This is the authors' submitted version of an article in press:

Davis, Farooq, Hayes, John, Lee, MacCabe, McIntish, Osborn, Stewart and Woelbert "Pharmacoepidemiology Research: delivering evidence about drug safety and effectiveness in mental health" **Lancet Psychiatry**

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Pharmacoepidemiology Research: delivering evidence about drug safety and effectiveness in mental health

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Abstract

There is a need for research that provides an evidence base for the pharmacotherapy of people with mental disorders. The abundance of digital data in recent years has facilitated pharmacoepidemiology in the form of observational comparative effectiveness studies at the population level. Advantages are large patient samples, coverage of under-researched sub-populations and naturalistic conditions. Pharmacoepidemiology is also cheaper and quicker to carry out than RCTs, meaning that issues regarding generic medication, stopping medication (deprescribing) and long-term outcomes are more likely to be addressed. Methods can also be extended to pharmacovigilance and drug repurposing.

Drawbacks of observational studies come from the non-randomised nature of treatment selection, and the inherent risk of confounding by indication. Potential methods for managing this may include active comparison groups, inter-individual designs, propensity scoring and instrumental variables. Many of the more rigorous pharmacoepidemiology studies have been strengthened through multiple triangulated analytic approaches to improve confidence in inferred causal relationships.

With these developments in data resources and analytic techniques, it is encouraging that guidelines are beginning to include evidence from robust pharmacoepidemiogical studies alongside RCTs. Collaboration between guideline-writers and researchers involved in pharmacoepidemiology may help researchers ask the questions that are important to policy-makers and ensure that results get integrated into the evidence-base. Further development of statistical and data science techniques, alongside capacity building in terms of data resources, a wider researcher base and public engagement, will be necessary to take full advantage of future opportunities.

Keywords: Pharmacoepidemiology, comparative effectiveness research, evidence-based medicine, psychiatry

Pharmacoepidemiology is the use of epidemiological techniques to study pharmacological treatments at the population level. The availability of large, representative datasets (see box 1) has facilitated a recent increase in pharmacoepidemiological approaches in mental health research, while the application of specialist statistical techniques has improved the robustness and validity of findings from these studies. This paper aims to provide an overview of the advances and challenges in this emerging field, and the extent to which such research can contribute to the evidence base for medication decisions in people with mental health needs.

Many academics hold the view that pharmacoepidemiological studies are less scientifically reliable than clinical trials; and hence that the results of such studies cannot be trusted.[1] While pharmacoepidemiological research has its pitfalls, it also has many advantages over clinical trials, especially in mental health. Many modern comparative efficacy studies (CES) using pharmacoepidemiological techniques have sophisticated study designs which "design out" issues of confounding that would otherwise restrict the interpretation of findings. We argue that pharmacoepidemiology should be viewed as a contributory resource, alongside randomised-controlled trials (RCTs), in developing an evidence base for some key clinical questions. This has implications for capacity building in this field and the development of clinical guidelines.

[insert Box1 around here]

/H1/ Benefits of Pharmacoepidemiology

The RCT is considered the "gold-standard" design for testing clinical treatments, because randomisation of participants to treatment groups and tight control of the conditions account for both measured and unmeasured confounders.[2] However, this high level of experimental control introduces selection and artificiality, with potential limitations in generalisability. Long-term efficacy and chronic harms of medication, as well as rare adverse effects are also difficult to study using RCTs.

/H2/ Sample Size

Recruiting and retaining participants in trials of psychiatric treatment can be difficult, especially when this involves asking doctors and patients to forgo treatment or attend frequent follow-up. The CUtLASS-1 trial of second vs first generation antipsychotics reported that recruitment was hampered when clinical preference shifted towards second generation antipsychotics, as clinicians were reluctant to enter patients into a trial that might randomise them to the older first-generation antipsychotics.[3] The BALANCE RCT[4] addressing the use of lithium and/or valproate treatment in bipolar affective disorder type 1, was initially designed to recruit 3000 people,[5] but later changed the primary outcome and sample size. It eventually took them six years across 41 sites to recruit 330 people, of which 167 completed the two year protocol.[4] In contrast, Hayes and colleagues performed an observational CES of 5,089 patients prescribed lithium, valproate, olanzapine or quetiapine for bipolar disorder, with up to 17 years of follow-up using a primary care database.[6] The CUtLASS example also demonstrates that the time taken to perform RCTs can be an issue, whereas the retrospective nature of pharmacoepidemiology can offer prompt answers to current dilemmas.

