The emerging landscape of health research based on biobanks linked to electronic health records: Existing resources, statistical challenges, and potential opportunities

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Biobanks linked to electronic health records provide rich resources for health-related research. With improvements in administrative and informatics infrastructure, the availability and utility of data from biobanks have dramatically increased. In this paper, we first aim to characterize the current landscape of available biobanks and to describe specific biobanks, including their place of origin, size, and data types. The development and accessibility of large-scale biorepositories provide the opportunity to accelerate agnostic searches, expedite discoveries, and conduct hypothesis-generating studies of disease-treatment, disease-exposure, and disease-gene associations. Rather than designing and implementing a single study focused on a few targeted hypotheses, researchers can potentially use biobanks' existing resources to answer an expanded selection of exploratory questions as quickly as they can analyze them. However, there are many obvious and subtle challenges with the design and analysis of biobank-based studies. Our second aim is to discuss statistical issues related to biobank research such as study design, sampling strategy, phenotype identification, and missing data. We focus our discussion on biobanks that are linked to electronic health records. Some of the analytic issues are illustrated using data from the Michigan Genomics Initiative and UK Biobank, two biobanks with two different recruitment mechanisms. We summarize the current body of literature for addressing these challenges and discuss some standing open problems. This work complements and extends recent reviews about biobank-based research and serves as a resource catalog with analytical and practical guidance for statisticians, epidemiologists, and other medical researchers pursuing research using biobanks.

KEYWORDS

biobanks, electronic health records, Michigan Genomics Initiative, UK Biobank, selection bias

ABBREVIATIONS: EHR, electronic health record; eMERGE, Electronic Medical Records and Genomics Network; GREML, genomic relatedness-matrix restricted maximum likelihood; GWAS, genome-wide association study; ICD, International Classification of Diseases; KPRB, Kaiser Permanente Research Bank; MGI, Michigan Genomics Initiative; NIH, National Institutes of Health; MLMA, mixed linear model association analysis; NHGRI, National Human Genome Research Institute; PheWAS, phenome-wide association study; SNP, single nucleotide polymorphism; UKB, UK Biobank.

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1 | INTRODUCTION

Biobanks linked to detailed disease phenotype information such as electronic health records (EHR) provide rich data resources for health-related research. Biobanks, loosely defined, are biorepositories that accept, process, store and distribute biospecimen and/or associated data for use in research and clinical care.[1] The rise in the number and size of biobanks across the world in recent years can be explained by improvements in biospecimen analysis and the need for large and holistic datasets to address complex diseases and conditions.[1,2] Many types of biobanks exist, including commercial, single medical center, health system-based, and population-based biobanks. Some biobanks are disease- or organ-specific, while others encompass an extensive breadth of diseases.

Biospecimens are increasingly being linked with their donor's EHR. An individual's EHR contains basic demographic characteristics as well as data on symptoms, medical history, behavior and lifestyle factors, physical examinations, diagnoses, tests, procedures, treatments, medications, referrals, admissions, and discharges.[3] In addition to the structured data, there exist clinical notes, images, and other unstructured components of an EHR. An EHR is maintained by a health care provider primarily to plan and document care and to assess patient outcomes.[3] EHR are distinct from medical and pharmacy claims data, which are maintained by insurance companies. Pharmacy and claims data include billing codes assigned during visits, diagnoses, tests and procedures administered (but usually not test results) from any provider an insured individual interacts with along with prescription data, including dates of when prescriptions are filled or refilled. There are ongoing efforts to link claims data with EHR data to have both a "broad" as well as "deep" view of an individual's encounters with the health system. The possibility to link EHR with biospecimen, insurance and prescription claims, national disease registries, and death indices, creates the potential for generating an incredibly rich, longitudinal database for health researchers.

Access to such integrated data frames enables researchers to bypass expensive data collection and provide a quick, cost-effective option to explore associations related to diagnosis, patient-reported outcomes, prognosis, treatment response, and survival. While some of the questions answered using biobanks have been driven by *a priori* biological hypotheses, such biorepositories also allow for agnostic ("hypothesis-free") interrogations, new discoveries, and hypothesis-generating studies. Phenome-wide association studies (PheWAS), first introduced in Denny et al,[4] which explore the associations between a single genetic variant of interest and many EHR-derived phenotypes, are one example that highlights the power of phenotype-linked biobank data. PheWAS can be used to replicate known associations and has the potential to discover novel and previously unknown associations for further research.[4]

The growth and evolution of research around biobanks have led to thoughtful and accessible literature on the topic. Recent reviews briefly discuss statistical and computational considerations for studies involving genetic data,[5] limitations of traditional study designs, identifying real-world phenotypes,[6,7] and EHR enabled database linkages in making pharmacogenetic discoveries.[8] These reviews are limited in their discussion of statistical methods related to biobank and EHR-based research and, in particular, their exploration of critical concepts such as study design, sampling, missing data, and other analytic issues.

In this paper, we complement and extend recent reviews about biobank-based research with the ultimate goal of providing an extensive catalog of resources with analytical, conceptual and practical guidance to statisticians, epidemiologists, and other medical researchers pursuing biobank-based research. We will focus on EHR-linked biobanks, but many of the topics covered are relevant to other biobanks with detailed self-reported disease history information instead of medical records.[9] In Section 2, we characterize different types of biobanks and provide descriptions of specific biobanks, including their geographic location, size, data access and availability, data linkages, and more. In Section 3, we discuss general statistical issues related to EHR-linked biobank research, including study design, sampling strategy, phenotype identification, and missing data. We illustrate some of these issues using data from two biobanks: the Michigan Genomics Initiative (MGI)[10,11] and the UK Biobank (UKB).[12,13] In Section 4, we mention potential opportunities and promising future directions for expanded and principled biobank-based research through a discussion of novel and emerging uses of EHR data, the creation of improved analytic infrastructure, and the integration of EHR with external data sources.

2 | A CHARACTERIZATION OF MAJOR BIOBANKS

In this section, we describe the types of biobanks that are frequently discussed in the literature and provide detailed descriptions for several existing biobanks. An in-depth discussion of the literature search algorithm used to conduct this review is in Supporting Information Section **S1**. To get a sense of the existing landscape, Section S2 enumerates the common health outcomes receiving attention in the biobank literature. A table summarizing the differences in target populations, potential biases, EHR quality, and inferential goals between population-based and medical center/health care system-based biobanks can be found in Section S3. The rationale for providing this detailed Supporting Information is to create a comprehensive set of resources describing features of various biobanks for a researcher interested in pursuing new lines of inquiry using such data.

2.1 | Existing biobanks

Table 1 describes some notable major biobanks with detailed disease phenotype data in terms of their size, location, type, and data access. This table extends the biobank descriptions in Wolford et al to include additional information about data linkages and cohort characteristics, and it includes information for a broader set of biobanks.[5] Many of the biobanks listed in Table 1 provide access to data for outside researchers, while some offer linkages to additional data sources, such as death registries and detailed prescription information. The biobanks in Table 1 often fall into two general categories: population-based biobanks and medical/health care system-based biobanks. While we attempt to categorize biobanks that share important characteristics, there is substantial heterogeneity within each category. As with any data source, researchers should understand who the participants are, whom the data represents, how the data were collected, and how these factors impact the breadth, depth, quality, and quantity of data.

2.1.1 | Population-based biobanks

Population-based biobanks are large-scale biorepositories that aim to recruit subjects reasonably representative of the source population. Population-based biobanks recruit directly from the general population (eg, China Kadoorie Biobank), and subjects are eligible for enrollment irrespective of their disease status or healthcare utilization. Estonia,[14,15] Denmark,[16] Sweden,[17] Saudi Arabia,[18] China,[19] the Republic of Korea,[20,21] Qatar,[22,23] and Taiwan[24,25] are some of the countries that have invested in establishing population-based (or reasonably representative) biobanks. Their sampling strategy may include active recruitment for particular subpopulations; for example, BioBank Japan[26] recruits patients with particular current or past disease status, and the NIH *All of Us*[27] program's recruitment strategy targets underrepresented minorities.

Perhaps the most well-known population-based biobank is the UKB (used in illustrative examples in this paper).[12] With approximately 500 000 subjects, it is one of the largest biobanks in the world. All residents aged 40 to 69 who lived within 25 miles of one of their 22 assessment centers (∼9.2 million people) were invited to participate.[13] UKB takes advantage of the UK National Health Service to obtain follow-up data (eg, mortality, cancer registrations, hospital admissions, primary care data) and actively collect and verify conditions that are typically under-reported (eg, cognitive function, depression).[13] These data are linked with genetic, biomarker, and, for some, imaging data, all of which are accessible for research use.

