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Article

Genomics Research of Lifetime Depression in the Netherlands: The BIObanks Netherlands Internet Collaboration (BIONIC) Project

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Abstract

In this cohort profile article we describe the lifetime major depressive disorder (MDD) database that has been established as part of the BIObanks Netherlands Internet Collaboration (BIONIC). Across the Netherlands we collected data on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) lifetime MDD diagnosis in 132,850 Dutch individuals. Currently, $N = 66{,}684$ of these also have genomewide single nucleotide polymorphism (SNP) data. We initiated this project because the complex genetic basis of MDD requires large population-wide studies with uniform in-depth phenotyping. For standardized phenotyping we developed the LIDAS (LIfetime Depression Assessment Survey), which then was used to measure MDD in 11 Dutch cohorts. Data from these cohorts were combined with diagnostic interview depression data from 5 clinical cohorts to create a dataset of $N = 29{,}650$ lifetime MDD cases (22%) meeting *DSM-5* criteria and 94,300 screened controls. In addition, genomewide genotype data from the cohorts were assembled into a genomewide association study (GWAS) dataset of $N = 66{,}684$ Dutch individuals (25.3% cases). Phenotype data include *DSM-5*-based MDD diagnoses, sociodemographic variables, information on lifestyle and BMI, characteristics of depressive symptoms and episodes, and psychiatric diagnosis and treatment history. We describe the establishment and harmonization of the BIONIC phenotype and GWAS datasets and provide an overview of the available information and sample characteristics. Our next step is the GWAS of lifetime MDD in the Netherlands, with future plans including fine-grained genetic analyses of depression characteristics, international collaborations and multi-omics studies.

Keywords: national cohort studies; MDD assessment; GWAS resource; cohort description paper

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Major depressive disorder (MDD) is a mental health condition characterized by decreased mood and anhedonia that severely impacts quality of life. It affects up to 20% of the population across the lifetime and is a leading contributor to disability worldwide (Kessler & Bromet, 2013; Marx et al., 2023; World Health Organization [WHO], 2017). MDD is referred to as a complex trait in that it is affected by numerous environmental and genetic factors. MDD runs in families and twin and family studies estimate that approximately 35% of the variation in MDD status is due to genetic factors (Flint & Kendler, 2014).

Similar to the efforts for many other psychiatric disorders, the significant heritability of MDD has stimulated large-scale genome-wide association studies (GWAS) and genomewide association meta-analyses (GWAMA) aimed at the identification of genomic

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variants associated with disease status (Uffelmann et al., 2021). One of the first GWA projects was initiated in the Netherlands (Sullivan et al., 2009) in 1738 MDD cases and 1802 controls. The sample size in this study was small by current standards, but the gene detected in this study (*PCLO*) was later confirmed in large collaborative projects (Howard et al., 2019). We now increasingly realize that identifying genetic risk factors for any complex trait within psychiatry, psychology or medicine requires very large sample sizes in order to detect the small effects of hundreds of variants scattered across the genome composing their polygenic architecture.

Due to the higher prevalence and lower heritability of MDD, three to five times as many cases are required to detect the same number of genomewide significant genetic variants as compared to less prevalent psychiatric disorders with a higher heritability, such as schizophrenia (Levinson et al., 2014; Wray et al., 2018). Recent GWA efforts for MDD have focused on boosting sample size by combining datasets with very broad phenotyping sources, including psychiatrically ascertained clinical diagnosis, self-reported clinical diagnosis or self-reported symptom/questionnaire data. This approach has indeed increased the number of significant hits in MDD and depression GWAS (Howard et al., 2019; Levey et al., 2021). However, there is an important and ongoing debate that considers the dilemma of broad phenotyping to maximize sample size and thus statistical power in genetic association studies, versus in-depth phenotyping, often resulting in smaller samples. Although the former approach has been successful in increasing the number of significant genetic hits, it has also been criticized for a possible lack of specificity; genetic variants associated with broad phenotypes may be nonspecific to MDD and instead apply to a wider spectrum of psychopathology (Cai et al., 2020). Flint (2023) suggested that employing minimal phenotyping strategies may render a substantial portion of the genetic foundation of MDD inaccessible, due to their limited specificity.

To help resolve the dilemma, larger datasets that include a uniform assessment of MDD and adhere to clinical criteria are warranted, such as those defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*; American Psychiatric Association, 2013). This need incited the establishment of the BIObanks Netherlands Internet Collaboration (BIONIC). BIONIC was established within the Biobanking and BioMolecular resources Research Infrastructure (BBMRI-NL). The BIONIC collaboration combines genotype and depression data from Dutch cohorts initiated by different academic groups across the Netherlands (see Figure 1) to study the causes of individual differences in MDD from a genetic perspective. With the inclusion of large population-based cohorts and some clinical studies, the participants in the BIONIC study form a good representation of the Dutch population. BIONIC sought to adhere to the clinical definition of MDD and initiated development of a new depression instrument to efficiently and uniformly assess MDD status in ongoing studies of which the majority has already gathered genomewide genotype information. This instrument, the LIfetime Depression Assessment Survey (LIDAS), was developed, validated and further tested in a series of studies with concurrent measures of depression and wellbeing (Barbu et al., 2021; Bot et al., 2017; Fedko et al., 2020; Huider et al., 2021; van de Weijer et al., 2022; Vreijling et al., 2023).