/H2/ Generalisability

The inclusion and exclusion criteria of clinical trials are typically restrictive. While this is designed to reduce random variation in the data and increase the likelihood of an intervention's effect being detected, this is at the expense of increased selection. The occurrence of comorbid conditions, which are common in people with mental health disorders, often means exclusion from RCTs. The drive towards personalised medicine, requires attention to patient characteristics, including comorbidities, to

provide evidence of what works for specific sub-populations. However, problems such as lack of capacity to consent to trial involvement, mean that there are important sub-populations for whom RCT evidence is practically nonexistent, such as mental health in learning disability and treatment-refractory schizophrenia.[7] Pharmacoepidemiological research has the potential to fill these gaps.

/H2/ Long-term, meaningful outcomes

Many mental health conditions first occur in adolescence or early adulthood with a relapsing remitting course, so effectiveness and safety of medicine need to be determined over long periods of time. Because of the implementation of fully digitalised records across English mental health services in 2005-10, many services have ten years' worth of routine service data available in 2019,[17],[8] which offers great opportunities to carry out studies of both length and depth. UK primary care databases can go back even further, which means that retrospective studies can be carried out, such as looking at the effect of anticholinergic medication exposure and the onset of dementia over 15-20 years.[9] Greater insight into real-world outcomes can be gained through linkage of electronic health record research databases to other administrative databases. For example, data on health service usage (e.g. Hospital Episode Statistics in England) and national mortality statistics linked to electronic health records have shown that the treatment of people with severe mental illness with guideline-recommended psychotropics are associated with better physical health outcomes,[10,11] and can be used to compare ongoing mental health of mothers with severe mental illness who continued or stopped maintenance medication during pregnancy.[12] Linkages of mental healthcare data to education, employment records, criminal records and more, are now taking place, enabling research to capture these wider long-term outcomes, which are of major public health importance.[8,13,14] Conversely, in most data sources there is very limited availability of routine outcome measure recording.

/H2/ Study of rare outcomes

Large studies with long-term follow-up offer the ability to quantify risks of rare outcomes. Examples include the association of clozapine treatment with reduced mortality,[11] or of selective serotonin reuptake inhibitors (SSRIs) with foetal abnormalities and adverse childhood outcomes.[15] Drug safety has always ultimately been tested on whole populations,[16] a special branch of pharmacoepidemiology termed pharmacovigilance. Studying the adverse events of current medications in large databases, has

also been used to produce models that can predict potential safety of new medications coming to market, which can be used to concentrate pharmacovigilance efforts.[17]

Adverse events arising from drug-drug interactions are difficult to identify in RCTs because of their rarity and the restrictions commonly placed on co-prescription of other drugs. They are likely to be better investigated in pharmacoepidemiological data. For example, Malik and colleagues were able to test the hypothesis that co-prescription of sodium valproate was associated with an increased risk of clozapine-associated neutropenia.[18] Complex harms such as a change in psychiatric risk from physical health medication are also only reliably detectable by the use of large observational datasets. This has been used to show that similar medications with incidental higher anticholinergic activity increase the risk of delirium[19] and that medications prescribed for asthma (leukotriene-modifying agents) rarely lead to psychiatric symptoms.[20]

/H2/ Questions that have not been answered using RCTs

For some important clinical questions, RCTs are not able to provide accurate answers. Examples include the choice of antidepressant in primary care and the long-term effectiveness of long-acting injectable antipsychotic (LAI) medication.

The Sequenced Alternatives to Relieve Depression trial (STAR*D) showed that the proportion of adults who respond to a first antidepressant was only 37%, but this rises to 67% after up to four trials of different antidepressant strategies[21]. Finding evidence to improve on trial-and-error for these antidepressant approaches has proved difficult. Datasets from large clinical trials such as STAR*D have been used to produce multi-variable models to predict treatment response with moderate success,[22] but generalizing predictive models across different datasets has proved challenging.[23] Pharmacoepidemiological research with larger and more representative samples may be able to offer richer data to these models allowing greater clinical applicability. Regarding harms from antidepressants, pharmacoepidemiology has played a part in exploring the issue of SSRIs and self-harm in vulnerable subgroups. SSRIs were previously thought to be safe for young people, based on RCTs mostly in adults. Observational data now shows a drug-by-age interaction that means young people are particularly at risk of developing self-harm and suicidal ideation when given SSRIs,[24,25] suggesting that

lives were being put at risk by extrapolating evidence-base practice from adults to children and young people.[26,27] This led to targeted warnings and a change in guidance. Pharmacoepidemiological techniques can also be used to note that these warnings have changed prescriber behaviour and highlight where improvement is needed.[26,27]

