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LEADING ARTICLE

Application of Healthcare 'Big Data' in CNS Drug Research: The Example of the Neurological and mental health Global Epidemiology Network (NeuroGEN)

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Abstract
Neurological and psychiatric (mental health) disorders have a large impact on health burden globally. Cognitive disorders (including dementia) and stroke are leading causes of disability. Mental health disorders, including depression, contribute up to one-third of total years lived with disability. The Neurological and mental health Global Epidemiology Network (NeuroGEN) is an international multi-database network that harnesses administrative and electronic medical records from Australia, Asia, Europe and North America. Using these databases NeuroGEN will investigate medication use and health outcomes in neurological and mental health disorders. A key objective of NeuroGEN is to facilitate high-quality observational studies to address evidence-practice gaps where randomized controlled trials do not provide sufficient information on medication benefits and risks that is specific to vulnerable population groups. International multi-database research facilitates comparisons across geographical areas and jurisdictions, increases statistical power to investigate small subpopulations or rare outcomes, permits early post-approval assessment of safety and effectiveness, and increases generalisability of results. Through bringing together international researchers in pharmacoepidemiology, NeuroGEN has the potential to be paradigm-changing for observational research to inform evidence-based prescribing. The first focus of NeuroGEN will be to address evidence-gaps in the treatment of chronic comorbidities in people with dementia.

1 Introduction

1.1 The Global Burden of Neurological and Mental Health Disorders

Neurological disorders such as cognitive disorders (including dementia), stroke and Parkinson's disease are leading causes of dependence and disability worldwide [1, 2]. Dementia has a global annual cost of US$818 billion [3]. The prevalence of age-related neurodegenerative disorders, including dementia and Parkinson's disease, is expected to double over the next 20 years [1]. It was estimated that 43.8 million people were living with dementia in 2016 [4], with 7.7 million new people being diagnosed every year [5]. Over 6 million people worldwide have Parkinson's disease, and the prevalence has doubled over a generation [6]. The total global burden of stroke is increasing, and close to 6 million people die because of stroke each year [7].

Psychiatric (mental health) disorders affect approximately 4.4% of the world's population at any one point in time, with an estimated 300 million people directly affected by depression in 2015 [8]. It is estimated that mental health disorders may be contributing to one-third of total years lived with disability, depression being the most common disorder [9].

Optimizing care and support through appropriate pharmacological and non-pharmacological management can reduce burden in people with neurological and/or mental health disorders, their families, healthcare systems and society.

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Key Points

Neurological and mental health disorders have a disproportionately large impact on global disease burden, but people with these disorders are often underrepresented in randomized controlled trials and real-world evidence is lacking.

International multi-database research using administrative data and electronic medical records provides an opportunity to conduct large and generalizable observational studies to generate new evidence to inform prescribing.

The Neurological and mental health Global Epidemiology Network (NeuroGEN) addresses evidence-gaps in the treatment of neurological and mental health disorders by bringing together researchers and data from Australia, Asia, Europe and North America.

1.2 Evidence Gaps in the Treatment of People with Neurological and Mental Health Disorders

Reducing the social and economic burden of neurological and mental health disorders, including dementia, is a global health priority [3]. The World Health Organization (WHO) Ministerial Conference on Global Action Against Dementia highlighted the need for research to determine and ensure the optimal use of pharmacological treatments for symptoms of dementia [3]. There are currently clear evidence gaps affecting the quality of medication use in certain vulnerable populations, such as those with dementia. For example, participants included in randomized controlled trials (RCTs) do not necessarily represent the characteristics of people prescribed medications in routine clinical practice. Older people with neurological and mental health disorders are often excluded from RCTs [10], resulting in a lack of evidence for medication safety and effectiveness. This is despite people with neurological and mental health disorders often experiencing high rates of multimorbidity and treatment with multiple medications [11, 12]. For example, few people with dementia were eligible to participate in the pivotal direct oral anticoagulant (DOAC) RCTs [13], despite a high prevalence of cardiovascular and cerebrovascular disease in this population [11]. In RCTs of acetylcholinesterase inhibitors, participants have been notably younger than the real-life population with Alzheimer's disease [14].

Specific evidence regarding the benefits and risks of medications in people with dementia is lacking [10], yet results of a recent nationwide study demonstrated that people with dementia were more likely to be exposed to polypharmacy (dispensed five or more medications) than people without dementia [15]. Insufficient evidence may lead to reliance on evidence extrapolated from other populations or settings, or prescribing decisions based on assumed benefits and risks. This could compound prescribing uncertainty or lead to inappropriate prescription of guideline-recommended medications for comorbid conditions. The UK primary care data suggest comorbid depression is diagnosed in 17%, 21%, 18% and 32% of people with coronary heart disease, stroke, diabetes and dementia, respectively [16]. Despite being highly prevalent, people with diagnosed depression are often excluded from RCTs related to the management of these conditions.

1.3 The Role of Administrative Claims and Electronic Medical Record Data in Central Nervous System Drug Research

The rapid increase in the availability of administrative and electronic medical record (EMR) data has resulted in new potential for 'big data' research in medication safety and effectiveness [10]. These data are collected from hospitals, primary care medical practices and pharmacies. Clinical registries have also been established in primary and secondary care, often with linkage to administrative data. High-quality, multi-database, observational studies of such 'big data' enable comparisons across geographical areas and jurisdictions, an increase in statistical power to investigate small subpopulations, rare outcomes, early post-approval assessment of safety and effectiveness, and an increased generalisability of findings.

