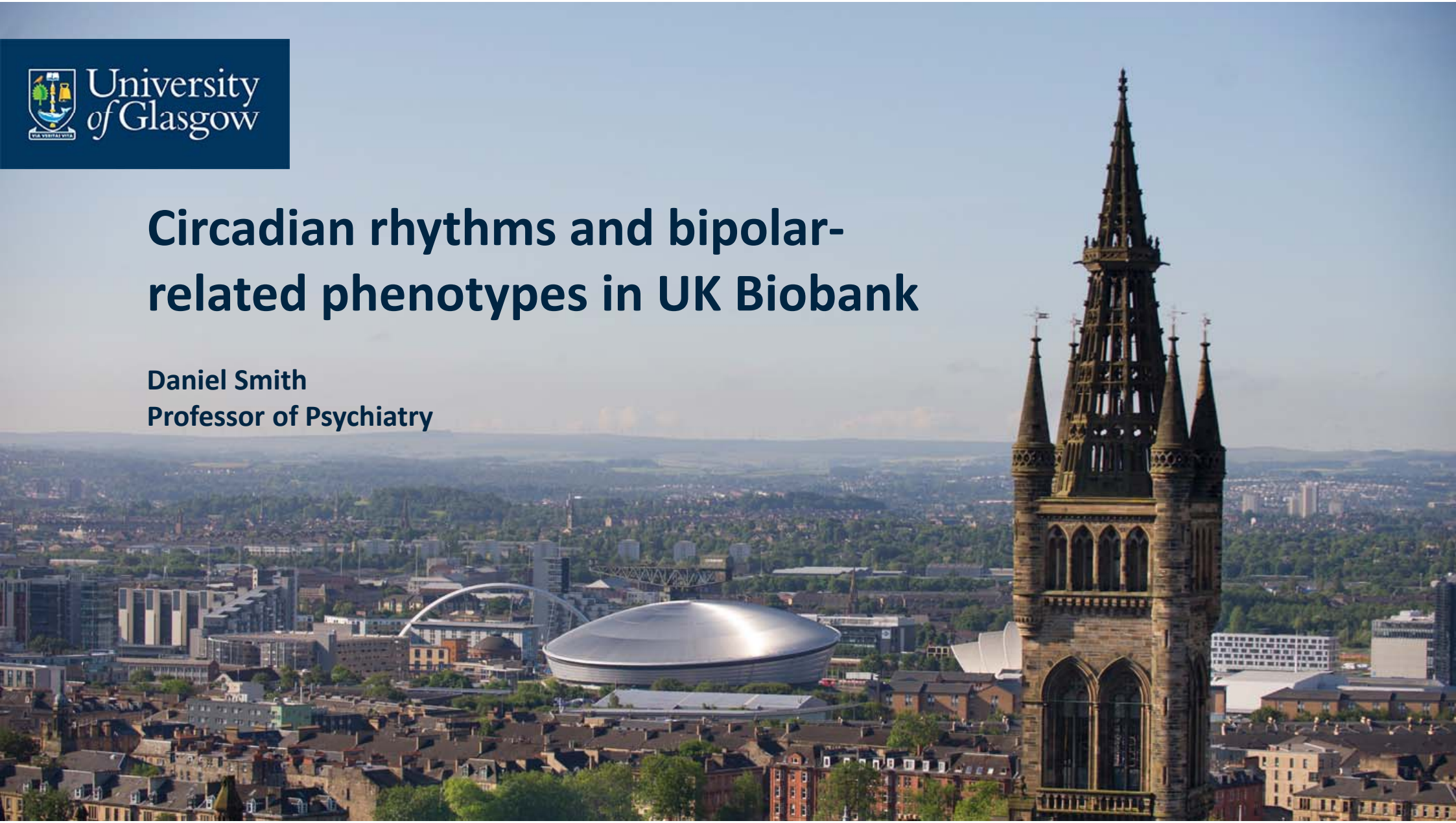
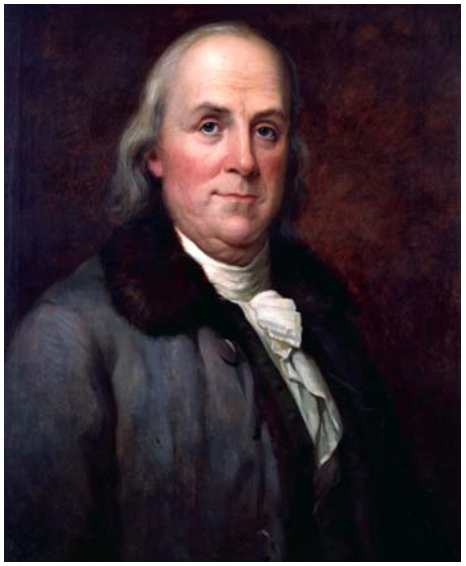


Circadian rhythms and bipolar-related phenotypes in UK Biobank

Daniel Smith
Professor of Psychiatry

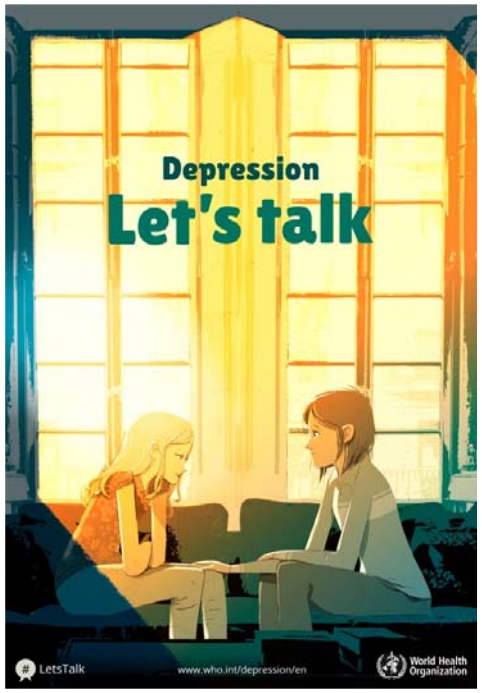
University of Glasgow

- Circadian rhythms and mental health
- UK Biobank analyses
- Precision medicine for bipolar disorder



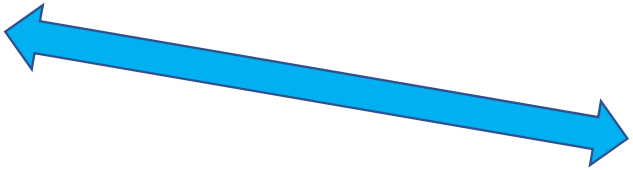
“Early to bed, early to rise makes a man healthy, wealthy and wise.”

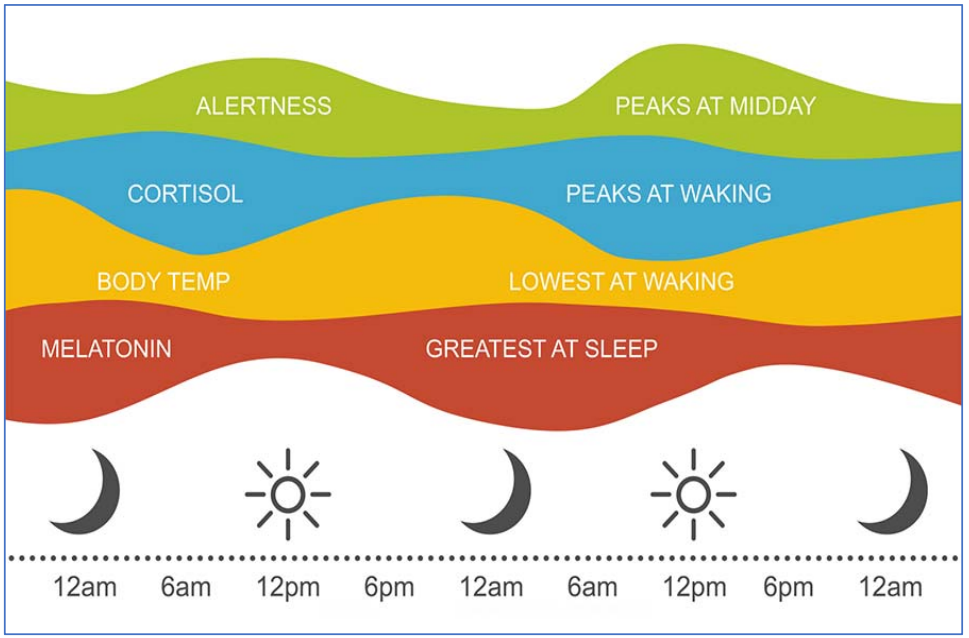
Benjamin Franklin
(1706 -1790)



Depression is now the single leading cause of disability worldwide

(WHO, Global Health Estimates, 2017)

