Use of large real-world databases - opportunities and challenges

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Conflict of Interest

- Consultant Cortechs.ai & Precision-Health.ai
- National PI Boeringer-Ingelheim, Compass, Janssen & MAPS/Lykos trials
- Speaker’s honorarium BMS, Janssen, Lundbeck, Otsuka, Lilly, Sunovion

Biological Psychiatry
A Journal of Psychiatric Neuroscience and Therapeutics
Biological Psychiatry

REVIEW | ARTICLES IN PRESS

How real-world data can facilitate the development of precision medicine treatment in psychiatry

Elise Koch • Antonio F. Pardiñas • Kevin S. O'Connell • Pierluigi Selvaggi • José Camacho Collados • Aleksandar Babic • Serena E. Marshall • Erik Van der Eycken • Cecilia Angulo • Yi Lu • Patrick F. Sullivan • Anders M. Dale • Espen Molden • Danielle Posthuma • Nathan White • Alexander Schubert • Srdjan Djurovic • Hakon Heimer • Hreinn Stefánsson • Kári Stefánsson • Thomas Werge • Ida Sønderby • Michael C. O'Donovan • James T.R. Walters • Lili Milani • Ole A. Andreassen • Show less

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Nordic opportunities (27 mill)

1. Personal identifiers
2. Health registries
3. Large biobanks
4. Public health system
5. Population surveys
6. Motivated population

=> Integrate research and healthcare

- data for pharma studies

› Lancet. 2009 Aug 22;374(9690):620-7. doi: 10.1016/S0140-6736(09)60742-X.

11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study)

Jari Tiihonen [1], Jouko Lönnqvist, Kristian Wahlbeck, Timo Klaukka, Leo Niskanen, Antti Tanskanen, Jari Haukka

Affiliations + expand

PMID: 19595447 DOI: 10.1016/S0140-6736(09)60742-X

Computational drug repurposing for mental disorders (MediMENT)

EP PerMed
European Partnership
for Personalised Medicine

Ryan Waples

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Large scale real-world data

Population-scale

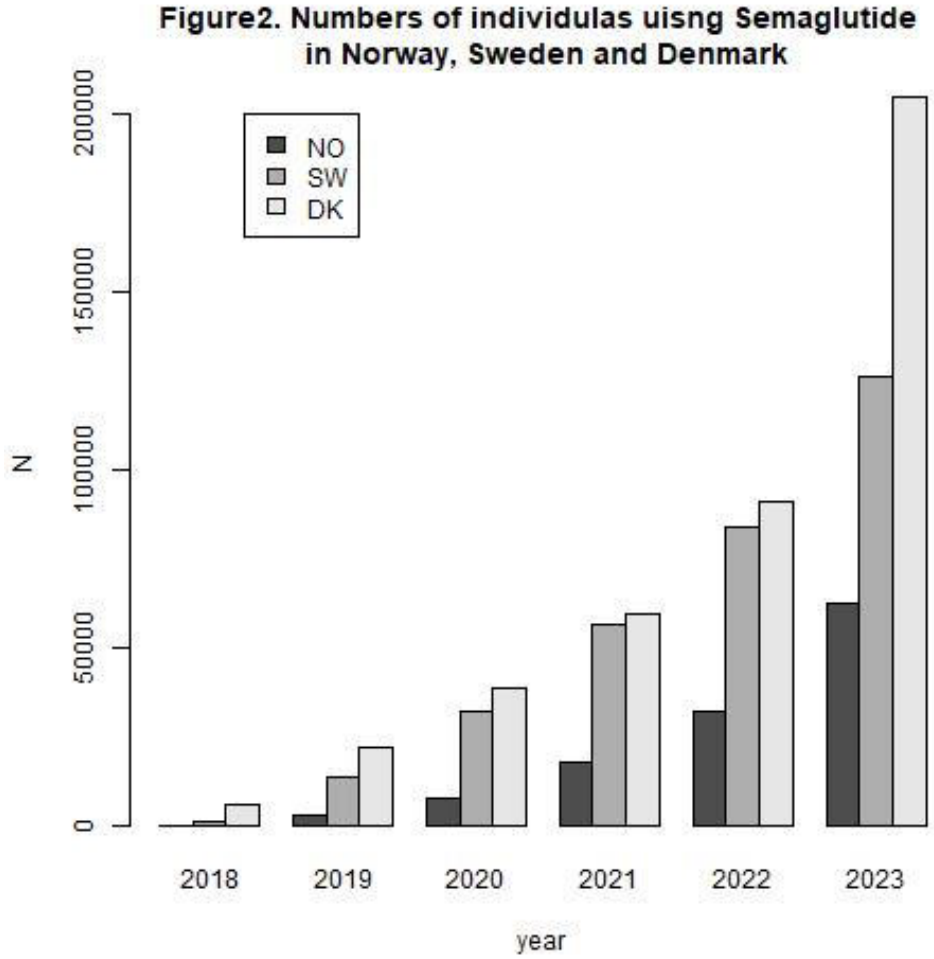
- National registers (~30M)
  - Electronic health records (e.g. diagnoses, prescriptions, etc.)
  - Familial relationships

Multimodal data

- Biobanks + Cohort studies (1.9 M+)
  - Genetic data
  - Biomarkers + rich phenotypes

