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Using Electronic Health Records for Population Health Research: A Review of Methods and Applications

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Abstract

The use and functionality of electronic health records (EHRs) have increased rapidly in the past decade. Although the primary purpose of EHRs is clinical, researchers have used them to conduct epidemiologic investigations, ranging from cross-sectional studies within a given hospital to longitudinal studies on geographically distributed patients. Herein, we describe EHRs, examine their use in population health research, and compare them with traditional epidemiologic methods. We describe diverse research applications that benefit from the large sample sizes and generalizable patient populations afforded by EHRs. These have included reevaluation of prior findings, a range of diseases and subgroups, environmental and social epidemiology, stigmatized conditions, predictive modeling, and evaluation of natural experiments. Although studies using primary data collection methods may have more reliable data and better population retention, EHR-based studies are less expensive and require less time to complete. Future EHR epidemiology with enhanced collection of social/behavior measures, linkage with vital records, and integration of emerging technologies such as personal sensing could improve clinical care and population health.

EHR: a software platform that contains individual-level patient-provider data captured during health care encounters. Epic, eClinicalWorks, McKesson, and Cerner are examples

Geographic information systems (GIS): a tool that allows researchers to combine and visualize spatial data and export analytic variables for merging with EHR data

Meaningful use: providers demonstrate they are meaningfully using their EHRs by meeting increasing thresholds for specific objectives, services, and activities

Primary data collection: new data collected for a specific research purpose, not for clinical care

INTRODUCTION

Epidemiologic research design and inference are shaped by prevailing theories, by available measures of risk factors, and by the cost of obtaining relevant data. Prior to the 1950s, researchers commonly used vital statistics to conduct cross-sectional and time series studies of noninfectious disease. The lack of longitudinal data limited causal inference. In the second half of the twentieth century, funding allowed researchers to develop cohorts of individuals who were followed over time. However, in the twenty-first century, declining research support and participation rates (42) complicate the conduct of traditional costly and time-consuming prospective studies.

The recent rise in the use of electronic health records (EHRs) offers a timely alternative. These databases provide a low-cost means of accessing rich longitudinal data on large populations for epidemiologic research. Not simply a digital version of a paper record (127), EHRs can be linked to contextual data using geographic information systems (GIS) and combined with self-reported data to address questions about complex networks of causation. Such work has the potential to evolve epidemiologic theory in the twenty-first century (69, 86).

In this review we describe the nature of EHRs and how they have been used in epidemiologic research. Since its recent inception, EHR data have made considerable contributions to a broad population health scholarship, from infectious disease research to social epidemiology. We summarize this literature and then contrast traditional and EHR-based studies to highlight specific strengths and weaknesses of each with the goal of informing future research.

EHR ADOPTION AND FUNCTIONS

EHRs were originally developed for billing purposes. However, their purview has expanded, motivated by meaningful use requirements expressed in the Health Information Technology for Economic and Clinical Health (HITECH) Act, part of the 2009 American Recovery and Reinvestment Act. Financial incentives to professionals and hospitals for EHR use are tied to existing and emerging requirements. Requirements include standard capture of vital statistics, an up-to-date problem list, and others relevant to patient engagement and data sharing (34, 127). The implementation of meaningful use will likely accelerate capture and standardization of data and benefit epidemiologic research (14).

In 2012, 69% of primary care physicians in the United States reported using EHRs, an increase of 23% from 2009 (110). Parallel changes have unfolded in other industrialized countries, and current usage ranges from lower levels in China and South Korea (115, 134) to nearly universal adoption in Australia, New Zealand, and northern Europe (110). Although the focus of this article is primarily on the use of EHR data for research in the United States, we draw on relevant research elsewhere.

EHR DATA AND DEFINING EPIDEMIOLOGIC PARAMETERS

Data included in EHRs are intended for clinical and administrative use. As discussed below, these data can be used effectively for research purposes, but doing so requires some caution and creativity.

EHR Data Collection and Content

Unlike standardized primary data collection in epidemiologic research, EHR data are collected for the purposes of the clinical encounter. Rather than being driven by research needs, the data collected are directly influenced by patient health status, by how and when they seek care, and by variation in physician care practices and documentation. Accordingly, the patient and physician,

