Major Depressive Disorder: Stage 1 Genomewide Association in Population-Based Samples.

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Critique

- Unrealistic sample sizes
- Sparse genotyping
- Imhomogeneity of samples
- Epidemiological sampling frame unknown
- Minimal phenotypes
- Controls not "draws from the same population" as cases
- Controls just unaffected, not at low liability
- Cases not directly evaluated by pros
- Replication not intrinsic

Primary phenotype definition

- Major depressive disorder (MDD)
- Dysphoria along with
  - Physical signs & symptoms
  - Impairment
  - Persistent & pervasive
  - Not normal sadness or grief
- Excludes depression due to other psychiatric and medical causes

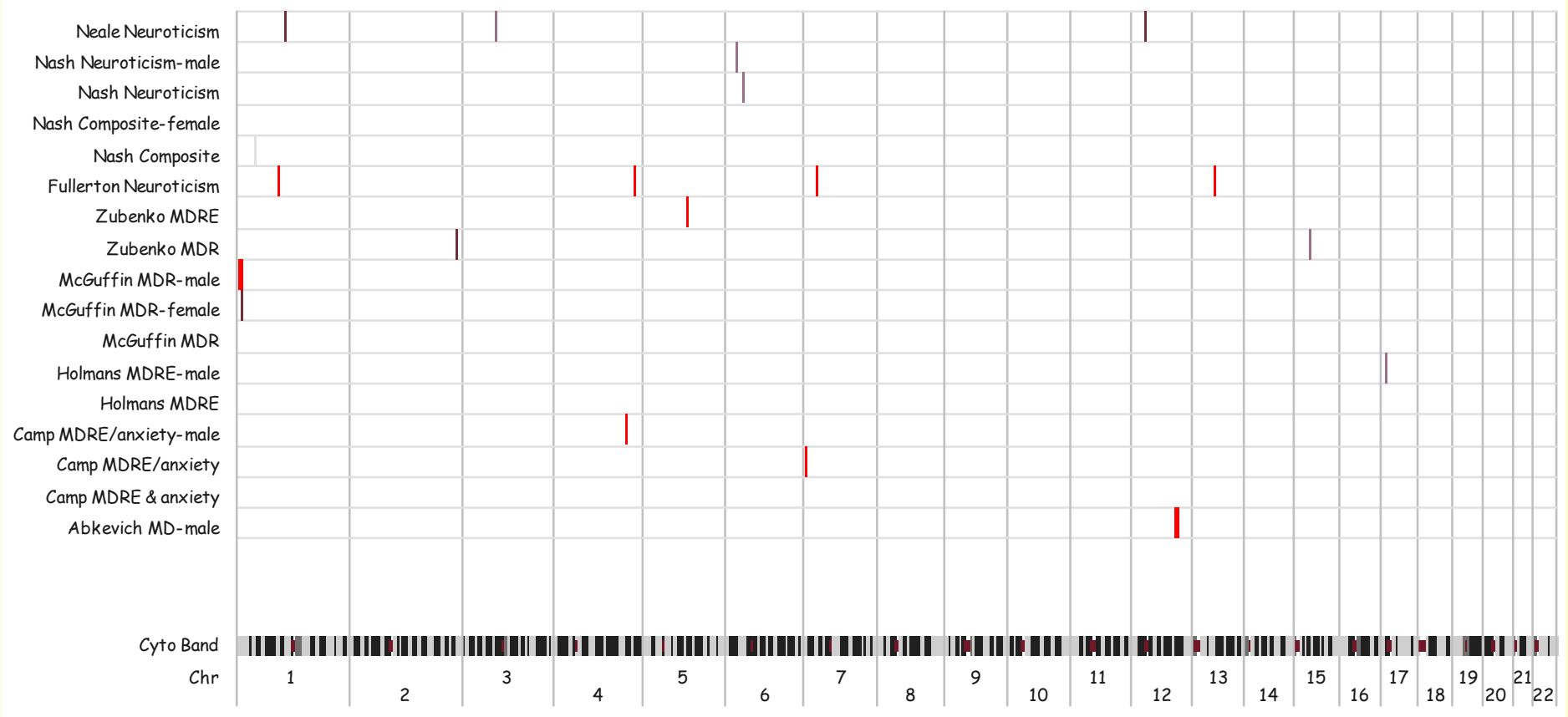
Importance of MDD

- Common
  - Lifetime prevalence ~15%
  - Increasing importance to psychiatry
- Chronic – recurrent for most (~75%)
- Increased mortality (suicide & other)
- Considerable morbidity
  - By 2020, projected to become 2nd leading cause of disability in world

