BNORC EPIDEMIOLOGY AND GENETICS CORE

Jorge E. Chavarro, MD ScD

Who we are

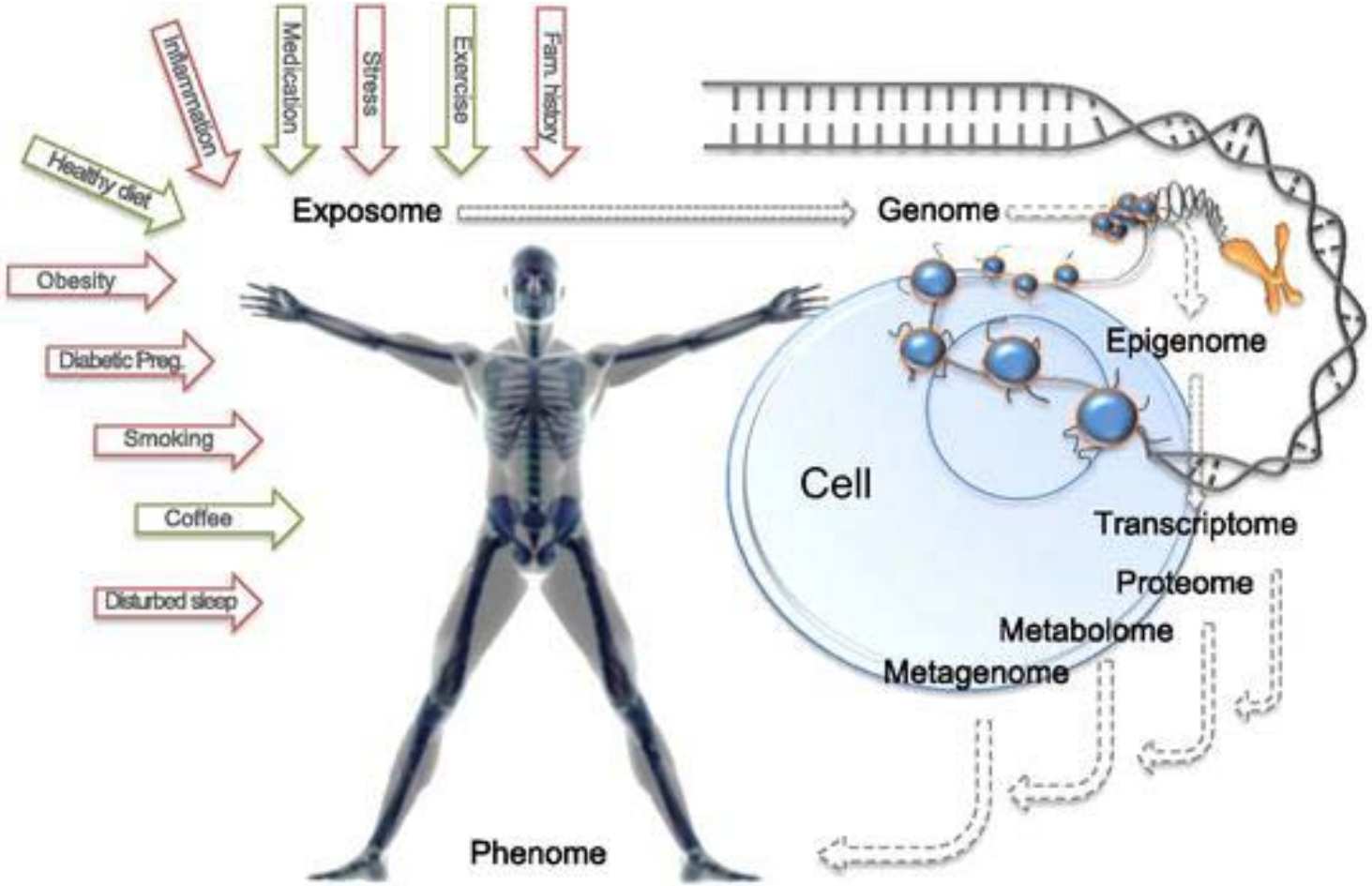
Director: Frank B. Hu, MD, PhD

Co-Director: Jorge E. Chavarro, MD, ScD

Assistant Directors

- Peter Kraft, PhD
- Liming Liang, PhD

What we do



Bennett et al. Ann NY Acad Sci 2015

What we do

- Provide access to large population-based prospective cohorts (and their bio-banks) to facilitate research on the causes and consequences of obesity
  - NHS, NHS-II, NHS3, HPFS, VIVA, …
  - Publicly available datasets (NHANES)

- Consultation on design, analysis and report of clinical trials and epidemiologic studies

What we do

- Provide access to high throughput genotyping facilities (subsidized) and support genetic and epigenetic data analyses for BNORC studies.

- Provide access to existing genotyping data for
  - Replication of novel genetic associations
  - Pooling analyses and meta-analyses
  - In silico replications
  - Human SNP associations from functional experimental studies

Services added during current cycle

- Bioinformatics support of epidemiologic studies analyzing next gen sequencing and exome SNP data
- Bioinformatics support of epidemiologic studies analyzing -omics data and other high-dimentional data
  - Epigenetics, metabolomics
- Support of studies evaluating developmental origins and life course origins of obesity and related phenotypes.
  - Planned expansion of biorepositoy
  - Novel data sources (digital phenotyping)

What does this actually mean?

Three examples:

- Access to data and specimens
- Human replication of animal models
- Support of novel data collection

Access to data and specimens

JAMA Network Open

Original Investigation | Diabetes and Endocrinology

Association of Birth Weight With Type 2 Diabetes and Glycemic Traits
A Mendelian Randomization Study

BIRTH-GENE (BIG) Study Working Group

Abstract

IMPORTANCE Observational studies have shown associations of birth weight with type 2 diabetes (T2D) and glycemic traits, but it remains unclear whether these associations represent causal associations.