For genetic projects, we have created an infrastructure to combine the MDD phenotype data obtained with LIDAS and other established psychiatric interviews and genotype data from participants from 16 Dutch cohorts into a dataset spanning over 130,000 individuals. Our aim was to reduce heterogeneity in phenotypic assessment of MDD and to carry out GWAS in a single, relatively homogeneous population. This article aims to serve as a description of the BIONIC resources; we describe the project establishment and infrastructure, the phenotype harmonization process across cohorts and genotype data pipelines, the features of the BIONIC database, and offer some reflections on the process and next steps.

Materials and Methods

Table 1 provides an outline of the multiple steps in our collaborative project. In step 1 we developed the project idea within the BBMRI-NL framework (https://www.bbmri.nl/). BBMRI-NL coordinates collaborations between Dutch cohort studies and biobanks to maximize the use of phenotype information, biosamples, imaging, omics and other data for genetic and health research. BIONIC is a collaborative effort with the two-part goal of providing a proof-of-concept for harmonized measurement of phenotypes in ongoing biobank studies, a key aspect of BIONIC's philosophy being the uniform online assessment of major depression status in studies and biobanks with existing genotype data. To this end we designed a structured and efficient online instrument to assess *DSM-5*-based diagnosis of depression: the LIfetime Depression Assessment Survey (LIDAS; Bot et al., 2017). The LIDAS was validated in step 2 against the Composite International Diagnostic Interview (CIDI; Kessler, Wittchen et al., 1998), considered the gold standard. The development of the LIDAS allowed for the efficient expansion of sample size for genetically informed approaches.

In step 3, cohorts and biobanks across the Netherlands were contacted and asked for their interest in participating in a uniform phenotyping effort for MDD, offering to facilitate the online data collection as well as financial reimbursement to the cohort. In step 4, the LIDAS data were analyzed and phenotype characteristics described. The prevalence based on the LIDAS data analyses was 6.7% for current depression and 18.1% for lifetime MDD. These percentages are in line with population estimates in the Netherlands (Bijl et al., 1998; Fedko et al., 2020; see also: https://www.trimbos.nl/kennis/cijfers/depressie/). Heritability based on a combined analysis of twin and extended family data was estimated at 34% for lifetime MDD (Huider et al., 2021).

To carry out genetic association studies, a challenging step (5) consisted of enabling cohorts and biobanks to share all phenotype and genotype data at the HPC Gearshift facility of the Genomics Coordination Center (GCC; https://docs.gcc.rug.nl/gearshift/cluster/) in Groningen, the Netherlands. All cohorts needed to sign data transfer agreements for this purpose. A standard operating procedure was developed to guide the initial preparation and upload of the phenotype data and genotype data to the HPC cluster.

In step 6, the phenotype harmonization involved defining case-control status based on LIDAS data or *DSM-5*-based interviews. A pipeline was developed to process the different genotype arrays and for imputation against the Human Reference Consortium panel (v1.1; McCarthy et al., 2016).

In a future step 7 we aim to carry out both a GWA analysis of the data in SAIGE (Scalable and Accurate Implementation of GEneralized mixed model; Zhou et al., 2018), which is suited for the analysis of binary traits in related individuals.

Phenotype Data

Harmonized assessment of major depression in the participating cohorts was primarily achieved through the LIDAS instrument.

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Table 1. Timeline of stages in the BIONIC project

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7
Study design, BBMRI-NL funding, instrument development (LIDAS).	Pilot study and LIDAS validation (Bot et al., 2017). $N = 245$	Study recruitment and LIDAS data collection.	MDD prevalence and SNP-h^2 in BIONIC LIDAS subsample (Fedko et al., 2020). $N = 22{,}624$	Non-LIDAS study recruitment and centralization of phenotype and genotype data.	Phenotype harmonization and genotype QC and imputation.	Genomewide association analysis of MDD in the Netherlands. $N = 66{,}648$
2015	2016–2017	2017–2019	2019–2020	2020–2022	2022–2023	2023–2024

Note: BBMRI-NL, Biobanking and BioMolecular resources Research Infrastructure; LIDAS, LIfetime Depression Assessment Survey; MDD, major depressive disorder; SNP-h^2, single nucleotide polymorphism heritability; BIONIC, BIObanks Netherlands Internet Collaboration; QC, quality control.