2.1.2 | Health care system or medical center-based biobanks

Another class of biobank is based on a particular medical center or health care system. In general, health system-based biobanks, such as Vanderbilt's BioVU biobank or Geisinger Health's MyCode Community Health and DiscovEHR initiatives, contain EHR and genotype data while others, like Partners HealthCare Biobank, also collect supplemental survey data. Some, like the large Kaiser Permanente Research Bank (KPRB), have additional linkages with detailed prescription information and feature-specific subcohorts (eg, pregnancy and cancer cohorts in the case of KPRB). A notable health-system based biobank is the Million Veteran Program. With already more than 600 000 enrolled,

TABLE 1 Description of selected major biobanks

Biobank	Start year	Location	Age	Size	Type*	Institution	Access	Linked with prescriptions?	Linked to death registry?	Biospecimen collected	Survey	Website
All of Us	2018	USA	18+	1 million (goal)	Health system	National Institutes of Health	Not yet available	Yes**	—	Blood, saliva, urine	Yes	https://www.joinallofus.org/en
BioBank Japan	2003	Japan	—	200 000+	Population	Ministry of Education, Culture, Sports, Science and Technology	Inquire with biobank	—	Yes	Blood (buccal swabs or nail/hair trimmings)	Yes	http://www.ims.riken.jp/english/projects/pj02.php
BioME	—	Mount Sinai Health System	—	42 000+	Health system	Mount Sinai Health System	Inquire with biobank	—	—	Blood	Yes	https://icahn.mssm.edu/research/ipm/programs/biome-biobank
BioVU	2007	Tennessee	18+	250 000+	Health system	Vanderbilt University	Inquire with biobank	No	No	Blood	No	https://victr.vanderbilt.edu/pub/biovu/?sid=194
China Kadoorie Biobank	2004	China	30-79	510 000+	Population	University of Oxford + Chinese Academy of Medical Sciences	Application for researchers	—	Yes	Blood	Yes	http://www.ckbiobank.org/site/
deCODE Genetics	1996	Iceland	—	~500 000	Commercial	deCODE (Amgen)	Inquire with biobank	—	—	—	—	https://www.decode.com/
DiscovEHR	2014	Geisinger Health System; Regeneron Genetics Center	18+	50000	Health system	Regeneron Genetics Center + Geisinger Health System	Inquire with biobank	No	No	Blood	No	http://www.discovehrshare.com/
eMERGE Network	2007	NHGRI	All	126 000+	Network of biobanks	National Human Genome Research Institute	Application for researchers	No	No	Genetic results obtained from external sources	No	https://emerge.mc.vanderbilt.edu/
Generation Scotland	2006	Scotland	18-65	30 000+	Population	University of Edinburgh	Application for researchers	Yes	Yes	Blood, urine (saliva for some patients)	Yes	https://www.ed.ac.uk/generation-scotland

(Continues)

TABLE 1 (Continued)

Biobank	Start year	Location	Age	Size	Type*	Institution	Access	Linked with prescriptions?	Linked to death registry?	Biospecimen Collected	Survey	Website
Guangzhou Biobank Cohort Study	2003	Guangzhou	50+	~30 000	Population	Universities of Birmingham and Hong Kong + The Guangzhou Occupational Diseases Prevention and Treatment Center	Inquire with biobank	No	Yes	Blood	Yes	https://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/PHEB/Guangzhou/index.aspx
HUNT—Nord-Trøndelag Health Study	2002	Nord-Trøndelag County, Norway	20+	125 000	Population	Norwegian University of Science and Technology	Application for researchers	Yes	Yes	Blood (urine for some patients)	Yes	https://www.ntnu.edu/hunt/hunt-biobank
Kaiser Permanente Research Bank	2008	Kaiser Permanente	18+	308 425	Health system	Kaiser Permanente	Application for researchers	Yes	—	Blood, saliva	Yes	https://researchbank.kaiserpermanente.org/
Michigan Genomics Initiative	2012	Michigan	18+	60 000+	Health system	University of Michigan	Inquire with biobank	No	Yes**	Blood	Yes*	https://www.michigangenomics.org
Million Veterans Program	2011	USA	—	600 000+	Health system	US Dept. of Veterans Affairs	Inquire with biobank	—	—	Blood	Yes	https://www.research.va.gov/mvp/
MyCode Community Health Initiaitve (Geisinger)	2007	Geisinger Health System	7+	190 000+	Health System	Geisinger Health	Inquire with biobank	No	No	Blood or saliva	No	https://www.geisinger.org/mycode#cgg
Partners HealthCare Biobank	2010	Brigham and Women's Hospital; Massachusetts General	18+	80 000+	Health System	Partners Healthcare	Inquire with biobank	No	No	Blood	Yes	https://biobank.partners.org/

(Continues)

TABLE 1 (Continued)

Biobank	Start year	Location	Age	Size	Type*	Institution	Access	Linked with prescriptions?	Linked to death registry?	Biospecimen Collected	Survey	Website
UK Biobank	2006	United Kingdom	40-69	500 000	Population	UK Biobank charity	Application for researchers	—	—	Blood, urine, saliva	Yes	http://www.ukbiobank.ac.uk/about-biobank-uk/
CARTaGENE†	2009	Quebec	40-69	43 000	Population	CHU Sainte-Justine Research Center	Application for researchers	No	Yes	Blood, urine	Yes	https://www.cartagene.qc.ca/en/about
Genes for Good†	2015	USA	18+	77 700+	Self-initiated	University of Michigan	Inquire with biobank	No	No	Saliva	Yes	https://genesforgood.sph.umich.edu
Lifelines†	2006	Northern Netherlands	All	167 000+	Population	Lifelines Biobank	Application for researchers	No	No	Blood, urine	Yes	https://www.lifelines.nl/researcher
Trans-Omics for Precision Medicine (TopMed)†	2014	USA (various sites)	—	~145 000	Consortium of studies	University of Washington	NIH Database of Genotypes and Phenotypes (dbGaP)	No	No	Genetic results obtained from external sources	No	https://www.nhlbiwgs.org/

Note: The information in this table is ascertained to the best of our knowledge. Where it indicates "yes," this means we were able to find a source that indicates this is a feature of the biobank. Where it indicates "no," this means that it was either absent or there was sufficient reason to believe the resource is unavailable at the biobank. It is best to contact the biobank to confirm the availability of resources that are unknown or indicated as not available.

— Indicates information is unknown; *We chose categories we thought best fit each biobank; **Indicates we found a source saying the resource is being developed or will be available in the future; †Indicates it is not connected to EHR.

it is one of the world's largest genomic biobanks and also allows for the investigation of military-related diseases and conditions. Other such biobanks recruit patients from a distributed network of health centers throughout the country.

MGI (used in illustrative examples) is an academic medical center-based biobank that started at the University of Michigan in 2012. It recruits surgical patients over the age of 18 using opt-in consent (allowing recontact for future research purposes), collects and stores blood samples, genotypes DNA samples, collects brief survey data related to pain, and is linked to EHR. This biobank can connect patient data to other data sources, including the cancer registry, prescription data, insurance claims, and the national death index. A very appealing feature of MGI is the consent of patients for future recontact. The biobank is also undergoing an effort to implement an extensive epidemiologic questionnaire designed to be comparable to other biobank survey data, namely the UKB.

For medical center and health system-based biobanks, it is crucial to understand how the participants are recruited and what type of services the health center/system provides. Participants recruited as surgical patients in a specialized medical center will often have very different breadth and depth of data available compared to those recruited from a general clinic at an integrated health system that serves as the patient's primary provider and offers a wide array of preventive services.

2.1.3 | Other types of biobanks

Initially planning to become the first nationwide biobank, deCODE Genetics is now a privately-owned *commercial* biobank. Launched in 2007 and funded by the National Human Genome Research Institute (NHGRI), the Electronic Medical Records and Genomics (eMERGE) Network combines a *network* of DNA biorepositories linked with EHR as a resource for genetic analyses. *Disease-specific* biobanks are also common, and these biobanks may focus on rarer conditions. Two examples are PcBaSe Sweden,[28] a prostate cancer cohort, and the Mayo Clinic Biobank for bipolar disorder.[29] While disease-specific biobanks may be better powered than other biobank types to study certain diseases, they are typically smaller in size and do not allow us to examine the associations and disease pathways across the medical phenome.

Biobank is a broad term that includes biobanks that are not linked to EHR. Many biobanks obtain disease and phenotype status through other means (usually self-reported through surveys).[9] Many of the analytic challenges discussed in this paper also apply to these non-EHR-linked biobanks that contain disease status and other behavioral and genotype data. We restrict our attention to solely EHR-linked biobanks.

In this section, we introduced the concept of biobanks, described some key characteristics of different types of biobanks while providing detail on some major biobanks, and provided summary information regarding data access and availability (Table 1). These are critical considerations for downstream statistical analysis

3 | STATISTICAL ISSUES RELATED TO BIOBANK RESEARCH

In this section, we discuss statistical issues and strategies for EHR-linked biobank data analysis following a general workflow for a well-designed research study. In Figure 1, we provide a flowchart describing the steps researchers generally take while conducting a study. The development of the research question, clarification of study goals, selection of study sample, and definition of the target population are critical stages of this process. With vast amounts of data becoming increasingly available, there is a tendency for researchers to try a large number of analyses and broadly define their research question based on an analysis that shows something *interesting*. This strategy is at odds with good statistical practice. We make a distinction between this strategy and large-scale agnostic hypothesis-generating studies such as PheWAS, where the research goal itself is to generate hypotheses or potential associations for future study.

