HHS Public Access

Author manuscript

Alzheimer Dis Assoc Disord. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Alzheimer Dis Assoc Disord. 2018 ; 32(1): 1–9. doi:10.1097/WAD.0000000000000237.

Population Neuroscience: Dementia Epidemiology serving Precision Medicine and Population Health

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Abstract

Over recent decades, epidemiology has made significant contributions to our understanding of dementia, translating scientific discoveries into population health. Here, we propose reframing dementia epidemiology as "population neuroscience," blending techniques and models from contemporary neuroscience with those of epidemiology and biostatistics. Based on emerging evidence and newer paradigms and methods, population neuroscience will minimize the bias typical of traditional clinical research, identify the relatively homogeneous subgroups that comprise the general population, and investigate broader and denser phenotypes of dementia and cognitive impairment. Long-term followup of sufficiently large study cohorts will allow the identification of cohort effects and critical windows of exposure. Molecular epidemiology and omics will allow us to unravel the key distinctions within and among subgroups and better understand individuals' risk profiles. Interventional epidemiology will allow us to identify the different subgroups that respond to different treatment/prevention strategies. These strategies will inform precision medicine. Additionally, insights into interactions between disease biology, personal and environmental factors, and social determinants of health will allow us to measure and track disease in communities and improve population health. By placing neuroscience within a real-world context, population neuroscience can fulfill its potential to serve both precision medicine and population health.

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Keywords

Aging; risk factors; protective factors; trends; cohort effects; life course epidemiology; molecular epidemiology; translational epidemiology

How will epidemiology contribute to our understanding of dementia over the coming decades?

The classic "seven uses" of epidemiology, proposed in the 1950s,[1] include completing the clinical picture of disease, community diagnosis, delineating new syndromes, computing individual morbid risk, charting historical trends, evaluating health services in action, and identifying causal/risk factors. Alzheimer's disease (AD) offers one of the best examples of epidemiology "completing the clinical picture." In 1906, Professor Alois Alzheimer reported a single case study of Auguste D, a 51-year old woman brought to his expert attention at the Frankfurt Asylum, suffering from the disease later named for him.[2] Based on his work, for the next several decades the condition was assumed to be a rare disease of middle-aged people. Not until 1964, when Professor Martin Roth and colleagues reported a population study of individuals aged 65 years and older in Newcastle-upon-Tyne, England, was it understood that it was also a common disease of older people, increasing in frequency with age.[3]

In dementia research, the classic "uses" have been accomplished through approaches generally categorized as descriptive epidemiology (completing the clinical picture, community diagnosis, charting historical trends, delineating new syndromes such as late-onset AD), and analytic epidemiology (computing individual risk, identifying risk factors). Experimental or interventional epidemiology (such as embedded randomized controlled trials and population-level field trials) is only now beginning to emerge, as we will describe later. The term translational epidemiology has been used to broadly summarize the role played by epidemiology in translating scientific discoveries into population health impact and in the synthesis of knowledge.[4] Building on the classic "uses" and study results to date, we offer a perspective on emerging directions in dementia epidemiology, leveraging new opportunities and resources than were unimaginable a decade ago, let alone half a century ago. We will show why contemporary dementia epidemiology is better characterized as population neuroscience, with implications for both population health and precision medicine. Although we will focus broadly on dementia, rather than on subtypes such as AD dementia, we will also discuss studies that investigated dementia subtypes using evolving research diagnostic criteria based on disease biology.

For the types of epidemiological investigations discussed here, sources of study cohorts have ranged from population-based, such as a census of a region, or a health insurance database where there is universal health care, to non-geographical community-based sources, such as members of religious orders or occupational groups such as nurses or military veterans. Their key characteristic is that they are not composed of patients seeking care for dementia, or research volunteers responding to advertisements. The cohort must be recruited in as unbiased a manner as possible from the source, to optimize its external validity, and should

have minimal attrition once it is recruited, to optimize its internal validity.[5] In these cohorts, the vast majority of individuals are free of dementia at the time of recruitment; they are thoroughly characterized at study entry and then followed prospectively to determine who eventually develops dementia and other outcomes of interest.