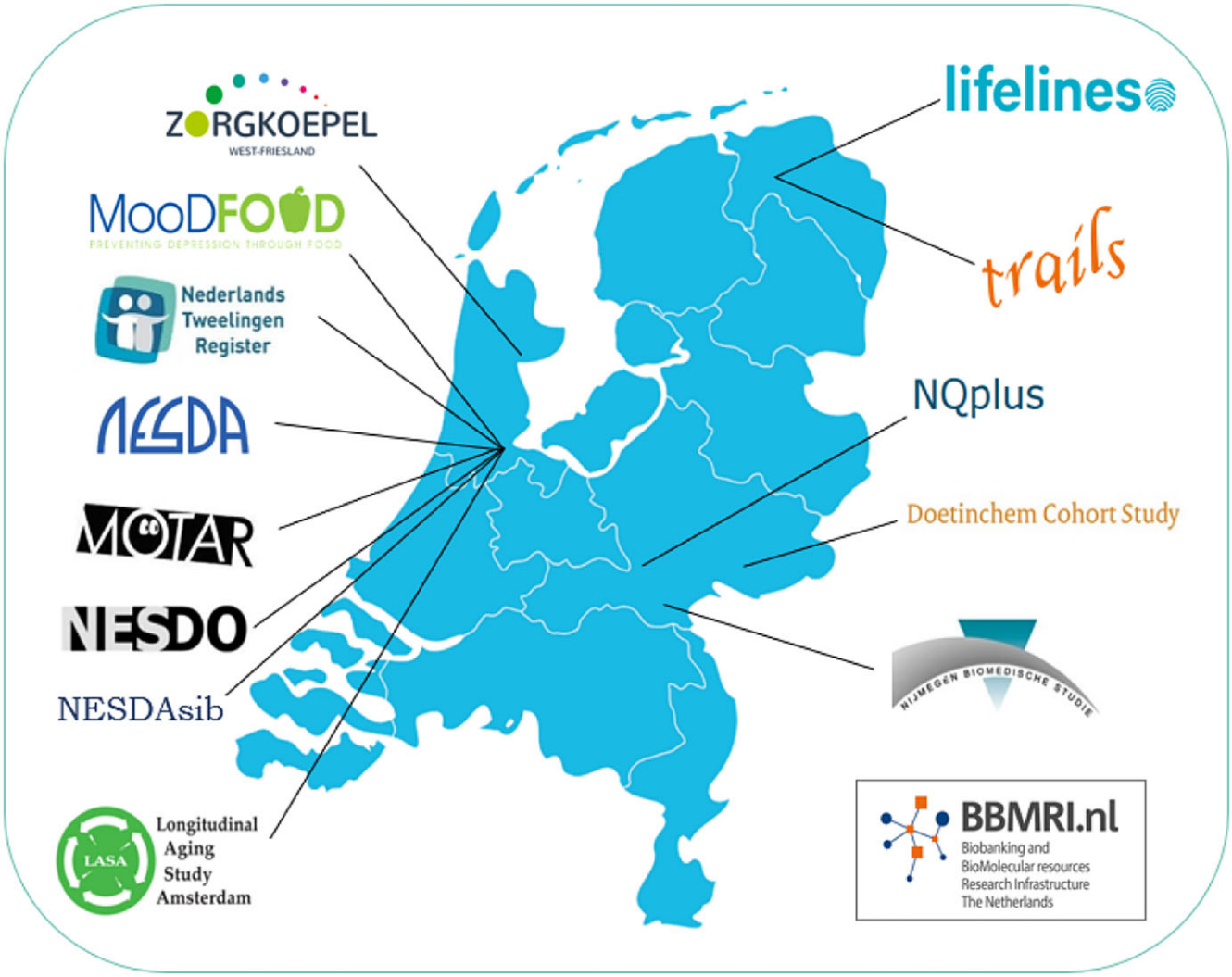

Figure 1. Map of the Netherlands and primary location of BIONIC cohorts.
Note: MooDFOOD, Multi-country cOllaborative project on the rOle of Diet, Food-related behavior, and Obesity in the prevention of Depression; NESDA, Netherlands Study of Depression and Anxiety; MOTAR, MOod Treatment with Antidepressants or Running; NESDO, Netherlands Study of Depression in Older persons; NESDAsib, Netherlands Study of Depression and Anxiety sibling cohort; TRAILS, Tracking Adolescents' Individual Lives Survey; NQplus, Nutrition Questionnaires plus.

A detailed description of the development and validation of the LIDAS instrument can be found in Bot et al. (2017). In short, LIDAS is an online self-report survey based on the CIDI short form (CIDI-SF; Kessler, Andrews et al., 1998), which assesses the presence of major depression symptoms as defined by the *DSM-5*. The LIDAS content can be divided into three sections: (1) demographics and lifestyle factors, (2) depression symptoms and episode characteristics, and (3) diagnostic and treatment history. Sections 1 and 3 are completed by all individuals. The first items of section 2 pertain to the cardinal symptoms of major depression,