Given our research question and data availability, the next step is generally to identify potential sources of bias. In this section, we describe several particular concerns of confounding bias, selection bias, and misclassification of EHR-derived phenotype variables. We then describe challenges and strategies for study design and discuss methods for data analysis, including modeling, correction for multiple testing, and handling of missing data.

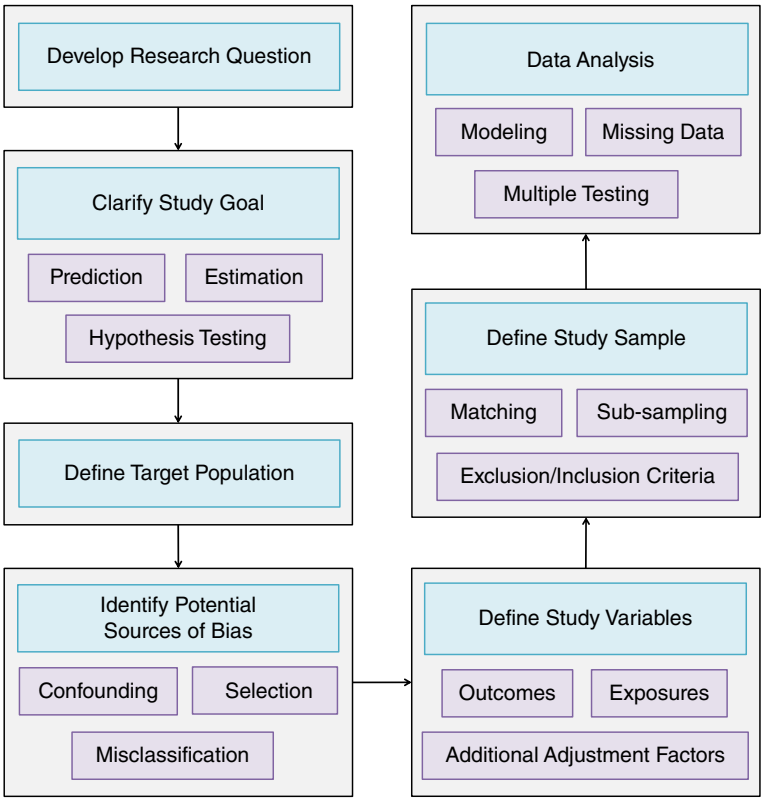

FIGURE 1 Flowchart of study planning, design, and analysis [Color figure can be viewed at wileyonlinelibrary.com]

3.1 | Potential sources of bias

3.1.1 | Selection bias due to nonprobability sampling

One challenge for research using EHR-linked biobank data is that the mechanism by which a patient from the population enters the biobank and when a visit appears in the EHR is often unknown and inherently patient-driven.[30,31] This phenomenon, called nonprobability sampling, has been studied extensively in the statistical literature, and certain mechanisms governing self-selected patient recruitment can introduce bias.[32] The extent to which the selection mechanism impacts study results depends on the estimand of interest and remains an open question.

The selection mechanism by which patient data are collected may vary widely across biobanks. Population-based biobanks are often large and obtain participants from a network of health or administrative centers across each country with the goal of being reasonably representative of the entire population. However, individual characteristics such as living near an assessment center (eg, UKB) or living in a specific region of interest (eg, China Kadoorie) may still impact inclusion. In contrast, medical center and health system-based biobanks attempt to recruit all patients meeting specific criteria within the center/health system, often through selected clinics. Generally, participation in these biobanks requires patients to use healthcare, which is indicative both of ability to access healthcare (eg, ability to overcome barriers to access including transportation and insurance) and health (ie, people with diseases and chronic conditions are more frequent users of healthcare). Compared to population-based biobanks, academic medical center-based biobanks tend to see more patients with rare or complicated diseases due to the availability of specialty care and, thus, are often useful for investigating rare conditions. For example, MGI[10,11] is enriched for analyses of some cancer types, most notably melanoma of the skin, since Michigan Medicine is known for its skin cancer treatment and care. In all cases, the data generating mechanisms have the potential to induce selection and participation biases into the analysis. These biases can have implications on the generalizability of the results and impact measures of association.[33] For guidelines and suggestions for diagnosing and handling nonprobability sampled data, we refer the reader to an American Association for Public Opinion Research task force report on nonprobability sampling.[34]

As a simple demonstration of the impact of different selection mechanisms, we consider prevalence rates for different disease phenotypes in two biobanks: MGI and UKB. As mentioned previously, MGI is a biobank of over 60 000 patients treated at an academic medical center. Patients in MGI were most commonly recruited through the

Anesthesiology department as patients were preparing to have a surgical procedure. The UKB is a population-based collection of over 500 000 patients. Table 2 provides comparisons of the patients in MGI and UKB in terms of demographics. Disease statuses were defined for MGI and UKB using aggregated versions of ICD codes, called PheWAS codes or phecodes.[35] This method of phenotype classification resulted in 1681 phecodes that are present in both MGI and UKB. A description of the phenotype generation process can be found in Section S5.

The different selection mechanisms in the various biobanks have implications for the observed disease prevalences across disease categories. Figure 2 shows the ratios of prevalences of various phenotype codes in MGI and UKB within different disease categories. We see that the majority of the prevalences are higher in MGI. In particular, prevalences for neoplasms, symptoms, endocrine/metabolic disorders, infectious diseases, and congenital anomalies are uniformly higher for MGI compared to UKB. Table 3 presents prevalences of some particular diseases in MGI and UKB along with published prevalences for their corresponding nationwide populations. MGI often captures subjects with many conditions at a higher rate than is observed in the general US population. The UKB has higher case counts than MGI for several conditions due to its size. The UKB is also often more representative of the rates observed in the population (at least for conditions common among ages 40 to 69, the age range of participants in UKB), with exceptions discussed in Section S6.

3.1.2 | Confounding bias

Measured and unmeasured confounding are common sources of bias in observational data. Careful use of existing analytical tools can help reduce or eliminate biases resulting from confounding. Here, we define a confounder as a variable

TABLE 2 Comparison of MGI and UKB patient populations

	MGI (academic medical center)	UKB (population-based)
Sample Size, n	30 702	408 961
Females, n (%)	16 297 (53.1)	221 052 (54.1)
Mean age, years (SD)	54.2 (15.9)	57.7 (8.1)
Median number of visits per participant	27	n/a[a]
Median days between first and last visit	1469	n/a[a]
Mean body mass index (SD)	29.7 (7.0)	27.4 (4.8)
Ever smoked, n (%)	17 044 (55.5)	246 320 (60.2)

[a]Data unavailable for UKB.

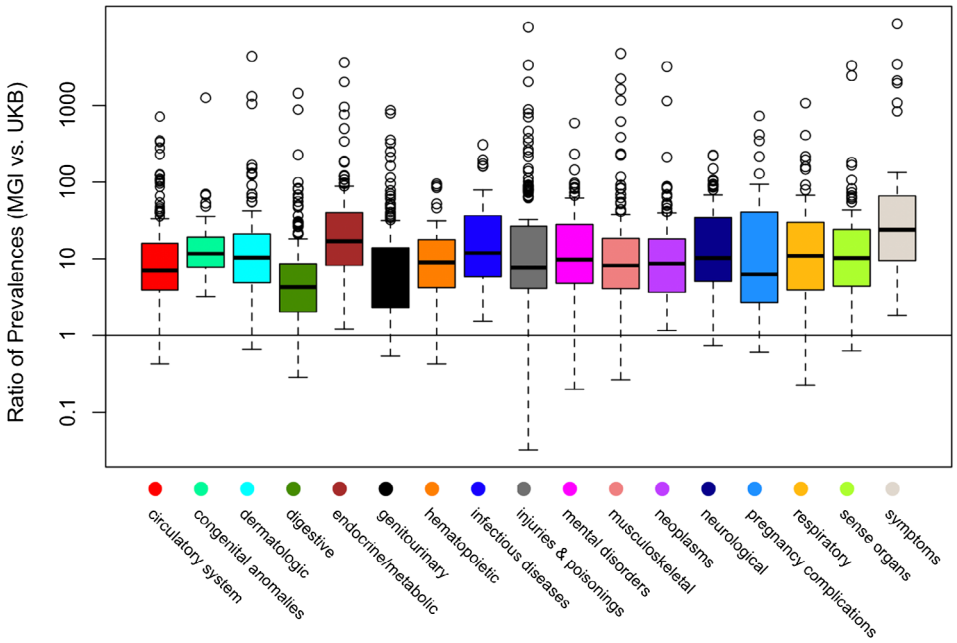

FIGURE 2 Boxplots of ratio of PheWAS code prevalences in MGI VS UK Biobank across phenome [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Prevalences of selected conditions in the Michigan Genomics Initiative and UK Biobank along with estimates from their respective national populations[a]