Example MediMent project - Denmark

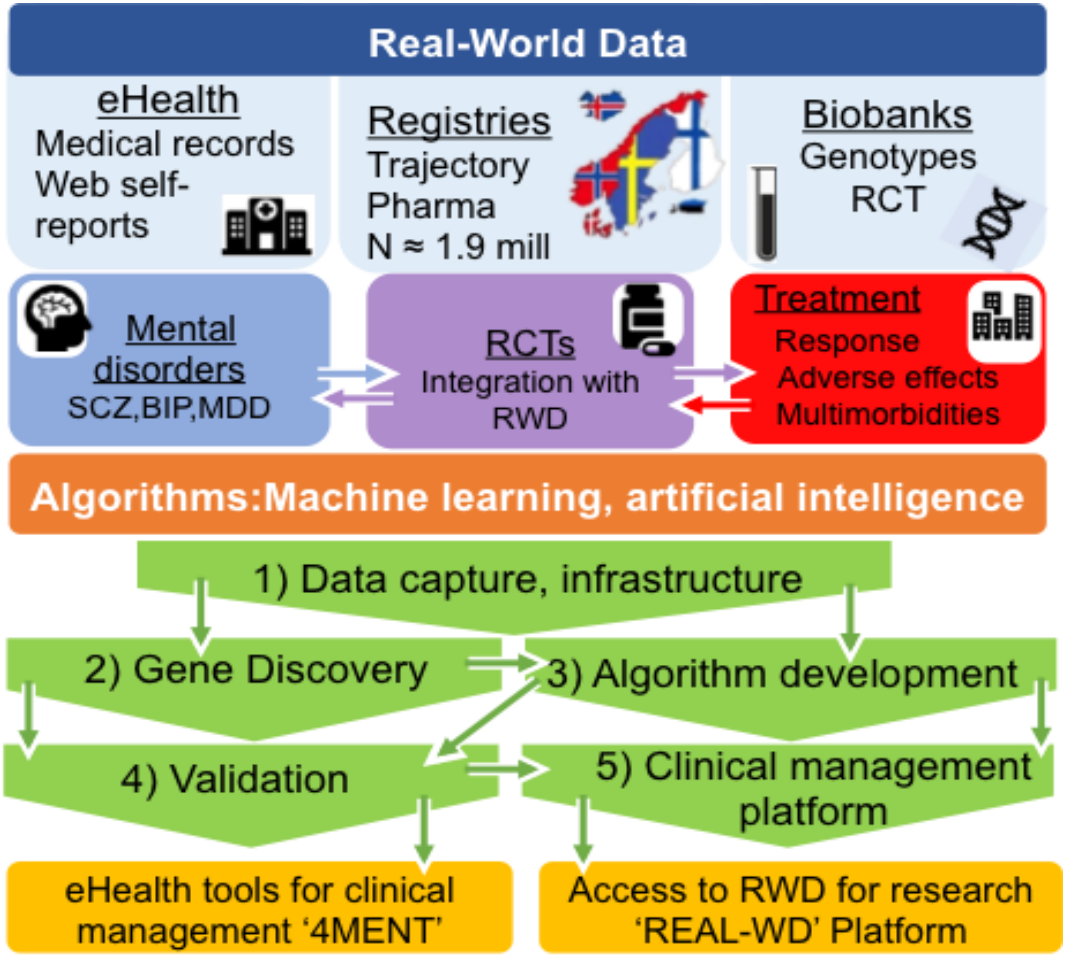
- All Danes born before 1950, data from 1995
- All prescriptions, n = 479,420,576
- All diagnoses, n = 80,865,480



Unnur Valdemarsdottir

Academia-industry

REALMENT



UiO : University of Oslo

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Oslo University Hospital

Real-world outcome

THE LANCET
Psychiatry

REVIEW · Volume 12, Issue 6, P457-468, June 2025 Download Full Issue

Recommendations for defining treatment outcomes in major psychiatric disorders using real-world data

Elise Koch, PhD [a,b] · Sophie Smart, PhD [c,†] · Guðmundur Einarsson, PhD [d,†] · Anders Kämpe, MD PhD [e,f,†] · Lina Jonsson, PhD [g,†] · Maris Alver, PhD [h,†] · et al. Show more

Challenges

- No standardized criteria
  - Outcome definitions
  - Measurements
- Different data sources
  - questionnaires, self reports, eHR, health registries
- Different measures across studies/data sources
- No validation

Koch et al. 2025

Schizophrenia, Bipolar disorder, Major depressive disorder

Panel 1: Recommendations for outcome definitions of antidepressant treatment in major depressive disorder

Non-response or treatment-resistant depression

Diagnosis of major depressive disorder, treatment adherence, and any of:

- Antidepressant switching (two or more antidepressant trials of adequate dose and duration)
- Admission to hospital during treatment
- Neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation)
- Treatment with ketamine or esketamine
- Self-reported non-response after two or more antidepressant trials

Response or non-resistance

Diagnosis of major depressive disorder, treatment adherence, or any of:

- History of stable treatment
- No history of neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation)
- No history of treatment with ketamine or esketamine
- No admission to hospital during treatment
- Self-reported treatment response

Panel 2: Recommendations for outcome definitions of antipsychotic treatment in schizophrenia

Non-response or treatment-resistant schizophrenia

Diagnosis of schizophrenia, treatment adherence, and any of:

- Lifetime clozapine use
- Antipsychotic switching (two or more antipsychotic trials of adequate dose and duration)
- Electroconvulsive therapy
- Admission to hospital during treatment
- Self-reported non-response after two or more antipsychotic trials

Response or non-resistance

Diagnosis of schizophrenia, treatment adherence, or any of:

- No history of clozapine treatment
- No history of electroconvulsive therapy
- History of stable treatment
- No admission to hospital during treatment
- Self-reported treatment response

Panel 3: Recommendations for outcome definitions of treatment in bipolar disorder

Non-response or treatment-resistant bipolar disorder

Diagnosis of bipolar disorder, treatment adherence, and any of:

- Medication switching—two or more trials of medications (different criteria for non-response and treatment resistance during maintenance treatment, mania, or bipolar depression), of adequate dose and duration
- Admission to hospital during treatment (maintenance, mania, or depression)
- Neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation) during treatment (maintenance, mania, or bipolar depression)
- Treatment with ketamine or esketamine
- Lifetime clozapine use
- Polypharmacy (combined treatment with three or more medications for maintenance treatment, treatment of mania, or treatment of bipolar depression)
- Self-reported non-response after two or more trials of medications (for maintenance treatment, treatment of mania, or treatment of bipolar depression)

Response or non-resistance

Diagnosis of bipolar disorder, treatment adherence, or any of:

- History of stable treatment
- No history of clozapine treatment
- No history of neurostimulation (electroconvulsive therapy or transcranial magnetic stimulation)
- No admission to hospital during treatment
- Self-reported treatment response