2 The Neurological and Mental Health Global Epidemiology Network (NeuroGEN)

2.1 Description of NeuroGEN

The Neurological and mental health Global Epidemiology Network (NeuroGEN) (https://www.neurogen.hku.hk/) is an international 'big data' collaboration platform established at a multidisciplinary meeting of 30 researchers from eight international geographical regions in Hong Kong in October 2018 [17]. NeuroGEN evolved out of the PharmAlliance collaboration in pharmacoepidemiology between Monash University, University College London (UCL) and University of North Carolina at Chapel Hill (UNC). PharmAlliance is a strategic partnership of staff and students at the Monash University Faculty of Pharmacy and Pharmaceutical Sciences, UCL School of Pharmacy and UNC Eshelman School of Pharmacy. PharmAlliance provides strategic seed funding

for multi-institutional initiatives in research, practice and education. The purpose of the October 2018 meeting was to explore data available in different jurisdictions, identify the breadth of clinical and methodological expertise, and to set research priorities. Research priority setting involved identifying 29 topics, of which six were prioritized highest. A second multidisciplinary meeting was held in London in August 2019 that included new member institutions and researchers. At this meeting, respective research groups presented and discussed their progress in relation to the existing and new topics. A map of current member regions is presented in Fig. 1. Initial seed funding provided by PharmAlliance has been supplemented by grants from the Victorian Medical Research Acceleration Fund, University College London (UCL)—Peking University Strategic Partnership Grant, and University of Hong Kong—UCL Strategic Partnership Grant and Research Grant Council of Hong Kong. The Dementia Australia Research Foundation—Yulgilbar Innovation Grant was received to investigate guideline-recommended medication use in people with dementia and chronic comorbidities. This Four Continents For Dementia (4C4D) program involves Australia, Hong Kong, the UK, and the US.

2.2 NeuroGEN Member Institutions and Databases

NeuroGEN facilitates access to a global network of administrative and medical record data for the purpose of conducting multi-database observational research with a focus on neurological and mental health disorders. Collectively, data are available for an estimated 100 million people with and without neurological and mental health disorders. There are considerable differences in national regulations and the application of ethical frameworks in different countries, and therefore each NeuroGEN partner works with the relevant data custodians and ethics committees to comply with the local legal and ethical requirements. Data included in each of the databases are described in Table 1.

2.2.1 Monash University, Australia

Monash University's Centre for Medicine Use and Safety (CMUS) comprises investigators in pharmacoepidemiology and clinical pharmacy. One of the research priorities of the CMUS involves analyses of administrative claims data to optimize medication use for dementia and cardiovascular diseases [18, 19]. The primary data source is a 10% random sample of national dispensing data from Australia's Pharmaceutical Benefits Scheme (PBS). Data are available for 10% (≈2.5 million) of Australia's population. This dataset is provided in a standard de-identified form by Services Australia, by application. Other data include Victorian-wide hospital data linked to the PBS, general medical practitioner data obtained through the Medicare Benefits Schedule (MBS), and emergency department and mortality data. Victoria is the second most populous state in Australia, with a population of 6.6 million. Analyses of linked Victorian data have been approved by all data custodians, with a waiver of informed consent due to the retrospective use of the data, data provided to researchers are de-identified, and consent would not be feasible to obtain.

2.2.2 University of Hong Kong, Hong Kong

The University of Hong Kong (HKU) team has conducted multi-database pharmacoepidemiological studies using EMRs [20–22]. The primary source of data is the Clinical

Fig. 1 NeuroGEN sites. *NeuroGEN* Neurological and mental health Global Epidemiology Network

Data Analysis and Reporting System (CDARS) managed by the Hospital Authority in Hong Kong. The Hospital Authority is the sole public-funded healthcare provider, whose primary, secondary and tertiary care services are accessible to all Hong Kong residents (> 7 million people). The CDARS includes records from all public hospitals, outpatient clinics and institutions under the Hospital Authority. Research proposals are approved by the Research Ethics Committee under the Hospital Authority. Informed patient consent is waived as the CDARS data used are de-identified.

2.2.3 University College London, UK

The UCL School of Pharmacy team's research focuses on neurodegenerative and cardiovascular diseases, diabetes, child health and pregnancy [23–25]. The main source of data is The Health Improvement Network (THIN). THIN is a nationwide database that contains electronic primary care records from UK general practices for 15 million individuals [26]. THIN covers a 6% representative sample of the UK population. Multiple diagnoses and lifestyle variables recorded in THIN database, including cardiovascular diseases, diabetes, obesity and smoking, have been used and validated for pharmacoepidemiological research [27]. THIN is subject to the UK Data Protection Act 2018 and EU General Data Protection Regulation (GDPR). Data obtained have been anonymised and consent was previously collected by the general practices where patients can opt-out.