OBJECTIVE To test the association of birth weight with T2D and glycemic traits using a mendelian randomization analysis.

Key Points

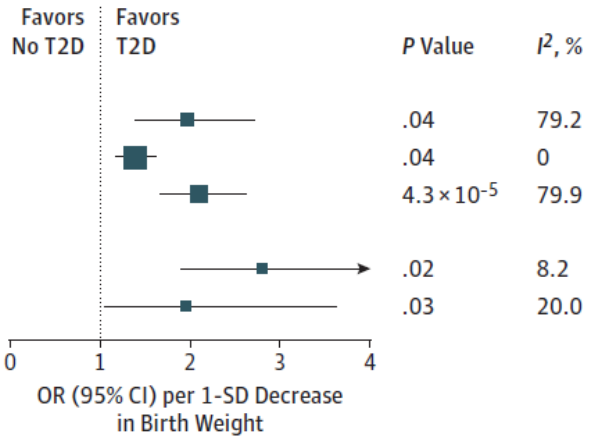
Question Is birth weight associated with type 2 diabetes and glycemic traits?

Findings This mendelian randomization study found that a 1-SD decrease in birth weight due to the genetic risk score was associated with a higher risk of type 2 diabetes among European and East

Access to data and specimens

Figure 2. Mendelian Randomization of Birth Weight and Risk of Type 2 Diabetes (T2D)

Data Sets	SNPs, No.	No. Cases/ No. Controls	OR (95% CI)	ARI (95% CI)	P Value	I^2, %
Study level data						
European participants	7	28 806/52 691	1.96 (1.42-2.71)	7.4 (3.27-13.3)	.04	79.2
Asian participants	7	12 349/27 317	1.39 (1.18-1.62)	3.0 (1.40-4.80)	.04	0
All participants	7	41 155/80 008	2.10 (1.69-2.61)	8.9 (0.23-9.0)	4.3×10^{-5}	79.9
Summary level data						
DIAGRAM A	7	34 840/114 981	2.79 (1.90-4.20)	13.9 (7.0-24.9)	.02	8.2
DIAGRAM B	43	34 840/114 981	1.96 (1.07-3.60)	6.7 (0.5-20.2)	.03	20.0



Human replication of animal models

nature COMMUNICATIONS

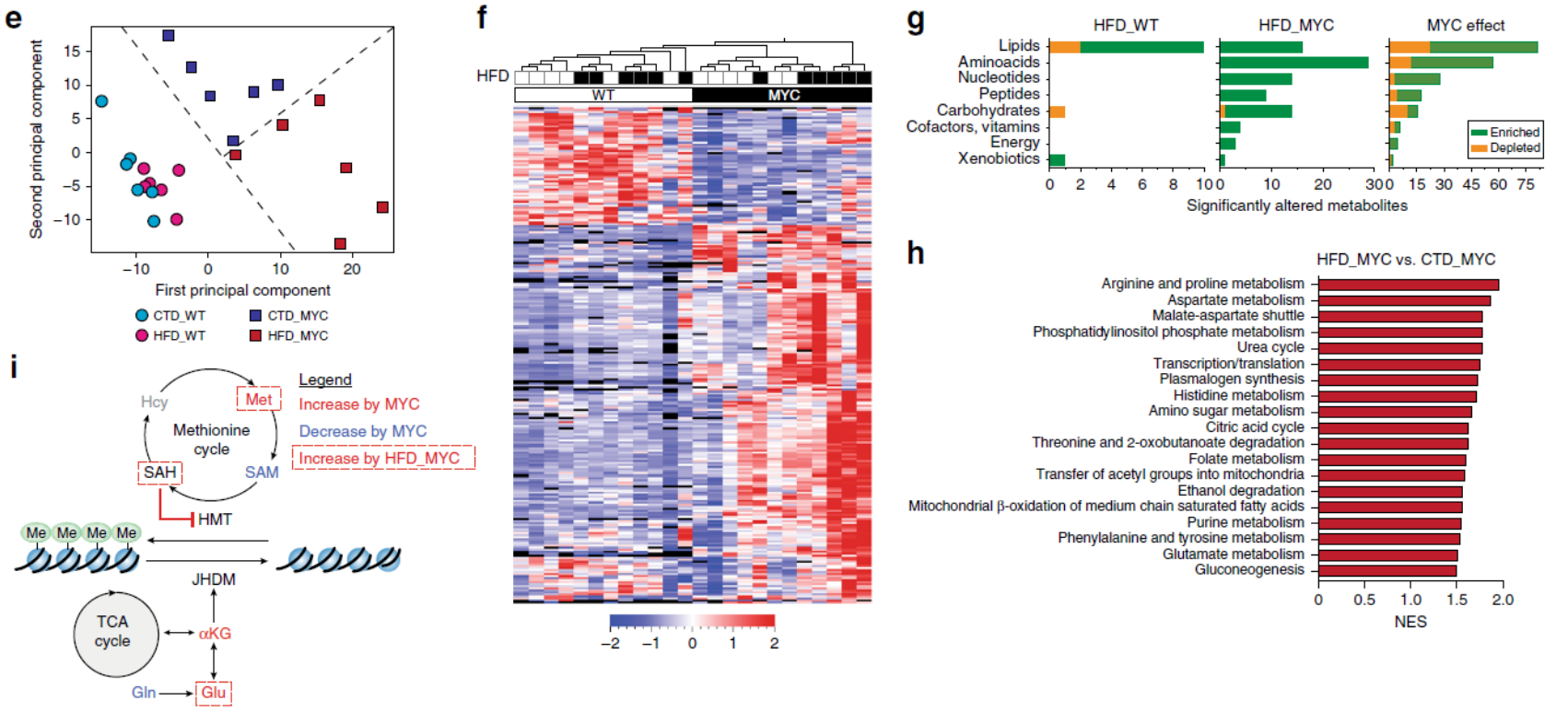
ARTICLE

https://doi.org/10.1038/s41467-019-12298-z OPEN

High-fat diet fuels prostate cancer progression by rewiring the metabolome and amplifying the MYC program