For readers unfamiliar with epidemiological terminology, prevalence is the proportion of a defined population that has the condition of interest at a given point in time; incidence is the rate at which new cases of the condition develop within a defined population; risk (and protective) factors are variables associated with subsequently higher (and lower) incidence rates, respectively; exposures are variables which might turn out to be risk or protective factors.

Recent epidemiological reports have dramatically changed longstanding concepts in the science of dementia (Table 1). For example, the age-specific incidence of dementia may be declining in high-income countries; this decline is not entirely explained by declining cardiovascular risk factors or increasing education.[6, 17, 18] Also, most dementia at the population level is not due to any single pathological process, but, rather, represents the sum of two or more pathological processes arising in brains with varying degrees of resilience against disease.[9] In contrast, many individuals with only one pathology remain free of dementia. In a study comparing the brains of individuals with clinically probable AD dementia from research clinics vs. community samples, the community cases were older, had less severe AD pathology, and were more likely to have infarcts and mixed pathologies, than the clinic cases.[19] Clinical research studies are understandably skewed towards younger individuals with earlier onset of disease, who are more likely than older persons to seek services and participate in clinical research. Regrettably, as a result, clinical research is deprived of the opportunity to consider the many characteristics of AD that change with aging, including clinical presentation and course, comorbidity, underlying pathology, and mortality risk. Further, incidence continues to rise exponentially into the tenth decade of life, but many of the known risk factors are associated only with dementia onset before age 85 or so, and not with dementia of later onset.[20] Community-based brain donor programs have been able to associate long-term lifestyle and risk factor data (such as diet) both with specific neuropathology and with apparent resistance to pathology.[21, 22] With aging, neuropathology becomes almost ubiquitous and dementia risk increases dramatically, and yet most older people do not develop dementia.[23] Since healthy seniors do not seek psychiatric and neurologic services, factors associated with healthy cognitive aging, like dietary patterns or education, can only be investigated at the population, and possibly primary care, levels.[24, 25] Such insights have clear implications for prevention and treatment strategies in dementia, and are transforming basic research and clinical trial design in AD.

Over the past decade, epidemiological or population work in dementia has become increasingly allied with clinical and basic neuroscience, including biofluid and imaging biomarkers and genomics. More recently, molecular genomics has been incorporated into community-based studies of aging and dementia. This interdisciplinary approach is consistent with the relatively recent concept of “Population Neuroscience” which, in essence, is the study of the full range of brain disease, risk factors, and underlying biological pathways as they present in the population at large.[26, 27] Neuroscience has made great

strides in social, cognitive, clinical, affective, economic, developmental, and communication areas; however, most of its findings are based on studies of convenience samples which differ systematically from the populations from which they were drawn. These systematic differences can bias the observed associations and thus distort our inferences about brain-behavior relationships.[28] Meanwhile, traditional population studies, including epidemiologic and social science research, have made major contributions towards understanding the associations of behavior with a range of external factors; however, these studies have treated the brain like the proverbial "black box." By marrying the two approaches, population neuroscience leverages interdisciplinary expertise and emphasizes interactional models which explore moderators of brain-behavior links and predictors of relevant outcomes.[26] We can use not only the tools of traditional epidemiology and biostatistics, but also detailed structural, functional and chemical brain imaging, electronic monitoring (i.e., wearable technologies), cognitive neuroscience, and various molecular genomic techniques using both ante-mortem and post-mortem biofluids and biospecimens including brain samples. It is becoming possible to integrate multi-level brain omics (genome, epigenome, transcriptome, proteome, lipideome, metabolome[29]) using systems biology and data mining techniques, at the population level.[30]

We therefore propose that the broad concept of "population neuroscience" supplant the traditional models of "neuroepidemiology" and "psychiatric epidemiology," in dementia research. Although a modest paradigm shift, it highlights the translational aspects that are informing the molecular epidemiology of AD and other dementias at the population level, and more clearly establishes the epidemiology of brain dysfunction as a branch of neuroscience.

One example could be integrating brain imaging, genetic, and biomarker studies to identify the biologically relevant subgroups in the population which best respond to a preventive or therapeutic intervention. Another might be devising methods to scale up imaging and biomarker studies to larger and more representative samples of the population. A third example could be using multi-level brain omics to identify novel therapeutic targets, including those related to resilience. Thus, population neuroscience can serve as a bi-directional bridge between clinical and basic research, develop frameworks and models to generate and test hypotheses across disciplines, and provide tools for translational medicine.[31] Table 2 shows some emerging directions that we believe represent the future of population neuroscience over the coming decades; in essence, the new avatars of the classic "seven uses of epidemiology." The proposed directions are complementary and have some overlap since they represent different approaches towards the same broad scientific goals.