Table 1 Data domains available from electronic health records^a

Domain	Examples	Utility to epidemiologic research
Demographics ^b	Age, sex, race/ethnicity, residential address	Exposures, confounders, effect modifiers and/or mediators; address used to link to environmental and community data for individual-level or contextual exposures
Health behavior ^b	Tobacco, alcohol, and injection drug use	Outcomes, exposures, confounders, effect modifiers and/or mediators
Vital signs ^b	Pulse, systolic and diastolic blood pressure, height, weight (used to derive BMI)	Outcomes, exposures, confounders, effect modifiers and/or mediators
Outpatient encounters ^b	ICD-9 codes for a wide variety of diagnoses, including diabetes, hypertension, asthma, kidney failure, migraine	Diagnostic codes used to construct variables; encounter type can indicate disease severity; timing of diagnoses in relation to one another and interval between visits may provide signals about the disease course
Inpatient encounters ^b		
Emergency department encounters ^b		
Laboratory data ^b	Lipid panel, basic metabolic panel, microbiologic culture with antibiotic resistance tests, liver function tests, microalbuminuria, hemoglobin A1c	Laboratory orders and results used to identify primary outcome or as covariates and can improve diagnostic accuracy of ICD-9 codes and to evaluate disease progression, severity, and control
Medication order ^b	Type, dose, frequency, duration	Medication orders provide information about disease course and severity, control, and prevention (e.g., hypercholesterolemia, statins, and cardiovascular disease)
Procedures ^b	Electrocardiogram, pulmonary function tests	Procedural data can improve diagnostic accuracy of ICD-9 codes and evaluate disease severity and control
Problem list	ICD-9 code for depression, heart failure, hypertension	Ongoing patient health problems are used to confirm diagnoses in other locations and can also be helpful in defining disease onset
Free text	Encounter notes, imaging notes	Text analysis can provide information on symptoms, onset, duration, and severity; notes can also have information not available elsewhere, e.g., Apgar scores; labor and delivery notes can also be used to link mothers and infants
Imaging	Echocardiogram, magnetic resonance imaging, CT scan	Data used to verify diagnosis and subtype and detection of other health problems

^aAbbreviations: BMI, body mass index; CT, computerized tomography; ICD-9, International Classification of Diseases.

^bLongitudinal data or repeated measures can be used to construct time-dependent variables.

not the researcher, stipulate the amount of time a patient is under observation (person-time), which impacts calculation of prevalence, incidence, and risk ratios.

EHRs used by different health systems vary in the number of domains (e.g., vital signs, laboratory data) of health care data that they collect. Over time, systems tend to add functionality to their EHR and expand the number of domains collected (**Table 1**). Longitudinal research is made possible by using the dates associated with specific EHR entries. Doing so allows researchers to study not only disease onset, but also disease severity and progression.

Diagnostic codes warrant special consideration in EHR research. Physicians use codes to depict a patient's condition, to document indications for orders (i.e., medications, laboratory tests, imaging), and to justify the levels of service and billing. The location of a code in the EHR can

Incidence rate: the number of disease onsets divided by the person-time at risk; health care encounters determine if a patient is contributing person-time

ICD-9: International Classification of Diseases code

Natural language processing: A technology that extracts information from free text, e.g., detecting sentence boundaries, segmenting text into meaningful groups, inferring temporal relationships

also provide useful information. Image and laboratory order codes indicate what the physician suspects about the patient's condition that requires validation or what the physician knows about the patient (e.g., hypercholesterolemia) and is monitoring (e.g., low-density lipoprotein). Medication orders/dosages or scheduling of return visits may represent the degree of physician concern, reflected in the explicit action required to manage the health condition. Even though diagnostic codes provide critical information on an individual's health status, providers may not use them consistently, and the meaning of any given code may vary among providers and across time.

Study Design and Study Population Assembly

EHR-based studies involve predominately case series, nested case-control studies, and prospective and retrospective cohorts. Researchers can use EHR data to rapidly identify cases and assess eligibility for individual or frequency matching in nested case-control studies (130). EHRs capture data on an open cohort in which patients may enter or leave care at any time. A patient can contribute person-time only if they are under observation and are at risk for the outcome of interest. Although the notion "under observation" will vary, at a minimum it requires that a patient be documented as having an encounter with a qualified provider (e.g., primary care physician). Researchers may find it difficult to interpret gaps in care in the EHR. When a patient lacks data, one cannot distinguish between patients who have left care, who have been well and have not sought care, or who have missed routine visits for other reasons. This ambiguity in whether patients are under observation is relevant to the person-time documentation required for estimating incidence rates. If patients enter care before an EHR has been implemented in a given system, some domains or events may not be captured and available for study (i.e., left-censored). Conversely, if they exit care, EHR data will lack information on events occurring after that time (i.e., right-censored).

Constructing Epidemiologic Variables

Outcomes and exposures. EHRs can be used to define disease onset and outcomes and to determine case and control status on a selected outcome, exposure measures, and covariates. For numerous reasons, the single appearance of a diagnostic code does not necessarily indicate that a patient has a disease. For example, in identifying chronic rhinosinusitis, Hsu and colleagues found that the positive predictive value (PPV) for the ICD-9 (International Classification of Diseases) code 471.x for nasal polyps was 85%, whereas 473.x for chronic sinusitis had a PPV of only 34% (54). With additional information—evaluation by an otorhinolaryngologist, for example—the PPV rose to 91%. The accuracy of disease definition is often improved by using ICD-9 codes and other information over time and is often better in relation to more severe disease (e.g., myocardial infarction). Aspects of the EHR may enhance data validity. For example, alerts, commonly used in clinical decision support (122), can also be used to notify clinicians of input errors to support real-time data correction.