2.2.4 University of Glasgow, UK

The University of Glasgow has expertise on vascular neurological and cardiometabolic diseases [28–30]. The primary source of data is the UK Biobank, which recruited 502,536 participants, aged 39–72 years, from the general population between 2007 and 2010. Participants attended one of 22 assessment centres across England, Scotland, and, where they completed a self-administered questionnaire and face-to-face interview, and trained staff took a series of measurements, including height, weight and blood pressure. Mortality, hospitalization, and primary care consultations are available through data linkage. The UK Biobank has acquired explicit informed consent from all participants.

2.2.5 University of Dundee, Scotland

The MEMO (Medicines Monitoring Unit) Research group at the University of Dundee and Ninewells Hospital conducts observational studies [31, 32] and large decentralized clinical trials. MEMO currently have approximately 40,000 patients randomized into clinical trials. For pharmacoepidemiological studies, MEMO researchers use data from the Information Services Division (ISD) of National Services Scotland, which is part of the public National Health Service (NHS). The ISD provides health information, health intelligence, statistical services and advice that support the NHS with the goal to improve Scotland's health. The Service holds health-related data, which in some cases cover an individual from before birth (with the mother's antenatal records) to their death. The ISD complies with the NHS Scotland Information Security Policy set out by the Scottish Government (https://www.informationgovernance.scot.nhs.uk/isframework/). Senior staff in the ISD have the role of 'Caldicott Guardian' (https://www.gov.uk/government/groups/uk-caldicott-guardian-council) for the Organization to ensure that not only the appropriate steps to protect the confidentiality of personal health information is observed but also that sensitive information is handled properly. In order to access personal health information, investigators are required to obtain a special authorization, and, once obtained, strict rules are in place to how information should be managed.

2.2.6 National Cheng Kung University, Taiwan

The National Cheng Kung University (NCKU) focuses on pharmacoepidemiology and big data research using claims data based on the National Health Insurance program in Taiwan [33, 34]. The National Health Insurance Database (NHID) was launched in 1995. The program covers over 99% of Taiwan's population (25 million people) and enrolled more than 90% of hospitals and clinics. The Ministry of Health and Welfare (MOHW) established a Health and Welfare Data Centre (HWDC), a data repository site that centralizes the NHID. The NHID includes medications, medical visits and procedures recorded in ambulatory, in-patient and emergency services. In addition, a multi-institutional EMR database, the Chang Gung Research Database (CGRD) [35] containing clinical data such as pathological and laboratory results, is available to serve as external validation data for the NHID. The CGRD includes 1.3 million outpatients and 0.2 million inpatients in Taiwan [36, 37]. Due to the retrospective nature of the analyses, informed consent is not required for either the NHID or the CGRD.

2.2.7 Sungkyunkwan University, South Korea

The Korean team focuses on analyses of the National Health Insurance System (NHIS) claims database [38, 39] and multi-database studies. The NHIS in South Korea achieved universal coverage of the entire population in 1989. The database contains diagnostic and prescribing data for approximately 50 million Koreans. The claims database includes data on each individual's age, sex, diagnoses (International Classification of Diseases, Tenth Revision [ICD-10]) and prescription medications. Information

Table 1 Summary of the content of the databases and their geographical locations

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
Victorian linked health data (cohort extracted from a statewide Victorian Admitted Episodes Dataset)	Australia	450,000 people hospitalised for myocardial infarction, ischaemic stroke, diabetes or hip fracture	2006–2018	Age, sex, ethnicity, language spoken, geographic area, marital status	Dispensed reimbursed medications, PBS item code, date of dispensing, quantity, strength	Hospital diagnoses and procedures (ICD-10-AM)	Referrals only (Medicare)	NA	NA	Month, year and cause of death
10% random sample of national PBS dispensing data	Australia	2.5 million	2005–2019	Year of birth, sex, state	Dispensed reimbursed medications, PBS item code, authority code where relevant, date of dispensing, quantity, strength, prescriber	Selected medical conditions can be inferred from medication dispensings using the Rx-Risk Index tool and prescriptions requiring specific diagnosis for reimbursement (authority)	NA	NA	NA	Year of death

Table 1 (continued)

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
MEDALZ (cohort and data linkages extracted from nationwide registers)	Finland	70,719 persons with AD and 282,862 comparison persons without AD (all community dwelling at the time of diagnosis); data linkage currently until 2015	Incident AD diagnoses from 2005 to 2011	Age, sex, hospital district, occupational social class (since 1970)	Reimbursed dispensings of prescription medications (1995 onwards) data on, for example, ATC codes, medication names, pack size, dispensed amount in defined daily doses, strength, formulation, costs	Hospital stays from 1972 onwards: diagnoses (ICD-8 until 1986, ICD-9 until 1995, ICD-10 Procedure codes (Sairaalaliitto until 1995, NOMESCO since 1996) Entitlement for special reimbursements for chronic conditions (since 1972, national criteria consistent with international guidelines) Detailed data on cancer from the cancer register	NA	Institutionalizations, required level of assistance at hospital discharge	NA	Date and cause of death
FinPark (cohort and data linkages extracted from nationwide registers)	Finland	21,683 persons with PD and 146,306 comparison persons without PD (all community dwelling at the time of diagnosis); data linkage currently until 2016	Incident diagnoses from 1996 to 2015	Same as MEDALZ	Same as MEDALZ	Same as MEDALZ	NA	Same as MEDALZ	NA	Date and cause of death