1. Expanding the phenotypes of dementia and mild cognitive impairment

1a. Characterize and investigate deeper and denser phenotypes

We must take greater advantage of growing opportunities to combine standard cognitive and other clinical measures with biofluid and neuroimaging biomarkers, in longitudinal population-based studies. The increasing use of relatively affordable structural and resting state functional MRI in population studies is an example of moderate progress along this path. Practically, large numbers of frail elderly individuals in the general aging population

cannot be imaged at academic medical centers; more neuroimaging research must be conducted at community hospitals and freestanding imaging centers, introducing new challenges which we must meet. Statistical methods have been developed, and more are under development, to correct for the biases that are inevitably introduced by multiple scanners, and by the non-randomness of the sample that agrees and is eligible to be neuroimaged.[32] Some groups in Europe and the US are incorporating CSF assays[33, 34] and amyloid and tau PET imaging[35] into subsets of population-based cohort studies. As *in vivo* methods for characterizing underlying pathologies become more reliable, affordable, and commonplace, we will be better able to observe the incidence and progression of biomarkers at the population level. We will also be able to measure their interactions with (or independence from) risk factors in contributing to cognitive dysfunction. Population studies employing such markers will further "complete the clinical picture of disease" in the community. By helping to identify the boundaries of neighboring syndromes and disease entities, they will improve the utility and prognostic value of our diagnostic groupings at the population level. These advances will help us hone in on the mechanisms by which risk factors lead to disease. Population studies are also needed to determine the external validity ("generalizability") of the substantial proportions of cognitively intact individuals with biomarker-positive preclinical AD or cerebrovascular disease, in both clinical and community studies[35, 36, 37, 34]

Through **deep phenomics**, population studies are broadening our understanding of links among organ systems, and establishing pathophysiological links among various previously siloed traits and conditions. Examples include insulin resistance in diabetes and Alzheimer disease,[38] and inflammation in visceral fat and brain glia.[39] Changes in glucose,[40] blood pressure,[41] and body mass index[42] have been reported to occur in the period preceding the emergence of dementia. There are also links with sleep and circadian rhythms,[43] pulmonary function,[44] chronic kidney disease,[45] and anemia.[46, 47]

Clearly, these relationships cannot be investigated in samples composed of the dementia patients typically recruited in clinical research settings. Further, since the ideal approach to chronic disease is prevention, it is only in people free of disease, at the community level, that we can apply preventive strategies. Studying deeper phenotypes at the community level will allow us to investigate emerging conditions that precede or coincide with preclinical (presymptomatic) disease, possibly in midlife; better understand the roles of aging and genetics in the above; and examine a wider range of relevant exposures than has been possible to date, for example, the role of stress.[48] Identifying the subgroups in which these factors influence the trajectory of cognitive decline, and the circumstances under which they do, will help target molecular analyses and bring us closer to precision medicine.[49] The intensive study of population-based samples can also help contextualize detailed phenotyping of volunteer and clinical samples. The aforementioned diversity of dementia in the population at large can be harnessed by identifying (for example) AD subtypes with different characteristics and outcomes, with implications for population health.

1b. Broaden the cognitive phenotype of dementia and mild cognitive impairment to include non-amnestic syndromes

Expanding the conventional dementia phenotype to include cognitive domains other than memory will allow population studies to capture atypical AD cases as well as non-AD dementias.[50] Non-amnestic mild cognitive impairment (MCI) also progresses to dementia, although at a slower rate than amnestic MCI.[51, 52] Susceptibility to delirium (e.g., post-operatively) in seemingly normal elderly is a potential preclinical marker of impending dementia.[53] Social cognition,[54] thus far primarily studied in clinical samples of younger people with conditions such as schizophrenia, autism, Huntington's disease, and frontotemporal dementia, is now recognized as a cognitive domain that can also be impaired in other forms of late-life dementia.[50, 55]

1c. Broaden the dementia phenotype to include neuropsychiatric and motor manifestations