Clinical text is also captured in the EHR, often in a notes section. It includes discharge summaries, treatment plans, and progress notes, which can contain information about patients that is useful for research purposes. However, this information may be inconsistently recorded. For example, Wasserman et al. (129) searched text notes for 465 children and found fever reported in 278 different ways (e.g., "fever," "pyrexia," "elevated temp"). One approach to deal with nuanced clinical text is to use open source natural language processing tools. These can extract text relevant to defining disease stage, severity, and progression or symptoms (6, 124), which may not be well captured by diagnostic codes. For instance, Anderson et al. (6) used natural language processing

Table 2 Selected examples of electronic health record study population data sources from cohort studies

Data source	Sample size	References
Single psychiatric inpatient unit	728–2,010	82, 97
Specialized center/clinic	544–10,017	15, 40
Prison network	370,511	8
Single hospital	467–55,492	23, 47
Multiple hospitals	1,074–25,241	53, 105
Multiple primary care practices	7,925–345,143	44, 74
Health care system	2,537–919,873	25, 48
Consortium	8,709–233,844	28, 83
Centralized anonymized repository	923–5,244,402	39, 101

to extract suicidal ideation from clinical notes on >30,000 Americans with a clinical diagnosis of depression.

Disease etiology. Whereas disease status is often well documented in EHRs, disease etiology, including fundamental causes of disease (70) (e.g., social, behavioral, environmental factors), is often not well documented. Some data are not retained, including, for example, residential addresses over time (only the current address is used for billing). Researchers have used health insurance status (e.g., commercial versus Medicaid) as a proxy for individual socioeconomic status (SES) (13, 18, 36, 44, 67, 83) and have assigned neighborhood SES on the basis of the median income or an index of deprivation in patients' communities (13, 18, 29, 35, 38). Although data on physical activity and other important behaviors and social risks are not routinely captured (2, 16), the Institute of Medicine has recommended that these and other domains be integrated into routine EHR data collection, including four existing (i.e., race/ethnicity, current address, alcohol use, and tobacco use) and eight new domains (e.g., stress, social isolation, physical activity) (27).

DIVERSE USES OF EHR DATA FOR EPIDEMIOLOGIC RESEARCH

Researchers have applied extract, transform, and load algorithms to EHRs to assemble study populations from a variety of settings (Table 2). The most successful EHR research to date has used deidentified databases in UK and US health care systems whose patient populations receive most or all of their care within the system. Researchers initially used EHRs for comparative effectiveness and health services research, pharmacoepidemiology and genetics epidemiology [e.g., the Electronic Medical Records and Genomics (eMERGE) Network], and disease surveillance. These efforts have been summarized elsewhere (12, 49, 66, 81, 95, 120) and are not covered in this review.

Assembling Research Cohorts from EHR Data

Researchers can use EHRs to form standard cohorts and to assemble groups of patients with specific diseases. Kaiser Permanente in the United States has several EHR-based cohorts (7, 30, 31, 89), including the Diabetes Study of Northern California (DISTANCE) study (85). DISTANCE involves 20,000 patients with diabetes and has addressed wide-ranging issues, including diabetes outcomes among Asians and Pacific Islanders (59), the impact of neighborhood deprivation on cardiometabolic health indicators (68), and the relationship of SES to risk of hypoglycemia (9).

SES: socioeconomic status

Extract, transform, and load: a tool that reads desired clinical EHR data, converts it into a usable form, and then writes it into the research database

Deidentified data: deidentification of protected health information occurs when all the HIPAA identifiers are removed from the data set

Normalized (data):

consistently structured and bounded data that link logically with other data available in the system

BMI: body mass index (kg/m²)

Researchers from two or more health systems are increasingly collaborating and assembling multisystem cohorts; the HMO Research Network has been a leader in this type of research since 1994 (112). Three other US examples are the Consortium on Safe Labor (28, 78, 83, 106), which uses EHR delivery and birth data from 19 hospitals; the Clinical Assessment, Reporting, and Tracking system in Veterans Administration (VA) hospitals (128); and the Chronic Hepatitis Cohort Study, which combined data from four health care systems on more than 1.6 million adults to identify a cohort of hepatitis B and hepatitis C patients (87). With Chronic Hepatitis Cohort data, Mahajan et al. (77) found that only 30% of hepatitis C–positive patients who died with documented liver disease had hepatitis C on their death certificate, uncovering huge underestimates of the role of hepatitis C on mortality in the United States (77).

Researchers have also assembled study populations from central repositories of anonymized data including the Clinical Data Analysis Report System in Hong Kong (22) and the Clinical Practice Research Datalink (CPRD) (4, 50, 102), the Health Improvement Network (THIN) (35, 93), and QResearch in the United Kingdom (125). The CPRD, which gathers data from more than 500 UK general practitioners, has data on more than 5 million active pediatric and adult patients. Repositories provide researchers with normalized, longitudinal data, enabling greater opportunities for research, as evidenced by the >1,000 peer-reviewed published papers using CPRD data.

Parallel rise in available EHR data and concern about obesity spurred some of the first population health research with EHRs (13, 52, 57, 64, 72, 96, 107, 111, 131). Weight and height used to calculate body mass index (BMI) is recorded during many clinical encounters. Additionally, BMI data in EHRs have relatively low error rates; notably, errors in child BMI are generally <1% (119). Not surprisingly, few studies have focused on cancer (46, 62, 114, 121), given the availability of cancer registries worldwide. In the following sections, we provide specific examples of EHR research and their major areas of contribution to date.