Table 1 (continued)

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
PHARMO database network	The Netherlands	4.2 million active (prior to linkage)	Pre 2000–2019	Age, sex, geographic area	Pharmacy dispensing data (sample of in-hospital treatments available) [date of treatment, quantity, duration, daily dose]	Linkage to nationwide hospitalization database, in-patient hospital pharmacy database (2 million), GP database (2.5 million)	Linkage to clinical laboratory database (1.2 million)	Linkage to nationwide registries (cancer, pathology, perinatal)	NA	Date of death
The Health Improvement Network (THIN)	UK	>4 million active, 13 million in total	1990–2018 (best-quality data 2004–2018)	Age, sex, year of birth, registration status, transfer out date, region, ethnicity, language spoken, marital status, socioeconomic status	Primary care prescriptions (ATC codes/BNF product codes) [date, quantity, duration, daily dose]	Primary care clinical data, referral data, immunisation data (READ codes)	Test results (type of test, result, normal range of result, unit of measure)	Possible linkage to HES	GP recorded BMI, smoking, alcohol consumption	Date of death
Clinical Practice Research Datalink (CPRD)	UK	4.4 million active, > 11.3 million total patients meeting quality criteria	Pre 2000–2019	Age, sex, month and year of birth, registration status, transfer-out date, region, ethnicity, deprivation index (linked)	Primary care prescriptions (Gemscript/BNF product codes) [date of treatment, quantity, duration, daily dose]	Primary care clinical data, referral data, immunization data (READ codes)	Test results (type of test, result, normal range of result, unit of measure)	Possible linkage to HES, ONS, National Cancer Registry	GP recorded BMI, smoking, alcohol consumption	Date of death (possible linkage to ONS for death statistics/cause)

Table 1 (continued)

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
UK Biobank	UK	0.5 million	2007–2010 for baseline data	Age, sex, ethnicity, area-based deprivation index, education, income, and occupation	Self-report at baseline and linked primary care data on prescription	Self-report at baseline and linked mortality, hospitalization, and primary care data	Majority of participants at baseline; $n = 18$ K repeated measures in 2012–2013; additional from linked primary care data	Brain and heart MRI data from subset of participants; cognitive tests, genetic/genomic data	Self-report lifestyle at baseline; small subset in repeated measurements	Date and cause of death
Information Services Division (ISD) Scotland	Scotland	5 million	2000–2019	Date of birth, sex, ethnic group, marital status, GMC no. of referring Dr/Dentist/Nurse, Allied Healthcare Professional, GP Practice Code, NHS number, postcode, UCPN	PIS; dispensing system. Prescription and dose duration are decoded	Hospital episodes of care data for acute conditions consisting of ICD and OPCS codes. There are also databases on maternity/birth record/child health/cancer registration/Office for National Statistics death certification; data by ICD codes, birth, death, marriage. Via a separate system (Albasoft), access to GP data across nearly all practices in Scotland	A series of regional databases called SCI-Store containing all laboratory data linked to the CHI number	PACS system, a Scottish-wide record of all imaging in Scotland; accident and emergency attendance data; vaccination records; ambulance calls databases	Via linkage to the national datasets for lifestyle alcohol brief interventions, drug and alcohol treatment waiting times, drug prevalence estimates, National Drug-Related Deaths Database, National Sexual Health System, Scottish Drug Misuse Database, Scottish School Adolescent Lifestyle and Substance Use Survey, Smoking Cessation Database; Social Deprivation data	Date and cause of death

Table 1 (continued)

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
Hospital Authority's Clinical Data Analysis and Reporting System (CDARS)	Hong Kong	> 7 million active, > 11 million total	1995–2019	Sex, year of birth, month of birth, Race, Ethnicity, Location of patient	Prescription and dispensing information including date, dispensing status, quantity, duration, daily dose)	Hospital diagnoses and procedure ICD-9-CM/ ICD-10	Laboratory test orders, laboratory test results	Diagnosis, inpatient, outpatient, accident and emergency department admissions and discharges records, payment method	Via linkage to family medicine records	Date and cause of death
National Health Insurance Database (NHID)	Taiwan	23 million	2003–2017	Age, sex, date of birth, geographic area	Prescription information, including medication code, strength, dose frequency, quantity, date of supply	Hospital and clinic diagnoses and procedure ICD-9-CM/ ICD-10	NA	NA	NA	Date of death
Chang Gung Research Database (CGRD)	Taiwan	1.3 million outpatients and 0.2 million inpatients	2008–most updated	Age, sex, year of birth, ethnicity, language spoken, marital status, socioeconomic status	Prescription information, including medication code, strength, dose frequency, quantity, date of supply	Hospital and clinic diagnoses and procedure ICD-9-CM/ ICD-10	All laboratory data	NA	Smoking, BMI, alcohol consumption	Date of death
National Health Insurance system (NHIS) Database	Korea	50 million	2003–2018	Age, sex, geographic area, insurance type, income level	Hospital medication order, pharmacy claims	Hospital diagnoses and procedure (ICD-10-CD)	NA	NA	Via linkage to the national health screening program database	Month and year of death