Koch et al. 2025

Major depression

	Criteria
Real-world data from population-wide health registries	
Diagnosis	Diagnosis of major depressive disorder is required and should be obtained from specialist health care or primary health care (ICD-10)
Antidepressant treatment	Medication use from prescription registry: ATC codes N06A, ketamine (N01AX03), and esketamine (N01AX14)
Indication	Indication can be extracted from free text of prescriptions; indications other than depression (eg, pain or sleeping problems) should not be considered as antidepressant treatment
Antidepressant switching	Medication use from prescription registry (ATC codes N06A); treatment-resistant depression should be defined as two or more antidepressant switches, and each switch should be between 6 weeks (for adequate treatment duration) and 14 weeks (to exclude treatment interruption) after the previous antidepressant prescription
Augmentation or combination therapy	Augmentation of (or combination with) another antidepressant or antipsychotic or lithium
Stable treatment (as proxy for response)	Treatment for ≥6 months
Adequate treatment duration	Obtained from prescription registry; should be ≥6 weeks to reduce the risk of switches due to side-effects
Adequate dose	Daily dose from prescription registry; should have minimal dose recommended for major depression
Admission to hospital	Admission to hospital due to a depressive episode (during or shortly after antidepressant treatment)
Comorbidity	Other psychiatric diagnoses should be excluded if one is the main diagnosis (eg, bipolar disorder)
Functional outcomes	Functional outcomes such as employment
Neurostimulation (ECT or TMS)	Neurostimulation during antidepressant treatment
Ketamine or esketamine treatment	Treatment with ketamine or esketamine during antidepressant treatment
Adherence	By using prescription registry data , the ratio between prescribed and dispensed medication can be calculated to estimate adherence; from therapeutic drug monitoring, non-detectable drug concentrations can be used as indicator of non-adherence; non-adherence should be excluded
Real-world data from routinely collected questionnaires or self-reports	
Treatment with antidepressant, ketamine, or esketamine	Patient-reported medication history can be used if registry data are incomplete
Treatment non-response or treatment resistance	Self-reported non-response after two or more antidepressant trials
Side-effects	Switches due to side-effects should not be considered as non-response
Adherence	Adherence measured in patient reports should only be used when no other adherence measures (such as drug concentrations from therapeutic drug monitoring) are available; for therapeutic drug monitoring, non-detectable drug concentrations can be used as indicator of non-adherence; non-adherence should be excluded

ATC=Anatomical Therapeutic Chemical classification system. ECT=electroconvulsive therapy. TMS=transcranial magnetic stimulation.

***Table 1*: Recommendations for measuring treatment outcomes in major depressive disorder**

Koch et al. 2025

Schizophrenia

	Criteria
Real-world data from population-wide health registries	
Diagnosis	Diagnosis of schizophrenia is required and should be obtained from specialist health care or primary health care (ICD-10)
Lifetime clozapine treatment	Medication use from prescription registry (ATC code N05AH02) or from clozapine registries
Antipsychotic switching	Medication use from prescription registry (ATC codes N05A); treatment resistance is defined as two or more antipsychotic switches, and each switch should be between 6 weeks (for adequate treatment duration) and 14 weeks (to exclude treatment interruption) after the previous antipsychotic prescription
Stable treatment (as proxy for response)	Treatment for ≥6 months of the same antipsychotic
Adequate treatment duration	Obtained from prescription registry; should be ≥6 weeks to reduce the risk of switches due to side-effects
Adequate dose	Daily dose from prescription registry; should have minimal dose recommended for schizophrenia
Admission to hospital	Admission to hospital due to schizophrenia during antipsychotic treatment
ECT	ECT during antipsychotic treatment
Comorbidity	Other psychiatric diagnoses should be excluded if one is the main diagnosis
Functional outcomes	Functional outcomes such as employment
Adherence	By using prescription registry data, the ratio between prescribed and dispensed medication can be calculated to estimate adherence; from therapeutic drug monitoring, non-detectable drug concentrations can be used as indicator of non-adherence; non-adherence should be excluded
Real-world data from routinely collected questionnaires or self-reports	
Lifetime clozapine treatment	Patient-reported medication history can be used if registry data are incomplete
Treatment non-response or treatment resistance	Self-reported non-response after two or more antipsychotic trials
Side-effects	Switches due to side-effects should not be considered as non-response
Adherence	Adherence measured in patient reports should only be used when no other adherence measures (such as drug concentrations from therapeutic drug monitoring) are available; for therapeutic drug monitoring, non-detectable drug concentrations can be used as indicator of non-adherence; non-adherence should be excluded

ATC=Anatomical Therapeutic Chemical classification system. ECT=electroconvulsive therapy.

Table 2: **Recommendations for measuring treatment outcomes in schizophrenia**

Koch et al. 2025

Bipolar disorder

	Criteria
Real-world data from population-wide health registries	
Diagnosis	Diagnosis of bipolar disorder is required and should be obtained from specialist health care or primary health care (ICD-10)
Bipolar treatment	Medication use from prescription registry: ATC code N05AN01 (lithium), N03A (antiepileptics), N05A (antipsychotics), N06A (antidepressants), ketamine (N01AX03), and esketamine (N01AX14)
Polypharmacy	
Non-response or treatment resistance in maintenance treatment	Combined treatment with three or more medications to treat bipolar disorder (lithium, antiepileptics, antipsychotics, or antidepressants)
Non-response or treatment resistance in mania	Combined treatment with three or more antimanic drugs (lithium, antiepileptics, or antipsychotics with indication for mania)
Non-response or treatment resistance in bipolar depression	Combined treatment with three or more treatments for bipolar depression (antidepressants, antiepileptics, ketamine, esketamine, or antipsychotics with indication for bipolar depression)
Medication switching	
Non-response or treatment resistance in maintenance treatment	Two or more switches between different medications to treat bipolar disorder (lithium, antiepileptics, antipsychotics, or antidepressants), regardless of monotherapy or combination therapy
Non-response or treatment resistance in mania	Two or more switches between different medications to treat mania (lithium, antiepileptics, or antipsychotics with indication for mania), regardless of monotherapy or combination therapy
Non-response or treatment resistance in bipolar depression	Two or more switches between treatments for bipolar depression (antidepressants, antiepileptics, ketamine, or antipsychotics with indication for bipolar depression), regardless of monotherapy or combination therapy
Lifetime clozapine treatment	Medication use from prescription registry: ATC code N05AH02
Stable treatment (maintenance)	Treatment for ≥6 months with one or two drugs to treat bipolar disorder (lithium, antiepileptics, antipsychotics, or antidepressants)
Adequate treatment duration	Obtained from prescription registry; should be ≥6 weeks to reduce the risk of switches due to side-effects
Adequate dose	Daily dose from prescription registry; should have minimal dose recommended for bipolar disorder
Admission to hospital	Admission to hospital during mania (to identify manic episodes), during bipolar depression (to identify depressive episodes), or during maintenance treatment for bipolar disorder (to identify treatment strategies that did not prevent future episodes)
Comorbidity	Other psychiatric diagnoses should be excluded if one is the main diagnosis
Functional outcomes	Functional outcomes such as employment
Neurostimulation (ECT or TMS)	Neurostimulation during pharmacological treatment for bipolar disorder
Ketamine or esketamine	Treatment with ketamine or esketamine during a depressive episode (to define non-response or treatment resistance in bipolar depression)
Adherence	By using prescription registry data, the ratio between prescribed and dispensed medication can be calculated to estimate adherence; from therapeutic drug monitoring, non-detectable drug concentrations can be used as indicator of non-adherence; non-adherence should be excluded
Real-world data from routinely collected questionnaires or self-reports	
Bipolar treatment	Patient-reported medication history can be used if registry data are incomplete
Polypharmacy	Patient-reported history on combination treatment for bipolar disorder (lithium, antiepileptics, antipsychotics, or antidepressants) to define non-response or treatment resistance in mania, depression, maintenance (same criteria as for registry data)
Lifetime clozapine treatment	Patient-reported medication history can be used if registry data are incomplete
Treatment non-response or treatment resistance	Self-reported non-response after two trials or more of pharmacological treatment for bipolar disorder to define non-response or resistance in mania, depression, maintenance (same criteria as for registry data)
Functional outcomes	Patient-reported information about functional outcomes such as employment
Side-effects	Switches due to side-effects should not be considered as non-response
Adherence	Adherence measured in patient reports should only be used when no other adherence measures such as drug concentrations from therapeutic drug monitoring are available; non-adherence should be excluded