Reevaluating Prior Findings

Researchers have employed large EHR data sets to reevaluate conclusions drawn from smaller studies. For example, many small studies reported positive or inconsistent associations between midlife BMI and later-life dementia. Qizilbash et al. (102) used longitudinal CPRD data on 2 million people and found that higher midlife BMI was associated with a decreased risk for dementia, which suggested that obesity could be protective for dementia or that weight loss may result from early dementia, both important areas for future research. In another study, Hibbard and colleagues (28) used Consortium on Safe Labor EHR data ($N = 233,844$ deliveries) to control for factors missing from prior birth outcome studies (e.g., maternal medical conditions). They found that late preterm birth compared with birth at term was associated with increased respiratory morbidity, but the association was smaller than reported in prior studies (28). Similarly, studies with small samples from fertility clinics had previously linked celiac disease to infertility. Dhalwani et al. (35) calculated incidence rates of infertility in >2 million UK women and found no evidence of such a connection.

Multiple Risks, Subgroup Differences, and Rare Outcomes

The large patient samples from EHRs enable researchers to evaluate multiple risk factors and/or outcomes simultaneously, to test associations in subpopulations, and to study rare outcomes.

For example, researchers in the Netherlands evaluated access to green space in relation to disease diagnoses with >10% prevalence. Using 12 months of EHR data on more than 300,000

patients from 195 general practitioners (74), this team found that green space was protective in 15 of 24 disease clusters, including musculoskeletal and neurological clusters with the strongest associations for anxiety and depression, especially among children and individuals of low SES.

In a subgroup analysis, Scherrer et al. (109) used seven years of VA EHR data and found that major depressive disorder and type 2 diabetes alone each increased the risk of myocardial infarction by about 30%. However, evidence of having both health problems increased risk by more than 80%, with important clinical implications. Rapsomaniki et al. (103) studied >1 million UK adults using CALIBER (CArdiovascular research using Linked Bespoke studies and Electronic Health Record) data to evaluate age category–specific risk of 12 acute and chronic cardiovascular diseases (CVDs) related to systolic and diastolic blood pressure. The study was able to provide an adequate sample size to evaluate important subgroups (e.g., those with low blood pressure or who were on blood pressure–lowering drugs) and found varying associations across subgroups between systolic and diastolic blood pressure and CVD end points (e.g., between systolic, but not diastolic, blood pressure and stable angina). Because the health data covered the majority of the UK population, these findings had excellent external validity (103) and were in contrast to prior studies that evaluated fewer CVDs (132) across narrower age and blood pressure ranges.

Rare disease research can also benefit from EHR data, which help alleviate methodological constraints. Thomas et al. (125) used four UK EHR databases to study chickenpox as a risk factor for stroke, a rare event in children. Using patients as their own controls, they observed a fourfold increase in risk of pediatric stroke in the first 0–6 months after chickenpox. This study identified avenues for future research on links between infections and vascular injury and their role in stroke.

Environmental and Social Epidemiology

EHR data sets have allowed environmental and social epidemiologists to leverage data on patients distributed across a wide range of physical, built, and social environments. Because patient addresses are routinely checked and updated at each encounter for billing and communication purposes, researchers can readily link geocoded addresses to location-specific data and use GIS to study an individual's proximity to hazards related to disease. This process can be used to study negative health impacts from both direct exposure, e.g., air pollution, and contextual exposure, e.g., residential zip code poverty rates.

Physical environment. EHR studies have evaluated exposures to risks and resources in the physical environment (e.g., air pollution, green space) and health outcomes (e.g., hypertension, diabetes, migraines) (72, 74, 78, 80, 88, 106). For example, in a novel study of exposure to acute air pollution, Männistö et al. (78) used EHR data on 151,276 deliveries from 19 hospitals across the United States from the Consortium on Safe Labor and found elevated odds of high blood pressure at delivery in normotensive women exposed to higher levels of 4 air pollutants in the 4 hours preceding hospitalization. Casey et al. (19) obtained data from the Geisinger EHR on more than 10,000 births to evaluate objectively recorded health risks associated with unconventional natural gas development. They identified significantly increased odds of preterm birth in women exposed to more unconventional natural gas development activity during their pregnancies.

Built environment. Studies of the built environment have focused on land use (e.g., street connectivity, population density, agriculture), food (e.g., density of fast-food restaurants, food deserts), and physical activity environments (e.g., access parks, diversity of physical activity establishments) (18, 19, 38, 71, 72, 107, 111, 118). Duncan et al. (38) found greater increases over time in BMI

CVD: cardiovascular disease

Geocode: the process of taking a patient address and assigning it to a spatial location with geographic coordinates

Machine learning:

algorithms used to predict outcomes based on features of the data; methods include support vector machines and regression trees

z-scores for 50,000 children and adolescents who were residing in less walkable neighborhoods versus those in more walkable neighborhoods, after controlling for age, sex, race/ethnicity, and neighborhood median household income. Casey et al. (18) reported that living near high-density, industrial livestock production or the crop fields to which manure was applied increased the risk for methicillin-resistant *Staphylococcus aureus*; this study provided the first evidence of agricultural risk for antibiotic-resistant infections in a general population sample.