Table 1 (continued)

Database name	Region	Size	Years of data	Demographic variables	Source for medication use	Source for medical conditions	Source for laboratory results	Availability of other clinical data	Availability of lifestyle information	Date and cause of death
20% sample of the Medicare	US	10 million per year	2007–2017	Date of birth, sex, county of residence, race, enrolment information	Outpatient dispensings, including dates of dispensing, National Drug Codes, strength, quantity dispensed, days' supply	Inpatient data ICD-9-CM/ ICD-10 codes for diagnoses and procedures	Laboratory tests ordered	Medical equipment, home care, long-term care	NA	Date and cause of death
Medicaid Analytic Abstracts (MAX), 45 states	US	> 152 million	2001–2012; 2013 (26 states); 2014 (14 states)	Date of birth, sex, state and county of residence, race/ethnicity, enrolment information (e.g. basis of eligibility, dual Medicare status)	Paid prescription drug claims, including national drug codes, dispense dates, quantity dispensed, and days supplied	Inpatient, outpatient and long-term care claims with ICD-9-CM/ ICD-10-CM codes for diagnoses and procedures	Inpatient, outpatient and long-term care claims with ICD-9-CM/ ICD-10-CM, HCPCS, CPT procedure codes	Long-term care and diagnostic codes for palliative care, drug overdose, emergency visits	NA	National Death Index date and ICD-10 cause of death codes for 2001–2007

PBS Pharmaceutical Benefits Scheme, *ICD* International Classification of Diseases, *ICD-8* ICD, Eighth Revision, *ICD-9* ICD, Ninth Revision, *ICD-10* ICD, Tenth Revision, *ICD-9-CM* ICD-9, Clinical Modification, *ICD-10-AM* ICD-10, Australian Modification, *NA* not applicable, *MEDALZ* MEDication use and ALZheimer's disease, *AD* Alzheimer's disease, *ATC* Anatomical Therapeutic Classification, *NOMESCO* Nordic Medico-Statistical Committee, *FINPARK* Finnish Medication and Parkinson's disease, *PD* Parkinson's disease, *GP* general practitioner, *GMC* General Medical Council, *NHS* National Health Service, *UCPN* Unique Care Pathway Number, *PIS* Prescribing Information System, *OPCS* Office of Population Censuses and Surveys, *SCI* Scottish Care Information, *CHI* Community Health Index, *PACS* picture archiving and communication system, *BMI* body mass index, *BNF* British National Formulary, *MRI* magnetic resonance imaging, *HES* Hospital Episode Statistics, *ONS* Office for National Statistics, *HCPCS* Healthcare Common Procedure Coding System, *CPT* Current Procedural Terminology

on prescription medications includes generic name, date of prescription, duration, and route of administration. Due to the retrospective nature of the analyses, informed consent is not required.

2.2.8 University of Eastern Finland, Finland

The Kuopio Research Centre of Geriatric Care focuses on pharmacoepidemiology in people with Alzheimer's disease and Parkinson's disease. This includes aetiological research, drug utilization studies and outcome studies [40, 41]. Primary sources of data are the nationwide MEDication use and ALZheimer's disease (MEDALZ) study [42] on people with Alzheimer's disease, and the Finnish Medication and Parkinson's disease (FINPARK) study on people with Parkinson's disease [43]. Both studies include a matched cohort to facilitate comparisons to persons without these conditions and are derived from Finnish nationwide databases including medication dispensing data, hospital discharge data and mortality data. The MEDALZ cohort includes incident cases of Alzheimer's disease diagnosed from 2005 to 2011, and the FINPARK study includes incident cases of Parkinson's disease diagnosed from 1996 to 2015 with ongoing follow-up. Both MEDALZ and FINPARK data are used in pseudonymised form. The research proposals are approved by data custodians. According to Finnish legislation, other approvals or informed consent are not needed as the study is based on pseudonymized register data, and participants are not contacted.

2.2.9 Utrecht University, The Netherlands

The Pharmacoepidemiology and Clinical Pharmacy group at Utrecht University (UU) has a clinical, policy and methodological focus. The UU group has methodological expertise in preventing and/or controlling for confounding, analysis of effect modification and conducting multi-database analysis. The primary data sources used for large pharmacoepidemiological studies include the Dutch PHARMO database (http://www.pharmo.nl) and the UK Clinical Practice Research Datalink (CPRD) [44]. The CPRD is subject to the UK Data Protection Act 2018 and the EU GDPR. Data obtained have been anonymised and consent was previously collected by the general practices where patients can opt-out. In PHARMO, patient information is de-identified and the requirement for individual consent is waived unless an intervention is planned. All use of the data requires approval by the independent Compliance Committee STIZON/PHARMO Institute, in compliance with the Netherlands Personal Data Protection Act and Medical Treatment Contract Act. Data access is funded by the Utrecht Institute for Pharmaceutical Sciences. The UU group coordinate the European Research Network of Pharmacovigilance and Pharmacoepidemiology (EU PE&PV) and have developed novel methodologies for the conduct of multi-country, multi-database studies on variability of medication use and health outcomes [45–47].