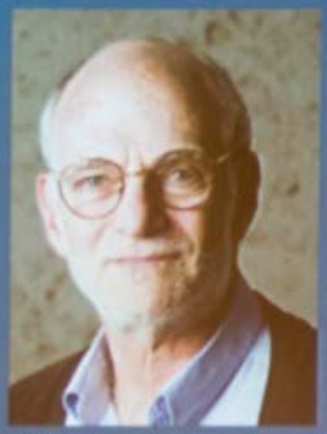




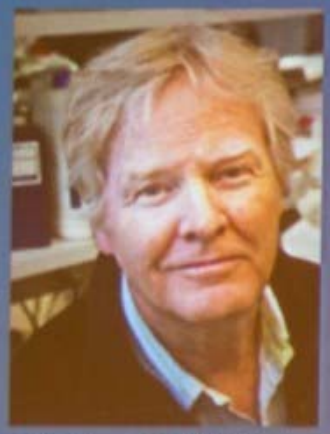
Circadian rhythms are vital for health and wellbeing, especially mental health

The 2017 Nobel Prize in Physiology or Medicine

Jeffrey C. Hall
Born in New York, USA
in 1945



Michael Rosbash
Born in Oklahoma City, USA
in 1944



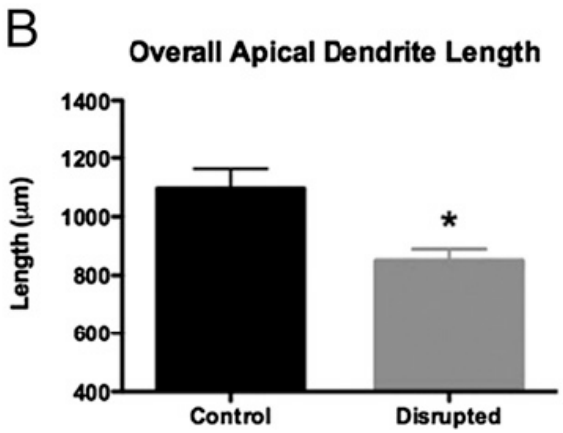
Michael W. Young
Born in Miami, USA
in 1949

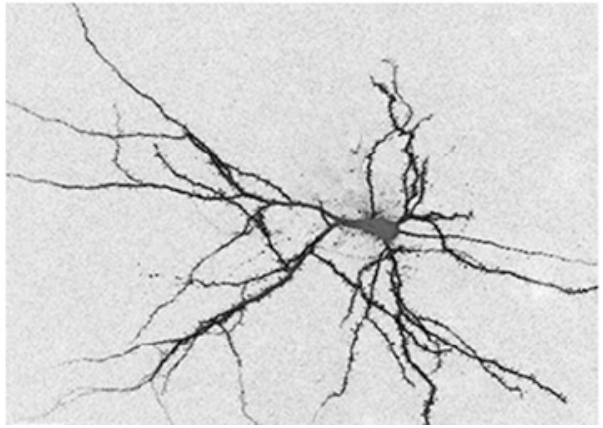
for their discoveries of mechanisms controlling circadian rhythms

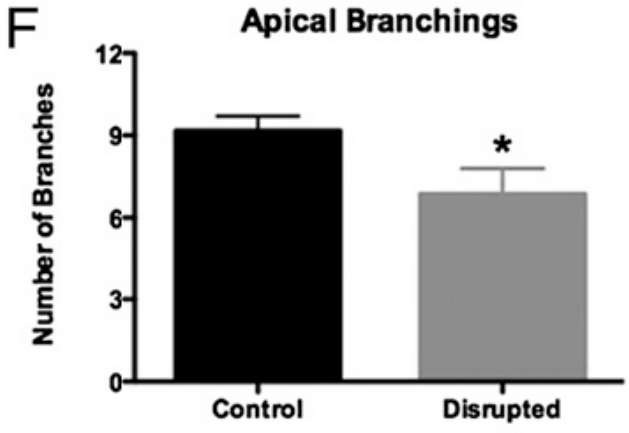
Disruption of circadian clocks has ramifications for metabolism, brain, and behavior

Ilia N. Karatsoreos[a,1], Sarah Bhagat[a], Erik B. Bloss[b], John H. Morrison[b], and Bruce S. McEwen[a,1]

PNAS







- **Prefrontal cortex: loss of dendritic length, decreased neuronal complexity**
- **Associated with decreased cognitive flexibility and changes in emotionality**

Circadian disruption:

Obesity

Cardiovascular disease

Diabetes

Hypertension

Addiction

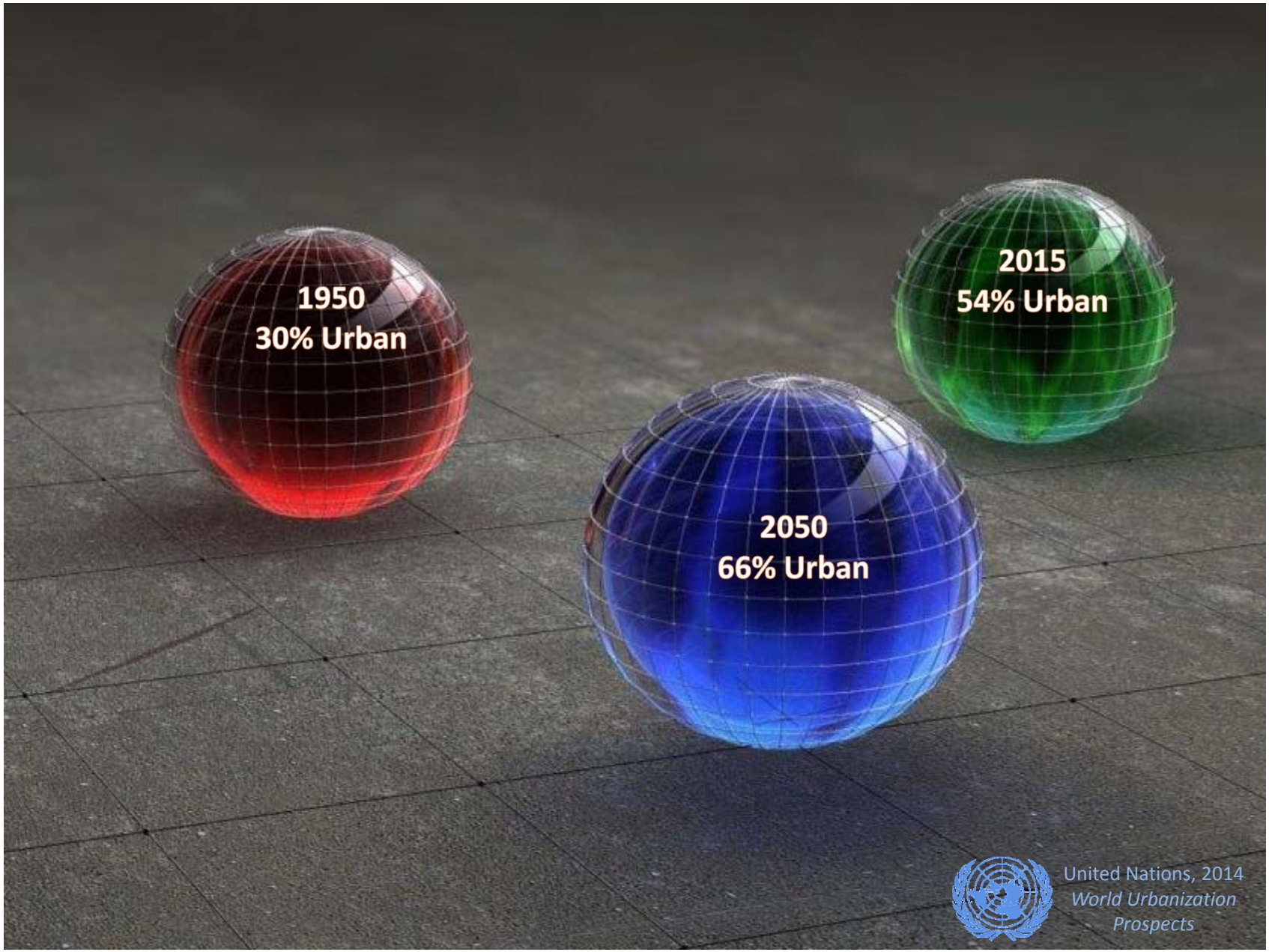
Breast cancer

Depression
Bipolar Disorder

Cognitive impairment

Chronic pain

Alzheimer's Disease
Parkinson's Disease


1950
30% Urban
2015
54% Urban
2050
66% Urban
United Nations, 2014
World Urbanization
Prospects

Urban = Light Disruption = Circadian Disruption

An Underestimated Anthropogenic Effect……


sedentary lifestyle
Poor diet
pollution
URBAN
RISK
FACTORS
stress
photoperiodic disruption