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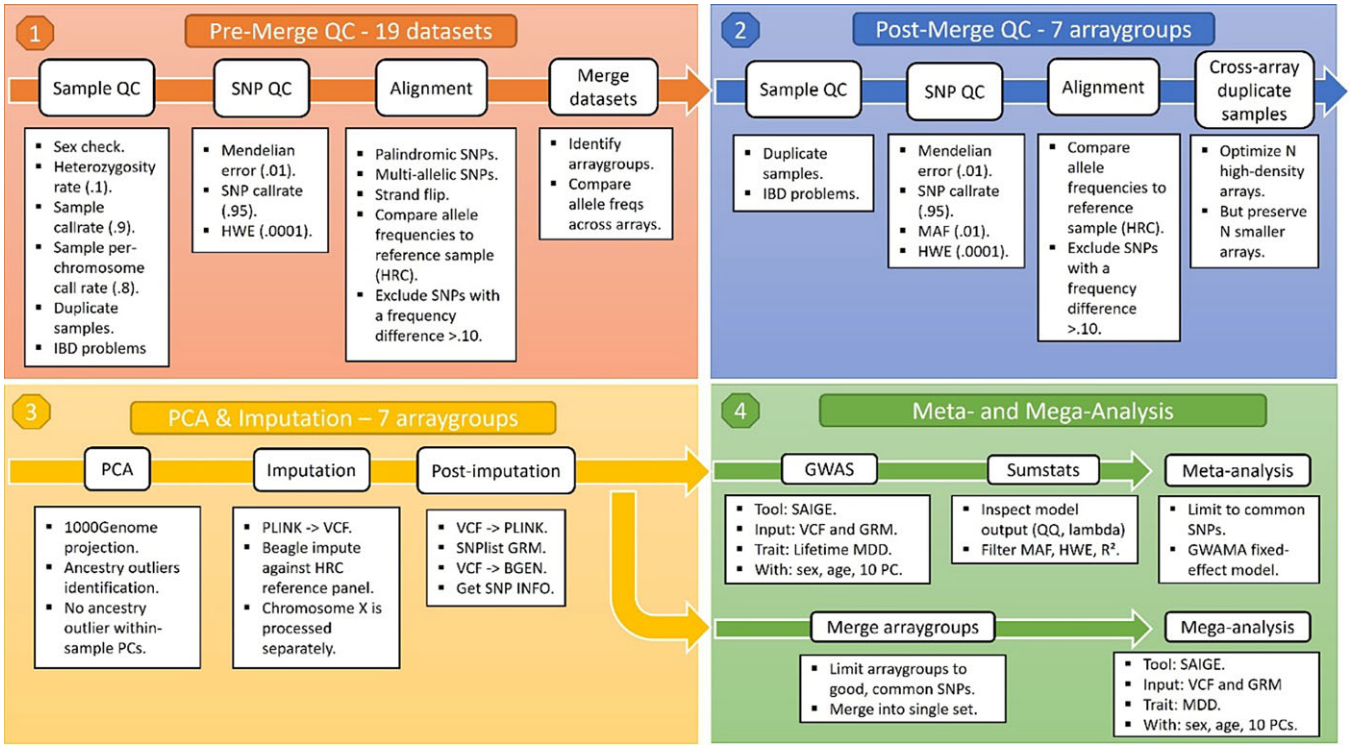

Figure 2. Overview of BIONIC genotype pipeline.
Note: QC, quality control; SNP, single nucleotide polymorphism; HWE, Hardy Weinberg equilibrium; PC, principal component; GRM, genetic relationship matrix; HRC, human reference consortium; MAF, minor allele frequency; GWAS, genomewide association study; GWAMA, genomewide association meta-analysis; MDD, major depressive disorder.

decreased mood and anhedonia; individuals with one or more cardinal symptoms are asked about accessory symptoms and episode characteristics, while individuals without cardinal symptoms are immediately redirected to the next section for efficient control identification. Cohorts were offered the option to add extra items to the online instrument, such as questions about wellbeing or zygosity. The LIDAS showed good sensitivity (.85) and specificity (.80) when compared to the CIDI (Bot et al., 2017). In BIONIC, additional depression information was obtained from the CIDI and Mini-International Neuropsychiatric interview (MINI; Sheehan et al., 2018) diagnostic interviews provided that *DSM-5* criteria could be applied in the identification of cases, as discussed below.

MDD Definition

We settled on a uniform definition of lifetime MDD cases in accordance with *DSM-5* criteria, where a case is defined as having at least five out of nine clinical depression symptoms, of which at least one is a cardinal symptom (by definition), with dysfunctionality for a period of at least two weeks. Controls were defined as having fewer than five depression symptoms, having no cardinal symptoms (by definition), or experiencing functional impairment for less than two weeks as a result of symptoms. Extra controls, who did not complete the LIDAS, were identified based on conservative cut-offs for sum scores on depression symptom questionnaires, such as the Beck's Depression Inventory (BDI; Beck et al., 1961). Controls were screened for the presence of psychopathology when such information was available. This included screening for a diagnostic or treatment history of depression, anxiety disorder, bipolar disorder, any eating disorder, schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, phobia, attention deficit hyperactivity disorder (ADHD) or attention deficit disorder (ADD), any personality disorder, alcohol or drug addiction, or use of antidepressant medication. The presence of any one of these was sufficient for exclusion as a control.