Evidence for genetic influence on phenotype

- Complex trait
- Indirect data from genetic epidemiological studies
  - Twin studies, heritability ~40% (or higher)
  - Adoption studies consistent
  - Familial - risk to 1st degree relatives RR=2.8
- Evidence from the Netherlands consistent

Genomewide Linkage Studies (MDD & N)



Genomewide Association Studies

Study	N_{total}	IP?	Ancestry	Status	Comments
GAIN	3,200	No	EUR	In progress	4,600+Stage 2
Pfizer	500	Yes	EUR	Complete	No controls
GSK	2,000	Yes	EUR	?	
Academic 1	3,000	No	EUR	In progress	Pooling
Academic 2	2,000	No	Mixed	?	
Academic 3	2,000	No	Mixed	Planned	

Restrictions on data use

IRB approvals & consents :

- Allow the future use of DNA samples/phenotype data and information derived from them for genetic studies;
- Permit the use of the samples and information derived from them for research on phenotypes other than MDD;
- Do not impose any restrictions on sharing samples and information derived from them with other investigators; and
- Do not restrict the use of the samples and information derived from them in any other way, **as long as the anonymity of the participants is guaranteed**.

1,600 CASES with MDD: Netherlands Study of Depression and Anxiety (NESDA, www.nesda.nl, 2003-present)

- Collaborative study within the Netherlands (4 academic centers, 2 non-academic centers)
- Longitudinal cohort study following 2,850 persons, 18-65 years
- Five assessments: baseline and after 1, 2, 4 and 8 years
- Designed to be representative for MDD patients → Covers different range of psychopathology and settings

Inclusion & exclusion criteria for MDD cases

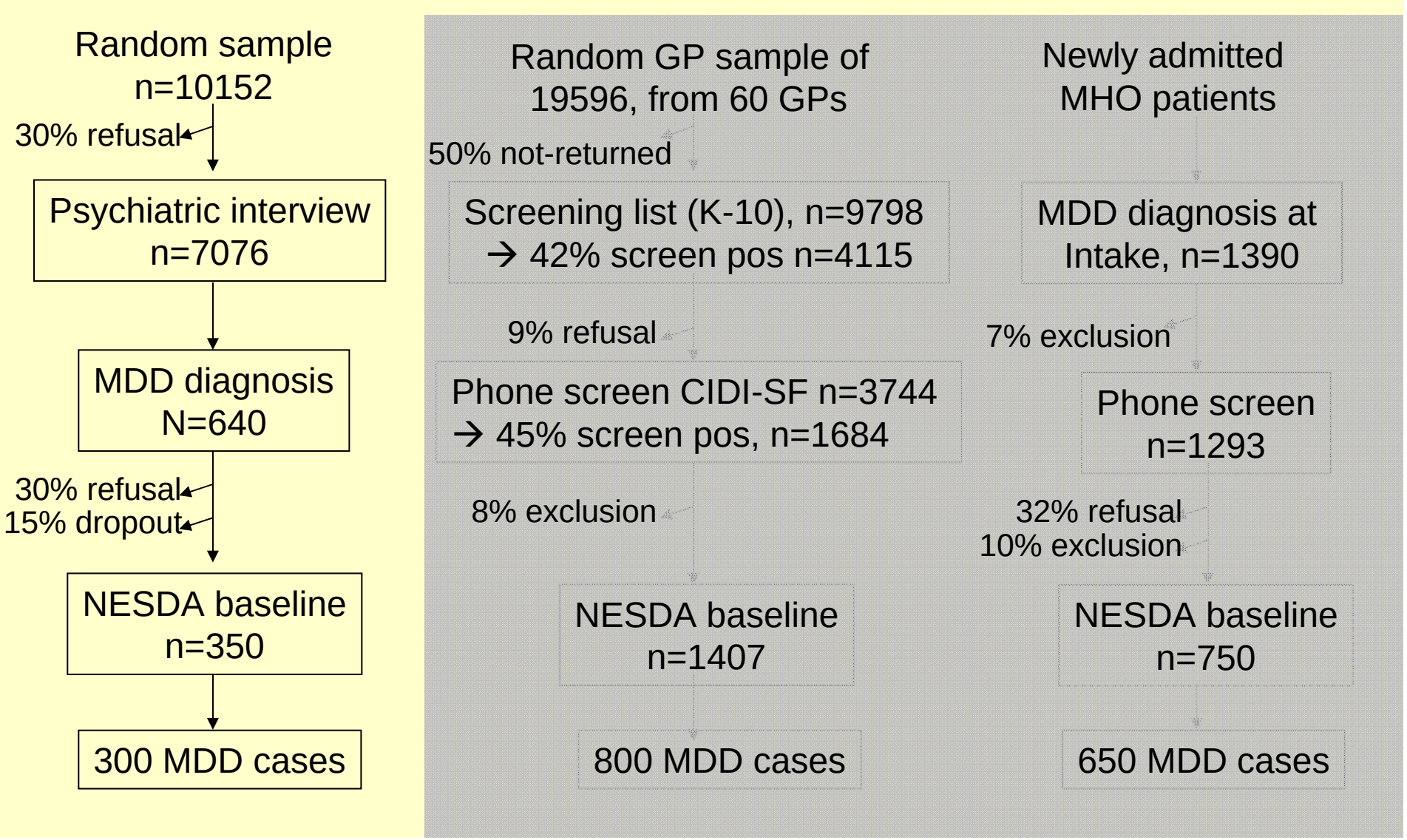
Inclusion criteria:

- Confirmed MDD diagnosis according to CIDI interview, version 2.1
- Age 18-65 years

Exclusion criteria:

- Insufficient knowledge of Dutch language
- Ancestry other than North-European
- Other psychiatric disorder, e.g. bipolar disorder, OCD, severe addiction, psychosis, mood disorder due to a general medical condition

Recruitment of MDD cases



Key clinical features for MDD

Positive family history(%)	71%
Recurrent episode	≥2 episodes: 47% 1 episode of >3 years: 31%
Age of onset	>30: 39% 22-30: 40% <22: 21%
Any of these	95.1%

CONTROLS: Netherlands Twin Register (NTR)

	1991	1993	1995	1997	2000	2002	2004
Twins	3386	4225	3413	3231	4610	4523	4017
Siblings	n/a	n/a	1481	1517	1474	1454	1264
Fathers	1439	1774	1572	n/a	n/a	1266	1058
Mothers	1607	1920	1688	n/a	n/a	1529	1333
Spouses	n/a	n/a	n/a	n/a	708	1527	945
Total	6432	7919	8154	4753	6795	10299	8617

In total, questionnaire data available for 20,496 individuals.

Selection of 1,600 controls

- DNA, mRNA (challenged/unchallenged) and lymphocytes (immortalized cell lines) present
- Only unrelated individuals are selected
- Proband & parents born in the Netherlands or Western-Europe
- NEVER a high score (> mean + 0.6 SD) on personality traits associated with depression (neuroticism, anxious depression, trait anxiety, borderline personality) in the 15 year follow-up period
- NO reports of clinical depression (YASR/Beck inventories, CIDI interview) or use of antidepressant medication EVER, up to biobanking

Matching of cases and controls

- All cases and controls are drawn from the same population

- Very homogeneous subject ancestries

- Cases and controls come from ongoing prospective studies

- Comparable composition across age, sex, marital status, SES

Matching of cases and controls

	MDD cases (NESDA)	Controls (NTR)
Age (mean ± SD)	41.6 yrs ± 12.8	43.9 yrs ± 13.3
Female	68.9%	66.5%
Married/partner	66.5%	75.8%
Educational level	Lower: 33.3% Middle: 31.4% Higher: 33.5%	Lower: 25.3% Middle: 31.7% Higher: 38.6%
North-European ancestry	100%	100%

Phenotype	NESDA Cases	NTR Controls	GAIN Deposition
CIDI – MDD information (episodes & age of onset)	Yes	n/a	Initial
Depression severity (Inventory of Depressive Symptoms)	Yes	n/a	Initial
Family history of MDD	Yes	Yes	Future
Anxiety severity	Yes	Yes	Initial
Personality (neuroticism & extraversion)	Yes	Yes	Initial
Prospective follow-up	Yes	Yes	n/a
Demography – age, sex, ancestry, marital status, & educational attainment	Yes	Yes	Initial
Stressful life events	Yes	Yes	Future
Leisure time exercise behavior	Yes	Yes	
Licit & illicit substance use	Yes	Yes	Initial
Thyroid function (TSH & free T_3, 99% of subjects)	Yes	No	Future
Cortisol profile (six time points, 75% of subjects)	Yes	No	Future
Heart Rate Variability (and other indices of autonomic nervous system functioning via VU-AMS system, 95% of subjects)	Yes	No	Future

Future Plans

- Increase Stage 1 sample (N=3,200 now)
  - Can increase now to total of 4,600 or 8,000
- "Stage 1b" – alternate genotyping
  - Subset of best SNPs
  - Promising SNPs with technical issues
  - Fill in sparse regions
  - "Too hard" – MHC & mitochondrial tag SNPs
- Stage 2 – N=14,000 & special samples
- Stage 3