Social environment. Social epidemiology's rich history of studying the influence of neighborhoods and communities on health (75, 123) has expanded through the use of EHR data. EHR-based studies have generally used an administratively defined surrogate for neighborhoods, such as census tracts, and then used census data to link community-level exposures to EHR data through geocoded patient addresses (21, 43, 92, 100, 107, 111, 126). For example, Nau et al. (92) used data on Geisinger Clinic children and adolescents ($N=163,473$) and found that community socioeconomic deprivation was associated with steeper BMI trajectories. Pujades et al. (100) used CALIBER data on nearly 2 million patients and confirmed prior associations between socioeconomic deprivation and myocardial infarction and CVD mortality, with new evidence of heterogeneity by age groups, CVD types, and sex. Most EHR social epidemiology has evaluated associations of community SES (e.g., median household income or education level) and health, but some have studied other exposures, including intimate partner violence (98, 104), sexual abuse (24), and community violence (116).

Predictive Modeling

The convergence of machine learning tools and big data methods is motivating development of predictive models that can readily use diverse, high-volume EHR data to guide decision making for individual patients (56). Researchers have used EHR data to assign Framingham Heart scores (45) and QScores (<http://www.qresearch.org/>), which predict the risk of outcomes such as cancer, diabetes, and stroke. Better cardiac prediction has been achieved by adding variables available in the EHR that were not included in the traditional prediction models (32, 63, 93, 133). Osborn et al. (93) developed an algorithm to predict CVD in patients with severe mental illness, and their model outperformed the Framingham model, which significantly overpredicted events in mentally ill men. Other algorithms have been developed to predict treatment failure among HIV-positive patients to better target interventions (101, 105). Most algorithms have utilized only EHR data; the addition of place-based predictors of patient health (i.e., social and environmental variables) could improve performance.

Research on Stigmatized Conditions

EHRs can be used to study stigmatized conditions, such as mental health outcomes or HIV, where patient recruitment and follow-up can sometimes pose challenges. For example, McCoy et al. (82) used EHR data to classify psychiatric inpatients using Research Domain Criteria Project criteria. Loadings on cognitive, arousal, negative valence, and social domains predicted the length of hospital stay and readmission, whereas ICD-9 codes did not, exemplifying the promise that information extracted from EHRs can improve diagnosis and predict health outcomes (55). In Rwanda, Betancourt et al. (10) used EHR data and information from community health workers to compare mental health outcomes in HIV-positive children, children living with HIV-positive parents, and HIV-unaffected children. They demonstrated that children living with HIV-positive parents require the same mental health services as do children who are themselves infected (10).

Natural Experiments

The widespread use of EHRs enables the rapid collection of data when natural experiments occur. Johnson & Beal (58) exploited the isolation of Altru Health System in North Dakota, where a comprehensive smoke-free ordinance went into effect. Using EHR data from the only acute care center in a 70-mile radius, the investigators found a significant decrease in the heart attack rate after the ban. In the Netherlands, Dirkzwager et al. (36) assessed health problems one year prior and two years after a fireworks disaster using data from family medical practices. In addition to finding poorer health overall postdisaster, they identified groups in need of priority postdisaster care: those with preexisting mental illness and those forced to relocate.

EPIDEMIOLOGIC PRINCIPLES: COMPARING TRADITIONAL AND EHR STUDIES

Compared with studies using primary data collection, EHR-based studies are considerably less expensive, require less time to complete, and involve substantially larger and more generalizable populations with fewer limitations to follow-up (Table 3). However, traditional studies offer more

Table 3 Comparison of traditional and EHR epidemiology studies^a

Study feature	Traditional study	EHR study
Original purpose of data collection	Research; requires primary data collection.	Clinical care; research relies on secondary data.
Cost	More expensive, primarily government-funded.	Less expensive; data collection is funded by health care system; research can be funded with a variety of sources or may not require funding at all.
Access	Open to all researchers at a minimal cost.	Central repositories in Europe are open to all researchers; access to US health care data is constrained.
Common study design	Prospective cohort, nested case-control, cross-sectional.	Retrospective or prospective cohort, nested case-control; cross-sectional less common because longitudinal data are available.
Time frame	Further follow-up restricted by funding; must wait for health outcomes to occur for prospective studies.	Retrospective data availability restricted by date of EHR implementation; additional years of data available at low cost.
Study population	Based on recruitment; may involve incentives or suffer from healthy volunteer effects; fewer participants than EHR.	Based on patient use of a specific health system, and the system's opt-in or opt-out participation; many more participants are available; can use EHR data to prescreen patients for eligibility; various population designs are available, e.g., primary care patients, specialty cohorts.
Data on family members	Sometimes available.	Not linked owing to confidentiality but possible to reconstruct relationships with EHR data; no restrictions on future capture in EHR as part of a research study.
Follow-up	Scheduled; continues as long as funding supports, often with standardized timing between visits.	Occurs during health care encounters; in general, will have more unique encounters, with variable timing between visits.

