers were published from 1985 through 2012. We used this resource to generate interaction networks (Figure 1). Every active ADC investigator was represented as a node, and coauthorship of a publication with another ADC member was considered an edge linking 2 nodes. By categorizing these networks on a year-by-year basis, trends in the evolution of ADCs become apparent. In 1985, the first year of the ADC program, there were several dozen active investigators linked by preexisting collaborations (Figure 1A). During the next 10 to 15 years, the number of active nodes grew rapidly as additional centers opened and new investigators were recruited into the program (Figure 1B-D). By 2010, growth in the number of active investigators had begun to plateau. Nevertheless, the total number of interactions between these nodes continued to increase, resulting in considerably larger and more connected networks (Figure 1E-F). In 2012, for example, there were 857 ADC publications originating from 662 active investigators linked by 9018 unique collaborative interactions. In contrast, in 1985, there were 88 ADC publications from 113 active investigators and 139 unique edges.

These data are analyzed in more detail in Figure 2. As would be expected from a growing research initiative, the total number of collaborative ADC publications per year has increased nearly linearly from 1985 to the present (Figure 2A). In part, this is the result of recruitment of new centers and investigators. Nevertheless, the total number of active ADC investigators per year has leveled during the past 10 years, suggesting that the average productivity of each investigator has increased during this time (Figure 2B). This possibility is supported by the growth in the total number of “edges per year” between ADC investigators during the past 25 years (Figure 2C). Presented differently, these data indicate that the total number of collaborative interactions has grown consistently regardless of changes in the total number of investigators. These collaborative interactions include coauthorship with members of the same institution (intra-ADC edges) as well as coauthorship with members of different institutions (inter-ADC edges). There has been a modest increase in the total number of intra-ADC edges during the past 25 years. More interesting, however, is the striking increase in the total number of inter-ADC edges during the same time (light blue bars in Figure 2C). The proportion of inter-ADC edges reached a minimum during the early 1990s and roughly corresponded to the peak recruitment of new centers (Figure 2D). Since that time, the percentage of inter-ADC edges has grown dramatically, comprising more than 80% of collaborative publications in 2011 and 2012 (Figure 2D). Taken together, these data suggest that membership in the ADC program encourages collaborative interactions, particularly among investigators in different institutions.
The percentage of nodes connected to the largest cluster, ie, the main cluster size, of these interaction networks has grown as well (Figure 2E). Judged by this metric, the degree of connectivity within ADC copublication networks has dramatically increased to the point that more than 90% of ADC investigators are connected either directly or indirectly to other ADC investigators in any given year. Similarly, we calculated the NDT, a measure of the interconnectivity of a network that is largely independent of the number of nodes. We found that the ADC network has an NDT of 0.274, which indicates a clear, positive trend in the degree of interconnectivity (Figure 2F). Most interesting, the NDT can be separated into the individual contributions of inter-ADC and intra-ADC edges. As would be expected based on the growth of inter-ADC edges described above, the major contribution to the NDT has come from collaborations established between different institutions (Figure 2F, inset). We cannot formally exclude the possibility that these changes reflect an underlying alteration in the nature of the AD field without a carefully matched control population of non-ADC investigators. Nevertheless, we can conclude that the growth in collaborative studies during this time is consistent with the goals of the ADC program, especially with respect to the rapid increase in interinstitutional connections.

To extend these results, we generated interaction networks at the level of institutions rather than single investigators (Figure 3). When integrated over the entire tenure of the ADC program, we found a remarkable degree of interconnectivity between different institutions (Figure 3A). Most active ADCs had at least 1 collaborative connection to at least 26 other ADCs (Figure 3B). In fact, 323 of the 351 potential connections (92.0%) between active ADCs were represented by at least 1 collaborative publication. The total number of collaborative publications shared between different ADCs was more variable than the number of unique edges (Figure 3C). Nevertheless, we found that each active ADC has a mean of 122 collaborative publications shared with its sister ADC institutions. Therefore, we conclude that productive links between different ADCs are the norm rather than the exception.

This analysis can also be used to assess the evolution of research interests and methodologies over time. To this end, we

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**Figure 1. Copublication Networks of Alzheimer Disease Center (ADC) Investigators, 1985-2012**

Publications from active ADC investigators were harvested from public databases, and networks of coauthorship were generated for every year from 1985 to 2012. Each red circle (ie, each node) represents a single active ADC investigator. Each blue line linking 2 nodes (ie, each edge) represents shared coauthorship of an article between 2 investigators. Blue edges with increased width represent coauthorship of more than 1 publication. Representative networks are shown for 1985 (A); 1990 (B); 1995 (C); 2000 (D); 2005 (E); and 2010 (F). These networks illustrate the growth of ADCs over the past 25 years in terms of the number of active investigators as well as the collaborative interactions among them.
Figure 2. Network Statistics for Collaborative Alzheimer Disease Center (ADC) Publications