Behavioral and psychological symptoms are integral parts of the phenotype, and not mere epiphenomena, of dementia and mild cognitive impairment. They often precede, and are more distressing and burdensome than, the cognitive symptoms; they are frequently the first reason for which services are sought. The unfortunate Auguste was not taken to the psychiatric hospital to see Dr. Alzheimer because she was forgetful. Families report that personality change precedes the development of cognitive decline,[56] although they are likely referring to behavioral changes such as apathy, rather than personality traits such as neuroticism (which appear stable).[57] Population studies have also identified apathy as a common feature of mild cognitive impairment and a budding prodrome of dementia.[58] Work has begun to characterize a primarily behavioral phenotype of the dementia prodrome (currently labeled "Mild Behavioral Impairment") that may precede or coexist with the more familiar cognitive phenotype of MCI.[59, 60] Similar to the application of amyloid PET imaging to study memory loss, studies could perhaps be undertaken with dopamine PET to investigate apathy. Such investigations would be best initiated in clinical epidemiology studies, to clearly describe the phenotype in well-characterized patients before moving to detect preclinical and subclinical phenotypes in the population at large.

In addition, changes in mobility[61] and motor function, such as extrapyramidal signs,[62] are harbingers of subsequent cognitive decline and dementia including AD. These changes are related to the pathology of AD as well as Lewy Body disease and cerebrovascular disease.[63]

2. Explore links between disease patterns and the modifiable macro-environment

We still know relatively little about environmental influences on AD pathology, in contrast to what we know about Parkinson's disease (e.g., the pesticide paraquat).[64] Longitudinal epidemiological studies are the only feasible approach to investigate the impact of environmental factors such as lead or mercury exposure,[65, 21] air pollution,[66, 67] and effects of the built, social, and economic environments on heart and brain disease.[68, 69] A recently coined term, the 'exposome,' refers collectively not only to these various externally experienced factors, but also to the exposures that individuals may generate or experience

within themselves (such as variability in blood pressure, physical activity, diet, gut microbiome). Traditionally, epidemiology has partnered with public health to identify a few high impact risk factors that could be modified to drastically reduce individual and population risk; for instance, the impact of smoking on lung cancer, or possibly of early education on resilience to clinical dementia in the face of neurodegenerative pathology. However, for the complex condition of aging-related dementia, it appears more likely that a large number of interacting factors exert joint impacts. Different factors may contribute in different clusters of individuals; their investigation will require the development of new analytic and computational tools.[70] This is a potentially high-impact target for public health and public policy interventions.

3. Molecular epidemiology and Omics

It has been suggested that an optimistic outlook for epidemiology is being offered by the "convergence of striking developments in biotechnology, the increasing availability of biobanked samples, and advances in biostatistics and bioinformatics."[71] We need to move these rapidly evolving investigations out of case-control studies within specialty clinics and into the larger community where AD cases can potentially be identified at all disease stages including preclinical disease, and with all the common comorbidities with which therapeutics must contend. Omics provides an opportunity for precision medicine,[72] in that it can identify subgroups with different pathways defined, for example, by different polygenic scores. Expanding the procurement of brain autopsies in community/population studies will help this cause. Beyond the genome, multi-level brain omics must be derived from the biospecimens of interest. For cognition, this is the brain; however, in Lewy Body disease there is interest in examining the autonomic nervous system where peripheral specimens such as cutaneous nerves and parasympathetic ganglia may be usefully examined.[73]

4. Life Course Epidemiology

The population neuroscience of dementia has to begin in early life. Signals from highly selected clinical samples with autosomal dominant AD suggest that the neuropathology of AD begins to develop decades before the onset of symptoms or detectable deficits.[74–76] Links between developmental and aging processes have been identified;[77–79] *in-utero* conditions may influence the risk of age-related diseases through epigenetic changes.[80, 81] Replicating these findings in very long-term population studies, starting in early adulthood, will allow us to identify antecedents and true risk factors for the more common, non-dominant, late-onset AD; these data will have direct implications for prevention trials. Longitudinal population studies reveal that cognitive change is not linear, and that different aspects of these non-linear trajectories are associated with different risk factors[82, 83] and brain pathology.[84] These studies not only shed light on disease biology but also reveal the critical windows over the life course during which the different exposures exert their effects on risk on late-life dementia[85] and on the underlying neuropathologies.[86, 87] This approach can identify risk factors that play out over many years, exerting small but cumulative effects that are far below the resolution of shorter-duration randomized clinical trials. Following cognitively intact individuals in the population longitudinally, as they age, allows us to