University of Glasgow

- ✓ Circadian rhythms and mental health
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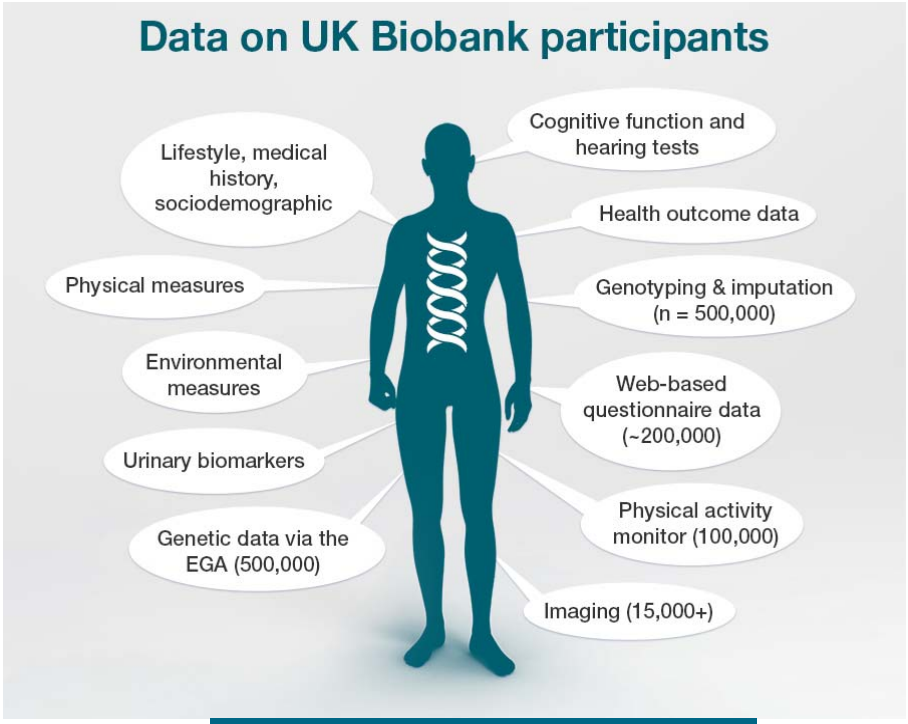


ANNALS OF MEDICINE, 2017
VOL. 49, NO. 5, 411–420
http://dx.doi.org/10.1080/07853890.2017.1292045

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Adverse metabolic and mental health outcomes associated with shiftwork in a population-based study of 277,168 workers in UK biobank*

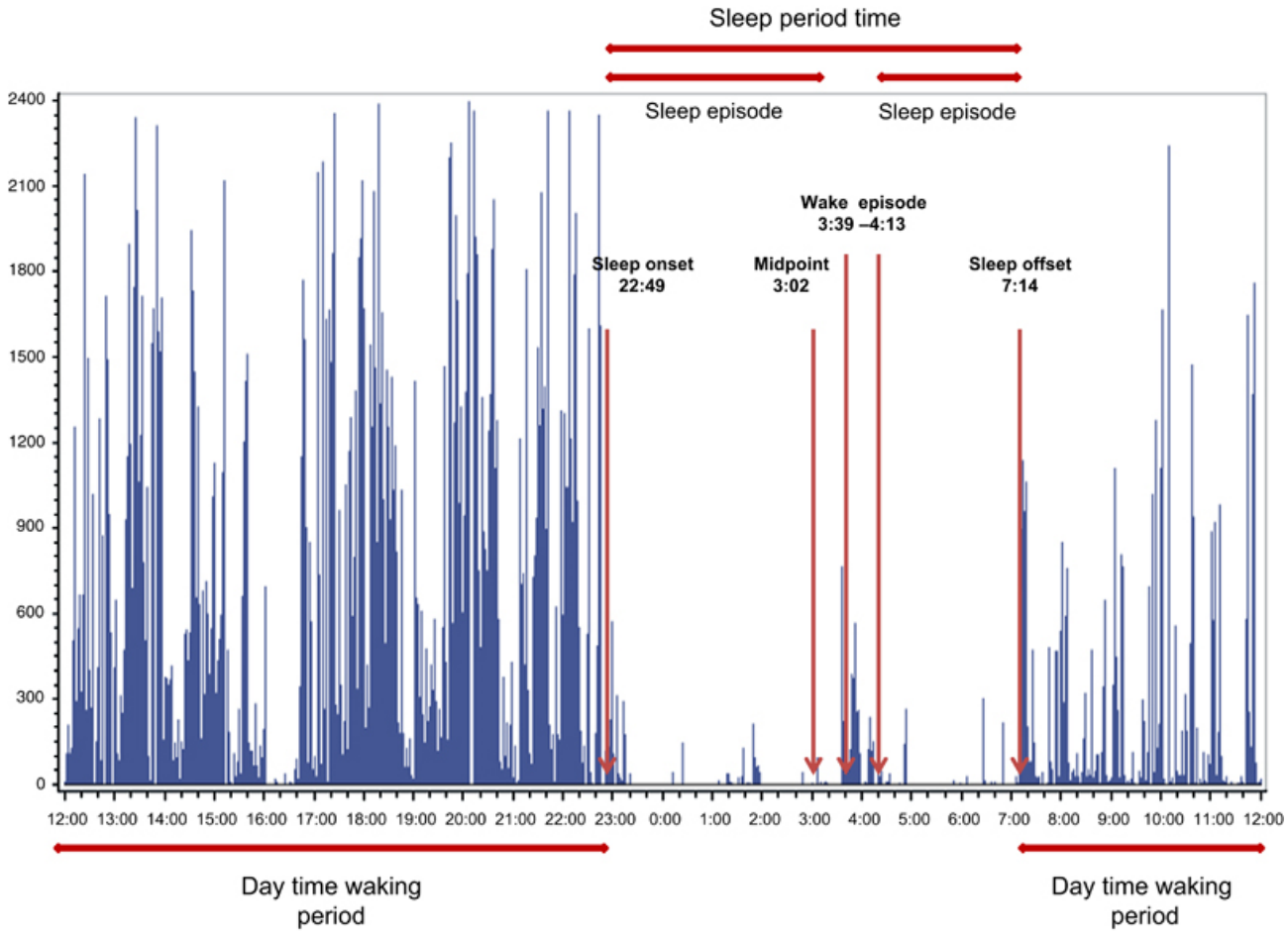
Cathy A. Wyse[a,b], Carlos A. Celis Morales[c], Nicolas Graham[d], Yu Fan[c], Joey Ward[d], Anne M. Curtis[a], Daniel Mackay[d], Daniel J. Smith[d], Mark E. S. Bailey[e], Stephany Biello[f], Jason M. R. Gill[c] and Jill P. Pell[d]

- 17% of the employed participants in UK Biobank are shift-workers
- More likely to be male, smokers, higher social deprivation
- Shift-workers more likely than controls to be:
  - Obese
  - Depressed
  - Higher neuroticism score
  - Reporting disturbed sleep