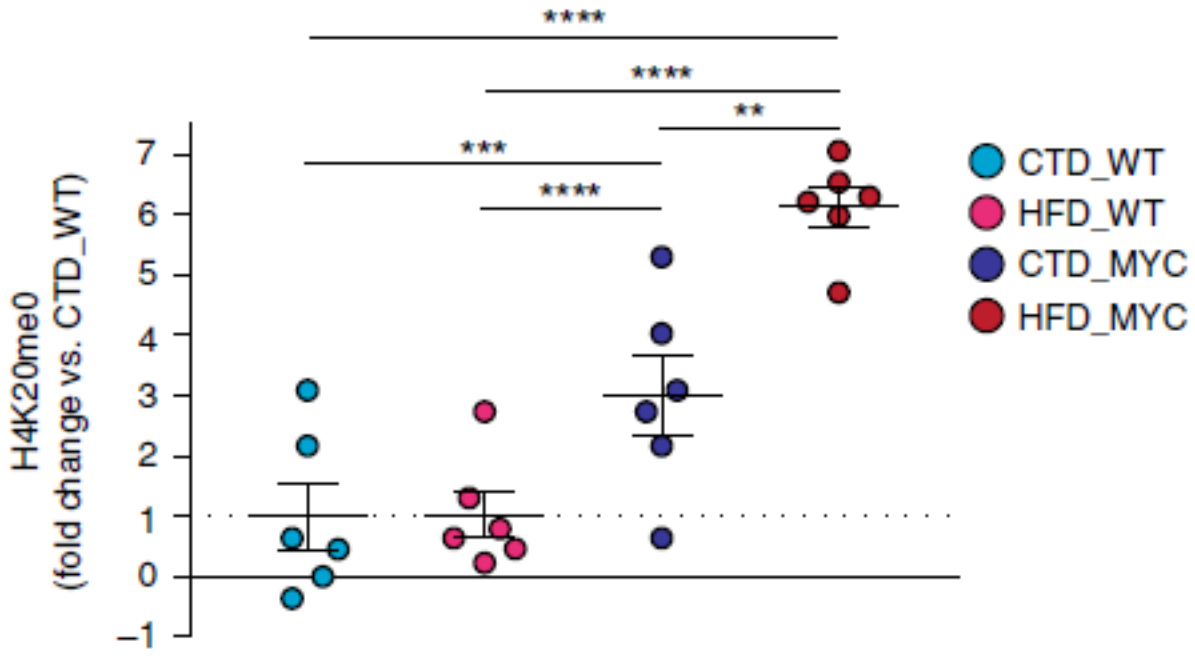
David P. Labbé et al.#

Human replication of animal models



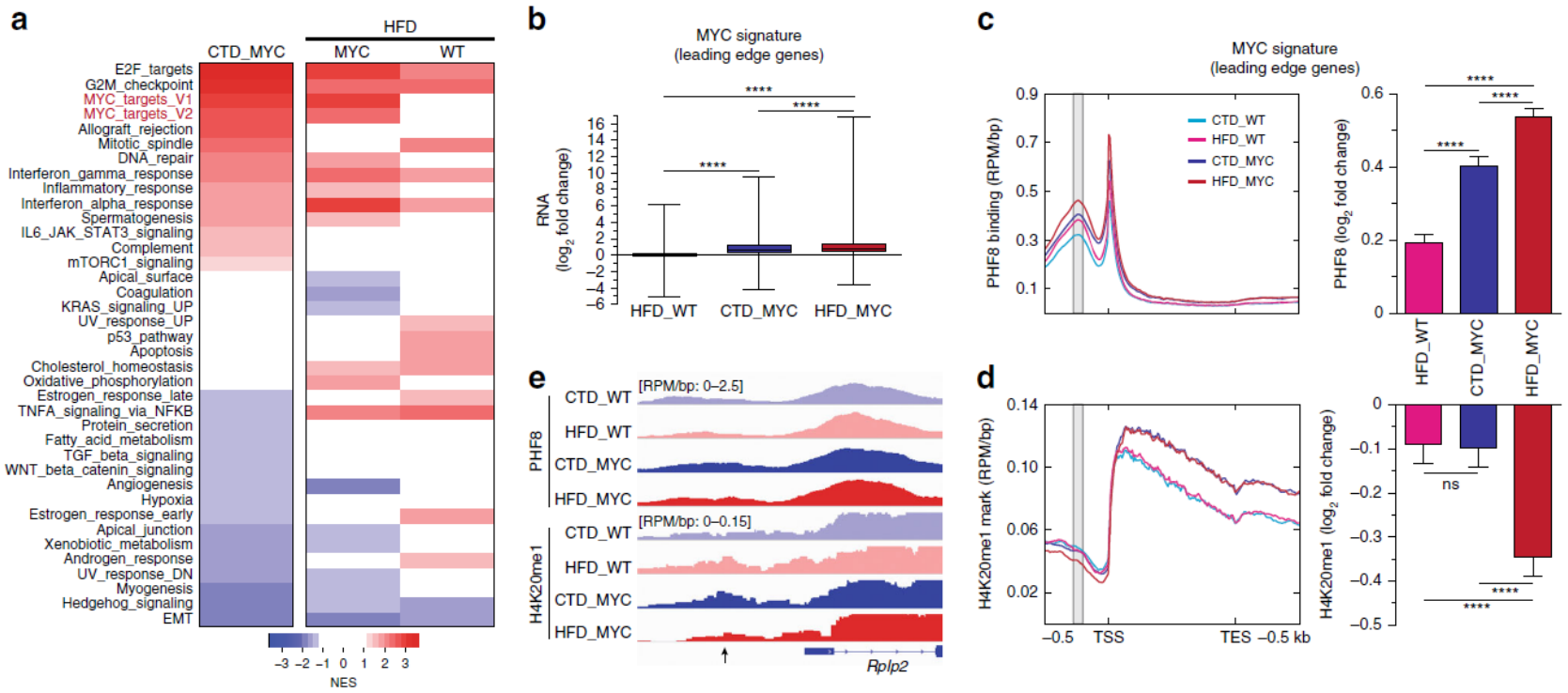
HFD under MYC overexpression results in a characteristic metabolomic profile suggestive of dampened histone methylation