	MGI (academic medical center)	United States	UKB (population-based)	United Kingdom
	N = 30 702		N = 408 961	
Psychiatric/neurologic				
Depression	21.7 (6651)	16.9**	2.9 (11 918)	3.3†
Alzheimer's	0.2 (60)	1.6***	0.1 (433)	1.3‡
Anxiety*	22.1 (6782)	31.2****	1.6 (6945)	5.9†
Schizophrenia	0.3 (78)	.7-1.5	0.1 (573)	0.2-0.59§
Bipolar Disorder	2.9 (886)	4.4****	0.2 (1064)	2.0†
Cardiovascular disease				
Atrial fibrillation	9.5 (2919)	2-9	3.6 (14 839)	1.2-1.3
Coronary heart disease	14.3 (4396)	6	5.0 (20 539)	3-4
Myocardial infarction	5.5 (1702)	4.7**	3.0 (12 099)	.87-2.46
Obesity	33.7 (10 351)	39.8	2.6 (10 820)	26.2
Diabetes	21.4 (6571)	12.6	5.0 (20 260)	6.2
Cancer				
Colorectal	2.6 (806)	4.2****	1.1 (4627)	5.3-7.1****
Breast (female)	12.4 (2025)	12.4****	5.7 (12 680)	12.5****
Lung	2.3 (707)	6.2****	0.5 (2243)	5.9-7.7****
Pancreatic	1.0 (313)	1.6****	0.2 (749)	1.4****
Melanoma of skin	6.2 (1896)	2.3****	0.7 (2724)	1.9 ****
Prostate (male)	12.4 (1794)	11.2****	3.6 (6762)	12.5****
Bladder	3.7 (1147)	2.3****	0.6 (2433)	0.9-2.6****
Non-Hodgkins lymphoma	3.1 (937)	2.1****	0.4 (1827)	1.7-2.1****

Notes: Ranges for schizophrenia represent the minimum and maximum point estimates from several estimates included in the source material; ranges for myocardial infarction and cancer estimates provided indicate the range of sex-specific point estimates; lack of representativeness in UKB for obesity phenotype discussed in Section S6.

*Any anxiety disorder; **adults 40 and older; ***adults 65 and older; ****lifetime risk of developing disease/condition; †past week prevalence, refers to the presence of symptoms in the past week; ‡point prevalence, refers to the prevalence measured at a particular point in time (proportion of persons with a particular disease at a point in time); §estimate is from England.

Sources for US and UK estimates can be found in Table S4.

[a]Phenotypes were defined using ICD-based PheWAS codes[35] for MGI and UKB. A description of the phenotype definitions can be found in Section S5.

that impacts both our outcome and our predictor(s). Failure to adjust for the confounder may result in biased inference regarding the association between the predictor and the outcome. Confounding is of particular concern for EHR data as some well-established measures routinely collected in population-based studies may not be available. In the EHR setting, confounders of interest (eg, comorbidities) may also often be crudely measured, incomplete, or not measured at all. On the other hand, many potential confounders may be extracted from an EHR database, and variable selection to identify important confounders or adjusting for a high dimensional confounder set in the analysis model are issues specific to EHR studies.[36,37]

There are many analytical strategies in the statistical literature for dealing with confounding. Popular methods for general observation studies include adjusting for or stratifying analyses by confounders,[38] selection propensity weighting, and adjustment and matching on known confounders. Because of the large sample sizes, matching or stratification with respect to levels of confounders still may entail adequate power for a specific hypothesis, leading to new design issues to consider in such studies. Techniques in causal inference such as instrumental variable analysis can also be used to address issues of confounding in EHR.[39,40] Recently, researchers have used particular genetic variants as instrumental variables in analyses relating variables such as hormone levels to phenotypes of interest.[41] Mendelian randomization analysis is

then used to explore potential causal relationships.[42] Marginal structural models can be used to address confounding by time-dependent variables and has recently been applied to EHR in Sperrin et al.[43,44] Techniques for reducing and eliminating confounding often assume that the potential confounders are measured. When key confounders are not measured, sensitivity analyses and related statistical methods can be used to explore the impact of and to correct for potential unmeasured confounding.[45-48]

3.1.3 | Defining the phenome

A central challenge for research involving EHRs is in defining phenotypes. The data available falls into two broad categories: structured and unstructured. Some examples of structured data are billing and procedure codes, numeric lab and test results, and prescription information. Some examples of unstructured data are narrative notes made by physicians/nurses, radiological/pathological notes, and images.

ICD9 and ICD10 diagnosis codes are the most common source for defining phenomes. They are universally defined, which make them appealing (although there may be differential usage across institutions).[49] Incorporating other structured data, such as continuous lab values, is more challenging and may require pre-processing. The development and use of automated algorithms for making these data useful for phenotyping are essential.[50] Additional expert input (eg, through a consortium) can be used to create phenotype definitions, however, establishing a well-accepted definition requires time, careful thought, and discussion. The eMERGE Phenotype Knowledgebase[51] (PheKB) details existing phenotyping algorithms for individual phenotypes that incorporate additional patient information. Due to the complexity of these phenotyping algorithms, the simpler ICD-based phenotyping method is common for PheWAS studies, but the incorporation of these external phenotyping resources may help improve phenotype definitions in the future.

Unstructured data have also been used to define phenotypes, particularly for diseases with unreliable ICD9 classifications such as some psychiatric diseases, using natural language processing methods.[52-60] Such methods can also be used to obtain patient measures such as smoking status.[52] Natural language processing methods mine free text such as narrative doctor's notes for words or phrases to develop a model combining structured and unstructured data to classify each patient as having or not having the phenotype of interest.[52,53] Some challenges include dealing with misspellings, tenses, alternative phrasing, negation, and defining a trained dictionary of words and phrases that may correspond to a particular phenotype. Algorithms are usually trained using expert annotations, but new methods have attempted to automate this step as well.[58,59] Additional machine learning methods have also been used to define phenotypes (eg, imaging analytics from medical imaging datasets) using a broad spectrum of patient information.[61-63]

Recent works propose phenotyping strategies to overcome hurdles using multiple data sources to more accurately ascertain disease status.[64-72] However, future work is needed to provide statistical methods for incorporating data of different types for phenome generation. For a detailed review of phenotyping procedures, see Bush et al.[7] Figure S8 provides some examples of the types of structured and unstructured EHR information that can be used to construct phenotypes.

3.1.4 | Misclassification and information bias

While we have discussed methods for the *assignment* of phenotype status, there exist many nuanced challenges to consider when before analyzing these data. Disease status determination is usually performed across subjects who have different lengths of follow-up time, who have different numbers of visits, and who are being seen in different types of medical clinics. The EHR cannot capture future diagnoses, and information on past medical history and treatment by external providers may be incomplete. Generally, the observation process can be complicated and may be related to patient- and provider-specific information such as gender and underlying disease status (Figures S3-S5).[73,74] Misclassification of the disease status may depend on this observation process, where subjects followed for a longer period of time or more often may be more likely to have their disease recorded in the medical record. Some statistical tools have been developed to try to deal with outcome misclassification and related issues, but computational restrictions may make these methods difficult to apply to large-scale biobank data.[57,75] In addition, symptoms occurring between visits may not always be reported, and the use of diagnostic guidelines and assessment of the phenotype may vary from doctor to doctor.[76,77] These underlying patient- and provider-specific properties are often ignored when classifying subjects as cases and controls for a particular disease.

ICD-based phenotype misclassification is common for psychiatric disorders, where a diagnosis can be particularly challenging.[55,76] For diseases with burdensome treatments such as cancer, we may expect that all subjects receiving a cancer diagnosis truly do have cancer, and there may be only a few cancer cases without a corresponding ICD code. In contrast, ICD codes for psychiatric disorders such as anxiety may be sometimes attributed to some subjects that do not meet the ICD definitions for the disorder. There may also be a tendency for patients to receive ICD classifications that result in reimbursement from the insurance provider. Additionally, disease ICD codes are sometimes assigned when a disease is suspected prior to further diagnostic testing, so it may be unclear whether a given ICD code refers to the final diagnosis.[7,78]

Figure 3 provides a visualization of the relationship between phecode-based diagnosis and the length of follow-up in MGI within age strata for anxiety and heart attack. We observe a greater rate of anxiety diagnoses among subjects followed for a longer period of time. Many factors may contribute to this, but one explanation is that more anxiety diagnoses are missed in subjects followed for a shorter period of time. In contrast, the proportion of subjects with a heart attack phecode was not appreciably related to the length of follow-up, and these acute events are captured when they happen.