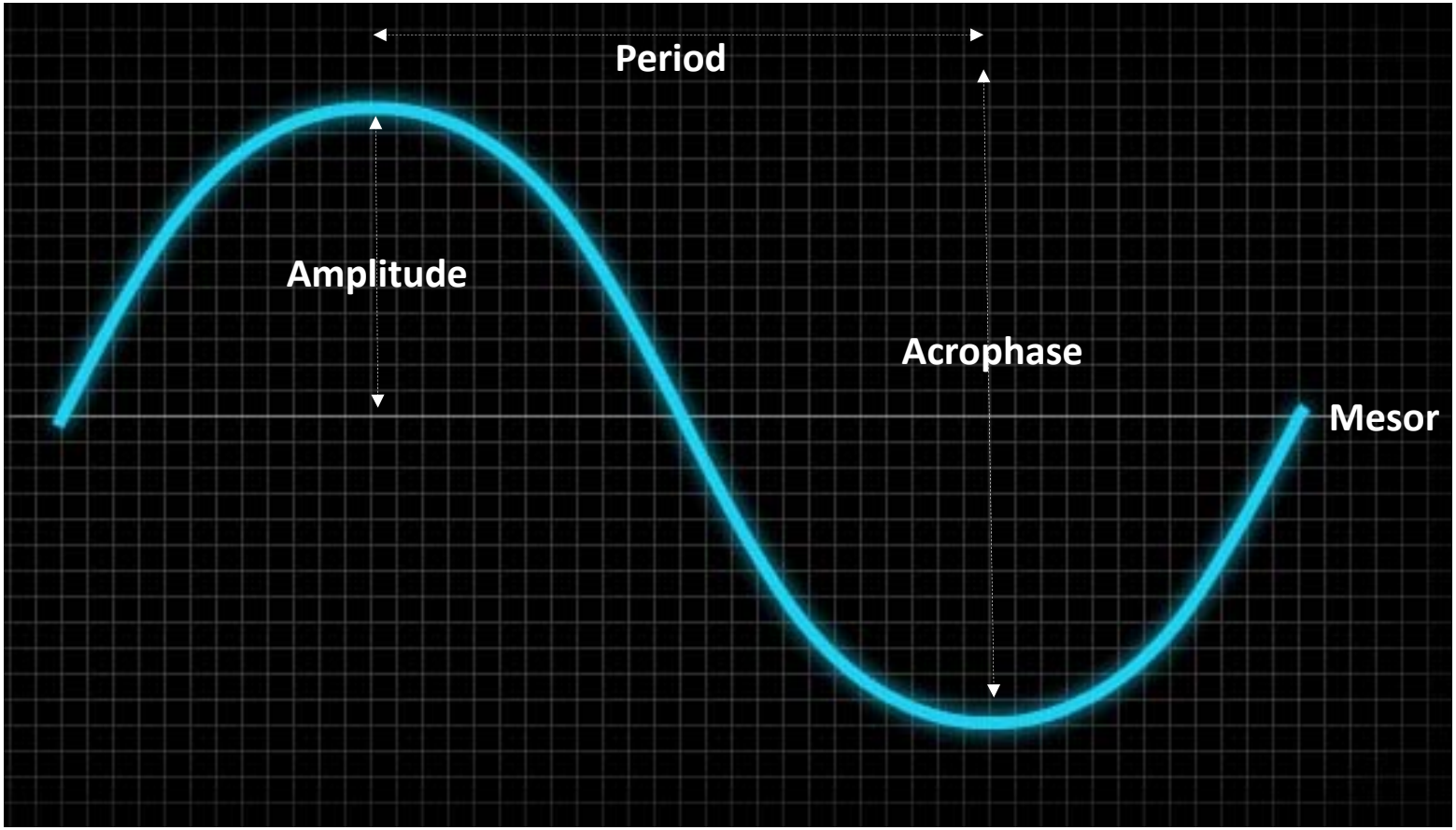
University of Glasgow

Activity monitoring in UK Biobank
(100,000 participants)

Sleep parameters:



Circadian rhythmicity parameters:



Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing and cognitive function in UK Biobank

- **Relative amplitude (RA):** relative difference between the most active continuous 10-hour period (M10) and the least active continuous 5-hour period (L5) within an average 24-hour period:

$$\mathbf{RA} = \frac{\mathbf{(M10-L5)}}{\mathbf{(M10+L5)}} = \text{measure of } \mathbf{rhythmicity} \text{ of rest-activity cycles}$$

- Outcomes assessed: major depressive disorder (MDD); bipolar disorder; mood instability; neuroticism score; loneliness; subjective happiness; health satisfaction scores; reaction times.
- Controlling for confounders (demographic, lifestyle, education, overall activity)

Lyall et al, in submission.

Low relative amplitude and mood disorder phenotypes in UK Biobank

	Model 1			Model 2		
	N (cases; controls)	OR (95% CI)	p	N (cases; controls)	OR (95% CI)	p
MDD	13,880; 39,154	1·16 (1·14, 1·18)	<0·0001	13,805; 38,968	1·08 (1·07, 1·10)	<0·0001
Bipolar Disorder	585; 39,154	1·24 (1·16, 1·32)	<0·0001	582; 38,968	1·15 (1·06, 1·24)	<0·0001
Mood instability	36,960; 52,948	1·07 (1·06, 1·08)	<0·0001	36,695; 52,672	1·04 (1·02, 1·05)	<0·0001
Neuroticism	76,413	1·02 (1·02, 1·03)	<0·0001	76,025	1·01 (1·01, 1·02)	<0·0001

Model 1 adjusted for age, season, sex, ethnicity and Townsend score.
Model 2 additionally adjusted for alcohol intake, smoking status, degree, and overall mean acceleration

Lyall et al, in submission.

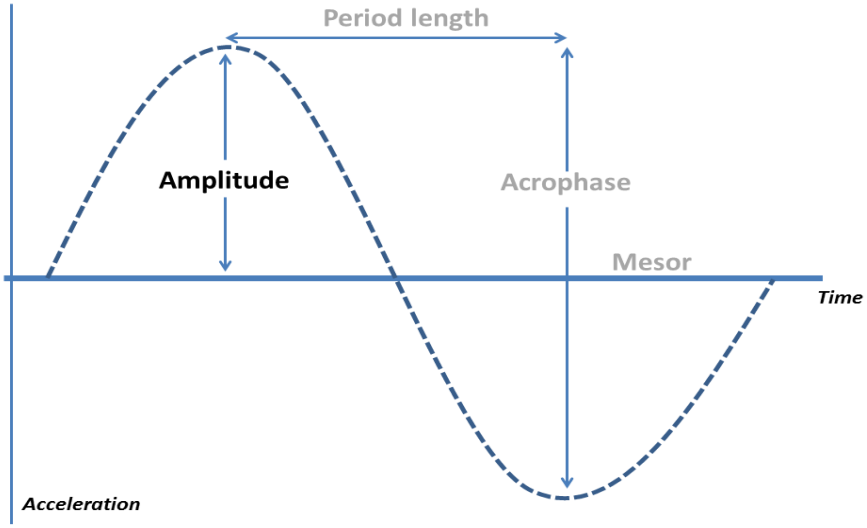
Low relative amplitude and subjective happiness, health satisfaction, loneliness, reaction time:

	Model 1			Model 2		
	N	OR (95% CI)	p	N	OR (95% CI)	p
Happiness	34,614	0·89 (0·88, 0·90)	<0·0001	34,378	0·92 (0·90, 0·94)	<0·0001
Health satisfaction	34,629	0·78 (0·77, 0·79)	<0·0001	34,393	0·88 (0·87, 0·90)	<0·0001
Loneliness	14,115; 76,247	1·14 (1·13, 1·16)	<0·0001	14,003; 75,800	1·11 (1·09, 1·13)	<0·0001
Reaction time	91,234	2·17 (1·71, 2·64)	<0·0001	90,656	1·71 (1·13, 2·29)	<0·0001

Model 1 adjusted for age, season, sex, ethnicity and Townsend score.
Model 2 additionally adjusted for alcohol intake, smoking status, degree, and overall mean acceleration

Lyall et al, in submission.

Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing and cognitive function in UK Biobank



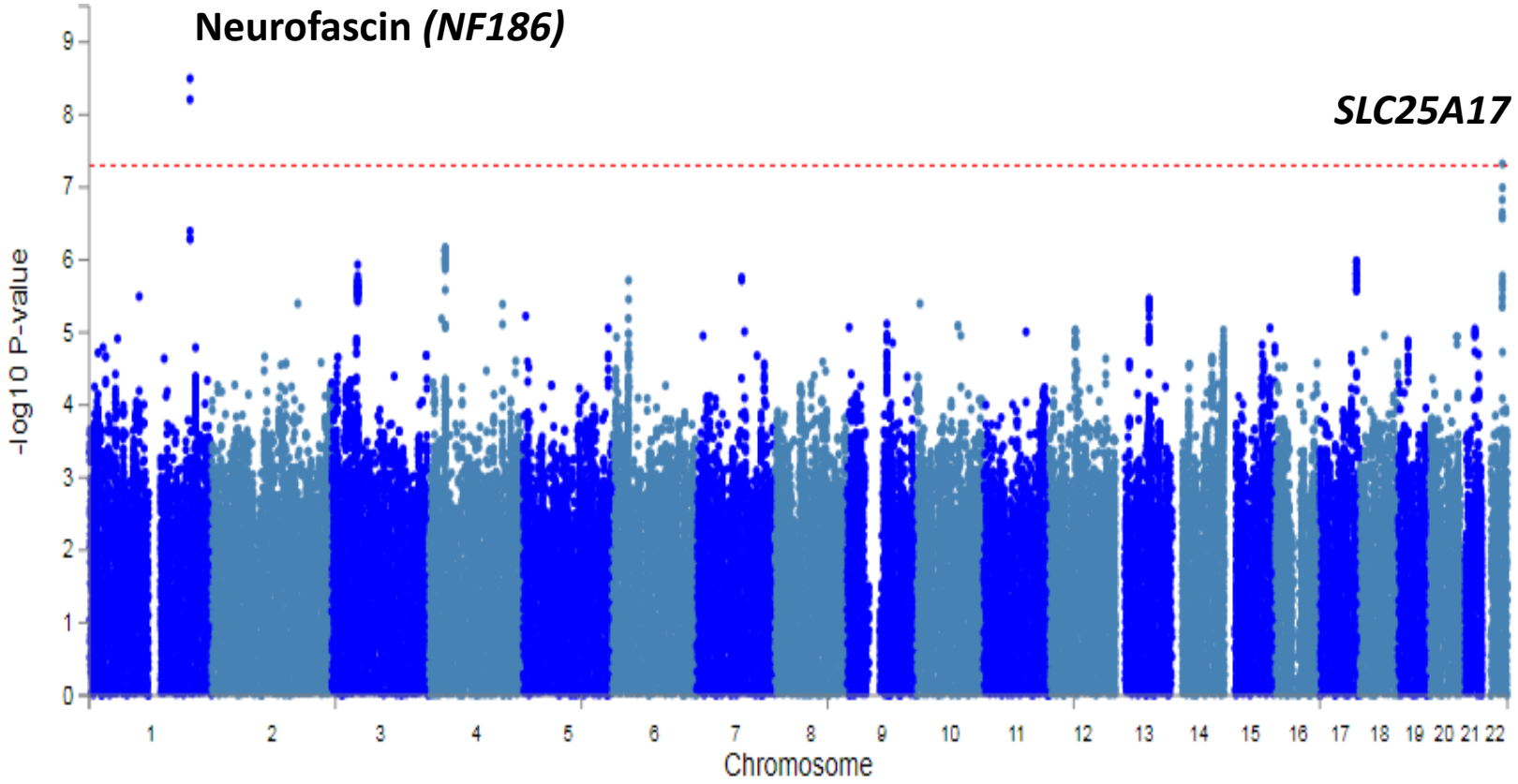
Low relative amplitude:

- Increased risk of depression
- Increased risk of bipolar disorder
- Greater mood instability
- Higher neuroticism

- Lower overall happiness
- Lower health satisfaction
- Greater loneliness
- Longer reaction time

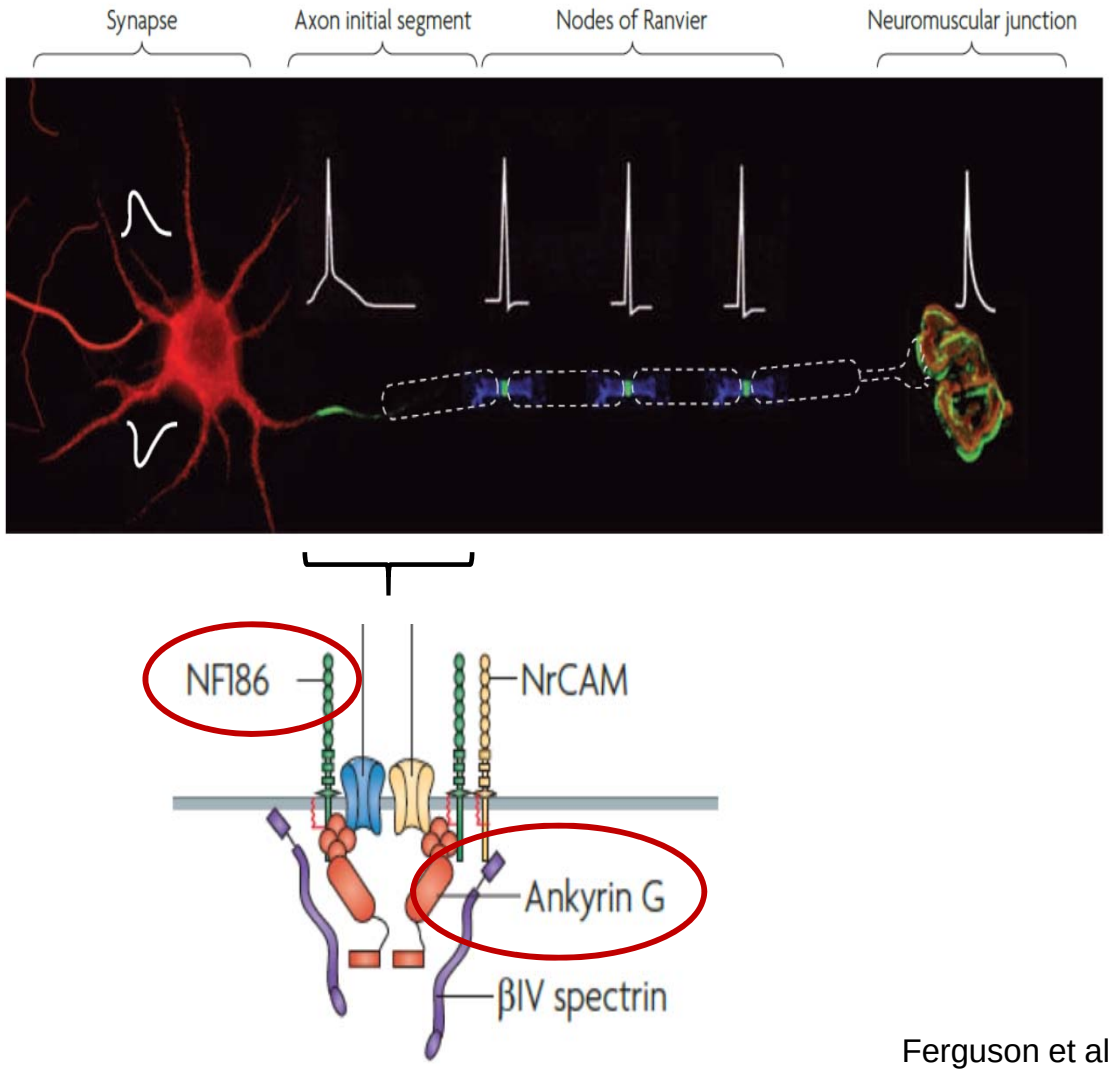
Lyall et al, in submission.

Genome-wide associations with low relative amplitude in N=74,137 UK Biobank participants



Ferguson et al, in preparation

Neurofascin *(NF186)* is a key component of the Axon Initial Segment:

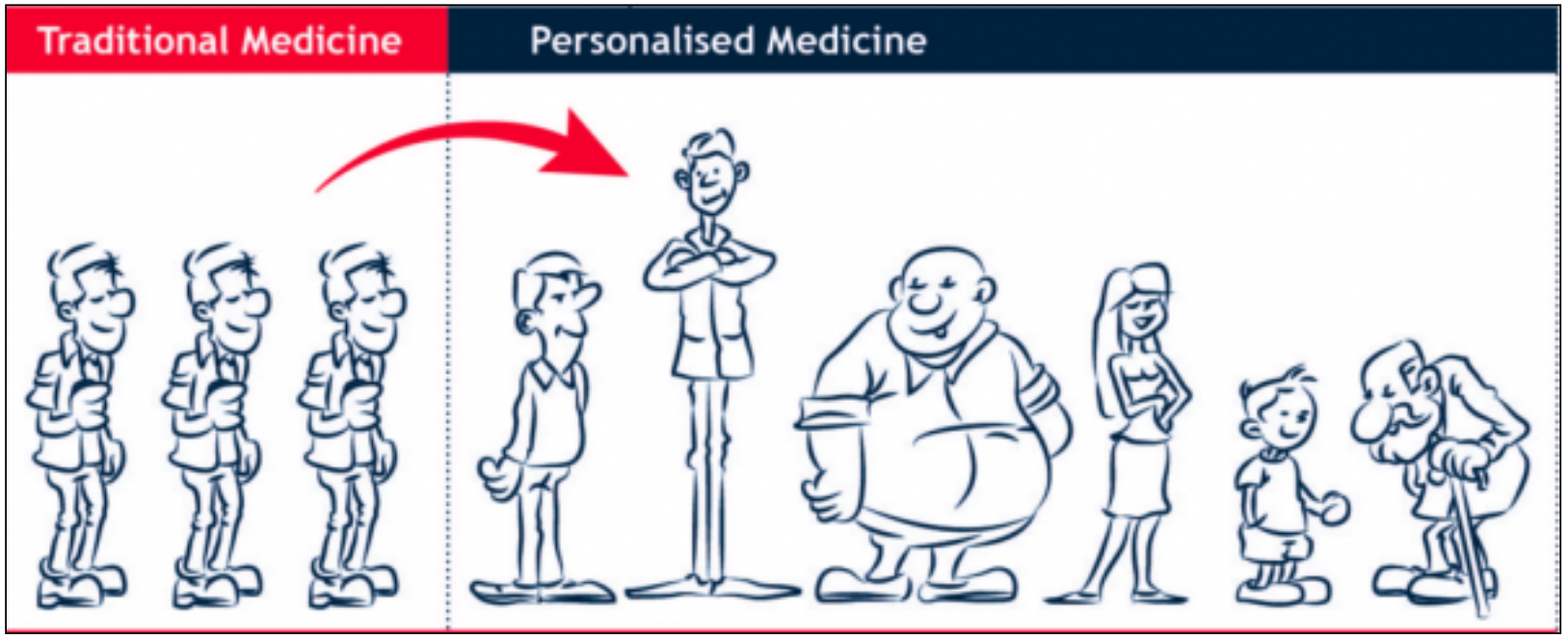


Ferguson et al, in preparation

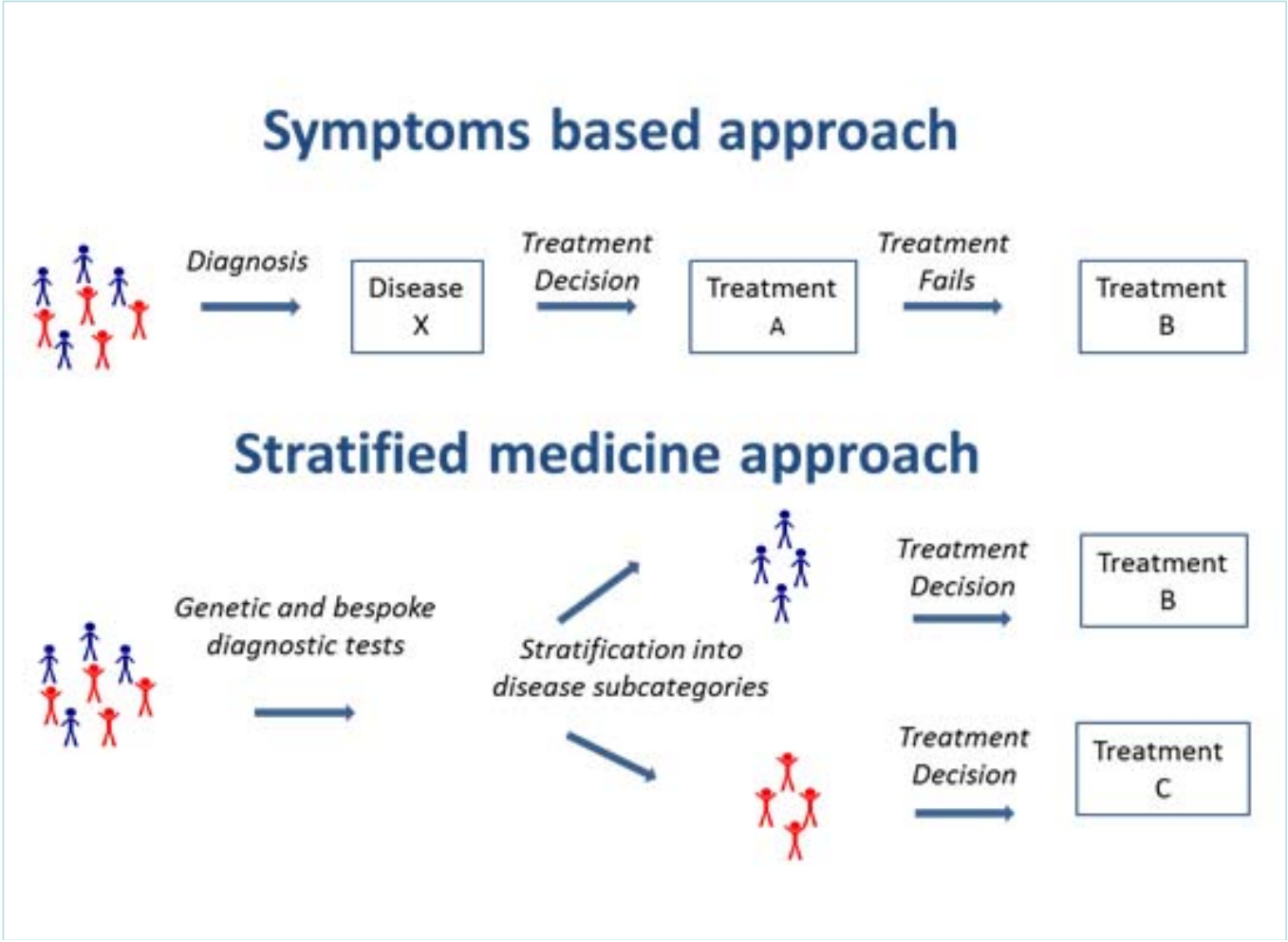
University of Glasgow

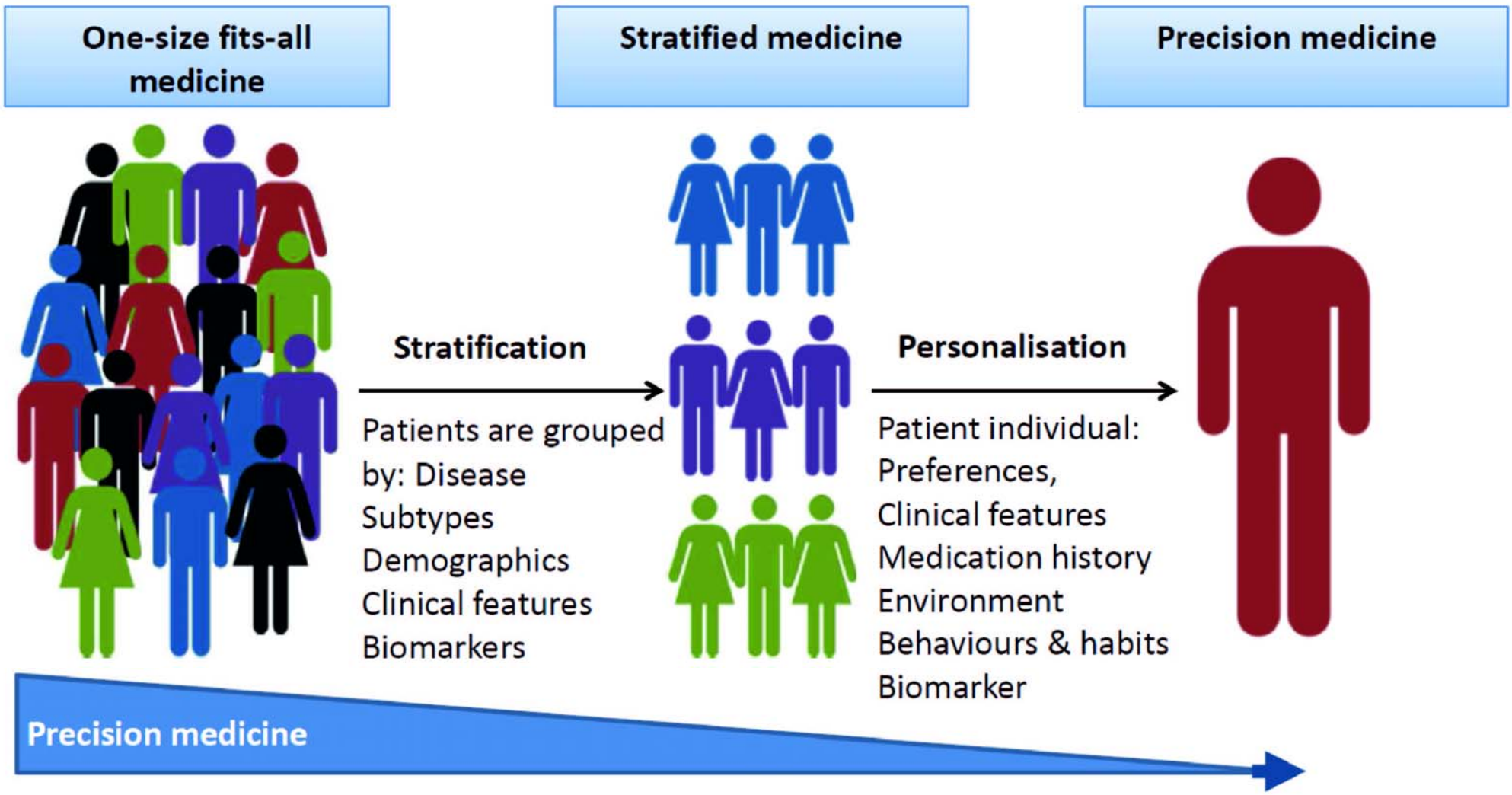
- ✓ Circadian rhythms and mental health
- ✓ UK Biobank analyses
- Precision medicine for bipolar disorder

University of Glasgow



University of Glasgow




One-size fits-all medicine
Stratified medicine
Precision medicine
Stratification
Patients are grouped by: Disease
Subtypes
Demographics
Clinical features
Biomarkers
Personalisation
Patient individual:
Preferences,
Clinical features
Medication history
Environment
Behaviours & habits
Biomarker
Precision medicine

Clinical predictors of good lithium response:

- Episodic/remitting pre-treatment clinical course
- Positive family history of bipolar disorder
- Low rates of medical and psychiatric comorbidity (and substance misuse)
- 'Typical' clinical presentation (severe mania and severe depression)
- Good compliance with medication
- Higher social class
- Good social support
- Being in employment
- Low number of life events
- Less childhood trauma