In the case of LAI antipsychotics, a large RCT[28] and subsequent meta-analysis[29] found no benefit of LAI over oral antipsychotics in preventing relapse in schizophrenia. Conversely, mirror image studies (within individual design comparing outcomes prior to and after initiation of LAIs), find LAI superior to oral antipsychotics in preventing hospitalisation.[29] The reason for this anomaly may be that a key advantage of LAI antipsychotic is improved adherence, but this may not be well captured in an RCT. Firstly, people with issues that affect concordance with medication may be less likely to agree to take part in RCTs, making the trials unrepresentative of normal clinical caseloads; secondly, the nature of the trial follow-up itself goes beyond normal clinical practice, which can be predicted to result in increased adherence.

/H2/ Funding and non-standard treatment

Testing pharmacological treatments with RCTs can be staggeringly expensive.[31] The RCTs required to bring novel treatments to market require considerable investment, funded by the pharmaceutical industry, often jointly with the public sector.[32] There are many important clinical research questions which are unlikely to attract such funding; for example, the impact of discontinuing medications or guiding the use of medications after the expiry of commercial patent rights.[33] This may inadvertently weight the evidence base towards newer and indefinite treatments. Furthermore, the effects of conflicts of interest on the reporting of clinical trials are well documented,[30] and were partially responsible for the late discovery of the risks of SSRIs in children.[31] Observational CES are much cheaper than RCTs and are only rarely funded by pharmaceutical companies. They therefore have the potential to redress this imbalance in evidence and are less likely to present conflicts of financial interests.

A further benefit is the ability to identify of drugs that might be repurposed to treat mental disorder. For instance, Hayes et al found that people with serious mental illness in the national Swedish database who were taking statins (HGC A reductase inhibitors) for cardiovascular health were less likely to be hospitalised when taking statins than during periods when they had not been taking them.[32] Prescribing

practices that contravene guidelines, but are nevertheless common, such as antipsychotic polypharmacy, are rarely tested in randomised controlled trials, but can readily be studied using pharmacoepidemiological techniques.[36]

/H1/ Limitations of observational data and emerging methods of correction

It is important to recognise the limitations of pharmacoepidemiology. All studies have biases, but the biases of an observational trial may differ from RCTs.[33] Differential surveillance between the groups, inequitable observation windows and confounding may be issues; guidance is available[37-40] to minimise or provide a sensitivity analysis for some of these issues through selection of active treatment arm, selection of comparison group, choice of start dates and the definition of outcomes. As this article about the association between SSRIs and atrial fibrillation explains, multiple strategies may need to be employed for confidence.[35] We will concentrate on the issues that have affected pharmacoepidemiology in mental disorders.

/H2/ Data quality

The quality of data gathered for observational research may be different to experimental data that was collected specifically for research purposes, and this may be a limitation of pharmacoepidemiology. Data collected for administrative purposes will have record-keeping that varies between coders / clinicians and over time.[36] Most outcomes will need some form of validation to determine to what extent they reflect true disease, and this may be considered more problematic in mental health, where there is a reputation for subjectivity.[37]

/H2/ Confounding

Confounding by indication and/or severity is one of the most important challenges for observational studies of different treatments.[1] This is because people are not given treatment 'at random', but related to the presence and severity of a medical or psychiatric disorder. In an uncorrected analysis this would confound treatment effectiveness with the presence and severity of a disorder. For example, consider testing the effectiveness of clozapine for control of psychotic illness by looking at time to admission to a psychiatric ward. If one was to compare people on clozapine to random people in the same registry who were not taking any antipsychotic, people in the control group are likely not to have a psychotic illness and so unlikely to have psychiatric admissions. So clozapine treatment and psychotic illness are confounded. Equally, comparing people on clozapine to people on first-generation antipsychotics would also be unfair, as clozapine treatment is only indicated in the case of treatment-resistant psychosis.