Genotype Data

Cohorts had collected genotype data through a variety of arrays, including the Illumina Infinium General Screening Array, the Illumina Infinium Core Exome chip, the Illumina Infinium CytoSNP chip, the Illumina Infinium OmniExpress-24 Beadchip, the Affymetrix SNP array 6.0, the Affymetrix AXIOM-NL array, and the FinnGen ThermoFisher Axiom custom array. Combining multiple genotype datasets means risking stratification, which is a well-known source of false positive and false negative results in GWAS (Marchini et al., 2004). The possible sources of stratification can be controlled for at the analysis level but are best addressed during data preparation. To this end, cohorts performed only minimal preprocessing before genotype data were shared and subjected to the same quality control (QC) pipeline. The genotype pipeline is summarized in Figure 2.

Sample and single nucleotide polymorphism (SNP) QC were conducted using PLINK v1.90 and KING v2.24 (Manichaikul et al., 2010; Purcell et al., 2007). In short, samples were excluded in case of discrepancy between reported and biological sex (PLINK FchrX-coefficient < .8 for males and FchrX > .2 for females), excess heterozygosity (Fautosomes > .10 or < -.10), insufficient sample call rate (<.90) and call rate by chromosome (<.80), or incorrect

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identity-by-descent sharing between relatives. SNPs were excluded based on Hardy Weinberg Equilibrium ($p < 1 \times 10^{-4}$) and SNP call rate (<.95), as well as Mendelian error rates above 1%. Palindromic SNPs were excluded with minor allele frequency > 0.30. SNPs were aligned to the Haplotype Reference Consortium (HRC) panel (v1.1; McCarthy et al., 2016) and SNPs with an allele frequency difference > 0.10 with the reference data were also excluded.

An important caveat of a multi-cohort GWA approach is that some genotype datasets may have small sample size or contain an overrepresentation of either cases or controls, thus risking chance findings when the data from these cohorts are analyzed independently. As a solution, genotype data derived from the same genotype array were combined into seven array groups, so that each group had sufficient size for analysis and a similar case-control distribution. The new genotype array groups underwent the same SNP QC again, including the thresholds above and a minor allele frequency (MAF) threshold of 0.01. Some individuals were genotyped multiple times, sometimes across different arrays. These duplicate observations were resolved by favoring the more modern arrays. Genotype data were then phased and imputed against the HRC reference panel using the BEAGLE software (v5.1; Browning et al., 2018).

The Netherlands has a population of nearly 18 million people, living within a total area of 41,850 km^2 (16,160 sq miles) and has seen historical immigration over the centuries. In the 20th century, immigration was mainly from Indonesia; in the 1960s, from Turkey, Morocco, Italy and Spain; and in the 1970s from Suriname and the Netherlands Antilles. The Netherlands also retains regional differences; for example, a north-south gradient, which may lead to stratification and hence to false positives in GWAS (Abdellaoui et al., 2013; Francioli et al., 2014). We conducted a standard 1000 Genomes projection genetic principal component analyses (PCA) in the array groups to identify and exclude ancestry outliers (>4 *SD*s from mean of the first standardized 6 PCs). Subsequent PC analyses will be conducted in the HRC imputed data to accommodate the Dutch population substructure, as well as post-imputation platform differences and other sources of genetic stratification.

Results

Sixteen cohorts were combined in the BIONIC project: The Doetinchem Cohort Study (DCS; Picavet et al., 2017), the Hoorn Study and the New Hoorn Study (Rutters et al., 2018), the Hoorn Diabetes Care System cohort (Heijden et al., 2017), Longitudinal Aging Study Amsterdam (LASA; Hoogendijk et al., 2020), Lifelines (Sijtsma et al., 2022), the Multi-country cOllaborative project on the rOle of Diet, Food-related behavior, and Obesity in the prevention of Depression study (MooDFOOD; Cabout et al., 2017), the MOod Treatment with Antidepressants or Running study (Lever-van Milligen et al., 2019), the Netherlands Study of Depression and Anxiety (NESDA) and its sibling cohort (NESDAsib; Penninx et al., 2021), the Netherlands Study of Depression in Older Persons (NESDO; Comijs et al., 2011), the Nutritional Questionnaires plus study (NQplus; Brouwer-Brolsma et al., 2018), the Nijmegen Biomedische Studie (NBS; Galesloot et al., 2017), the Netherlands Twin Register (NTR; Ligthart et al., 2019), and the Tracking Adolescents' Individual Lives Survey (TRAILS) and its clinical cohort (TRAILS-CC; Oldehinkel et al., 2015). The Hoorn Diabetes Care System cohort, The Hoorn Study, and The New Hoorn Study were combined into one Hoorn Studies cohort, and the TRAILS and TRAILS-CC cohorts were combined into one TRAILS study cohort. A brief overview of each cohort is presented in the supplementary material. Together, these cohorts have recruited participants across the entire country of the Netherlands.