ATC=Anatomical Therapeutic Chemical classification system. ECT=electroconvulsive therapy. TMS=transcranial magnetic stimulation.

***Table 3*: Recommendations for measuring treatment outcomes in bipolar disorder**

Koch et al. 2025

Presicion psychiatry

REALMENT

- Psychiatry: difficult with stratification based on mechanism
- Data access: RCT too small – need real-world data
- Academia – Industry: validation

Genetics and drug response – «stratification»

Large variation in treatment response

Large variation in adverse effects

Trial-and-error approach

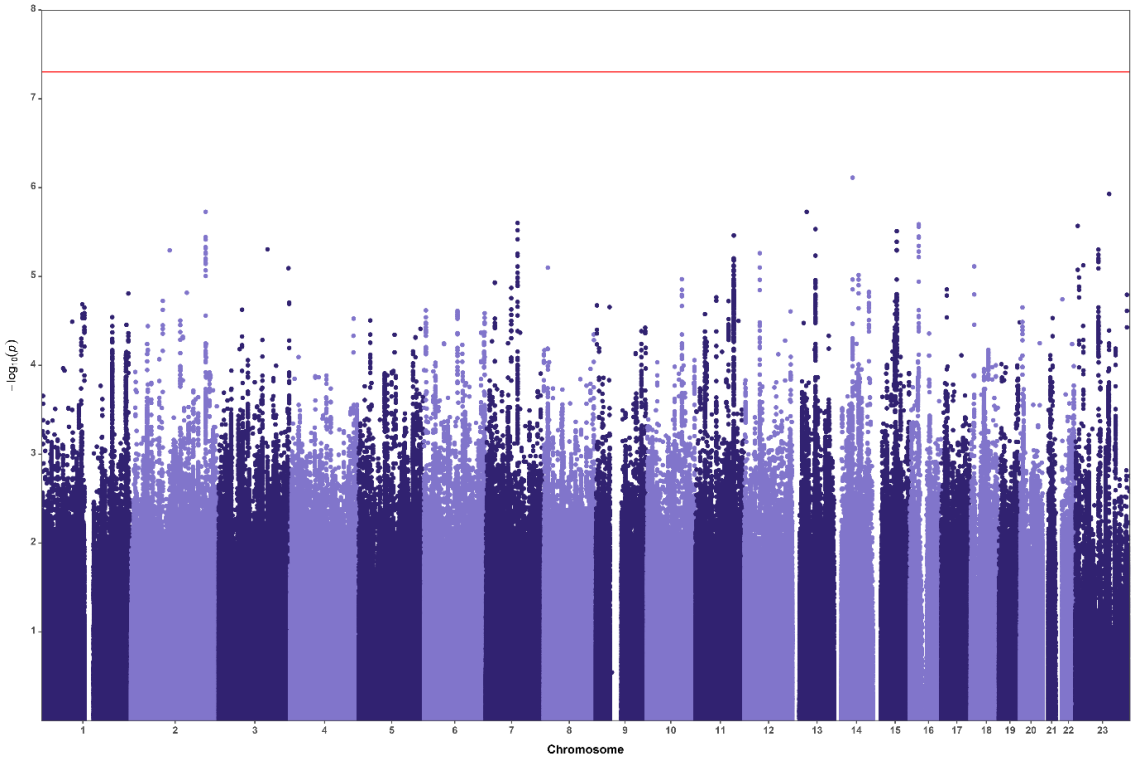
Can genetic variants predict response/adverse effects of psycho-pharmacology agents?

- precision medicine in psychiatry

Need large training data (GWAS)

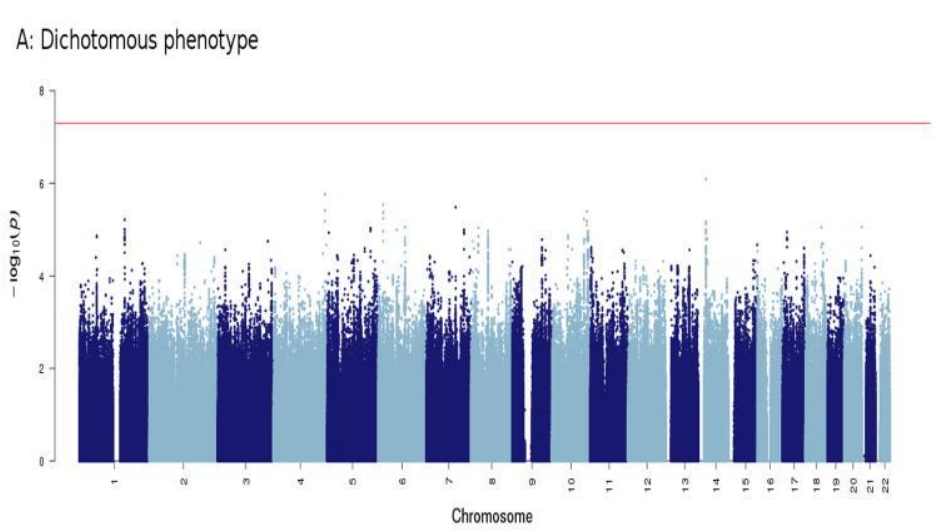
Meerman et al. *J Affect Disord 2022,*
McIntyre *et al. Lancet 2020,*
Jauhar *et al. Lancet 2022*