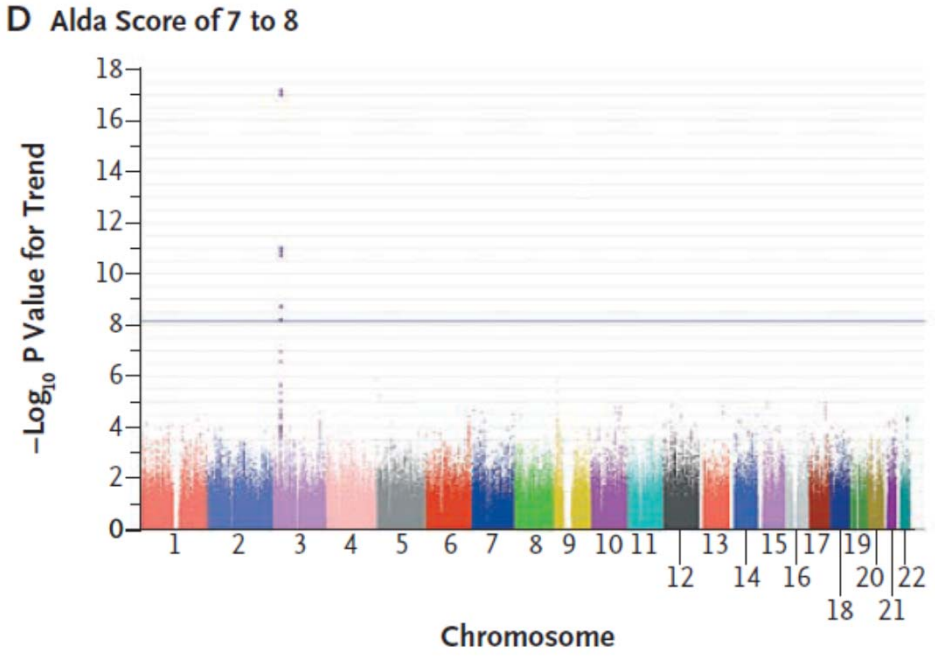
Alda, M., 2015, *Molecular Psychiatry*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variant *GADL1* and Response to Lithium Therapy in Bipolar I Disorder

C.-H. Chen, C.-S. Lee, M.-T.M. Lee, W.-C. Ouyang, Chiao-Chicy Chen, M.-Y. Chong,



- Han Chinese sample
- Not replicated since
- *GADL1*

OPEN

Molecular Psychiatry (2015), 1–8

www.nature.com/mp

ORIGINAL ARTICLE

Genome-wide association study identifies *SESTD1* as a novel risk gene for lithium-responsive bipolar disorder

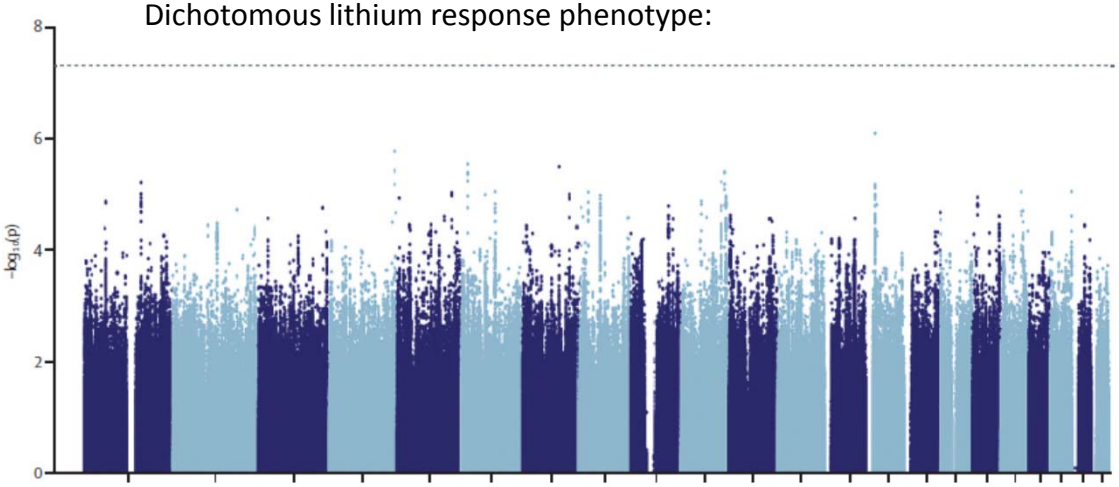
J Song[1,11], SE Bergen[1,2,11], A Di Florio[3], R Karlsson[1], A Charney[4], DM Ruderfer[4], EA Stahl[4], The International Cohort Collection for Bipolar Disorder (ICCBD)[12], KD Chambert[2], JL Moran[2], K Gordon-Smith[5], L Forty[3], EK Green[6], I Jones[3], L Jones[5], EM Scolnick[2], P Sklar[4,7,8], JW Smoller[9], P Lichtenstein[1], C Hultman[1], N Craddock[3] and M Landén[1,10]

Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study

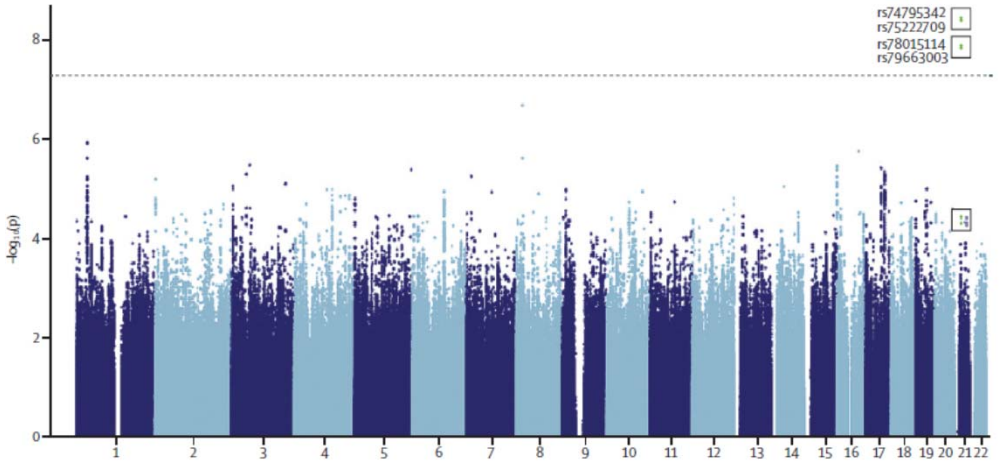
Liping Hou, Urs Heilbronner*, Franziska Degenhardt*, Mazda Adli, Kazufumi Akiyama, Nirmala Akula, Raffaella Ardau, Bárbara Arias, Lena Backlund, Claudio E M Banzato, Antoni Benabarre, Susanne Bengesser, Abesh Kumar Bhattacharjee, Joanna M Biernacka, Armin Birner, Clara Brichant-Petitjean, Elise T Bui, Pablo Cervantes, Guo-Bo Chen, Hsi-Chung Chen, Caterina Chillotti, Sven Cichon, Scott R Clark,*

Two genes for long non-coding RNAs

Dichotomous lithium response phenotype:



Continuous lithium response phenotype:



JAMA Psychiatry | Original Investigation

Association of Polygenic Score for Schizophrenia and HLA Antigen and Inflammation Genes With Response to Lithium in Bipolar Affective Disorder
A Genome-Wide Association Study

International Consortium on Lithium Genetics (ConLi+Gen)

ConLi+Gen
The international Consortium on Lithium Genetics

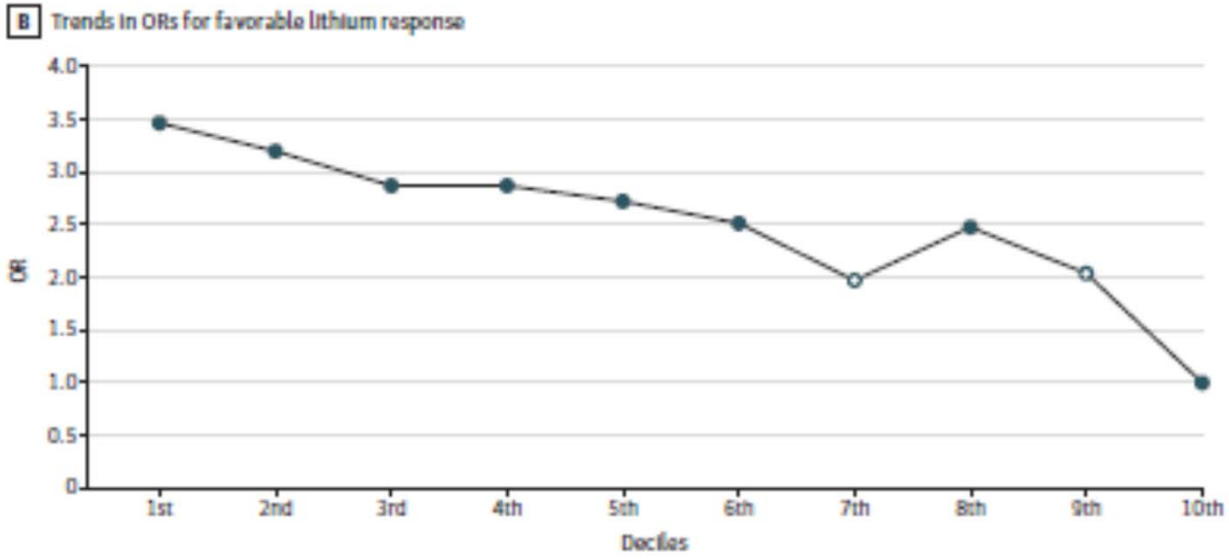


Table 2. Odds Ratios (ORs) of Favorable Treatment Response to Lithium in Patients With BPAD