Depression, age and sex information was available for a total of $N = 132{,}850$, and lifetime MDD status could be determined for $N = 123{,}950$, with 29,650 cases and 94,300 screened controls; 4361 potential control participants were excluded as part of the screening process because they met diagnostic criteria for anxiety and/or bipolar disorder, had a history of psychopathology or had taken antidepressants. Eleven cohorts administered the LIDAS (in one, or in multiple stages; $N = 70{,}982$) and five cohorts relied on diagnostic interviews. An overview of the instruments can be found in the supplementary material. There were 79,213 women and 53,637 men, with MDD case prevalences of 28.2% and 17.6% respectively. Mean age was 48.8 years (16.1 *SD*). The sex-averaged prevalence of MDD in the full sample (23.9%) is slightly higher than that of the general population, which is primarily explained by the inclusion of the clinical depression cohorts, and the screening of controls.

Genotype information was available for $N = 66{,}648$ individuals with European ancestry, and so the BIONIC MDD GWAS sample has 16,847 cases and 49,801 screened controls. Table 2 describes the participating BIONIC cohorts in the MDD GWAS set, with number of participants by cohort, depression instruments used, cohort type, percentage female, mean age and percentage MDD cases. The relatively high percentage of cases in Lifelines can be explained by the fact that data were in part derived from the MINI questionnaire, which measured current depression and so only allowed for lifetime MDD cases to be identified. The higher prevalence in TRAILS is explained by the combination of the population-based and clinical TRAILS cohorts. The prevalence of MDD prevalences in other cohorts seems in line with expectations, with population cohorts ranging between 11.5% and 27.2% and clinical cohorts having a higher prevalence by design.

Table 3 contains an overview of the available information in the BIONIC GWAS set as well as its full phenotype dataset. Besides MDD status, available variables include individual symptoms, episode characteristics, psychiatric history, and demographic and lifestyle factors. There is a noticeable shift in the availability of symptoms 1 and 2 versus symptom 3 and beyond. This difference reflects the fact that the former were used as screening questions and so are available for nearly everyone. Subsequent symptoms and episode characteristics are generally available only to those who passed the screening questions, which predominantly comprises MDD cases but also some controls (at a ratio of about 2.5 to 1). The psychiatric history category includes information on ever having been diagnosed for (and/or subsequently treated for) a range of psychopathology, including depression, bipolar disorder, schizophrenia or psychosis, eating disorder, anxiety disorder, ADD/ADHD, post-traumatic stress disorder, phobia, personality disorder, panic disorder, obsessive compulsive disorder, and alcohol or drug addiction. In addition, 'ever treated with ...' includes the treatments of antidepressant medication, psychotherapy, online help program or e-health intervention, running therapy or physical activity, light therapy, hospitalization in psychiatric hospital, and electroconvulsive therapy.

Table 4 contains a descriptive overview of the full MDD GWAS sample as well as separately for MDD cases and screened controls. From descriptives it appears that MDD cases and controls were comparable in their educational attainment and body size. Mean age was similar in both groups although cases may be slightly

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Table 2. Overview of BIONIC cohorts in the GWAS set

Cohort	Abbreviation	*N*	Instrument(s)	Type	% women	Age (mean)	% MDD case
Lifelines Cohort Study	Lifelines	39,610	LIDAS, MINI	Population	61.6%	52.2	27.2%
Netherlands Twin Register	NTR	16,261	LIDAS, CIDI, ASR, HADS, BDI	Population	63.3%	42.1	14.3%
Doetinchem Cohort Study	DCS	2,320	LIDAS	Population	51.1%	65.6	16.3%
Nijmegen Biomedische Studie	NBS	1,343	LIDAS	Population	51.0%	63.4	21.1%
Tracking Adolescents' Individual lives Survey	TRAILS	958	LIDAS	Population, clinical	56.1%	24.5	26.2%
The Hoorn Studies	HRN	784	LIDAS	Population	38.4%	68.0	17.3%
Nutrition Questionnaires plus	NQplus	347	LIDAS	Population	34.3%	65.8	11.5%
Multi-country collaborative project on the role of Diet, Food-related behaviour, and Obesity in the prevention of Depression	MooDFOOD	183	LIDAS, MINI	Clinical	74.9%	50.5	37.2%
Netherlands Study of Depression and Anxiety	NESDA	2,115	CIDI	Clinical	66.7%	42.2	84.4%
Longitudinal Aging Study Amsterdam	LASA	1,879	CIDI, DIS, CES-D	Population	52.4%	72.3	20.6%
Netherlands Study of Depression in Older Persons	NESDO	445	CIDI	Clinical	65.2%	70.4	73.9%
Netherlands Study of Depression and Anxiety sibling cohort	NESDAsib	295	CIDI	Clinical	54.2%	51.9	41.7%
MOoD Treatment with Antidepressants or Running	MOTAR	108	CIDI	Clinical	53.7%	43.2	60.2%
Total:		66,648					25.3%

Note: MDD, major depressive disorder; LIDAS, Lifetime Depression Assessment Survey; CIDI, Composite International Depression Inventory; MINI, Mini-international neuropsychiatric interview; DIS, Diagnostic Interview Schedule; CES-D, Center for Epidemiological Studies Depression scale; ASR, Adult Self Report - Achenbach System of Empirically Based Assessment; BDI, Beck's Depression Inventory; HADS, Hospital Anxiety and Depression Scale.