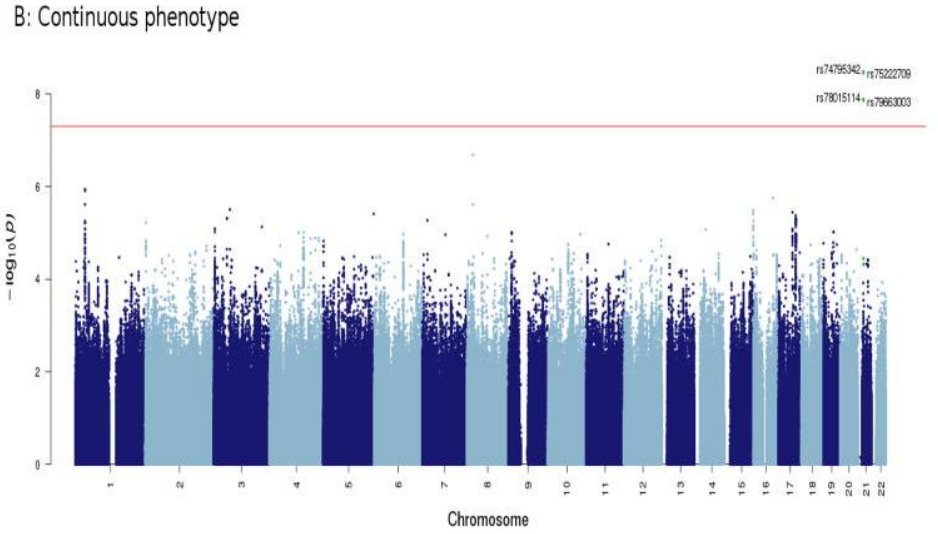
Genetic variants associated with non-response antipsychotics



Pardinas et al., *JAMA Psychiatry* 2022

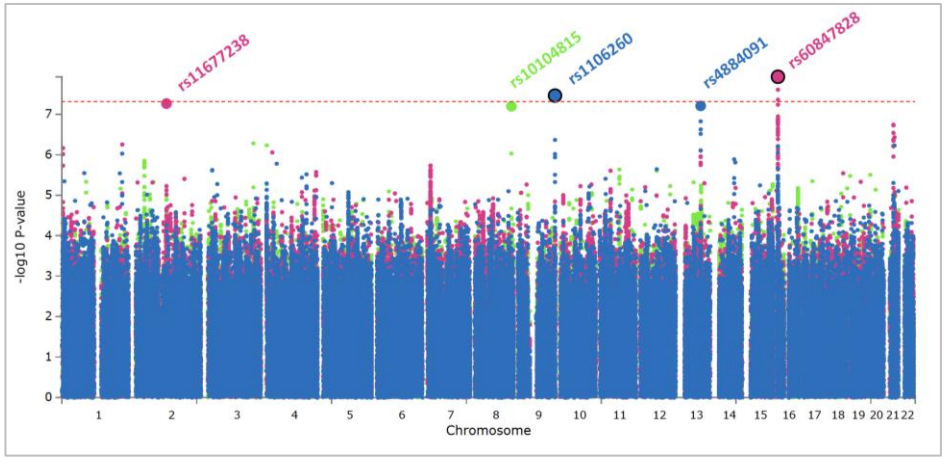
Genetic variants associated with lithium response



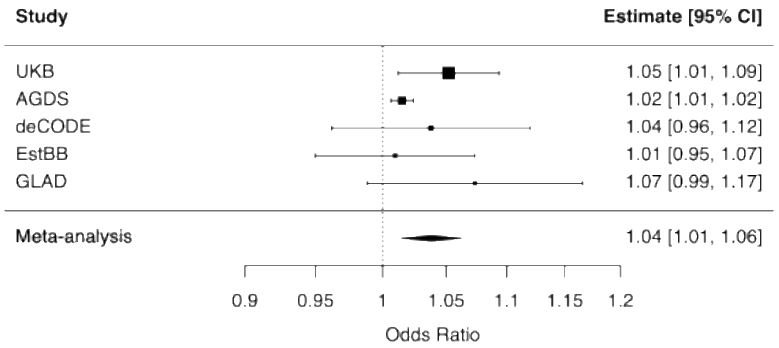


Hou et al., *Lancet* 2016

Genetic variants associated with antidepressant non-response



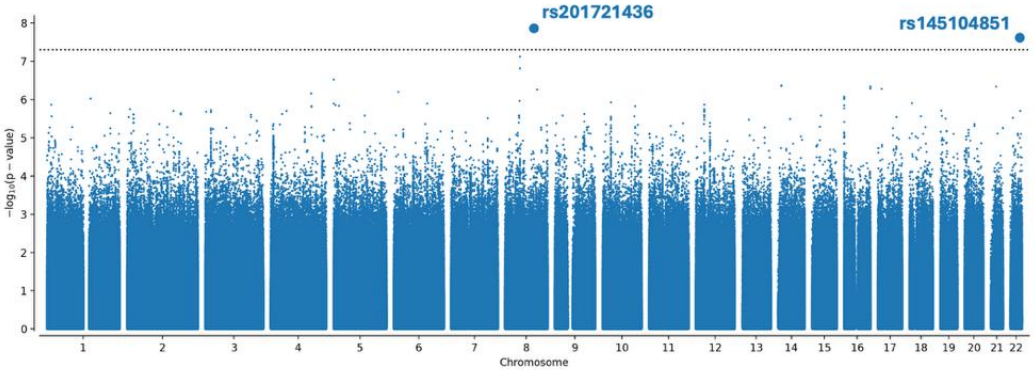
Non-response to SSRIs (blue), SNRIs (green), and SSRIs or SNRIs (pink).