When comparing between different treatments, it may also be the case that treatment A is chosen over treatment B due to the presence of a comorbidity or the side-effect profile of treatment B. An example is in antipsychotic use. A primary care database study of weight gain comparing olanzapine, quetiapine and risperidone found that patients newly prescribed olanzapine tended to have lower weight at baseline than the other groups,[38] showing an apparent inclination to choose olanzapine for people of lower weight. This type of factor needs to be taken into account when planning and interpreting observational studies.

/H2/ Causal inference techniques

Causal inference is the central aim of both the RCT and observational CES. Over the last thirty years, a formal statistical language has been developed in which causal effects can be unambiguously defined, and the assumptions needed for their identification clearly stated,[39] and a number of techniques are particularly pertinent in pharmacoepidemiology.[40,41]

A causal inference technique that accounts for confounding by indication is propensity scores. The propensity score is the probability that a particular patient would receive the treatment of interest (i.e. treatment A rather than treatment B) given the characteristics of the patient and the clinical environment.[42] Returning to the comparison of second generation antipsychotic agents above an unadjusted analysis suggested that olanzapine was associated with a significantly lower risk of cardiac events compared to risperidone. However, after matching people taking different antipsychotics based on their propensity to be prescribed olanzapine (including body mass index, diabetes and contact with mental health services), there was no significant difference in cardiovascular event risk.[43]

When using electronic health records or other rich sources of information, there may be advantages in using machine learning to come up with a high-dimensional propensity score; performance of naïve models can be as high as expert-informed propensity score.[44] Conversely, in some databases, not enough data might be available on the profile of the people in different treatment groups to build a propensity score, which case external adjustment can be used, by collecting this information on a

subsample of individuals and using that to correct for unmeasured confounders in the main study.[45] Studies may also contain an extra arm that is a "negative control", defined by an exposure that is known to be unrelated to the outcome under study, in order to detect bias and confounding in the data source and model being used.[51] This was done when evaluating in utero exposure to SSRIs and foetal abnormalities by looking at the association of abnormalities with fathers' use of SSRI, which could not have an effect through the proposed pathway. [15]

Within-individual designs also address the issue of confounding by indication.[46,47] By having individuals acting as their own controls, all time-invariant confounding is eliminated. This approach has been used in the studies mentioned above regarding LAI antipsychotics[29] and repurposed agents for the treatment of severe mental illness[32]. It has also been used to solve the dilemma of comparison group for clozapine users outlined above, using data from Queensland Australia[48] and finding that continued clozapine use was associated with an average 0.71 fewer admissions (10 bed-days) over two years, compared to the two years prior to commencement.

Methods which have not been widely used in pharmacoepidemiology in mental health research, but are ripe for exploitation include instrumental variable approaches, including the sub-types of regression discontinuity designs and Mendelian randomisation. An instrumental variable is something that influences which treatment people receive, but has no independent or confounding relationship with the outcome, except by affecting the likelihood of the treatment.[54] Using the instrumental variable as a proxy for exposure can help remove confounding. Common instruments exploit inter-regional or inter-facility availability of treatment, but regression discontinuity uses the presence of an artificial cut-off point on a continuous scale,[40] and Mendelian randomisation uses common genetic mutations.

/H1/ Pharmacoepidemiology as an evidence base for guidelines

Despite the progress made in terms of both data and analysis, and the unique strengths of pharmacoepidemiology, guidelines for clinical treatment still rely heavily on RCTs for their evidence-base, using an evidence pyramid that places RCTs above observational studies to justify not searching for observational research if any relevant RCT is found. However, RCTs may not be superior; observational CES can be complementary, or able to address different questions. The reliance on RCT is also reflected in the "research recommendations" included in guidelines, which frequently request RCTs unlikely to be feasible. For example, despite the difficulties described above in recruitment, retention, generalisability and lack of funding for trials of medication in common usage, the NICE 2014 schizophrenia guideline[56] contains a recommendation for RCTs to test the physical health benefits, risks and costs of discontinuing or reducing antipsychotic medication among young adults with first episode psychosis who have achieved remission. For these and other questions, time and energy may be wasted on underpowered RCTs that are unlikely to be definitive. Future guidelines may benefit from encouraging evidence from rigorous pharmacoepidemiology instead.