Phenotype misclassification can result in bias ("information bias") and negatively impact the statistical power to detect associations. Differential misclassification of disease status can also result in inflated type I error.[79] The extent of misclassification can be described using quantities such as sensitivity, specificity, and negative and positive predictive values (provided a gold standard exists for comparison). Researchers have explored methods for incorporating external information about sensitivity/specificity to account for outcome misclassification.[80-82] However, these quantities can vary from population to population and from phenotype to phenotype, and it is difficult to know the extent of phenotype misclassification in a particular population without performing further phenotype validation.[82,83] Among other examples,[57,82,84-86] Beesley et al proposed a sensitivity analysis approach for exploring the potential impact of phenotype misclassification and disease-dependent patient selection on logistic regression effect estimates simultaneously.[33]

We demonstrate the potential bias induced by phenotype misclassification and disease-dependent patient selection using data from MGI in Figure 4. We consider a logistic regression model for whether the patient was diagnosed with cancer and the association of having cancer with gender. On the entire sample, we estimate the gender odds ratio as 0.89 (95% CI: 0.85, 0.93). We suppose the observed cancer diagnosis status is the truth and artificially induce misclassification and disease-dependent selection of the MGI patients. We then calculate the corresponding association between gender and the misclassified outcome in the selected patients. We impose misclassification under 90% specificity and ∼70% sensitivity, and subsampling was imposed under an average 50% sampling rate for the entire cohort. If we compare the three analyses without any outcome misclassification, we see that subsampling dependent only on disease status does not induce bias in the association estimate (OR 0.89, 95% CI: 0.82, 0.94), but it does result in a less efficient estimate due to the smaller sample size. However, we do see bias when subsampling depends on *both* disease status and gender (OR 1.01, 95% CI: 0.95, 1.08). This provides a demonstration of biases expected under different sampling mechanisms.

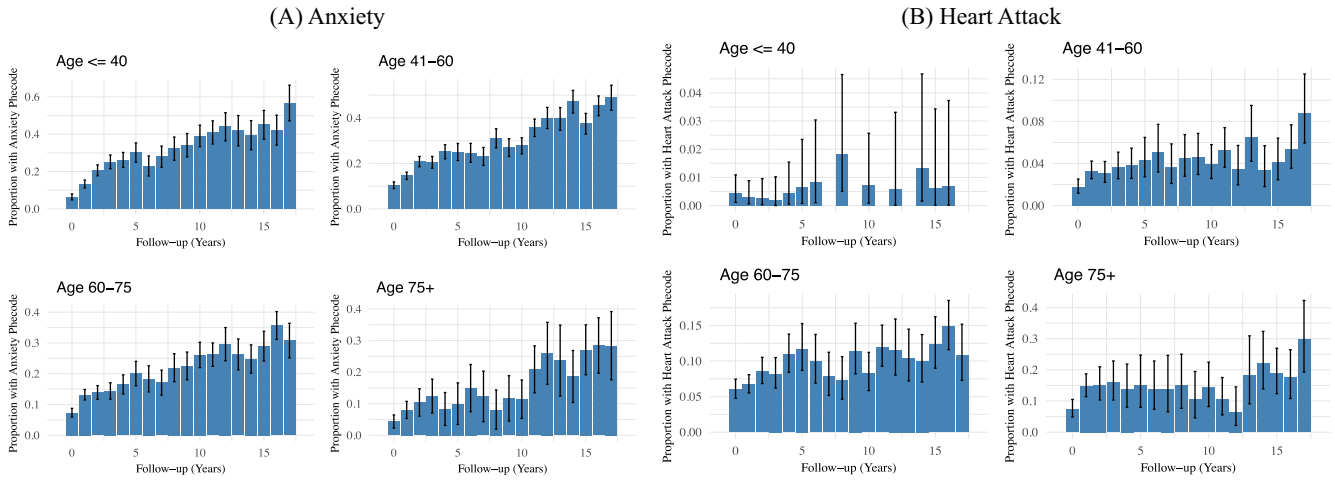

FIGURE 3 Relationship between (A) anxiety or (B) heart attack diagnosis and length of follow-up within age strata in MGI. Plotted intervals indicate 95% confidence intervals for each proportion [Color figure can be viewed at wileyonlinelibrary.com]

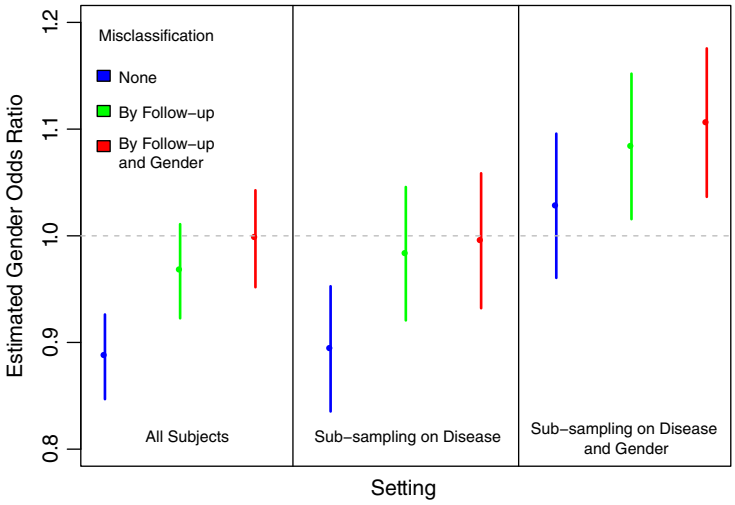

FIGURE 4 Impact of selection mechanism and phenotype misclassification on estimated association between gender and cancer diagnosis in MGI. 95% confidence intervals are plotted[Color figure can be viewed at wileyonlinelibrary.com]

Additionally, when we compare the odds ratio estimates for a particular subsampling setting, we see that outcome misclassification is associated with bias in all settings, and this bias is not always towards the null.

3.2 | Study design

3.2.1 | Defining the study sample

A vital issue to consider when performing a biobank-based investigation is study design. Design choices can have implications for the analysis and interpretation of the study results. In this section, we describe several approaches for study design used in biobank research and describe some design-based strategies for dealing with common sources of bias.

Within pre-existing biobanks, researchers seek to sample patients for inclusion in a particular study. A common study design involves phenotype-specific case-control sampling, where all observed cases for a particular phenotype are selected and some subset of (possibly matched) controls for that phenotype are sampled from the biobank.[10,87] Cases are often defined as subjects receiving a particular diagnosis code a prespecified number of times, for example, twice. An advantage of case-control sampling is that it does not require additional longitudinal information and instead relies on dichotomized phenotypes, but it is heavily dependent on the "case" and "control" definitions. One crucial aspect of case-control sampled data is the validity of secondary analyses of related outcomes, and many methods exist for addressing this issue.[88-91] In addition, the choice of controls should be considered carefully. Controls might be defined as all patients without the primary phenotype, or we may exclude patients with related diseases from being included as controls. Another common practice is to restrict the analysis to patients with a certain amount of follow-up, which can bias sampling toward sicker patients.[92] In the presence of many competing control definitions, one strategy is to evaluate internal validity by performing inference using many different control group definitions to "bracket" the association of interest.[93,94] Another common study design is cohort sampling, where all biobank patients with available data meeting the inclusion criteria are included in the analysis.[38,95]

Self-controlled designs in which each patient serves as his/her own control are emerging as an appealing design paradigm for some scientific problems.[96,97] Two variations of self-controlled designs are the self-controlled case series design and the case-crossover design. Recently, Schuemie et al developed an adapted self-controlled case series design that uses the notion of accumulated exposure to study long-term drug effects.[98] A detailed comparison of the self-controlled case series and case cross-over designs can be found in MacClure et al,[99] and additional exploration of self-controlled case series can be found in Petersen et al[100] and Simpson et al.[101] An advantage of this design is that it controls for confounding due to time-invariant variables. Unlike cohort and case-control designs, however, this method requires longitudinal data to be available for all patients, which may be missing, incomplete, or insufficient in some EHR-linked databases.

Due to finite resources, some biobanks may collect data, for example, genotype data, on a subset of their cohort. The strategy of collecting data on a subset of patients enriched for certain characteristics and related issues are explored in detail in Sun et al[102] and Schildcrout et al.[103,104] Two-phase designs also result in missing data by design, where more expensive assays or time-consuming surveys may be administered to a subset of the patients determined based on results from the first phase. Exposure-dependent (eg, when we have rare exposures of interest) and other stratified trait-dependent sampling designs can also be used. For example, extreme phenotype sampling designs collect additional data only for patients with extreme values of a continuous variable.[105,106]

Another critical concept to consider when defining the study sample is the independence between patients. Longitudinal outcomes are expected to be correlated *within* patients, and outcomes may be correlated *between* patients due to relatedness, nesting within doctor or clinic, belonging to a common social network, or other reasons. The software KING (Kinship-based Inference for GWAS) uses genotype data to determine pairwise kinship between patients.[107] We might then define the study sample restricted to unrelated patients and apply methods that rely on independence between patients (eg, Firth-corrected logistic regression in Fritsche et al[10]). Statistical modeling approaches such as mixed modeling (eg, SAIGE) can also be used to account for residual correlations between individuals.[108]

Many variations and alternative strategies for designing the study sample exist in the statistical literature and can also be applied in the EHR setting. For a review of many general study design strategies, see *Modern Epidemiology: study design and data analysis*.[109,110]

3.2.2 | Considerations related to study design

Madigan et al compares effect estimates resulting from several study designs in a particular setting and demonstrates that the choice of study design can have substantial impacts on effect estimates.[111] These study design choices also impact the statistical power and generalizability of the results. Therefore, the study design should be considered carefully. In addition to impacting power, the method by which the patients are included in the study sample may result in biased inference (with respect to the target population), called sampling bias. Haneuse et al provide a general framework for exploring and dealing with design-based sampling bias for EHR analyses.[112] Haneuse et al focus on characterizing the mechanism by which patients were included in the dataset by breaking it into smaller observation mechanisms, which may be impacted by different factors. Possible sources of sampling bias arising from each mechanism can be explored in detail in a sensitivity analysis framework.