Leave-one-out polygenic prediction of non-response to SSRIs

Koch et al., *Molecular Psychiatry* 2025

Genetic variants associated with treatment-resistant depression

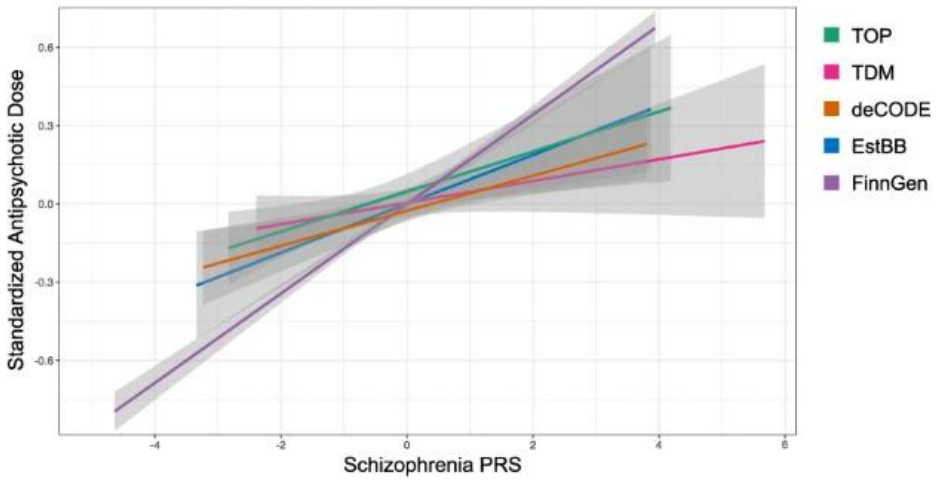


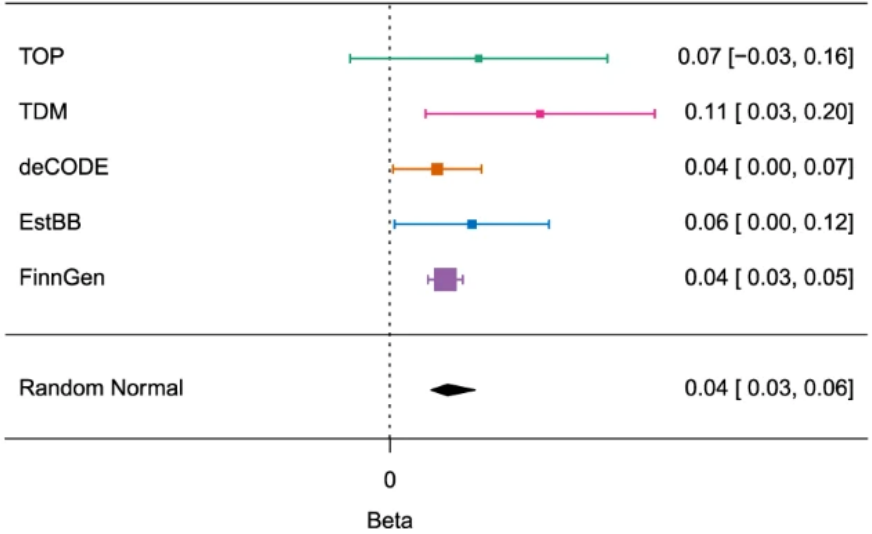
Genome-wide meta-analysis of treatment-resistant depression (registry-based and harmonized across cohorts) identifies two novel loci

Cohorts with prescription registry data and genetics	N total
Estonia (EstBB)	200,000
Sweden (various)	200,000
Finland (FinnGen)	500,000
Iceland (deCODE)	173,000
Denmark (iPsych)	300,000
Norway (MoBa, HUSK, Tromsø)	350,000
UKB	230,000
AGDS*	13,000
AllofUS (v8)	450,000

Koch et al. subm.

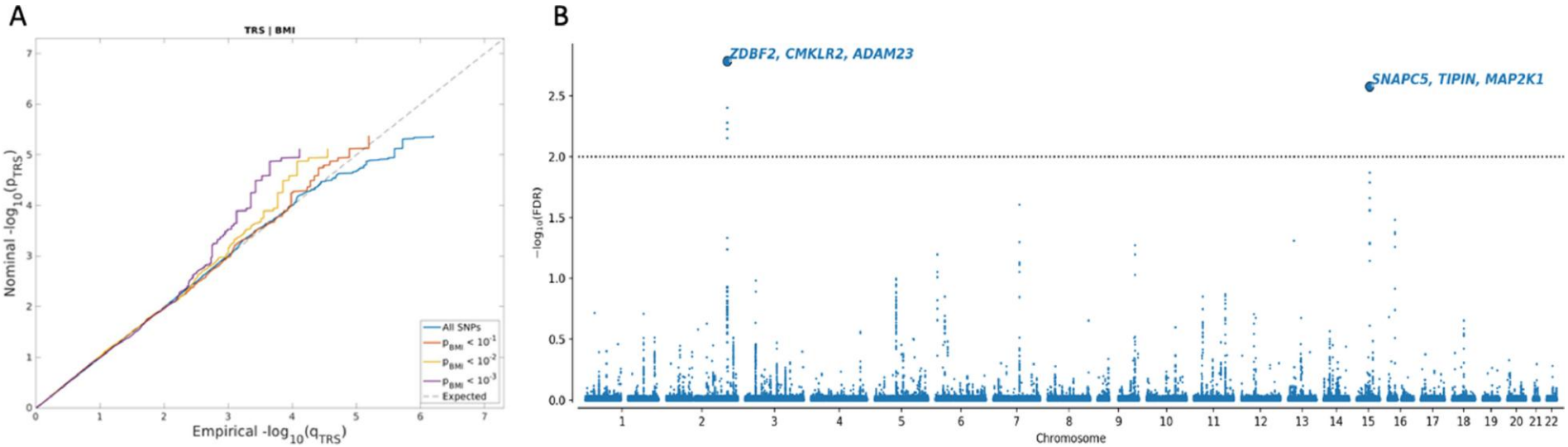
Association between schizophrenia polygenic risk score (PRS) and standardized antipsychotic dosage (DDD method) across all antipsychotics





Koch et al. *Neuropsychopharmacology* 2024

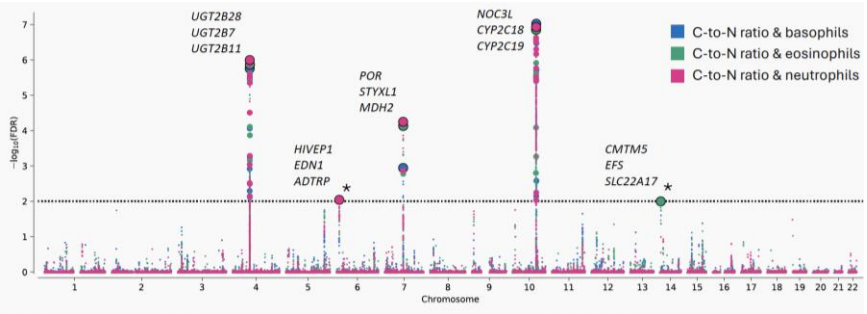
Polygenic overlap with body-mass index improves prediction of treatment-resistant schizophrenia (TRS)