Human replication of animal models



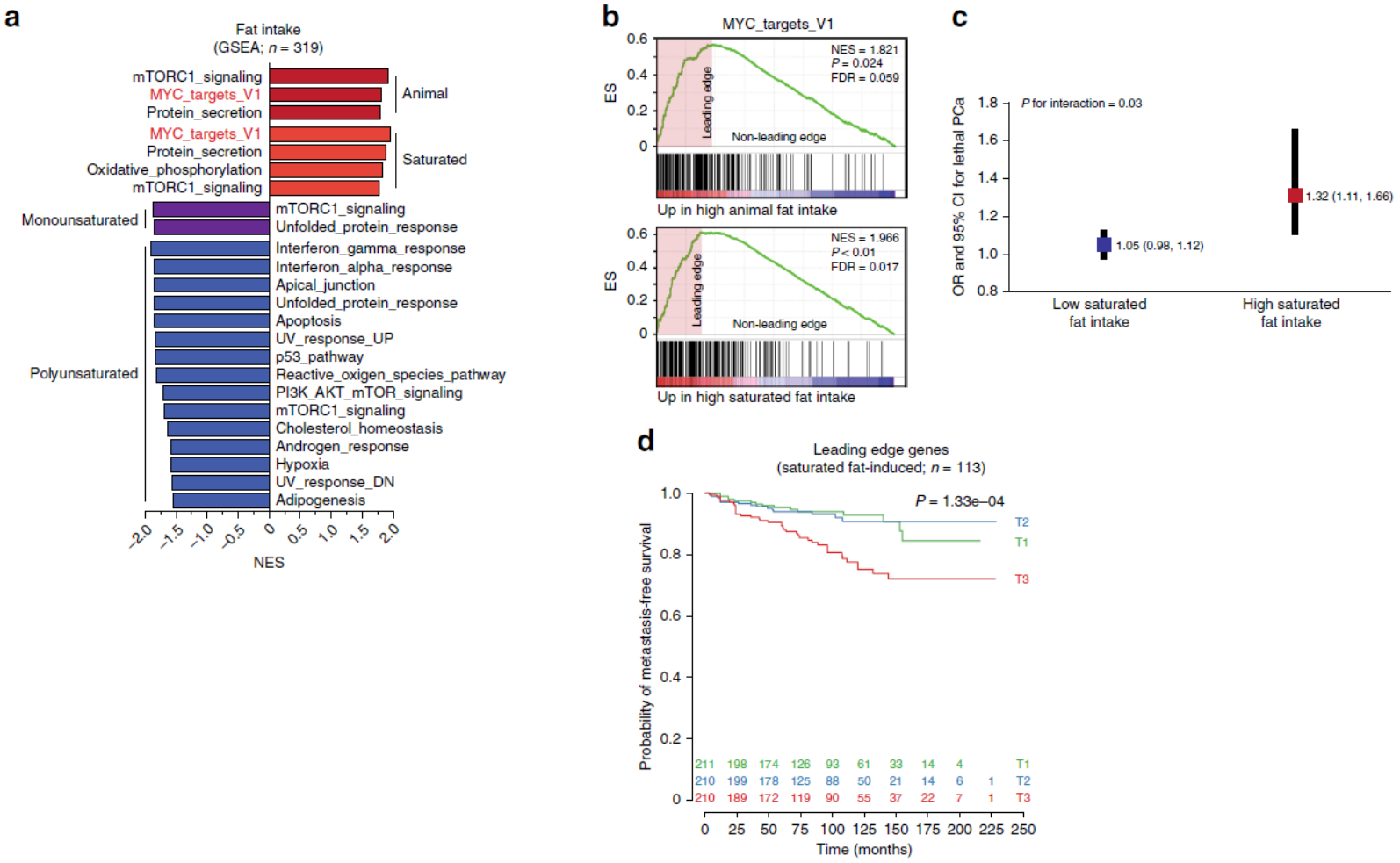
HFD increases hypomethylation of MYC target genes in a MYC overexpression model