2.2.10 Rutgers University, US

The Center for Health Services Research and Center of the Pharmacoepidemiology and Treatment Sciences at Rutgers' Institute for Health are interdisciplinary groups with research focusing on the use and outcomes of medications across large, diverse usual-care populations in the US and other countries [48, 49]. Researchers at Rutgers have worked on studies particularly on the use and outcomes of central nervous system (CNS) drugs, including opioid use disorders; use and outcomes of antipsychotics; treatment of adults with severe mental illness; use and safety of selective serotonin reuptake inhibitors in pregnant women; and psychotropic treatment for children. The main data sources include health insurance data from the Center for Medicare and Medicaid Services, which is updated annually: a 20% sample of Medicare patients representative of the US older people and people with end-stage renal diseases, and 45 State Medicaid Analytic Extracts (MAX) representative of a low-income population, including pregnant women and children. According to the US Health Insurance Portability and Accountability Act (HIPAA) of 1996 privacy rules, informed consent was not required as the data were originally collected for insurance purposes, and secondary use of the data for researchers is conducted without person identifiers.

2.3 Ongoing Case Studies and Initiatives

2.3.1 Case Study 1: Adherence and Persistence to Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors (AChEIs) are the most widely prescribed medications for dementia, although efficacy [50, 51] and cost effectiveness [51, 52] are modest. Non-adherence and non-persistence reduce potential benefits, with a systematic review of five RCTs reporting that discontinuation is associated with a significant decline in cognition and worsening of neuropsychiatric symptoms [53]. This highlights the importance of persistence in maximising benefit. This study will investigate adherence and persistence to AChEIs across the NeuroGEN partners. Australia, South Korea and Taiwan have analysed their respective data using a common study protocol. The study will utilize the proportion of days covered to estimate adherence from medication dispensing and prescribing databases. Persistence will be estimated using a prespecified gap of no dispensing or prescribing. This study will permit a comparison adherence and

persistence using standardized definitions and methodology. This program of work is funded through the National Health and Medical Research Council (NHMRC) Boosting Dementia Leadership Fellowship Scheme.

2.3.2 Case Study 2: Predicting Dementia and Survival from Cognitive Footprints of Electronic Health Records Using Machine Learning

Based on the 'cognitive footprint' of medical history, this population-based, case-control study will aim to develop and validate an algorithm for predicting dementia using machine learning [54]. The algorithm will be trained using territory-wide EMRs from the CDARS in Hong Kong, and tested both locally and externally in other databases (e.g. the UK THIN and the Finnish MEDALZ). The CDARS currently hosts records from more than 70,000 people with dementia diagnoses between 2001 and 2018. Potential protective/risk factors, which will be selected based on the cognitive footprint theory, will be modelled holistically. It is anticipated that the modelling will include analyses of diagnostic data, laboratory test results and the prescription of antidepressants, antipsychotics, statins and polypharmacy. Other than a set of Hong Kong-specific factors, a set of common factors that are shared by other databases will be identified to maximize interoperability. The subsequent common algorithm, to be derived from real-world data in Hong Kong, may then be suitable for embedding into other health information systems. Patients with a high risk or likelihood of dementia can be efficiently identified to permit targeting of risk-reduction programs. A secondary objective of this project is to estimate survival from the point of a recorded diagnosis of dementia in Hong Kong, Canada, Finland, Germany, Korea, Taiwan, UK and US. This project will aggregate large population-scale data from different geographical regions. The project is ongoing and is expected to be completed by June 2022. This project is funded by the Research Grant Council of Hong Kong under the Early Career Scheme.

2.3.3 Case Study 3: Mortality of People with Parkinson's Disease Across Geographical Areas

In a meta-analysis of inception cohorts, Parkinson's disease was associated with 1.5 times higher mortality [55]. The same meta-analysis demonstrated major heterogeneity in mortality ratios stratified by sex, and identified a need for further high-quality studies of mortality in Parkinson's disease. Specifically, there is a lack of large-scale, population-based inception cohorts with long-term follow-up. This study will investigate the survival of people with Parkinson's disease following diagnosis, as well as possible geographical differences in mortality ratios and factors that predict higher mortality. The project is in its initiation phase. This project will be coordinated from Finland, and data from Finland, Hong Kong, Korea, Australia and the UK will be utilized. Additional countries will be included once confirmed with the corresponding investigators. Funding applications for this project have been submitted. Once secured, the development of the common study protocol will commence.

2.3.4 Case Study 4: Capacity Building

One of the objectives of NeuroGEN is capacity building and training the next generation of pharmacoepidemiologists. This is being achieved by providing opportunities to early career researchers, including PhD candidates and post-doctoral researchers. For example, PhD students from Monash University, Naresuan University (Thailand) and Princess Norah Bint Abdul Rahman University (Saudi Arabia) have conducted exchanges to UCL to conduct pharmacoepidemiological studies [56–59]. Similarly, a PhD student from Monash University has conducted an exchange to HKU, and researchers from Utrecht University and UCL have conducted exchanges to Monash University. A bi-lateral exchange of post-doctoral researchers from University of Eastern Finland and Monash University has taken place [60]. These exchanges have been funded through the Royal Golden Jubilee PhD Program (Thailand), Newton Fund (UK), Saudi Arabian Ministry of Higher Education, the Australian Government Endeavour Fellowship Scheme, Monash Doctoral Program and the NHMRC Boosting Dementia Leadership Scheme.