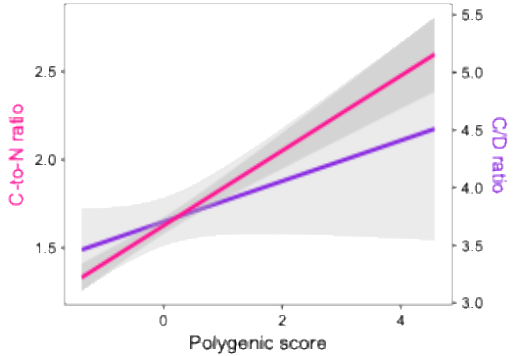


O'Connell et al. *Psychiatry Res* 2023

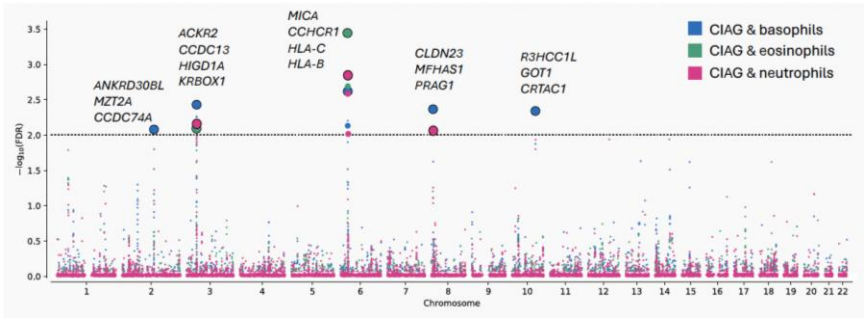
Polygenic overlap with granulocyte counts identifies novel loci for clozapine metabolism and clozapine-induced agranulocytosis

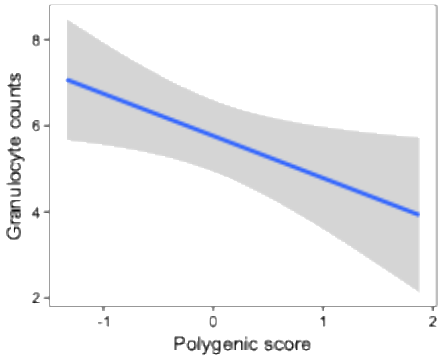
Clozapine metabolism (C-to-N ratio)