Table 3. BIONIC variables

Variable	Available in MDD GWAS set (*N*)	Available as GWAS set (*N*)	Available as phenotype (*N*)
Major Depressive Disorder	66,648	66,648	123,950
Screening symptoms			
1: Decreased mood	59,079	62,733	110,262
2: Anhedonia	59,147	63,129	111,134
Accessory symptoms			
3: Anergia	22,882	24,758	44,054
4: Change in weight/appetite	22,039	23,478	41,102
5: Sleeping problems	24,596	26,404	46,863
6: Psychomotor changes	21,769	23,139	40,621
7: Cognitive disturbance	21,056	22,206	38,548
8: Guilt/worthlessness	21,971	23,426	41,224
9: Suicidal thoughts	20,351	21,388	36,650
Episode characteristics			
Number of episodes	11,248	12,079	20,549
Age at onset	11,204	12,033	20,469
Dysfunction	11,166	11,997	20,974
Longest episode	11,136	11,947	20,348
Sought professional help	11,175	12,008	20,453
Contacted support agency	40,638	43,066	73,239

(*Continued*)

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Table 3. (*Continued*)

Variable	Available in MDD GWAS set (*N*)	Available as GWAS set (*N*)	Available as phenotype (*N*)
Psychiatric history			
Ever diagnosed with . . . ?	33,733	35,621	63,089
Ever treated for . . . ?	6,656	8,401	14,073
Ever treated with . . . ?	32,384	34,268	60,633
Demographic/Lifestyle			
Educational attainment	43,865	46,703	78,002
Smoking	40,980	43,498	74,105
Physical activity	40,962	43,474	74,081
Height	50,842	53,586	85,573
Weight	48,711	51,197	82,555
BMI	51,512	54,308	86,329

Note: MDD, major depressive disorder.

Table 4. Variables descriptives in full MDD GWAS sample and for MDD cases and controls

	MDD GWAS sample	MDD cases	MDD screened controls
Sample size	66,648	16,847	49,801
Sex (% women)	60.8%	70.5%	57.6%
Age (*M*, *SD*)	50.7 (16.0)	48.7 (14.3)	51.3 (16.5)
Educational attainment			
Lower	11.3%	11.6%	11.1%
Middle	45.0%	45.8%	44.7%
Higher	43.8%	42.6%	44.2%
Smoking			
Never	50.6%	43.9%	52.7%
Former	12.6%	16.2%	11.5%
Current	36.8%	39.9%	35.8%
Body size			
Height (*M*, *SD*)	174.4 (9.7)	173.4 (9.6)	174.7 (9.8)
BMI (*M*, *SD*)	25.6 (6.1)	26.0 (6.8)	25.4 (5.8)

Note: MDD, major depressive disorder; GWAS, genomewide association study.

younger on average. Women were overrepresented among cases, and cases seemed more likely to be smokers. These descriptives are in line with formal testing in an earlier subsample of BIONIC (Fedko et al., 2020).

The sample with complete phenotype data for MDD and covariates was genotyped across 22 genotype arrays. Table 5 describes the seven array groups that were derived from these datasets. Array group sample sizes appear sufficient for independent analysis before being pooled in meta-analysis. Lifetime MDD prevalence across the seven array groups varied between 18.2% and 31.8%, forming a well-balanced range around the ideal 1-to-4 case-control ratio for binary trait GWAS (Hong & Park, 2012).

Table 5. Overview genotype data

Array	*N*	Cohort(s)	% case
Affymetrix SNP array 6.0	8,082	NTR, NESDA	31.8%
FinnGen ThermoFisher Axiom custom array	12,789	Lifelines	28.9%
Affymetrix AXIOM-NL array	1,261	NTR, HRN, LASA	18.6%
Illumina Infinium General Screening Array	32,742	DCS, Lifelines, LASA, MooDFOOD, MOTAR, NESDAsib, NESDO, NTR	22.2%
Illumina Infinium Core Exome chip	727	HRN	18.2%
Illumina Infinium CytoSNP chip	9,357	Lifelines, TRAILS	27.8%
Illumina Infinium OmniExpress-24 Beadchip	1,690	NBS, NQplus	19.2%

Note: NTR, Netherlands Twin Register; NESDA, Netherlands Study of Depression and Anxiety; HRN, Hoorn Studies; DCS, Doetinchem Cohort Study; LASA, Longitudinal Aging Study Amsterdam; mooDFOOD, Multi-country cOllaborative project on the rOle of Diet, Food-related behavior, and Obesity in the prevention of Depression; MOTAR, MOod Treatment with Antidepressants or Running; NESDAsib, Netherlands Study of Depression and Anxiety sibling cohort; NESDO, Netherlands Study of Depression in Older persons; TRAILS, Tracking Adolescents' Individual Lives Survey; NBS, Nijmegen Biomedische Studie; NQplus, Nutrition Questionnaires plus.