detect the earliest changes and manifestations that occur well before patients appear in the clinical setting seeking services. To accomplish this goal cost-effectively, we can extend the study of "aging" backwards into earlier periods of life; leverage existing birth cohorts and cohorts of young adults, and follow them longitudinally throughout their lives, periodically measuring putative biomarkers where feasible. Well-established life-course studies, starting with the 1946 British Birth Cohort study[88] and including several others in Northern Europe[48, 89, 90] and North America,[91–96] and existing longitudinal studies that have followed young children through early adulthood,[97] all provide the opportunity to continue following these well-characterized cohorts with a change in research focus (and funding agency). These studies could delineate the long-term trajectories of cognitive and behavioral change, and also the evolution of biomarkers over time, thus helping elucidate the dynamics of the long induction and latency phases of degenerative dementias.

5. Cohort Effects

There is growing evidence that rates of dementia incidence,[6, 7, 17, 98] stroke incidence,[99] and cognitive decline[100] may have been dropping over recent decades in the high income countries.[101] The same may not be uniformly true across various ethnicities within those countries.[102] Intriguingly, a rare autopsy study suggested that amyloid deposition appeared to have declined in aging brains over recent decades.[103] However, given rising life expectancy and duration of survival with dementia, prevalence is unlikely to decline over the next few decades, although one national US study has reported a decline in prevalence.[104] Potential explanations for declining disease incidence include better early nutrition and control of infectious disease, better education, less exposure to environmental toxins such as lead, and lower rates of smoking, in more recently born cohorts. Plausible and testable hypotheses would relate to the downstream effects on brain function and dementia incidence of advances in cardiovascular disease management; specifically, diastolic blood pressure in the 1960s, systolic blood pressure and statins in the 1990s, and tissue plasminogen activator for acute stroke in the 2000s.[18] None of these developments have as yet been shown to explain declining dementia incidence.[6] Meanwhile, rising rates of obesity[12] and diabetes[105] may counteract the favorable trends by increasing dementia risk. Investigating such trends requires very long-term studies examining cohort effects, i.e. variations based on the year or decade of birth. Different exposures or levels of exposure in different birth cohorts may well lead to different rates of outcomes in those cohorts. Age-specific incidence may still be rising in low- and middle-income countries such as Brazil, India and China; incidence dropped among African-Americans but not among Africans (Nigerian Yoruba) between 1992 and 2001.[106] Generational or birth cohort effects will vary across regions and in accordance with locally applicable historical events and exposures, such as wars and famines. Caution should of course be exercised to ensure that apparent trends are not artifacts of shifts in study design, diagnostic criteria, population characteristics, or response rates over time.[107]

6. New generations

In addition to birth cohorts which have already reached the age of risk, coming generations will experience a range of different relevant exposures than preceding ones (e.g., nutrition,

immunizations, transportation, electronic media and digital devices). Potential new risk factors could include the more pervasive sleep disturbances[108] and increased stress experiences that result from stagnant wages, multiple jobs, intrusion of work into all hours of the day,[109] increased jet travel,[110] increased sedentary time,[111] and other lifestyle changes.[112] In mouse models, a "modern-life-like stress paradigm" has been found to exacerbate Aβ pathology and increase synapse loss.[113, 114]

New generations (e.g., "millennials") may be easier to recruit using social media, capitalizing on their increased propensity to share information. Social media are being found to be of value in infectious disease epidemiology, for disease surveillance and outbreak management,[115] and for pharmacovigilance of adverse drug reactions.[116] Twitter has been used to identify stigmatizing statements about AD;[117] potentially, ways can be found to use social media for the recruitment of community-based samples for longitudinal studies. Secure web-based data collection, m-health applications, and increasing comfort with allowing data to be collected passively, should make participation easier and less time-consuming.