The situation may be improving however. The British Association for Psychopharmacology guidelines for bipolar disorder issued in 2016[57] did not follow the traditional evidence pyramid, the reason stated by the authors being that "this approach explicitly downgrades non-experimental descriptive studies of treatment effects in favour of any randomised controlled trial; in so doing, it confounds design with quality". They instead employed an approach based on the Cochrane Collaborations GRADE system[58] that downgrades findings from small inconclusive RCTs and upgrades findings from observational studies in large samples with strong quasi-experimental designs. Other BAP guidelines may follow this example.

In maximising the opportunity for their research to be identified and inform guidelines, researchers need to make sure that it is easily identifiable as a quasi-experimental design testing a particular medication for a particular indication. Observational research must also use outcomes that guideline writers and regulators consider important, as well as accounting for all covariates considered important. This can be a little opaque, but there are examples where researchers have worked with regulators to define these variables, such as the Innovative Medicines Initiative (IMI) Realworld Outcomes across the

Alzheimer's Disease spectrum (ROADMAP) project, which attempted to identify what real-world evidence would be required when a regulator was considering a medication for early Alzheimer's dementia.[59]

/H1/ Future directions

In the UK, there are signs of the way forwards for pharmacoepidemiology. The research charity MQ: Transforming Mental Health data science group[60], aims to harness the power of UK data resources for mental health research by fostering collaboration and building capacity. A public-private partnership spear-headed by the Medical Research Council hosts a data-sharing platform, Dementias Platform UK,[61] providing quick access to multiple data sources for a single application, alongside a learning community. In February 2019 another platform project, supported by MQ, was launched supporting research into mental health in young people aged 10-24 years; this Adolescent Data Platform[21] will bring together billions of records in Secure Anonymous Information Linkage (SAIL). The next step may be a platform for mental health of all ages, possibly utilising resources from the MRC's Mental Health Data Pathfinder projects.[62] Any inclusion of prescription data would provide a valuable opportunity for pharmacoepidemiology research programmes.

Pharmacoepidemiology offers great advantage in reaching people who are under-represented in conventional research, is very cost-effective compared to conventional research, facilitates co-operation and open science. But "social license" is needed for the use of public and health data, and this requires researchers to earn the trust of both the public and health professionals.[63,64] Any new data platform must continue with public engagement that includes both the methods and the intended benefits, so that there is a two-way dialogue that promotes respect on both sides.[65,66]

/H1/Conclusions

Although RCTs are the bedrock of evidence-based medicine, there are some questions that cannot or will never be answered by RCTs. Pharmacoepidemiology meanwhile is flourishing in a world of increasing digitalisation of information. This is true for all healthcare specialties, but there are particular advantages of the digital era and data science in areas as complex as mental health, especially given the difficult funding environment for mental health research.[50] The availability of data, however, is not sufficient for robust studies; the development of methodology to address the biases and confounding inherent in observational studies is also essential. Similarly, the presence of high-quality studies is insufficient to influence clinical practice unless decision-makers are engaged with the evidence. In order to make use of the new capabilities of pharmacoepidemiology there is therefore a need to build awareness in two groups: first, the clinical and academic community to build capacity to produce more robust evidence based on real-world needs; second, the clinical and policy community so that they are equipped to appraise and integrate emerging findings into practice for the benefit of the community.

Author Contributions

Concept- KD, JHM, AM; Design- KD, SF, JH, WL, JHM, DO; Content- All authors; Editing and Approval- All authors.

Acknowledgements

KD and RJS are funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. JH is supported by the Wellcome Trust (211085/Z/18/Z). JH and DO are supported by the University College London Hospitals NIHR Biomedical Research Centre. AJ is funded by the Medical Research Council and MQ at Swansea University Medical School. WL is supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South West Peninsula. AM is supported by a Wellcome Trust Strategic Award (Reference 10436/Z/14/Z). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the MRC, the Wellcome Trust, or the Department of Health and Social Care.

Declarations of interest

All authors have completed an ICMJE Conflict of Interest form. The following was noted:

No authors had any potential conflicts of interest to declare within this work.

SF reports grants, personal fees and non-financial support from Sunovian Pharamceuticals and Lundbeck , outside the submitted work; AM reports grants from The Sackler Trust, outside the submitted work; RJS reported receiving grants from Janssen and Roche and co-supervision of a PhD candidate with GlaxoSmithKline.