Human replication of animal models



HFD enhances MYC transcriptional activity

Human replication of animal models

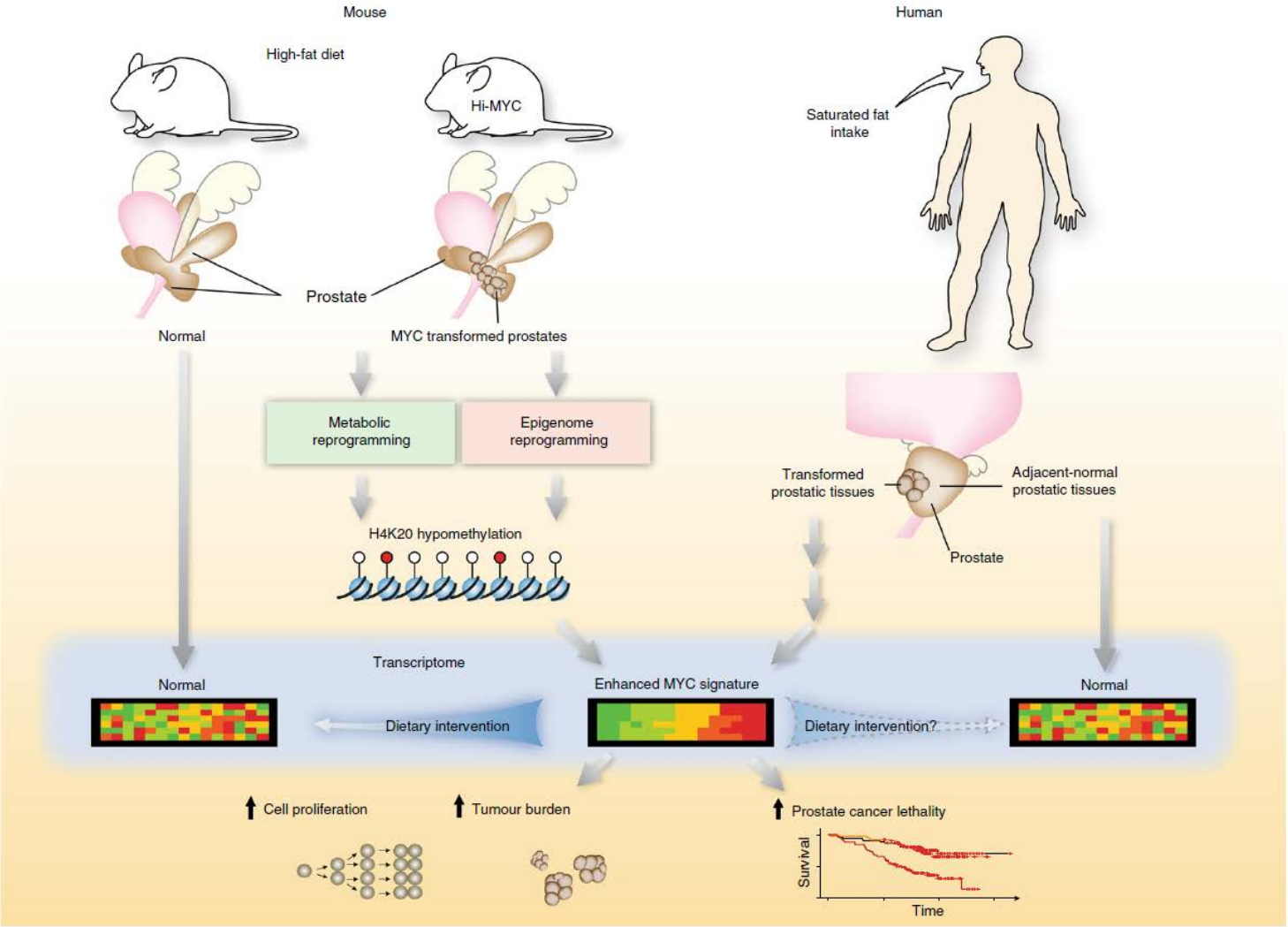


Human replication of animal models

Table 2 Fat-induced and non-fat-induced MYC signature score in relation to risk of prostate cancer death among men diagnosed with non-metastatic prostate cancer

MYC score	*n*	Leading edge genes (fat-induced)[a]			*n*	Non-leading edge genes (non-fat-induced)[b]		
		OR (95% CI)[c]	OR (95% CI)[d]	OR (95% CI)[e]		OR (95% CI)[c]	OR (95% CI)[d]	OR (95% CI)[e]
Animal fat								
Tertile 1 (low)	13	1.00	1.00	1.00	17	1.00	1.00	1.00
Tertile 2	18	1.58 (0.73, 3.53)	1.31 (0.57, 3.08)	1.27 (0.55, 2.99)	19	1.17 (0.57, 2.44)	1.03 (0.47, 2.30)	0.96 (0.43, 2.16)
Tertile 3 (high)	31	3.44 (1.69, 7.38)	2.50 (1.14, 5.70)	2.37 (1.07, 5.43)	26	1.79 (0.90, 3.64)	1.07 (0.81, 3.70)	1.66 (0.78, 3.61)
P, linear trend[f]		0.001	0.019	0.03		0.09	0.15	0.17
Saturated fat								
Tertile 1 (low)	13	1.00	1.00	1.00	16	1.00	1.00	1.00
Tertile 2	15	1.23 (0.55, 2.80)	1.07 (0.45, 2.59)	1.05 (0.44, 2.54)	18	1.24 (0.59, 2.64)	1.17 (0.52, 2.65)	1.09 (0.48, 2.48)
Tertile 3 (high)	34	4.02 (1.98, 8.63)	3.21 (1.47, 7.35)	3.04 (1.38, 7.01)	28	2.34 (1.18, 4.82)	1.93 (0.90, 4.23)	1.86 (0.87, 4.08)
P, linear trend[f]		0.0001	0.002	0.004		0.015	0.085	0.107