3 Discussion and Future Directions

3.1 Discussion

Multinational collaboration with data from multiple regions globally is a growing opportunity to conduct large, generalizable, observational studies that address research questions with international relevance. Use of a common protocol approach (CPA) and common data models (CDM) can facilitate large multi-database studies that address topics of international public health importance. NeuroGEN is currently using both the CPA and CDM. Although the CPA is more straightforward to implement, it requires close communication between investigators to ensure that all analyses are conducted consistently. A CDM is a sophisticated data platform supporting secondary use of data across multiple databases. The major advantage of CDM is that analyses are controlled by the use of a standardized data structure, terminology, variable definitions and an analytical program. Such a distributed network approach in which data partners

maintain physical and operational control over the data in their existing environments also addresses data privacy issues across jurisdictions because data are not shared. However, establishing the CDM requires a considerable investment of time and resources to convert native databases into the CDM.

Other examples of consortia include the Asian Pharmacoepidemiology Network (AsPEN). AsPEN uses modified distributed networks with a common data structure across databases to allow single analytic programs to be used in each site [61]. Some NeuroGEN investigators are also participating in AsPEN. Another example is the Canadian Network for Observational Drug Effect Studies (CNODES), where databases across different provinces are analysed using the same approach [62].

NeuroGEN investigators have created a CDM based on the Observational Medical Outcomes Partnership (OMOP) CDM [63], containing all relevant information to conduct analyses for ongoing projects. A stand-alone analysis programme for each study will be developed based on the NeuroGEN CDM. Because the data structure and terminologies are identical among the converted databases, the analyses can be conducted in each home institution. Each site will generate a standardized results file that will then be collected by the coordinating site. Figure 2 presents the structure of the NeuroGEN CDM. Previous applications of similar conversions include, for example, paediatric use of prescription medications [64].

Dementia Australia and the Yulgilbar Foundation have funded the development of the CDM for four databases focusing on dementia research. The databases include the Australian linked health data, the US Medicare data, the UK THIN data and the Hong Kong CDARS data. The respective investigators are currently working together synchronising the databases into the CDM format to investigate the use of guideline-recommended medications for chronic comorbidities in people with and without dementia.

3.2 Future Directions

NeuroGEN is planning an international symposium on multi-database pharmacoepidemiology and is currently in discussion with partner research groups in other geographical regions, including Oceania and South America. Currently the COVID-19 is posing significant challenges globally, a large volume of research has been produced on the acute effects and acute treatments. However, the medium and long-term direct and indirect effects of COVID-19, impact on the pandemic on management of non-COVID related conditions, and the mental health and wellbeing of society as a whole remain unknown. Partners of NeuroGEN are currently working together to develop research proposals for various funding bodies. These proposals will harness the power of big data in monitoring the medium and long-term outcomes of COVID-19 as well as other novel infectious diseases and the effectiveness and safety of future vaccines and interventions. The collaboration will continue to seek to address topics of global importance to better manage neurological and mental health disorders.

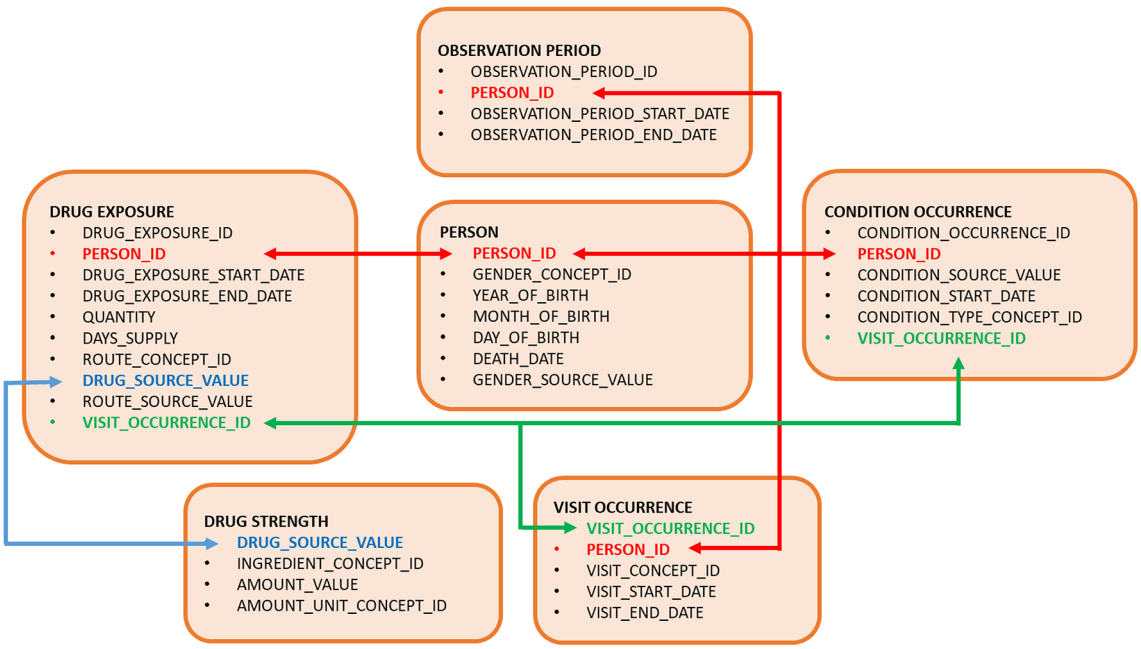

Fig. 2 Proposed common data model structure for the NeuroGEN. *NeuroGEN* Neurological and mental health Global Epidemiology Network