Role of funding source

There was no specific funding for this paper. The authors were solely responsible for the design, writing and decision to submit.

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Box 1: Data sources for pharmacoepidemiology with features and examples of use			
Data Source Type	**Examples**	**Features**	**Exemplar study/studies**
Population Databases	Nordic health registers: Denmark, Finland, Iceland, Norway, and Sweden Linked databases in Ontario, Canada Western Australia administrative databases	Wide coverage of general population. Many stretch back many decades. Large numbers to detect small signals or in rare sub-groups. Data consists of indices of healthcare usage, coded diagnoses and prescriptions – frequently linked to other public information.	Do antidepressants taken in pregnancy increase the risk of birth defects? Furu et al 2015 using combined Nordic registers[15] Can commonly prescribed medication for physical health help people with psychiatric illness? Hayes et al 2019 using Swedish register[3]
Reimbursement Databases	Gmünder ErsatzKasse (GEK), Germany Longitudinal Health Insurance Database of Taiwan Medicare / Medicaid, USA (public) PharMetrics / Market Scan, USA (commercial)	Large numbers to detect small signals or in rare sub-groups. Data consists of indices of healthcare usage, coded diagnoses and prescriptions. Biases can be introduced by reimbursement policies.	Is risk of self harm affected by the type of antidepressant, the dose, and the age of the patient? Miller et al 2014 using PharMetrics[4]
Electronic Health Records (structured info)	Canadian Primary Care Sentinel Surveillance Network The Health Improvement Network (THIN), UK.	Coverage of those people accessing care, good for most purposes. Temporal coverage varies, but up to 20 years in UK primary care. Data usually includes coded problems and treatments.	Which mood stabiliser is best for bipolar disorder? Hayes et al 2016 using THIN[5] Do anticholinergic medications increase the long-term risk of developing dementia? Richardson et al 2018 using CPRD[6]

	Clinical Practice Research Database (CPRD), UK. Secure Anonymous Information Linkage (SAIL), UK.	Data entry dependent upon clinicians. Different systems tend to collect different information, and this may change over time. Coding patterns can also change over time.	
Electronic Health Records (with Natural Language Processing, NLP)	South Verona Psychiatric Case Register Clinical Record Interactive Search (CRIS), UK Veterans Affairs, USA Individual Health Maintenance Organisations (HMOs, e.g. Partners HealthCare & Mayo Clinic) and virtual data warehouses with data from multiple HMOs (e.g. Health Care Systems Research Network), USA.	Coverage of those people eligible for and accessing care. Data still dependent on clinician, but coded data supplemented by free text, usually using via an NLP tool, allowing more in-depth phenotyping.	What is the risk of relapse among new mothers with a severe mental disorder who stop medication while pregnant? Taylor et al in 2019 using CRIS and linkages[7] How should we model adverse effects to enable better detection? Bean et al 2017 using CRIS[8]
Disease-specific cohorts	Can be derived from above data types, or may be from trials, e.g. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and International Study to Predict Optimized Treatment in Depression (iSPOT) Psychiatric Biobanks and Bioresources, e.g.	Narrow coverage of those with disorder who meet other inclusion criteria. May be poorly representative of the profile of all people with disorder, with less coverage of those with comorbidities, in minority groups, and those without capacity to consent.	Can we predict treatment outcomes in depression that translates to other settings? Chekroud et al 2016 using STAR*D and Combining Medications to Enhance Depression Outcomes[9]

	European Autism Intervention (EU-AIMS) and Genetic Links to Anxiety and Depression (GLAD) Study	In-depth, consistent information, tailored to condition.	
Large cohort studies	Nord-Trøndelag Health Study (HUNT), Norway UK Biobank & Generation Scotland, UK National Longitudinal Study of Youth, USA	Coverage will depend on methodology, likely to bias against those with more severe mental disorder. Information available may not be tailored to mental-health.	Do antihypertensive drugs cause depression and/or anxiety? Johansen et al 2012 using the HUNT 2 study[10]
Novel sources	Utilising data from wearables or collected by social media	Currently mostly theoretical.	Can we monitor response to treatment of depression using telemedicine devices? Callum et al from the Remote Assessment of Disease and Relapse (RADAR-CNS) study[11]

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