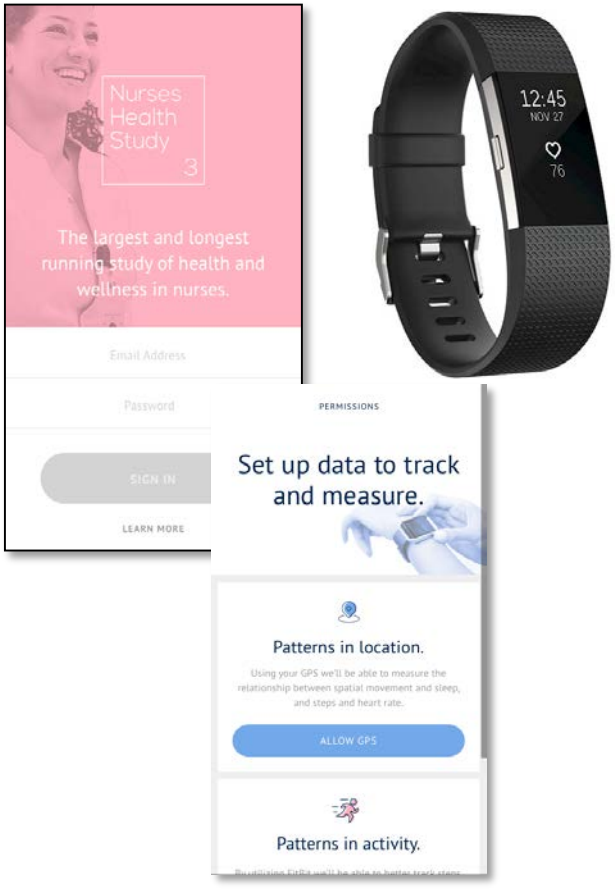
Human replication of animal models

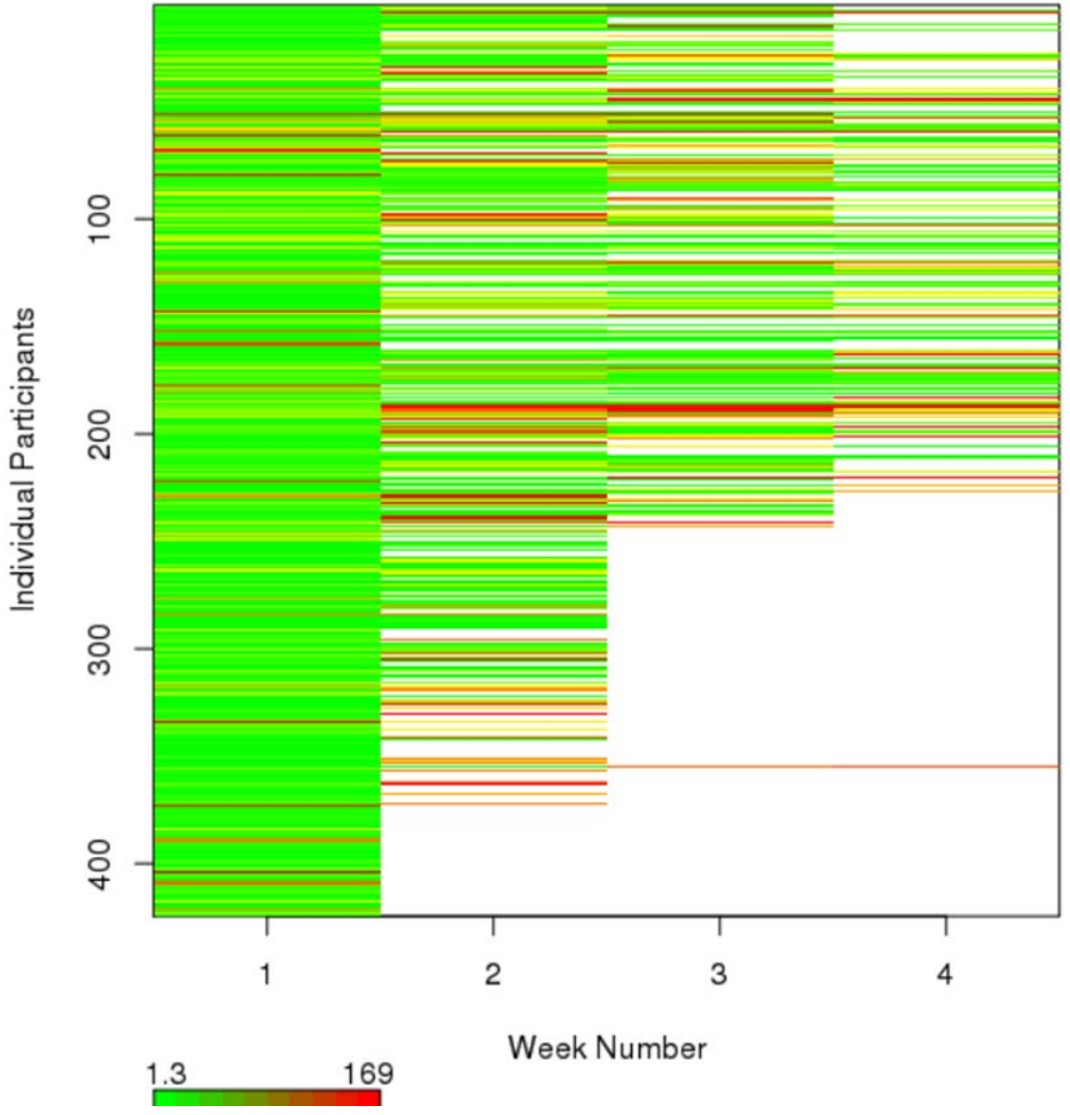


Support new data collection

- Digital phenotyping of obesity related behaviors
  - Physical activity
  - Sleep
  - Location (contextual factors)