(Continued)

Table 3 (Continued)

Study feature	Traditional study	EHR study
Data collection and storage	Established protocol; generally robust approach to data collection; often with primary focus in one area of epidemiology with specialized measurements, e.g., exposure assessment, genetics; biosamples stored for future analysis.	Recorded during health care encounter with varying levels of detail based on provider practices; stored in clinical diagnoses, laboratory results, current medications and medication orders, problem list, and notes; biosamples rarely banked.
Conditions captured	Any outcomes and all severities as specified at the beginning of the study by investigators as long as ascertainment can be validly operationalized.	Only those outcomes requiring care by a physician; data missing on mild, self-resolving, or short-lived conditions.
Outcome ascertainment	Consistent outcome definitions, identified in the same way for each participant; investigators can specify in advance outcomes to study and how to measure.	Based on physician-specific clinical diagnosis, identified from a variety of locations in EHR, diagnosis enriched with other clinical information, e.g., laboratory tests, medications.
Clinical covariate ascertainment	Prespecified variables.	Entire health record, tests, and treatments are available, but not random, and perhaps confounded by disease severity and other factors.
Nonclinical covariate ascertainment	Prespecified variables.	Limited or missing data on social and behavioral domains; GIS-based variables can substitute for some missing data.
Environmental exposures	Can capture exposures based on specific strategies in study design; more expensive; more labor-intensive; better specificity.	Can measure surrogates using GIS-based strategies with varying levels of quality and relevance; relies on temporal and spatial variability of exposures of interest.
Community conditions e.g., social, built, and food environments	Measured with GIS, or sometimes by direct observation if a small number of communities are under study.	Assigned based on GIS, generally for a large number of participants in many communities spanning large geographies.
Internal validity	<p>Attrition: participants must return for study visits.</p> <p>Statistical regression: participants with extreme initial values will regress toward the mean on subsequent visits.</p> <p>Data collection: standardized across sites; participation in study and barrage of health tests may affect subsequent health.</p> <p>Nonparticipation bias: systematic error related to participation, related to attrition bias where participants with certain characteristics are more likely to drop out.</p>	<p>Attrition: participants will continue to contribute as long as they remain in the health care system and seek care.</p> <p>Statistical regression: possible, but ameliorated by large sample size.</p> <p>Data collection: outcomes may be measured or recorded differently by different health care providers.</p> <p>Nonparticipation bias: systematic error related to participation, related to the population with access to, or that chooses to seek, care.</p> <p>Recall bias: reduced by using longitudinal EHR data prior to events.</p>
External validity	Representative sample: participants must agree to join the study, participation rates are declining overall; past strategies to identify population-representative samples, e.g., random digit dialing, are becoming obsolete.	Representative sample: participants must be enrolled in the system and receiving care; documented care is more likely for more serious or troublesome conditions and less so for mild conditions; most HMORN members can identify subsets of their cared-for patients that represent the general population in their regions.

^aAbbreviations: EHR, electronic health record; GIS, geographic information systems; HMORN, Health Maintenance Organization Research Network.

comprehensive and precise protocols for data collection and better study population retention. Below, we consider the comparative strengths and weaknesses of the two approaches.

Study Population Selection

Investigators who directly recruit study participants encounter several limitations to obtaining truly representative samples. One limitation is that the interest of individuals and groups with salient characteristics in participating in research varies (42). Women, married individuals, those of higher SES, and those to whom the research topic is most relevant are more likely to enroll, whereas those with risk behaviors such as smoking, drinking, and drug use are less likely to do so (42). In combination with the declining participation rates in recent decades, this occurrence raises concerns about selection bias and external validity of traditional population health studies.

EHR studies also experience challenges with representativeness and missing data. On the one hand, that EHR studies can include in the analysis every person who receives care reduces selection bias. However, patients enrolled in a given health care system may differ in meaningful ways from the general population. To test representativeness, researchers can compare the age, sex, race/ethnicity, and other relevant characteristics of their patient population to census data in the matching region. Missing data may introduce bias into all studies. Since EHR data collection is less standardized, missing data may be especially problematic. For example, Qizilbash et al. (102) began with CPRD data on 6.1 million individuals, but were forced to exclude 48% of eligible participants because of missing BMI data.

Issues of generalizability pose less of a problem for regional environmental or social epidemiology than for general disease surveillance efforts. Increasing standardization and interoperability of EHR records should allow for pooling of data from multiple systems, thereby increasing representativeness and strengthening external validity. In addition, efforts to implement the use of structured templates in EHR may improve data completeness (20).

Study Population Attrition

Both traditional and EHR cohorts suffer from attrition, which can be problematic for longitudinal research. Traditional cohort studies experience attrition if people withdraw from the study or are lost owing to a move, although actively managed studies can reduce loss. For example, participation rates in the four follow-up exams in the Multi-Ethnic Study of Atherosclerosis (MESA) over an 11-year period following the initial assessment were 91%, 87%, 84%, and 68% (84); this pattern is representative of retention in large cohort studies.

Attrition in EHR studies arises primarily because of patient disenrollment. Study subjects may leave care for a variety of reasons. Some instances of disenrollment may be due to patient or disease characteristics, whereas others may reflect modifications to insurance coverage due to changes in employment, legislation, or regulations. If researchers use sequential cohorts, there may be changes in composition. If individual patients are followed, those who disenroll will be lost to follow-up. For example, a study of 20–39.9-year-olds enrolled in Kaiser Permanente from 2007 to 2009 found that 68% of active members from 2007 were retained at the end of 2009 (65). Retention increased with age; 76% of those 35–39.9 years old remained.