7. Inadequately studied populations

Populations of low- and middle-income countries, and also ethnic/racial/social/geographic minorities in the high-income countries, may have different rates of both exposures and outcomes, and different secular trends. Epigenetics may also vary across populations.[118] Given increasing travel and migration, local factors from environmental pollution (e.g., lead-tainted paint and water)[65] to infectious diseases (e.g., zika)[119] can have global impacts. Previous cross-national studies of dementia[106, 120, 121] have made substantial contributions to our understanding of varying prevalence and incidence across the globe, and of similarities and differences in traditional risk factors. However, newer studies are needed that are of suitable scale, reflect current thinking, and harness current technologies, to collect data and appropriate biological specimens and explore unique exposures and modifiers/moderators in the local context.

8. Interventional Epidemiology

Interventional epidemiology can involve the application of epidemiologic principles to design and recruit for trials, to analyze the data, and to interpret the results.[122] Additionally, trials can be totally embedded in representative population-based cohorts,[123] or in distinct targeted subgroups of the cohort. Within heterogeneous general populations it is usually possible to identify latent homogeneous subgroups, among which associations and even mechanisms can potentially vary. Epidemiology can enhance trials by identifying different homogeneous subgroups in which different approaches may be beneficial. This, in fact, offers an approach to precision medicine, allowing us to understand how different individuals and groups arrive at dementia along different albeit not exclusive paths.

However, it is sometimes necessary to challenge the conventional hierarchy of evidence. Some exposures like smoking and head trauma cannot be randomized in clinical trials, and sufficiently long randomized clinical trials are not practical for midlife risk and protective

factors. In these cases, causal inferences must be drawn from observational data. Steps can be taken to enhance the reliability and validity of non-randomized study designs, e.g., Mendelian randomization, in which genetic polymorphisms associated with modifiable exposures are used to strengthen the robustness of causal inference in observational studies.[124] Their use may increase, thanks to the expanding availability of genetic data in large, representative samples. Observational epidemiologic studies often not only mirror findings of randomized clinical trials but also provide long-term data that cannot be obtained from trials.[125–127] "Evidence must be translated, whether or not complete."[128]

9. Big Data

This term has been used in various ways to refer to databases that are large in volume (for example data on hundreds of thousands of metabolites, gut microbes, or genetic variants), velocity of accrual (such as minute to minute data on a person's movements collected by an accelerometer) or variety (different types of data on diet or pollutants). Here, we use the term to refer to gigantic databases which were assembled for purposes other than the proposed research. Examples would include electronic health records (EHRs) of large health care systems, the Medicare claims databases in the US, and national health or pharmacy databases in other countries. The increasingly pervasive routine collection of health data will provide unprecedented opportunities to create registries that can be linked to data collected from individuals. On a larger scale, these could be large interlinkable data sets within a single country or networks of multinational databases.[129] Done right, judicious mining of these data can narrow the gap between individual health and population health; cost of research data collection and processing will decrease; epidemiology will acquire biological and imaging data that could be difficult to obtain on the same scale in independent population-based research.[72, 130] However, these opportunities should be approached with caution, and, the appropriate Big Data set identified for a given research question. Sound epidemiological principles and validated methods must guide data mining. The major drawback is uncertain confidence in the clinical phenotype that can be generated by EHR or claims data, which are not collected for research purposes, and could be driven by local vagaries of coding and billing. Thus, this approach may be the best fit for data that are recorded unequivocally, such medication dosages, serious adverse effects, and clinical procedure codes. Pharmaco-epidemiological interrogations of these data could allow post-marketing surveillance to answer questions for which RCTs cannot be employed. Data mining approaches may also be useful for agnostic digital data such as MRI images, actigraphic data, and retinal scans. Here too, it is critical to distinguish disease effects from independent risk factors for disease, and to recognize that patients who are selected to undergo non-routine testing are systematically different from those who are not ("confounding by indication"). A partial solution is to combine direct data collection in a very large sample of the target population with surveillance for events based on EHR. This hybrid approach is being used in the new generation of mega-cohort studies;[131–134] it works best when embedded in health care systems that maintain detailed records and provide most of the clinical care received by the target populations. Data from EHRs also potentially provide the opportunity for efficient "virtual trials" of interventions analyzed using

epidemiologic approaches, again setting the stage for precision medicine and, eventually, population health.