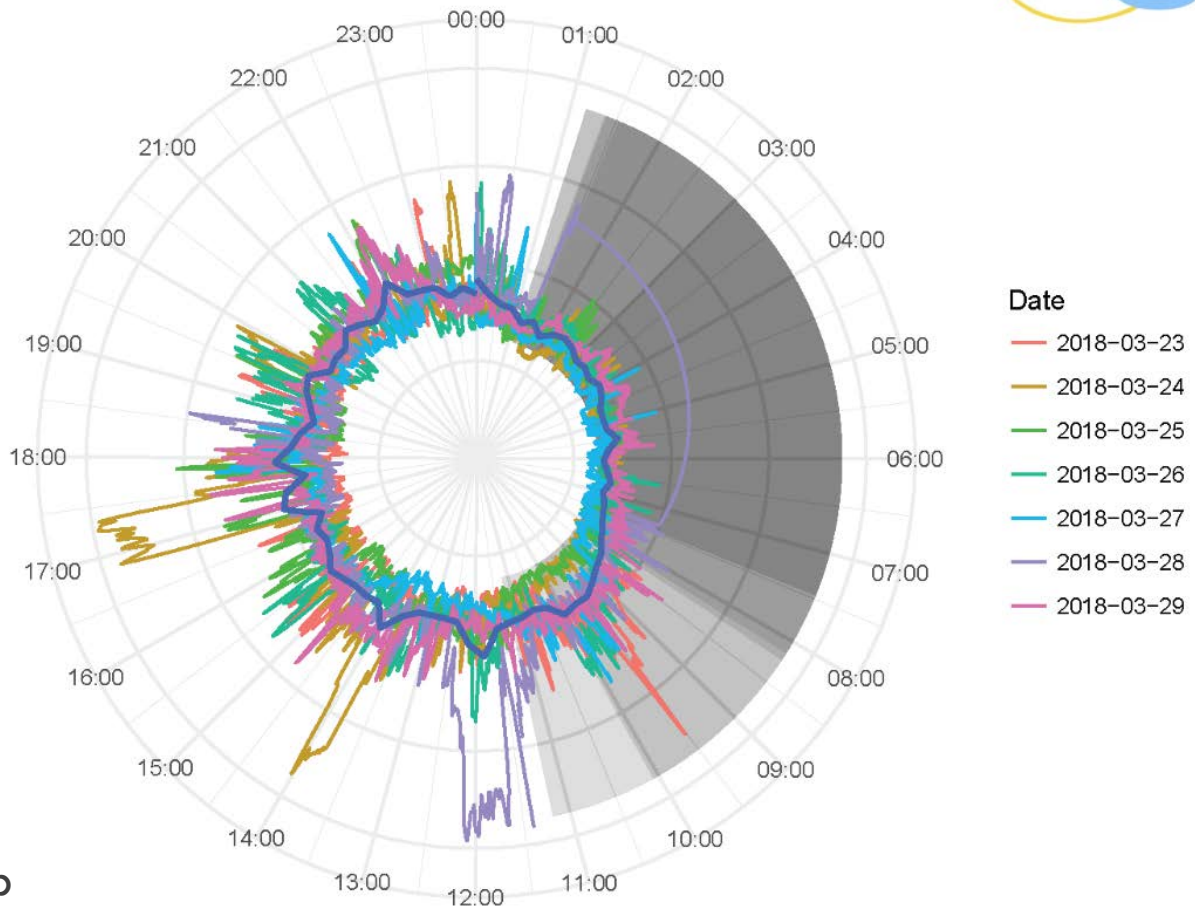
Mobile Health Technology (mHealth) in NHS3