A. Total ADC publications

B. Linked ADC investigators (total nodes)

C. Links between ADC investigators (total edges)

D. Inter-ADC links

E. Main cluster size

F. Node degree over time

Descriptive statistics were calculated from the copublication networks shown in Figure 1. A, Total number of unique ADC publications on a year-by-year basis, with data fit to a linear regression line. B, Total number of linked ADC investigators within each network, that is, active ADC investigators who published an article with another ADC investigator per year. These data were fit to a second-order polynomial. C, Number of links between ADC investigators per year. Columns in blue represent intra-ADC collaborations, that is, copublication links between 2 investigators within the same ADC. Columns in light blue represent inter-ADC collaborations, that is, copublication between 2 investigators in different ADCs. These data were fit to a linear regression line. D, Percentage of edges that came from inter-ADC collaborations. These data were fit to a second-order polynomial. E, The main cluster size of copublication networks, that is, the percentage of nodes connected by 1 or more edges to the largest subnetwork. These data were fit to a second-order polynomial. F, The number of edges per node for copublication networks. The growth of interconnectivity between ADC investigators is shown by the positive trend in node degree over time (NDT = 0.274). The inset bar graph shows that most of this increase in node degree originated from the increasing frequency of inter-ADC collaborations.
harvested MeSH terms for every ADC article and measured the rate at which their use changed between 1990 and 2012 (Figure 4). Although most MeSH terms are used too infrequently to identify meaningful trends, there were 700 terms represented in the ADC literature at least once per year on average. Most of these MeSH terms showed remarkable consistency over time. Nevertheless, the use of several dozen MeSH terms changed significantly over the past 2 decades (Figure 4A). For example, the frequency of articles dealing with human genetics underlying the susceptibility to AD has increased. This is seen in the increased use of MeSH terms such as AD genetics, single-nucleotide polymorphisms, and genetic predisposition to disease (Figure 4B). At the same time, there has been a modest decrease in the use of terms dealing with pharmacology and neuronal physiology.

As one would expect, the most common model organism has changed during this time given the shift in emphasis.
away from physiology and pharmacology toward molecular studies of disease genetics. With rats being the most common model 20 years ago, the more recent development of transgenic mouse models has allowed sophisticated investigations into molecular genetics (Figure 4C). Moreover, the emphasis on disease genetics has coincided with substantially changed for several dozen MeSH terms. B, The increased frequency of publications dealing with the human genetics of AD, including the terms AD genetics, single-nucleotide polymorphisms (SNPs), and genetic predisposition to disease, is evident. C, The shift in model systems from predominantly rats to transgenic mice is shown. D, An increased awareness of the influence of a patient’s sex on AD is illustrated. E, The growing focus on how a patient’s age affects the diagnosis and progression of AD is shown.
an increased awareness of patient-to-patient variability in the susceptibility to and progression of AD. Most notable has been a great increase in the frequency of sex-specific studies (Figure 4D), although patients’ age has become more significant as well (Figure 4E). Based on these trends, we expect that additional factors governing the interaction between genetics and environment—such as race and socioeconomic status—will take on more importance in the years ahead. The distribution of ADCs in major university hospitals throughout the United States should prove to be advantageous in recruiting patients for studies with a more refined appreciation for patient-to-patient variability.

Moreover, the extensive interconnectivity between ADCs suggests that there should be fewer barriers to the successful completion of unusually large or ambitious research initiatives. A critical test of this hypothesis is whether collaborative multi-ADC publications have a disproportionately large effect on the field. We therefore compared the number of citations received by collaborative ADC articles with articles from the AD field as a whole. Each red circle represents the citations received by a single multicenter ADC publication. B, The percentages of collaborative multicenter ADC publications and of all randomly sampled ADC publications reaching the 99th, 90th, 75th, or 50th percentile of citations received in any given year. Collaborative ADC publications have shown typically higher impact than the AD field as a whole.

Discussion

To our knowledge, this is the first study to use SNA to assess quantitatively the performance of the NIA ADC program over time by systematically harvesting every article published by ADC investigators to delineate copublication networks among the ADCs. The most significant conclusions we draw from this SNA of the ADC program are (1) the frequency of collaborations among ADCs and ADC investigators increased greatly since 1985, (2) collaborations among the active ADCs increased significantly between multiple different universities at which the ADCs are based, and (3) collaborative multi-ADC research articles are a signature of inter-ADC publications and they have a consistently higher impact compared with articles on AD as a whole. Although direct causality is difficult to demonstrate, these data are consistent with the conclusion that the ADC program has been successful in fostering high-impact multiuniversity collaborations, which is a major part of the mission of the NIA-funded ADC network. However, this SNA is not the whole story of the success of the ADCs. The Alzheimer’s Disease Neuroimaging Initiative, for example, is a spin-off of the social evolution of the collaborative culture of the ADC network, and is one of the most successful ADC-linked programs in the NIA AD research portfolio with a profound effect on driving AD biomarker research forward, especially to improve the conduct and efficacy of AD clinical trials.25
Conclusions

Since the establishment of the NIA ADC network, there have been tremendous basic science advances in understanding the neurobiology of the normal aging brain as well as mechanisms of AD and related neurodegenerative diseases. Highlights of these advances are provided each year by the Alzheimer’s Disease Education and Referral Center (http://www.niapublications.org/adear/), and many ADC scientists funded by this program have been instrumental in moving the AD research agenda forward.10 Our SNA of the ADC network provides quantitative data illustrating the success and impact of this program, and these findings suggest that the structural and administrative features of the ADC program could be successfully replicated in other fields of patient-oriented research funded by the NIH or through public and private partnerships, as is now taking place for AD research. In addition, we believe that the culture of the ADC program—one that encourages and rewards open sharing of resources, data, and ideas—has been very successful in fostering the research accomplishments that we have described.

REFERENCES