There is a belief in the literature that GWAS/PheWAS study results may be less susceptible to bias resulting from the patient sampling mechanism, since the opt-in consent is not likely to depend on the value of a single genetic marker. However, bias due to genotype relationships with the sampling mechanism can still arise in certain settings.[33,113,114] Additional work may help clarify settings in which bias is and is not expected in GWAS and PheWAS studies. In general, issues of sampling bias are not unique to EHR data, and many authors have explored the impact of sampling on inference. Some works exploring selection/observation biases in the EHR setting include Zheng et al, Phelan et al, Goldstein et al, and Rusanov et al.[30,31,92,115] However, additional characterizations of the mechanisms by which we can have sampling bias in biobank and EHR research may help guide study design in the future.

In terms of methods designed for large-scale EHR-based studies, Schuemie et al[116] and Schuemie et al[117] propose a *P*-value calibration method that may be able to account for both random and systematic (eg, confounding, sampling biases) sources of error using distributions of effect estimates believed to be null effects. Modern causal inference methods using the potential outcome/counterfactual framework are also being integrated in biobank analysis.[118-120]

3.3 | Data analysis and modeling

In performing statistical analysis, researchers may have a variety of goals, such as developing a prediction model, estimation (eg, finding candidate biomarkers, hypothesis-generating studies), causal inference, or hypothesis testing (eg, is drug A better than drug B). The analysis strategy and concerns will depend on the research goal and the data considered. In this section, we describe several common modeling challenges encountered in EHR-based data analysis, and we address specific issues, including multiple testing, handling of missing data, and comparison across different EHRs.

3.3.1 | Modeling

EHR data present many challenges concerning modeling and inference. For example, correlation structures between variables can be complicated, the number of adjustment factors can be large, and events of interest can be rare. In this section, we describe some popular and emergent modeling strategies.

A common goal of EHR-based analyses is to study the associations between specific phenotypes and variants at a particular gene region or across the genome, and this analysis is often performed using linear or logistic regression or using mixed linear model association (MLMA) analysis.[38,41,121-123] Firth-corrected logistic regression may prove useful for modeling rare binary outcomes or settings in which there is strong covariate separation, and its application to PheWAS is demonstrated in Fritsche et al.[124] Recently, Dey et al proposed a fast alternative to Firth-penalized regression to stabilize estimation for PheWAS studies using saddle-point approximation (SPA) that is useful for handling extremely unbalanced case-control data.[125] These methods can be applied in many other modeling settings as well. A saddle-point approximation approach for estimating mixed models (called SAIGE) was proposed for handling highly unbalanced case-control data with additional sample relatedness, which is typical for biobank data.[108] Another common target for these studies is to identify the proportion of variation in a particular phenotype that can be attributed to genetic variation, called heritability. Some popular statistical methods include polygenic profile scoring, univariate linkage disequilibrium regression, and genomic relatedness-matrix restricted maximum likelihood (GREML).[38,126-130]

A popular strategy for studying the *aggregate* association between genetic information and disease development is through polygenic risk scores (PRS). PRS involve summing the contributions of a potentially large number of genetic loci and can be used to stratify patients with respect to disease risk.[131] Many strategies exist for determining the genetic loci to include in the PRS and their relative contributions. Many PRS construction strategies and software packages exist, and we will not detail these various methods here.[124,132-143] For a recent exploration of PRS construction, we refer the reader to Choi et al.[144] Recently, statistical methods have been developed to leverage published GWAS and other omics summary statistics to improve the performance of prediction algorithms and perform analyses adjusting for many genetic loci simultaneously.[145-149]

Researchers may also be interested in studying relationships *between* phenotypes or joint relationships between phenotypes and other patient-level factors such as treatments or genotypes. Existing statistical methods for dealing with correlated outcomes such as mixed modeling and generalized estimating equations (when the model coefficients are of primary interest) can often be applied. Shaddox et al and Xue et al propose strategies for modeling correlated rare outcomes.[150,151] Recently, Bastarache et al developed a phenotype risk score-based method to study rare genetic variants associated with Mendelian diseases.[152] More generally, phenotype-based risk scores could be used to describe the combined association between secondary phenotypes and the primary phenotype and may prove useful for risk stratification in combination with PRS. However, construction of phenotype-based risk scores would involve modeling the relationship between many phenotypes, either pairwise or jointly, and this modeling would be complicated by phenotype misclassification. Additional statistical development is needed to handle many correlated, misclassified binary phenotypes.

In probabilistic phenotyping models, risk prediction models, and other modeling using EHR data, we are often interested in incorporating a broad spectrum of patient information. Variable selection and penalization methods along with sparse estimation strategies allow many predictors to be incorporated into statistical models, and there is an excellent opportunity for the use of such methods in the setting of EHR. Automated feature selection algorithms are often used within machine learning algorithms to determine which predictors to include, and this can also be combined with expert preprocessing of the candidate predictors.[153,154] Regularization techniques, including LASSO, ridge regression, and elastic net, have been applied in the EHR setting.[155,156]

Machine learning algorithms have also gained popularity in EHR data analysis, particularly in the development of risk prediction models. Traditional machine learning methods such as support vector machines and random forests with boosting are often used.[157,158] Deep learning, neural networks, and ensemble methods have emerged as attractive approaches to prediction using EHR data.[158-161] For a review of deep learning methods for EHR data, see Schickel et al.[158] Care must be taken when applying these machine learning techniques in the setting of rare outcomes, and additional model calibration may be needed. A disadvantage of machine learning algorithms is the difficulty in estimating prediction uncertainty. Some work has been done exploring uncertainty estimation in particular settings, but additional work is needed.[162] Machine learning algorithms can have excellent performance for prediction in some settings. When the goal of the analysis is to develop a prediction model for making predictions for new patients in the same EHR, challenges such as sampling bias and confounding, may be of less concern. However, the resulting model may be susceptible to

overfitting and may not always have good properties in terms of transportability to other EHRs and generalizability to other populations.

While we may conceive of many elegant modeling strategies for dealing with statistical issues for EHR data, these methods may not always scale well with respect to large samples, large numbers of variables, or a large number of repeated analyses (eg, in a PheWAS or GWAS). Computational feasibility will be an important factor to consider for applying statistical tools at scale. While computational efficiency strategies are outside the scope of this paper, we refer the reader to Thompson and Charnigo and Prive et al. for more information on phenome-wide computing for GWAS.[163-165]

3.3.2 | Missing data

Missing data is a common issue for biobank analyses, and data may be missing for a variety of reasons. A common source of missingness in GWAS/PheWAS studies is missingness in the genotypes. This can be handled by first excluding patients with missingness rates above a particular threshold (say, 2%) and then imputing missing values for patients with lower missingness rates.[38,128] Genotype imputation has improved over time due to larger and more diverse reference panels. While many of these biobank analyses reported their treatment of missing genotype data, missing information in the phenotype information or demographics is rarely discussed. Additionally, many studies define their analytical sample based on some subset of biobank participants, and it is sometimes unclear how these participants were chosen. A more transparent description of how the study sample was derived and the treatment of missing data may shed some light on the generalizability of study results.

Statistical methods for dealing with missing data in the EHR often rely on multiple imputation, a statistical approach in which the missing data is "filled in" using information from patients with observed values.[166-169] Such approaches can prove extremely valuable to EHR-based research, but implicit assumptions about the missingness mechanisms should be carefully considered. A common assumption behind many statistical methods for dealing with missing data is that data are missing at random, meaning that missingness depends only on fully observed information.[170] However, missingness in EHR data may often be related to a patient's underlying health state and other unmeasured individual or facility characteristics.[171] For example, healthier patients may be more likely to drop out of the EHR. Additionally, lab tests are only ordered for patients with suspected disease. This setting, called missing not at random, is more challenging to address in the statistical analysis. For a discussion of dealing with missing not at random data, see Little and Rubin.[170] In general, we cannot tell from the data what mechanisms generate the missingness, but additional data and subject matter experts can provide insight into the drivers of missingness. For example, Haneuse describes a survey-based strategy to explore the reasons for missingness in EHR data, which may help shed light on the validity of missingness assumptions.[172] McCullough and Neuhaus proposes a strategy for exploring outcome dependence in the mechanism by which patients visit the clinic.[171]

A common type of "missing" data is the true phenotype state of each patient. We can view the sampling mechanism that gave rise to our study population and the mechanism behind phenotype misclassifications (which we might call the observation mechanism) in a missing data framework, as discussed in Section S7 and Beesley et al.[33] Further work should be done to explore the impact of different sampling and phenotyping mechanisms on statistical inference.