Recall Bias

Disease diagnosis may skew a patient's recall of prior events. This lack of reliable information may be especially problematic in controversial areas such as childhood vaccination and autism

Hawthorne effect: changes in reports or behaviors due to awareness of being studied

Social desirability bias: reporting behaviors and beliefs believed to be more acceptable or valued by others

onset. Because EHRs can specify timing and risk, they may reduce recall bias and other types of information bias. For example, two studies used longitudinal data from the CPRD to assess the measles, mumps, and rubella vaccine as a risk factor for future autism diagnosis (61, 117), which assured no recall bias in vaccination reports. An additional advantage to using EHR data for social and environmental research is a reduction in possible diagnostic and reporting biases. Outcome data are obtained from reports of physicians and patients who are unlikely to be aware of the exposure of interest. EHR data can similarly reduce Hawthorne effects and social desirability bias.

Time, Cost, and Size

Because they use existing data, EHR studies require less time and money to conduct and can involve more participants than studies that require primary data collection. We contrast these factors in three traditional studies of CVD risk factors compared with a cohort drawn from a health system's EHR.

The traditional studies are the Framingham Heart Study (FHS) ($n = 5,209$ adults aged 30–59 years from Framingham, Massachusetts, enrolled in 1948 and followed up since); the Atherosclerosis Risk in Communities (ARIC) ($n = 16,000$ adults 45–64 years in 4 communities, 4 follow-up visits, one every 3 years); and the Multi-Ethnic Study of Atherosclerosis (MESA) ($n = 6,800$ adults aged 45–84 years in 6 communities, 5 follow-up visits to date over 12-year period) (91).

The EHR data were constituted from a retrospective data pull from the Geisinger EHR for the years 2006–2013. With institutional review board approval, we selected 138,514 patients aged ≥ 45 years at baseline. The data contained 12/13 domains (no imaging files) highlighted in **Table 1**.

Cost. Compared with direct recruitment and follow-up in traditional studies, obtaining data from the EHR is much less expensive. For example, as of 2012, the FHS had received \$140 million, ARIC \$189 million, and MESA \$121 million in funding from the National Heart, Lung, and Blood Institute (NHLBI) (91). In contrast, using an extract, transform, and load algorithm on the Geisinger EHR data cost about \$50,000. The approximate average cost per participant in the EHR sample was \$0.11 for 8 years of data compared with \$17,750 and \$11,800 per participant for 12 years of MESA and ARIC data, respectively, and \$2,732 per participant for 67 years of FHS data (unadjusted for inflation).

Time. The strongest cohort studies are prospective and wait for outcomes to develop; the FHS began in 1948 but did not have its first important research finding until 1960 (41). EHR-based retrospective cohort studies can produce results within a year or two. Since its origin in 2011, researchers have used the CALIBER database, which combines the UK's nationwide CPRD data with CVD procedure registries (33) to evaluate risk factors for 12 different CVDs in 1.3–1.9 million patients (99, 100, 103, 113).

Traditional prospective studies must recontact participants and may face difficulties with maintaining study samples, which can impact the length and/or depth of follow-up. For example, recent budget cuts have forced the FHS to eliminate in-person exams. EHR data could provide a solution. The NHLBI and others have identified health information technology as a way to rework large cohort studies to decrease costs and increase enrollment (69, 79).

As noted earlier, it may be difficult to follow patients for long periods of time within a specific EHR. However, there is increasing emphasis on greater linkage and record sharing across systems.

In addition to allowing prior clinical information to follow patients to wherever they seek care, these advances will also enable greater tracking of individuals for research.

Variables Available for Analysis

Traditional epidemiologic studies obtain data designed to address a specific research question. In an EHR, the same information may not be universally available or collected in a standard way. For instance, the MESA study used a standard intake form to assess smoking status, whereas the capture of smoking status in EHRs can be sporadic and varied in quality and detail. Relevant data on smoking may appear in different parts of the record. The social history section may contain time-varying data on pack-years, and encounters may provide diagnostic codes (e.g., ICD-9 305.1, tobacco use disorder), cessation counseling referral, and medication orders (e.g., varenicline) relevant to documenting smoking status (18).

Traditional studies can collect information that is not routinely included in EHRs. For example, the MESA study gathered sleep, psychosocial, employment, physical activity, and dietary data and biospecimens for biobanking at many of the follow-up visits, and participants completed computed tomography scans, magnetic resonance imaging, and carotid intima-media thickness tests (11). Such data are available on only a subset of patients in the EHR when tests are completed for diagnostic or treatment purposes.

In addition, EHR research can study only conditions that are routinely captured. EHR data collection is particularly weak for mild or remitting conditions (e.g., mild asthma, early diabetes, and sprains/strains) for which many patients do not seek care.

Finally, primary data collection often includes data on family members. Owing to confidentiality concerns, family members' EHRs are not directly linked. However, matching algorithms based on names, dates, birth weight, or other information may be used to link, for example, mothers to neonates (76).