4 Conclusions

NeuroGEN is a recent initiative addressing medication use and outcomes in people with neurological and mental health disorders. Compared with the other multi-database initiatives, NeuroGEN is the only global multi-database network that specifically addresses the management of neurological and mental health conditions, and with a broader focus on psychopharmacology. This will address significant evidence gaps in this under researched field. NeuroGEN covers countries and regions across four continents, Australia, Asia, Europe and North America, making the initiative truly global.

Compliance with Ethical Standards

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Conflict of interest Jenni Ilomäki has received consulting fees from AstraZeneca unrelated to the submitted work, and has received grant funding from the NHMRC, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation and National Breast Cancer Foundation. J. Simon Bell is supported by an NHMRC Boosting Dementia Leadership Fellowship, and has received grant funding from the NHMRC, Victorian Government Department of Health and Human Services, Dementia Australia Research Foundation, GlaxoSmithKline, and several aged care provider organizations, unrelated to the submitted work and all paid to the employing institution. Adrienne Y.L. Chan reports no receipt of research funding. Anna-Maija Tolppanen has received grant funding from the Academy of Finland. Hao Luo has received grants from the Research Grants Council (RGC; Hong Kong), as well as consulting fees from the Hong Kong Jockey Club Charities unrelated to the submitted work. Li Wei has received research grants from the European Medicines Agency and the UK Medical Research Council, National Institute for Health Research, and charities, outside the submitted work. Edward Chia-Cheng Lai has received research grants from the Ministry of Science and Technology (MOST) of Taiwan, National Health Insurance Administration of Taiwan, and National Cheng Kung University Hospital, outside the submitted work. Ju-Young Shin has received research funding from the Ministry of Food and Drug Safety, Ministry of Health and Welfare, National Research Foundation of Republic of Korea, Amgen, Pfizer, Hoffmann-La Roche, Dong-A ST, and Yungjin pharmaceutical, outside the submitted work. Giorgia De Paoli reports no receipt of research funding. Romin Pajouheshnia has no funding or conflicts of interest to declare. Frederick K. Ho has received research funding from the Wellcome Trust Institutional Strategic Support Fund via the University of Glasgow, outside the submitted work. Lorenna Reynolds is partly funded by the NHMRC Boosting Dementia Scheme. Kui Kai Lau has received grants from the Research Fund Secretariat of the Food and Health Bureau HKSAR, Boehringer Ingelheim, Pfizer, Amgen and Sanofi, as well as consulting fees and honorarium from Boehringer Ingelheim and Sanofi, all of which are unrelated to the submitted work. Stephen Crystal is supported by R01-HS026001, DA047347, R18-HS023258, and UL1TR003017. Wallis C.Y. Lau has no conflicts of interest to declare. Kenneth K.C. Man is supported by the C W Maplethorpe Fellowship and has received consulting fees from IQVIA Inc., unrelated to the submitted work. Ruth Brauer has no conflicts of interest to declare. Esther W. Chan has received research grants from the RGC (Hong Kong), Narcotics Division of the Security Bureau of the Government of the Hong Kong SAR, Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, NHMRC (Australia), Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, and Takeda, outside the submitted work. Chin-Yao Shen is supported by research grants from the National Cheng Kung University Hospital, Tainan, Taiwan. Ju Hwan Kim reports no receipt of research funding. Terry Y.S. Lum has received research grants from the RGC (Hong Kong), the Hong Kong Jockey Club Charities, the Social Welfare Department of the HKSAR Government, the Hong Kong Housing Society, the Simon KY Lee Foundation, and the Templeton World Charity Foundation, outside the submitted work. Sirpa Hartikainen has received lecturing fees from Astellas, unrelated to the submitted work. Marjaana Koponen has no conflicts of interest to declare. Evelien Rooke has no conflicts of interest to declare. Marloes Bazelier has no funding or conflicts of interest to declare. Olaf Klungel has no funding or conflicts of interest to declare. Soko Setoguchi has received research grants from the National Institutes of Health, Cystic Fibrosis Foundation, Pfizer and BMS, and served as a consultant for the US FDA, Pharmaceuticals and Medical Devices Agency (Japan), Pfizer, Merck, and Medtronic. Jill P. Pell has received research funding from the Scottish Government, Health Data Research UK, Medical Research Council, Wellbeing of Women, and National Institute for Health Research, outside the submitted work. Sharon Cook is supported by R01-HS026001, R18-HS023258, R01-DA045872, R01-DA047347 and UL1TR003017. Ian C.K. Wong has received research funding, outside the submitted work, from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong RGC, the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, and NHMRC (Australia), and has also received speaker fees from Janssen and Medice in the previous 3 years.

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