	Patients With BPAD (n = 2586)		
SCZ PGS by Decile	R/N, No.	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
First (lowest score)	83/175	1.97 (1.32-2.96)	3.46 (1.42-8.41)
Second	80/179	1.86 (1.24-2.79)	3.19 (1.32-7.74)
Third	78/180	1.80 (1.20-2.71)	2.87 (1.18-6.95)
Fourth	76/184	1.72 (1.14-2.59)	2.86 (1.18-6.91)
Fifth	76/180	1.76 (1.17-2.64)	2.71 (1.12-6.55)
Sixth	67/194	1.44 (0.95-2.18)	2.50 (1.03-6.05)
Seventh	58/200	1.21 (0.79-1.85)	1.97 (0.81-4.79)
Eighth	75/184	1.70 (1.13-2.55)	2.47 (1.03-5.96)
Ninth	61/198	1.28 (0.84-1.95)	2.03 (0.86-4.81)
10th (highest score)[b]	50/208	1 [Reference]	1 [Reference]

Ward et al. Translational Psychiatry (2017)7:1264
DOI 10.1038/s41398-017-0012-7

Translational Psychiatry

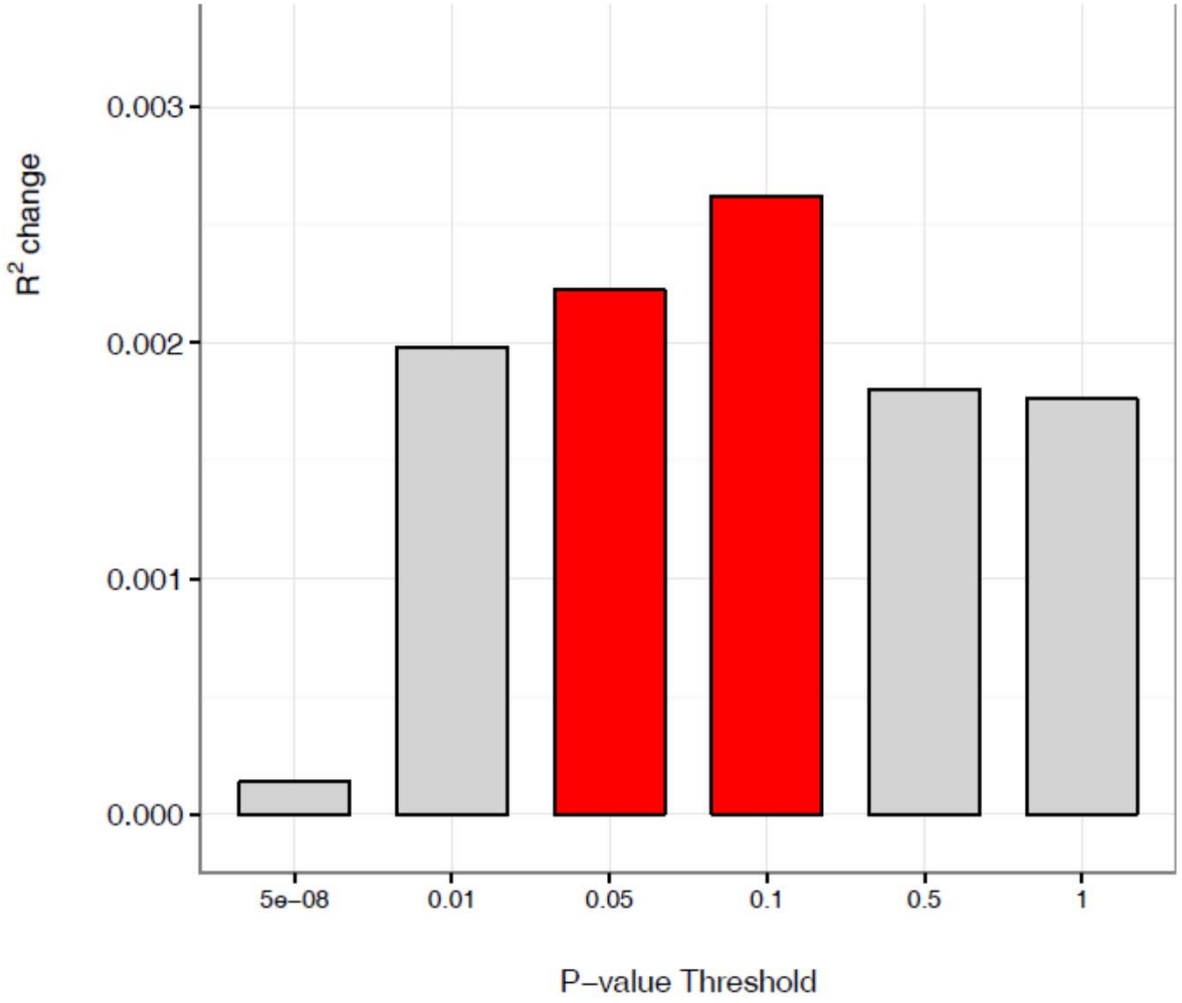
ARTICLE Open Access

Genome-wide analysis in UK Biobank identifies four loci associated with mood instability and genetic correlation with major depressive disorder, anxiety disorder and schizophrenia

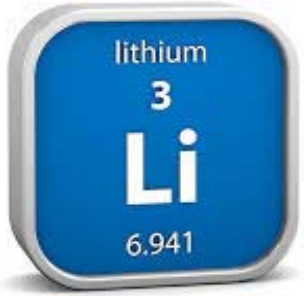
Joey Ward[1], Rona J. Strawbridge[1,2], Mark E. S. Bailey[3], Nicholas Graham[1], Amy Ferguson[1], Donald M. Lyall[1], Breda Cullen[1], Laura M. Pidgeon[1], Jonathan Cavanagh[1], Daniel F. Mackay[1], Jill P. Pell[1], Michael O'Donovan[4], Valentina Escott-Price[4] and Daniel J. Smith[1]

Mood instability: "Does your mood often go up and down?" (N=53,320 cases versus N=48,092 controls)

Polygenic risk for mood instability and non-response to lithium:

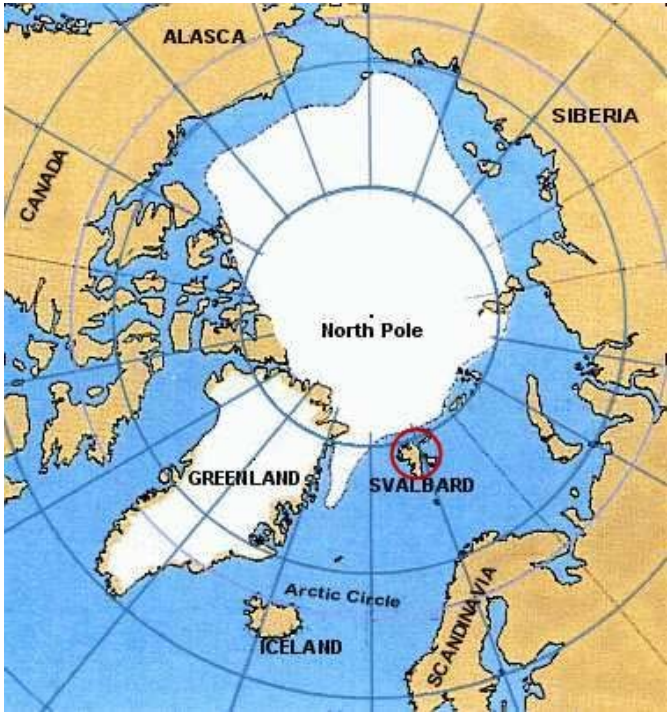


Bipolar disorder, severe depression



Stabilisation of circadian rhythms

Neuroprotective properties



"Five groups of two volunteers lived during four weeks under arctic summer conditions isolated in huts, without time information. They received lithium carbonate or placebo. All showed free-run of their circadian temperature and activity/rest rhythms with periods longer than 24 hours. Under lithium carbonate, a period-lengthening effect can be shown. This could help to understand the prophylactic effect of lithium salts in manic-depressive episodes."

Johnsson et al (1979) **Effect of lithium carbonate on circadian periodicity in humans.** *Pharmakopsychiatr Neuropsychopharmakol.* 12(6):423-5.

University of Glasgow

Future work:

1. Lithium may work for bipolar disorder because it stabilises circadian rhythmicity.

2. This property could be exploited to develop a stratified medicine approach for bipolar disorder.

3. This will require integrating multi-trait polygenic scores with environmental, clinical and demographic predictors of response.

University of Glasgow

- Circadian rhythms and mental health
- UK Biobank analyses
- Precision medicine for bipolar disorder

Thanks:


University of Glasgow
Thank you
daniel.smith@glasgow.ac.uk
@DrDanielJSmith