3.3.3 | Multiple testing of hypotheses

GWAS/PheWAS studies and many other types of EHR-based research often involve the simultaneous testing of many hypotheses. Failure to account for multiple testing can result in inflated type I error. Some methods for controlling the type I error include Bonferroni adjustment, false discovery rate-controlling thresholds,[41,173] and Benjamini-Hochberg thresholds.[84] However, many of these methods (in particular, the simple Bonferroni adjustment) are overly conservative when the many statistical tests are not independent. This is often the case in large-scale GWAS/PheWAS studies, where associations are explored for many related characteristics. In this setting, the goal may be to control for the effective number of independent tests rather than the number of correlated tests being performed. Such an approach may improve statistical power to detect significant associations while still controlling the type I error rate.

Several methods have been proposed to estimate the effective number of tests[174] or control for correlated tests. Good describes resampling-based testing via permutation or bootstrap to correct the *P*-values for multiple testing.[175] Gao et al. propose the simple *M* method to estimate the effective number of tests, which uses a combination of principal components

analysis and Bonferroni correction.[176] For a PheWAS study presented in Ge et al, the effective number of tests is estimated using principal components analysis of a matrix of pairwise correlations between pairs of phenotypes.[129]

Similarly, heuristic approaches have been suggested to identify a maximal independent set of uncorrelated phenotypes among pairwise correlations between pairs of phenotypes.[10,177] A popular method for identifying phenotypes is to aggregate ICD codes into a set of phenotype codes called "phecodes." For example, using 1578 phecodes in MGI, we identified a maximal set of 981 phenotypes with no pairwise Pearson correlation above 0.1. However, no general guidelines exist for multiple testing correction in the PheWAS setting. Alternative methods adjust for multiple testing using multivariate normal assumptions for the correlated test statistics.[178-180] In the context of correlated SNPs, some methods correct for multiple testing via analysis of the underlying linkage disequilibrium structure of the genetic data.[181] Johnson et al, Zhang et al, and Li et al provide some simulations comparing the performance of different methods.[174,182,183]

An emerging challenge is the correction of multiple testing across the medical phenome x genome two-dimensional landscape. With recent work regarding phenotype risk scores, there is increasing interest in studying phenotype-phenotype associations across the phenome.[184] As such, there is a need to develop a corresponding statistical methodology to correctly account for potentially strong cross-phenotype correlations, which are particularly common with hierarchically structured phenotypes.

Ultimately, the best strategy for correcting for multiple testing may depend on whether the goal is hypothesis generation/discovery or validation/hypothesis testing. In the former, we may be more willing to accept false-positive results for individual tests in exchange for higher power, while in the latter case, we may want to control the rate of false positives better.

3.3.4 | Heterogeneity between biobanks

Researchers often attempt to validate statistical findings from their data analysis using an independent dataset from a different population. For example, we may wish to validate results obtained using data from one biobank (eg, MGI) by performing the same analysis for another biobank (often, UKB). Here, we make a distinction between validation and replication, where replication involves comparing results in samples drawn with few systematic differences from the *same* population and validation involves comparing results in samples drawn from *different* populations or using different sampling approaches.[185] Systematic differences between the population characteristics or sampling mechanisms, however, could impact the generalizability of results between populations and impact our ability to validate findings.

In the meta-analysis literature, heterogeneity between studies is broadly grouped into three categories: *clinical heterogeneity* (differences in patients, interventions, and effects), *methodological heterogeneity* (differences in study design and sampling), and *statistical heterogeneity* (when the observed effects are more variable across studies than we would expect from random chance). Statistical heterogeneity may be a result of clinical and/or methodological heterogeneity.

Some analyses may be more impacted by differences between biobanks. As a demonstrative example, we compare the results of different data analyses using data from MGI and UKB. These biobanks exhibit substantial methodological heterogeneity concerning their sampling mechanisms, where MGI is based on an academic medical center and UKB is population-based. Suppose we are interested in comparing the odds ratio for having a particular phenotype based on the status of another phenotype, called phenotype co-occurrences. While prevalences will be impacted by the different sampling designs between MGI and UKB (see Figure 2), it is not clear how phenotype-phenotype associations will compare.

Figure S6 presents the estimated log-odds ratios of having a phecode diagnosis of melanoma regressed on other diagnoses in the phenome. See Section S5 for details on the phenotype generation procedure. The estimated odds ratios from the UKB data tend to be larger in magnitude compared to the odds ratios in MGI (for 70% of diagnoses). One possible explanation for this phenomenon is that in order for patients to get a phecode in UKB, they must visit a health care provider, during which time they may get multiple codes. When we compare UKB patients who did and did not receive a particular phecode (perhaps they did not visit a health care provider or did not visit as often), we may obtain inflated odds ratios. The patients in MGI are enriched with phecodes across the board, but patients with and without a particular phenotype may have many opportunities to collect other diagnoses through their interactions with the health care provider. In this melanoma example, the odds ratios for other neoplasms did not exhibit the same differences in MGI and UKB as seen for other classes of diseases. This may be due to enhanced screening of these diseases after diagnosis of melanoma in both MGI and UKB.

We predict the heterogeneity of the sampling mechanisms may not appreciably impact some associations; for example, GWAS results. In Figure 5, we compare GWAS results in MGI and UKB for several cancers. In this figure, points represent

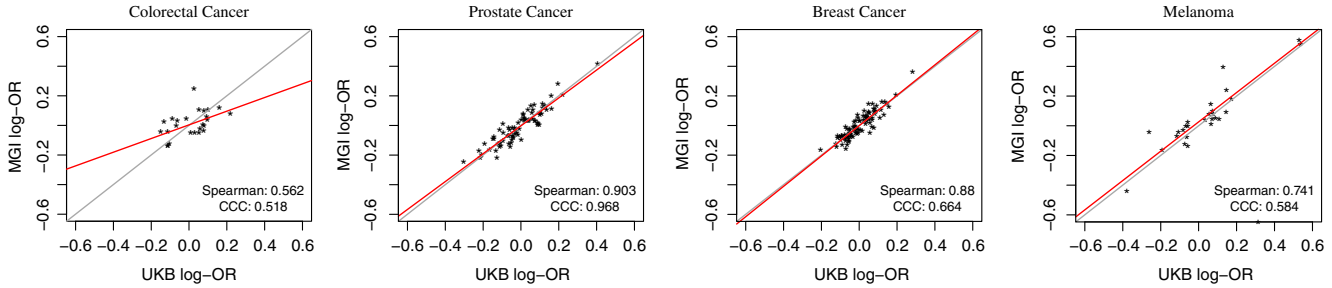

FIGURE 5 Comparison of GWAS results in MGI and UK Biobank for selected cancer phenotypes. Each point represents a SNP identified as being related to the corresponding phenotype in the NHGRI-EBI GWAS catalog. The point location corresponds to the log-odds ratio association between the SNP and the phenotype of interest in MGI and UK Biobank. The two lines correspond to equality of the estimates and a fitted line to the points (excluding any outlying points with absolute log-OR greater than 0.6). "Spearman" indicates the Spearman correlation and "CCC" indicates Lin's concordance correlation coefficient, which is a measure of agreement (with 1 being perfect agreement) [Color figure can be viewed at wileyonlinelibrary.com]

SNPs identified as being related to the corresponding phenotype in the NHGRI-EBI GWAS catalog.[186] See Section S8 for details. While MGI and UKB have very different sampling mechanisms, the GWAS results generally appear similar.

In addition to methodological heterogeneity, clinical heterogeneity could impact validation of results across biobanks. Some examples of clinical heterogeneity include differences in patient demographics, or the kinds of treatments prescribed, screening practices, and whether health care is public or private. An example of clinical heterogeneity for MGI and UKB is age, where MGI consists of patients aged 18 and up, while UKB consists of patients aged 40-69. If the association of interest depends on age, we would have different marginal associations in MGI and UKB. Another notable difference between biobanks/EHRs is how physicians encode diagnoses within the ICD framework. For a given patient, physicians in one EHR may tend to enter diagnosis A, while physicians in another EHR may enter related diagnosis B. This presents a problem for researchers seeking to validate diagnosis code-based phenotype associations across biobanks. Additionally, we may be interested in using biomarker or lab value measurements across biobank datasets, and these may be measured with different degrees of error.[187] When comparing this association overall between two different populations, a failure to adjust for the clinical heterogeneity across the two populations could result in biased inference.