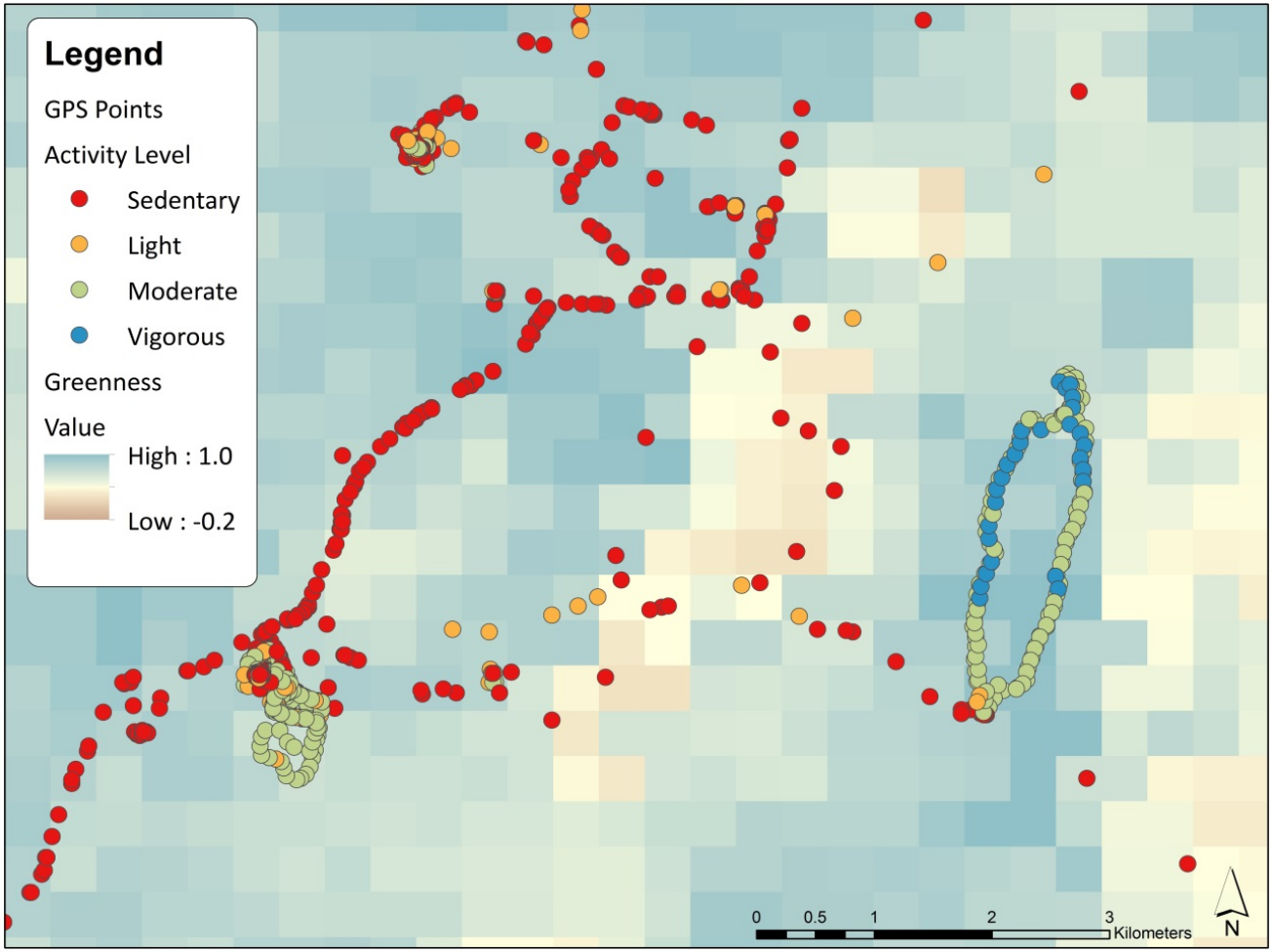


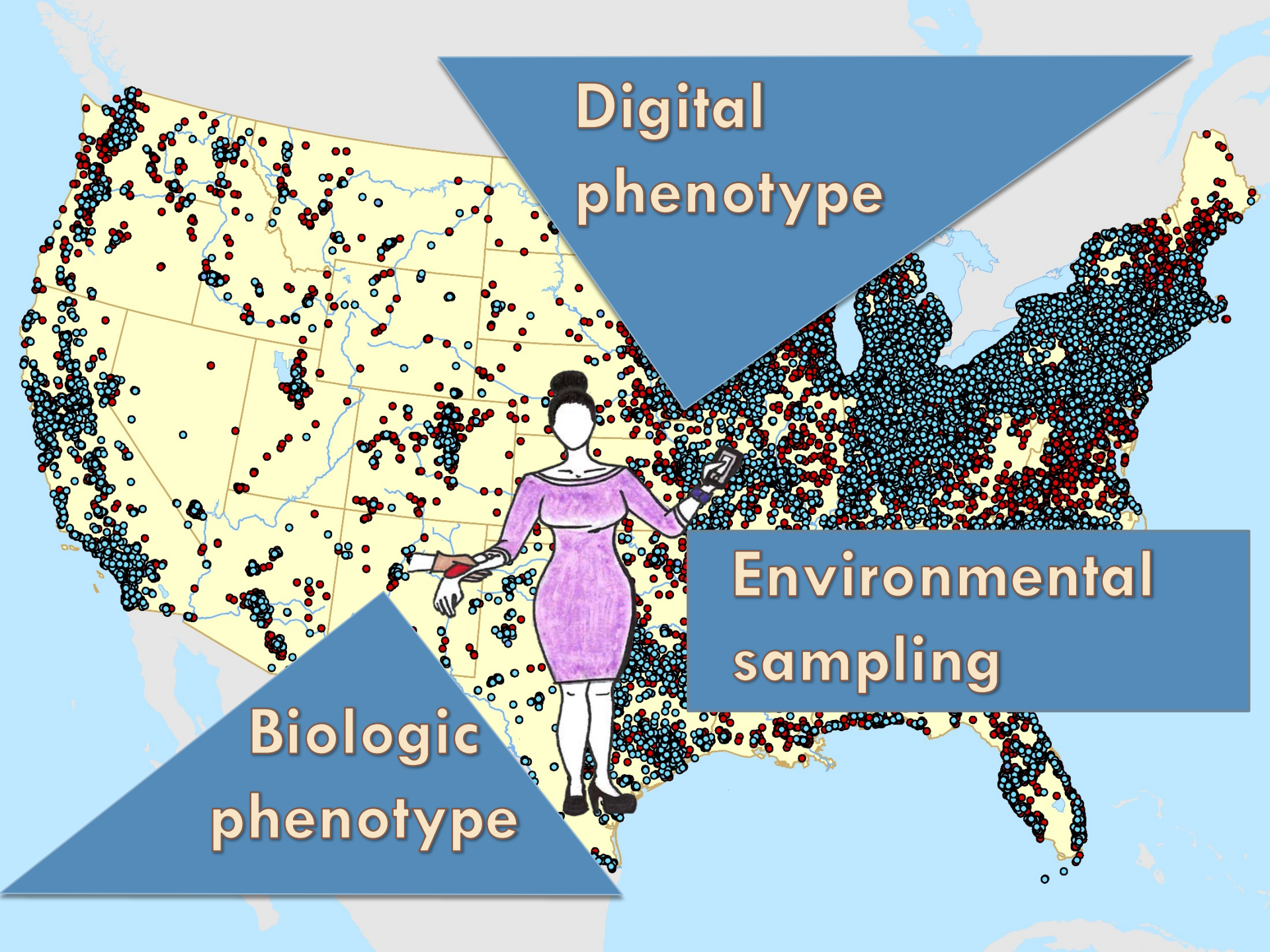
Sleep and Circadian Markers

- Activity, heart rate, and sleep periods across multiple days
- Can compare to questionnaire-based approaches
- Can use to derive circadian markers
- Examine variability in sleep timing, duration
- Novel metrics such as social jetlag
- Shift work
- Examine relationship between environmental factors and sleep



Heart Rate and Sleep Data for One Participant over One Week


Legend
GPS Points
Activity Level
Sedentary
Light
Moderate
Vigorous
Greenness
Value
High : 1.0
Low : -0.2
0
0.5
1
2
3
Kilometers
N


Digital phenotype
Environmental sampling
Biologic phenotype

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