Access to Data and Issues of Privacy and Security

Regulations requiring data sharing for federally funded research studies give researchers free access to the data from large cohorts such as the FSA, ARIC, and MESA. Whereas any researcher can pay to use the United Kingdom's CPRD, THIN, and QResearch databases, access to US-based EHR data is more difficult. In the United States, health care systems, not patients, typically own the property rights to EHR data. Systems then must decide who can access the data, which they generally limit to system affiliates. If access is granted to researchers, they usually bear the costs of data extraction and transfer and must develop data use agreements. However, given that sample size does not contribute to costs associated with using EHR data, large EHR studies can still remain inexpensive compared with similar studies using primary data collection.

When access is granted to use EHRs, special attention is needed to assure ethical use of the information. Population health research that relies on protected health information (PHI) may risk violating individuals' privacy rights (90). EHRs can both accentuate and ameliorate such risks. One issue is the nature of consent. Rather than obtaining active consent, many health systems require patients to opt out if they do not want their EHR data used for research purposes. As a result, some patients may unknowingly contribute their personal health data to research. Although this method has generally not been a problem, it can be if the research aims conflict with patients' moral or other values (108). Opt-in participation models protect privacy but require more time and funding and can lead to selection bias (51). Recently, a dynamic consent model has been proposed where patients can monitor how their data is used and change their consent over time (60). A second issue is maintenance of patient-provider confidentiality. This factor is especially

PHI: data generated in the health context, which relates to health and can be used to identify individuals, for instance names and addresses

Patient portal: an online application where patients can access their health information and communicate with their provider electronically

relevant when researchers merge data from multiple health systems, and it requires that reliable deidentification and security methods are in place. Third, because providers record PHI in many different formats, it may persist in free text despite efforts at deidentification. Finally, although not unique to EHRs, electronic data storage may lend itself to new forms of data breach, including laptop loss or inadvertent emailing of data.

At the same time, digitally stored data also offer safeguards. EHR data can be encrypted and require role-based access and authentication. Additionally, extracting EHR data with computer algorithms results in less researcher exposure to PHI and fewer opportunities for privacy breaches than do manual chart reviews or traditional data collection (17). While many patients support the use of EHRs in research (73), it is incumbent on researchers, clinicians, and policy makers to balance the benefits of having representative and informative samples with protecting individual privacy and confidentiality.

CONCLUSIONS AND FUTURE DIRECTIONS

EHR-based epidemiology has already produced a large body of important research and will only grow as EHR use expands, costs fall, linkage to vital or other records increases, and accessibility improves. Furthermore, opportunities will increase as new technologies allow patient data capture without input from medical professionals. For example, patients can self-report data on a patient portal that links to their EHR. Portal use has been associated with better care adherence, improved patient-provider relationships, and improved patient autonomy and self-efficacy (94). Empowered patients not only should make more informed health decisions, but may more readily participate in research to the benefit of both clinical care and population health (34).

Other advances in combination with EHRs can enable researchers to understand complex diseases with multifactorial etiologies. These could include improved capture of social/behavioral (2), environmental, and genetic data (56); phenotyping (37); clinical biobanks; improved natural language processing; personal sensing via smartphone; and social media. Such advances may enable researchers to incorporate variables such as racial segregation, exercise, and social networks into their studies and extend and modify epidemiologic theory.

In addition to informing population health research, EHR epidemiology and social-behavioral studies can advance clinical care and new precision medicine efforts (26). Imagine a child who presents with shortness of breath, wheezing, and cough. Diagnosis and treatment could be individualized and optimized if the clinician were aware, through real-time geocoding, linkage to secondary data sources, and messaging through the EHR, that the patient lived near a major industrial park [which had been shown, via EHR research, to be linked to higher risks of asthma (5)] and that sulfur dioxide levels in the vicinity are elevated. More generally, EHR research can help to evolve the concept behind and implementation of precision medicine to include important predictors of individual variability that lie outside the body and include occupational, environmental, and social determinants of health (1). EHR research can move such work forward in what we hope will become innovative approaches to precision public health.

As population health research with EHR makes use of new technologies, the work will raise ethical and practical issues. Privacy agreements and security must keep pace with research to achieve the full promise of such research. Although EHRs are designed and used for clinical care, their research utility goes beyond the hospital walls. Stage 3 of HITECH recognizes this potential; a proposed objective requires meaningful use participants to share health data with public health agencies or clinical registries (34). EHR epidemiology can help bridge the divide between individual health and public health and reduce health care spending on individuals while leading to direct improvements in population health.

SUMMARY POINTS LIST

1. EHRs provide researchers with low-cost sources of rich longitudinal health data on large geographically, socioeconomically, and culturally diverse populations.
2. EHRs offer particular advantages for environmental and social epidemiology where patient addresses can be linked to individual and contextual exposures that vary spatially.
3. The use of EHRs for epidemiology requires consideration of unique issues related to study population definition, population attrition, disease/case definition, and privacy concerns.
4. Major areas of population health EHR research include reevaluating prior findings; capitalizing on large sample sizes to analyze subgroups and to study rare diseases or multiple diseases simultaneously; social and environmental epidemiology; research on stigmatized conditions; predictive modeling; and exploiting natural experiments.
5. Future developments in EHRs including increased use and sophistication, improved capture of social and behavioral determinants of health, better standardization to allow data merging across health systems, and linkage to vital records and to other emerging technologies (e.g., personal sensing) and data streams (e.g., air pollution data, clinical biobanks) will improve data quality and expand research opportunities to improve public health.

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