Discussion

In this article we have described the establishment of the BIObanks Netherlands Internet Collaboration (BIONIC) project and its lifetime MDD and genotype databases. Through the collaborative efforts of 16 Dutch cohorts we established the largest depression dataset of its kind in the Netherlands; a dataset that comprises not only MDD status and genetic data but also symptom presentation, episode characteristics, and a range of demographic and lifestyle factors. We provided an overview of the project and its resources,

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including the development and validation of a standardized homogeneous online depression instrument and its heritability. We showcased the effectiveness of rapid phenotyping in ongoing biobanks, described MDD features in the dataset and established that the BIONIC sample is a good representation of the population of the Netherlands. Finally, we described a pipeline for the preparation of genotype data from multiple genotype arrays and the resulting MDD GWAS set. The GWAS in the Dutch BIONIC sample is underway and in the future we hope to expand these efforts to include analyses of more fine-grained depression information such as symptom presentation.

We expect that the BIONIC resource will make a valuable contribution to our understanding of the genetics of MDD. It can also serve as a resource for epidemiological studies that do not necessarily focus on genetics, as it has already in recent projects (van Loo et al., 2022, van Loo et al., 2023; Vreijling et al., 2023), and for studies of the exposome. The focus on a uniform MDD case definition will improve power in genetic association analyses, and the additional depression information will also allow us to dive deeper into the heterogeneous patterns in which depression manifests. That is not to say that the focus on increasing sample size has not been a successful endeavor; the number of genetic variants identified through international efforts is a testament to that (Howard et al., 2019). The focus on deeper phenotyping is a next step in refining our GWAS hits and understanding of MDD etiology (Cai et al., 2020; Flint, 2023).

Population-based studies such as this one will also benefit cross-ancestry projects in the future. An important caveat of GWASs published so far is that the majority has been conducted in European populations, which limits the utility of GWAS-derived findings such as polygenic scores for underrepresented groups (Martin et al., 2017; Martin et al., 2019). People in the Netherlands have a wide range of ancestral backgrounds, due to historical geographical differences within the population of the Netherlands as well as more recent population admixture. These complex ancestries are somewhat accounted for through principal components in GWAS, but approaches that exclude individuals with the more diverging ancestries, because of analytical difficulties, are not desirable. One of the future goals of our project is to include individuals from all ancestral backgrounds, as analytical approaches to include these are currently actively being studied and developed (e.g., see Peterson et al., 2019). The database we established originates from the Netherlands, and based on the genotype information we will analyze 66,648 participants of European origin. However, 953 individuals whose ancestry is different from this are also part of BIONIC, and we hope to add the full BIONIC resource to the ongoing efforts in cross-ancestry research that have been established so far.

Another future goal is to examine sex differences in depression. Around the globe, MDD is consistently more prevalent in women, yet existing research based on GWAS has not yet fully addressed this sex difference, and fails to offer an explanation or mechanism. Perhaps this is in line with the finding that female-dominated disorders receive less funding (Smith, 2023). Recently, there have been method developments and suggestions to incorporate the analysis of sex differences into GWAS projects (Khramtsova, Wilson et al., 2023; Khramtsova, Winham et al., 2023; Vink et al., 2012). Although our own project might not yet be sufficiently powered to implement these suggestions, we intend to address the analysis of sex differences in collaboration with similar efforts and examine, through sex-specific GWAS, the contribution of genetic variants to depression risk separately in men and women, possibly revealing unique biological pathways for each. Similarly, the X-chromosome has long been left unconsidered in GWAS because of analytical difficulties. We aim for the inclusion of the X-chromosome to allow us to search for genetic associations there.

Other goals are to obtain polygenic risk scores (PRS), based on MDD as well as other traits, and to test their associations with MDD in the Dutch population. Based on our meta-analysis we will estimate genetic correlations with a range of other phenotypes as well as with other indices of depression as a way to investigate shared etiology and comorbidity across traits and populations. This work will be carried out as part of an international collaboration with similar online population-wide MDD efforts, such as those that have been or are being carried out in the United Kingdom (the Genetic Links to Anxiety and Depression (GLAD) study; Davies et al., 2019) and Australia (the Australian Genetics of Depression Study (AGDS; Byrne et al., 2020). Both have a wide array of MDD and other phenotype data that will facilitate fine-grained analyses of MDD and its symptoms, episode characteristics, and sex differences, especially given the statistical power of the combined samples. Furthermore, we aim to contribute the BIONIC resource to the Psychiatric Genetics Consortium MDD group effort (Howard et al., 2019). Finally, we aim to integrate the MDD and GWA data with other biological ('omics') layers, which are available in many BBMRI-NL projects, including the metabolome (Bot et al., 2020), epigenome and transcriptome.

In conclusion, the BIONIC project launches an exciting new era of MDD research and collaboration in the Netherlands and beyond. We hope that this article serves to describe effective methodology in establishing such a database and to promote the dataset resource as well as invite future collaborations.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2024.4.

Data availability. Data are available upon reasonable request from the contributing cohorts.

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