10. Pooled and Coordinated Analyses

We use this term to refer to analyses of appropriately pooled data from multiple epidemiological studies conducted for similar purposes. This approach can increase reach and power to detect modest-sized effects which escape detection in smaller individual study populations. If eventual pooling is a long-term objective, participating studies should use shared core methods without stifling local strengths and innovation. Uniformly collected data and specimens can easily be shared. For *post hoc* data pooling where data were not uniformly collected,[135] sufficient time and effort should be budgeted for appropriate harmonization. Multi-level analyses should account for the clustered nature of the pooled data, and account for within-group as well as between-group effects with appropriate weighting, as is typically done in meta-analysis. For balance, it should be asked whether there is a reasonable upper limit to sample size. Is bigger always better? What is the smallest effect that is useful to detect? Are data quality and integrity more important than number of studies included or total sample size? How will we recognize spurious findings? Cross-validation approaches and appropriate simulations should be planned. Other cautions abound. The harmonizing of measurements has its rational limits; cohorts studied during different eras at different sites will have unique characteristics which cannot be harmonized or statistically adjusted; in many long-term studies, participation (response/refusal) rates are declining, and mortality/attrition rates will vary across studies, introducing different levels of potential selection bias and survival bias. These issues can lead to under- or over-estimates of incidents, and of risk estimates, when pooling data across cohorts.

In summary, we have proposed some 21st century extensions of Morris' classic seven uses of epidemiology. Descriptive and analytic epidemiology will allow us to identify and study longitudinally the relatively homogeneous subgroups within populations and identify potential therapeutic and prevention targets. Molecular epidemiology and omics will allow us to "unravel the key distinctions within and among subgroups" and "point the way toward better-targeted, safer, and more effective treatments, based on a deeper understanding of individual patients' risk profiles."[130, 136] Interventional epidemiology will allow us to identify the different subgroups that respond to different treatment/prevention strategies. These strategies will inform precision medicine, which can be applied at the community level – and only at the community level - to prevent disease. Insights into interactions between disease biology, personal and environmental factors, and social determinants of health, will allow us to measure and track disease in communities and improve population health, a translational approach that has been termed precision public health.[137, 138] Thus, by placing neuroscience within a real-world context, population neuroscience can fulfill its potential to serve both precision medicine and population health.

Acknowledgments

The authors thank Dallas Anderson, PhD, NIA Division of Neuroscience, for encouraging the writing of this editorial.

The authors thank Erin Jacobsen MS for assistance with manuscript preparation.

This work was supported in part by the following grants K07AG044395; U01AG016976; P30AG10133; R01AG045350; P50AG005146; R01AG054076; P30AG10161, and R01AG17917 from the National Institute on Aging, US DHHS; and grant 2015-02830 from Vetenskapsrådet, Sweden.

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Table 1

Some Examples of Recent Contributions from Dementia Epidemiology

Temporal trends. Discovering a trend towards decreasing age-specific incidence of dementia in high-income countries; factors underlying these trends could shed light on disease mechanisms and inform preventive strategies.[6, 7, 8]
Full spectrum of pathology. Community-based brain autopsy studies showing that neuropathologies are common in people without dementia, and that most dementia, particularly in the eighth and later decades of life, is due to multiple etiologies; this knowledge broadens the potential range of preventive and therapeutic targets.[9]
Life-course impact of risk factors. Demonstrating critical periods during which different risk factors exert their influences, identifying the windows during which preventive strategies are likely to be effective.[10, 11, 12]
Modifiable environmental risk factors, such as air pollution, shown to be associated with dementia.[13, 14]
Modifiable protective factors, such as cognitive and physical activity, shown to predict healthy cognitive aging.[15, 16]

Table 2

Future directions for population neuroscience of dementia

1.	Investigate **expanded phenotypes** of dementia and mild cognitive impairment.
2.	Investigate links between disease patterns and the **modifiable macro-environment**.
3.	Further develop **molecular epidemiology incorporating omics.**
4.	Investigate epidemiology of disease over the **life course.**
5.	Examine trends in disease and risk factors across **birth cohorts.**
6.	Employ novel approaches to study aging and disease in **new generations.**
7.	Expand the study of **inadequately studied populations** where novel risk and protective factors may exist.
8.	Expand the scope of **interventional epidemiology.**
9.	Appropriately use **Big Data** approaches.
10.	Use judicious **pooled and coordinated analyses**