In the presence of this heterogeneity between study populations, we may explore statistical methods to improve our ability to compare between different populations. There is a body of statistical literature for quantifying and handling between-study heterogeneity via meta-analysis.[188-191] Weighting-based and resampling-based methods for dealing with heterogeneity have also been explored.[192-194] The large number of subjects and the large number of available adjustment factors in EHR data provide an opportunity to effectively address more refined questions such as the relationship between treatment and molecular subgroups of disease (inherently a question of interactions) directly, potentially allowing clinical heterogeneity to be handled directly through a redefinition of the quantity of interest.[195] Recently, Shi et al developed a spherical regression-based method for handling heterogeneity in ICD code designation across different EHR systems.[196] Methodology in the data integration literature may also prove useful for addressing these challenges.[197] Future work may explore resampling-based methods to make studies more comparable in the presence of heterogeneity with respect to the sampling mechanism.

4 | EMERGING USES OF ELECTRONIC HEALTH RECORD DATA AND COMBINATION WITH EXTERNAL DATA

There is a tremendous opportunity to incorporate additional data to enrich EHR and enhance the scope of research. For example, we may link cancer and death registry information to the EHR to study survival and disease-related outcomes after clinical diagnosis. Local and national surgical registries offer opportunities for studying more granular health-related outcomes. When registry data is not available, claims data may also provide some insight for survival and disease-related research.[198] Recent work has developed methods for defining the exposome based on clinical narrative information or additional patient-level measurements.[199,200] Geo-coded data can provide a wealth of exposure information including social determinants of health, neighborhood characteristics, socioeconomic status, and pollution

information.[201-206] Freely available resources like the eICU Collaborative Research Database[207] are becoming more common and increasingly accessible, allowing for additional exploration of data and aggregation for larger analyses.

Longitudinal data within the EHR and beyond also offer many opportunities for research. Mobile fitness tracking devices provide an opportunity to incorporate longitudinal health metrics or even use text messages or game performance to define phenotypes.[208,209] Noren et al, Noren et al, and Boland et al use longitudinal health data to discover and adjust for temporal patterns.[210-212] Longitudinal EHR data has proven to be extremely useful in the fields of pharmacovigilance, pharmacoepidemiology, and pharmacogenomics.[211,213-217] Additional work leverages large-scale medical data to study potential new indications for existing drugs, called drug repurposing or repositioning.[218] Longitudinal EHR data can also be used to develop dynamic predictions for patient prognosis, adverse events, etc., over time.[219-222]

When combining data from multiple disparate sources, several problems arise. Most notably are issues regarding patient privacy. Additionally, we must consider issues such as data processing and rules for linking records for a single patient. Many statistical methods have been developed for linking records corresponding to individual patients across data sources, and many of these methods explicitly address issues of privacy.[223-227] Statistical methods have also been developed for combining data across distributed data sources where data from individual patients are not accessible.[228,229] Yang et al. developed methods for performing meta-analysis based on existing GWAS, and similar methods should be developed for PheWAS studies in the future.[230]

Large biobank datasets also provide an opportunity to study different treatment pathways and their corresponding outcomes.[231] Additional components such as treatment nonresponse and treatment adherence can also be explored.[54,232] While such studies are certainly not new, the wealth of information provided through EHRs provides opportunities to study treatment-related outcomes at scale. Additionally, these data sources provide a clearer look at treatment-related outcomes *in practice*, which may not always align with outcomes under more ideal settings of a clinical trial. These data can be used to analyze and/or predict various outcomes to treatments, medications, and/or dosages (sometimes stratified by patient characteristics).

EHR have also been used for disease forecasting, where researchers use electronic health records to determine population rates of disease and forecast future rates.[233,234] Disease forecasting is a challenging problem, and EHR-informed forecasts can prove extremely useful for medical staffing, vaccine production, and policymaking.[235]

5 | CONCLUSION

Biobanks linked to EHR provide rich data resources for health-related research, and scientific interest in biobank-based research has grown dramatically in recent years. As more researchers become interested in using biobank data to explore a spectrum of scientific questions, resources guiding the data access, design, and analysis of biobank-based studies will be crucial. This work serves to complement and extend recent publications about biobank-based research and aims to provide some statistical and practical guidance to statisticians, epidemiologists, and other medical researchers pursuing biobank-based research.[5-8]

In this paper, we provide a detailed characterization of many of the major EHR-linked biobanks to facilitate researchers' ability to obtain and investigate research-quality biobank data with some understanding of the associated population, sampling mechanism, and data linkages. This characterization provides a useful starting point for understanding the types of biobank data available and for requesting and accessing data. We also survey biobank-based papers that have been published. Future research can utilize increasingly large EHR-linked biobank cohorts to study a broad range of diseases. Biobank data also present an exciting opportunity to explore treatment and therapy schedules, drug repurposing, or gene-by-treatment interactions in the future. Such explorations can also be used to inform dynamic, patient-centric predictions for monitoring and treating future patients.

When using biobank data for health-related research, it is essential that researchers understand the statistical and practical issues that accompany such analyses and have resources to address them. There is a great need for statistical developments to address the many varied issues that go hand in hand with EHR-based research. Our discussion is structured to address statistical issues and strategies that researchers encounter when following a typical research study structure (see Figure 1).

Given our research question and data availability, the next step is generally to identify potential sources of bias. In this paper, we describe several particular concerns of confounding bias, selection bias, and misclassification of EHR-derived phenotype variables. Researchers should carefully consider issues of phenotype misclassification both in terms of ICD code-based phenotyping and in terms of the limitations of the EHR as a whole. A better understanding of the mechanisms

governing misclassification (in terms of under- and over-reporting of disease) may help shed light on the limitations of the EHR data and how to deal with potential information biases that result. Biases, in terms of patient selection into the biobank/EHR and in terms of study design using EHR data, need to be carefully considered. Many statistical methods exist for addressing issues of nonprobability sampling in particular, and additional work looking into the mechanisms driving patient selection for EHR may help researchers better generalize results to their target populations.

Historically, a large body of statistical work has focused on studying how we can most efficiently use available data to estimate our quantity of interest. As the size of the data grows, however, efficiency becomes less and less of a concern and characterization of bias becomes critical.[236] This is particularly important in the study of EHR, where many possible sources of bias can come into play and the data generation mechanisms are often difficult to characterize. The recent push away from *P*-values and dichotomization of study results in the statistical community reflects these changing perceptions. Increased emphasis must be placed on reproducibility and scientific rigor, particularly when large repositories of data are being made widely accessible.

Given a large pool of EHR and biobank data, the next step is to design our study using the data available. One considerable challenge involves defining the phenome, and future work can explore ways to incorporate a broader spectrum of EHR information into phenotype classification. Defining exposure and outcome variables can be particularly challenging for EHR-based data. For example, suppose we are interested in studying relationships between genetics and smoking behavior. Smoking behavior may not be directly recorded in the EHR, and careful thought is needed to determine how we can use EHR information to extract these data and the possible implications for the veracity of resulting statistical inference. We also need to clarify which patients we will include in our analyses. In many cases, this may consist of all available patients, but careful subsampling of the large pool of available to define our study dataset can also be used to help mitigate possible sources of bias, can reduce computational burdens of large data, and can identify subjects for additional data collection.

Once we have designed our study, the next general step is data analysis. Many issues need to be considered, including how we want to model the data, correction for multiple testing, and handling of missing data. The treatment of missing data in EHR-based studies is an area in particular need of additional statistical development. For example, analyses wishing to include lab values as predictors need to reconcile somehow the inherent relationship between missingness (whether a given test was ordered) and the test results. Data can be missing for a variety of reasons, and the mechanism generating the missingness can have serious implications on inference. Statistical methods tailored to handling issues of missing data in EHR could prove extremely useful. In general, reporting of how missingness was handled needs to be more explicit in studies using EHR. Additional statistical methods are also needed to handle multiple testing adjustment for studies involving many correlated phenotypes or studies exploring the phenome x genome landscape. In general, there is a strong need for the development of statistical methods to address the many and varied challenges we face when analyzing EHR-linked biobank data.

The combination of genetic and phenotypic information (eg, through polygenic and phenotype risk scores) presents a big opportunity for improving risk prediction, and future work can attempt to interrogate these different types of patient-level information to untangle the genetic and environmental factors related to disease generation and risk. With an increase in the volume and variety of data becoming available, emphasis should be placed on methods for incorporating data from external sources and emerging data streams (for example, geo-coded data, longitudinal biomonitoring data, mobile data, registry data, genomics/metabolomics data, imaging data, ecologic data, etc.). Such analyses can widen the scope of scientific questions we can address, and they necessitate a new wave of related statistical methods.

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AUTHOR CONTRIBUTIONS

L.J.B. wrote the manuscript, gathered papers regarding statistical methods and issues related to handling and analyzing biobank data, and prepared the figures. M.S. wrote the manuscript, gathered papers published about biobanks or those using biobank data, and prepared the tables. L.F. performed GWAS analyses, data preparation and provided critical comments and feedback. A.P. performed GWAS analyses, data preparation and provided critical comments and feedback. B.M. provided key guidance in the development of the manuscript throughout the entire process and performed detailed paper edits. A.R., C.B., C.J.W., and L.D.L. provided critical comments and feedback. All authors reviewed the manuscript.

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