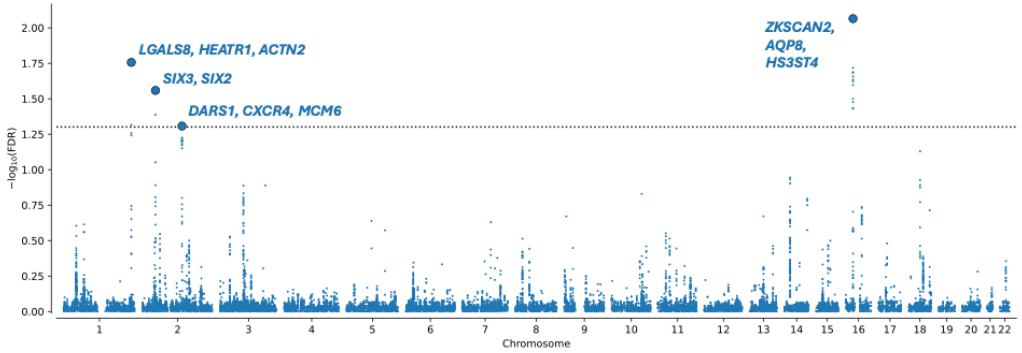
Clozapine-induced agranulocytosis

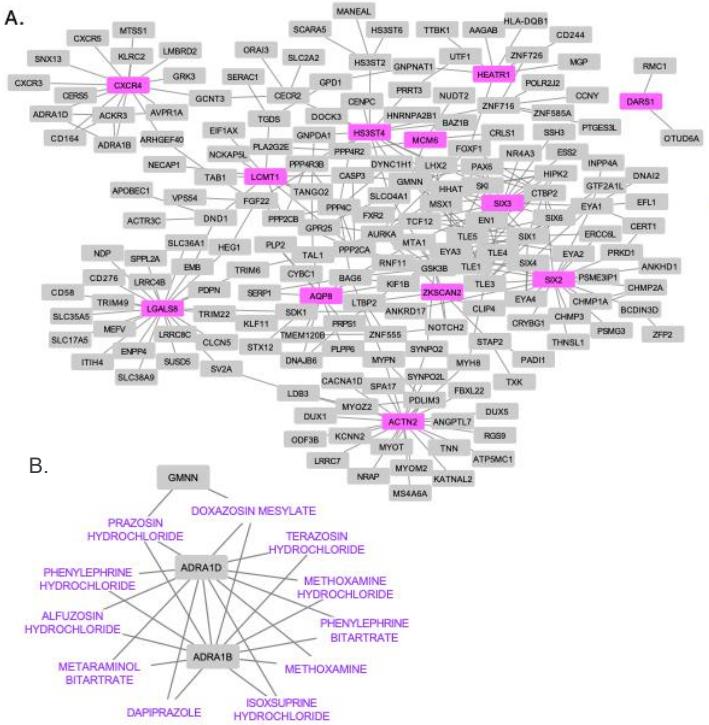




Koch et al. *Neuropsychopharmacology* 2025

Genetic overlap between treatment-resistant schizophrenia and smoking initiation



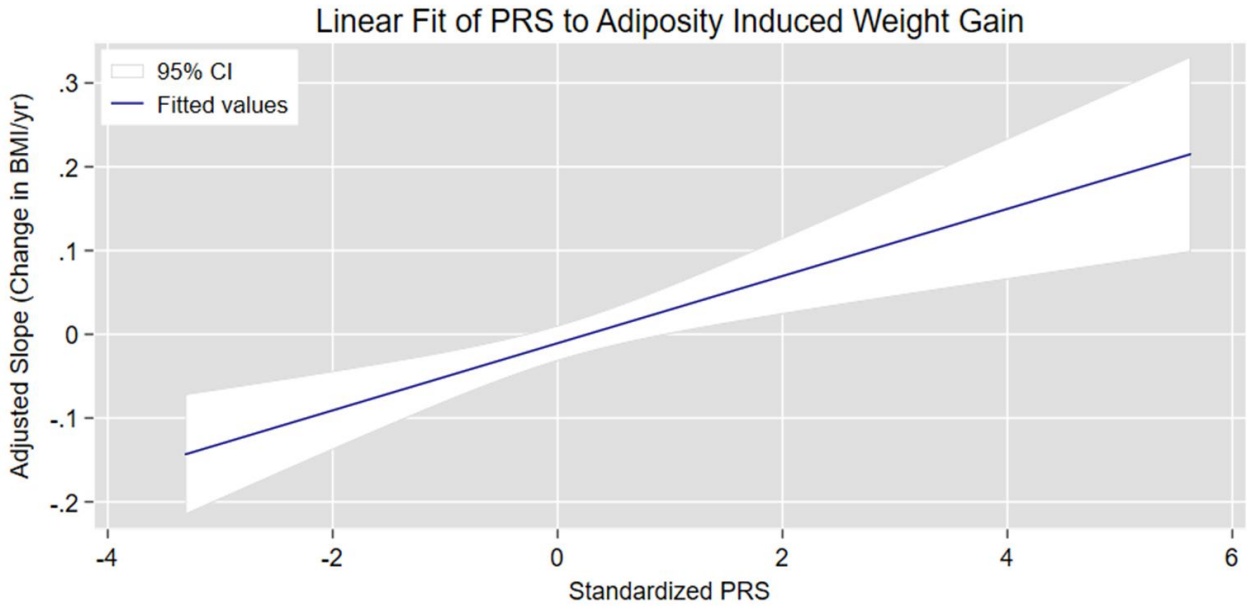


- Four novel loci jointly associated with treatment-resistant schizophrenia and smoking initiation
- Network-based analyses suggest alpha-1-adrenergic receptor antagonists for treatment-resistant schizophrenia

Koch et al, subm

Genetics of Antipsychotic-Induced Weight Gain

BMI PRS is positively associated with antipsychotic-induced weight gain.



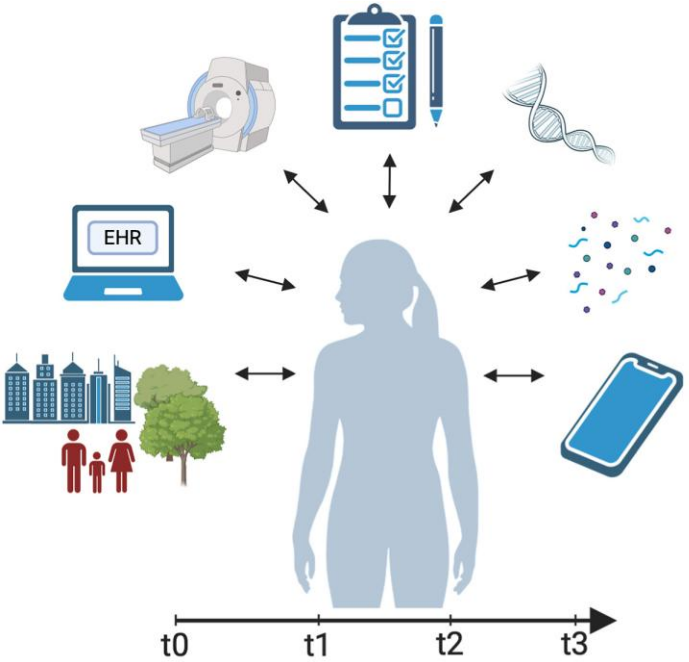
Nicol et al., *WCPG* 2023

Bottlenecks real-world Nordic data

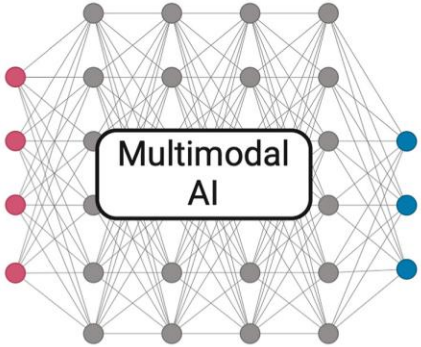
- Data access
  - no restriction who can access, but cannot move out of country
  - Need expertise on the system - how to apply
  - More complicated with multimodal data (biobank, registry)
- Data quality
  - Universal coverage, whole population
  - Presciption registry include also primary care
  - Building on real world data – Scandinavian hospital to ranked (Newsweek2025)
- Academia – Industry
  - New initatives in most countries, e.g. FinnGen
  - Governments support collaboration with industry – pharma companies

Real-world safety surveillance

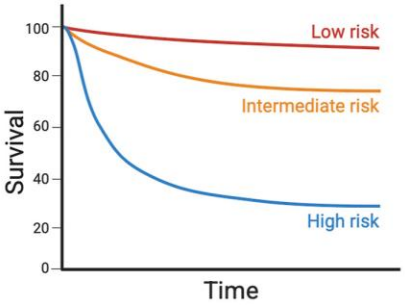
Artificial Intelligence (AI)



Multiple data modalities are relevant to bipolar disorder



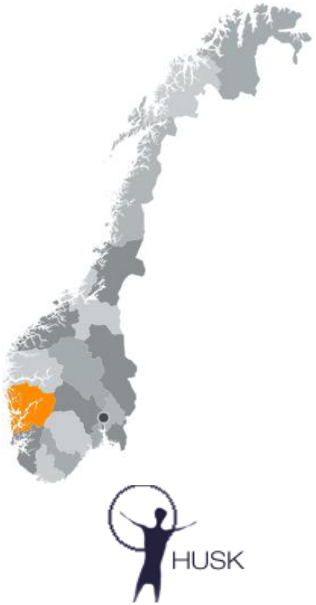
AI model processes and integrates multimodal data

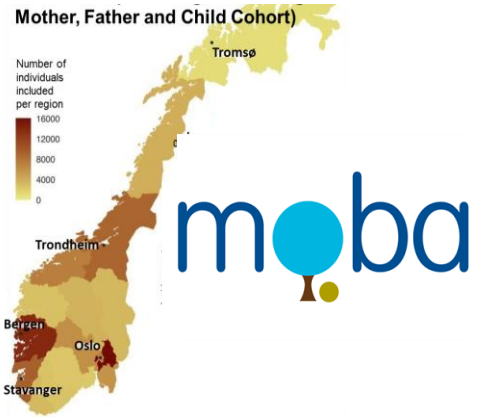


Improve diagnosis, prognosis, treatment, prevention

Smeland et al. *Biol Psychiatry* 2025

Norwegian population surveys: 400k RWD and genotypes





Norwegian population studies

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- JCVI – Anders Dale
- PGC
- ENIGMA

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EU H2020, Horizon Europe

NIH, Wellcome Trust

KG Jebsen

CoMorMent, RealMent

CoMorMent

The CoMorMent project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under Grant agreement 847776

PGC Psychiatric Genomics Consortium

Biobank Norway

REALMENT

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