

# BIG DATA INSTITUTE

Li Ka Shing Centre for Health Information and Discovery



## Mendelian randomization of objectively-measured sedentary behaviour in large-scale biobanks

Aiden Doherty

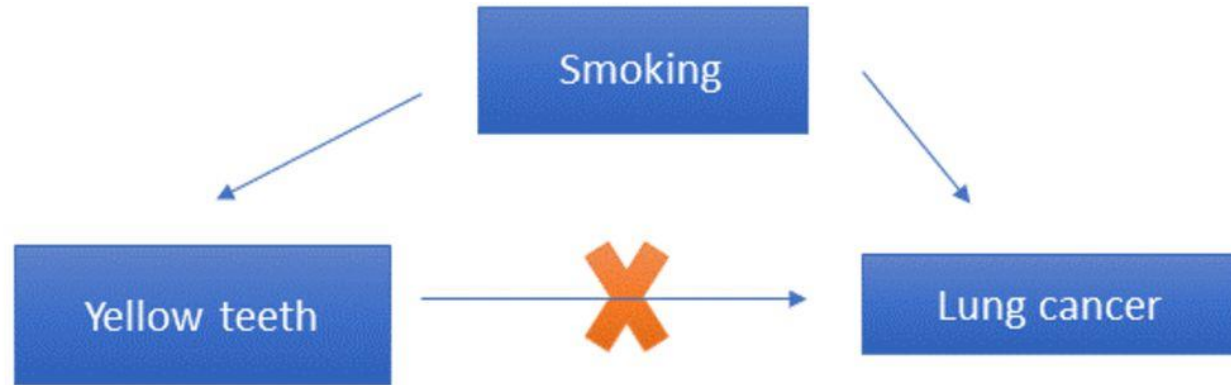
*Nuffield Department of Population Health  
NIHR Oxford Biomedical Research Centre*



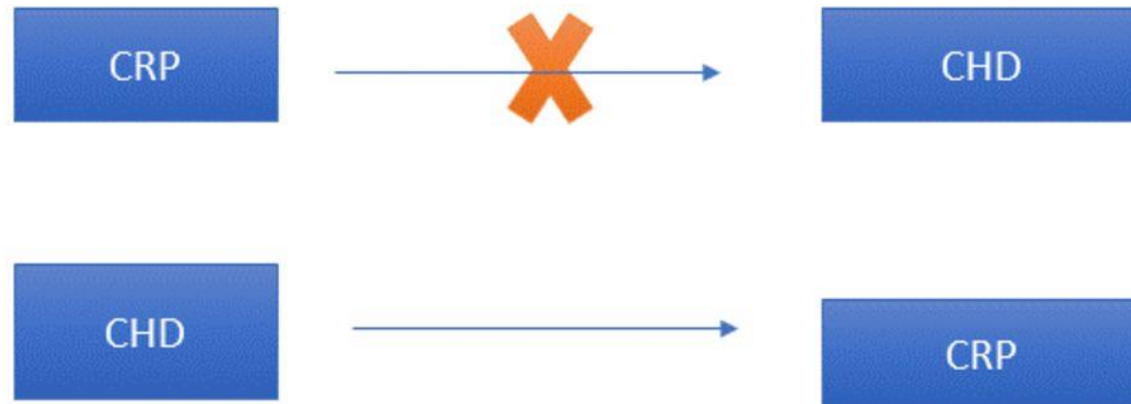
With thanks to: Cecilia Lindgren, Chris Holmes, Michael Holmes, Sara Pulit, Teresa Ferreira, Karl Smith-Byrne, Matthew Willetts, Louis Aslett, Nick Wareham, Soren Brage, Rory Collins, Gil McVean, Martin Landray, and many others...

# Examples of (A) confounding and (B) reverse causality in observational epidemiology.

## a) Confounding



## b) Reverse causality

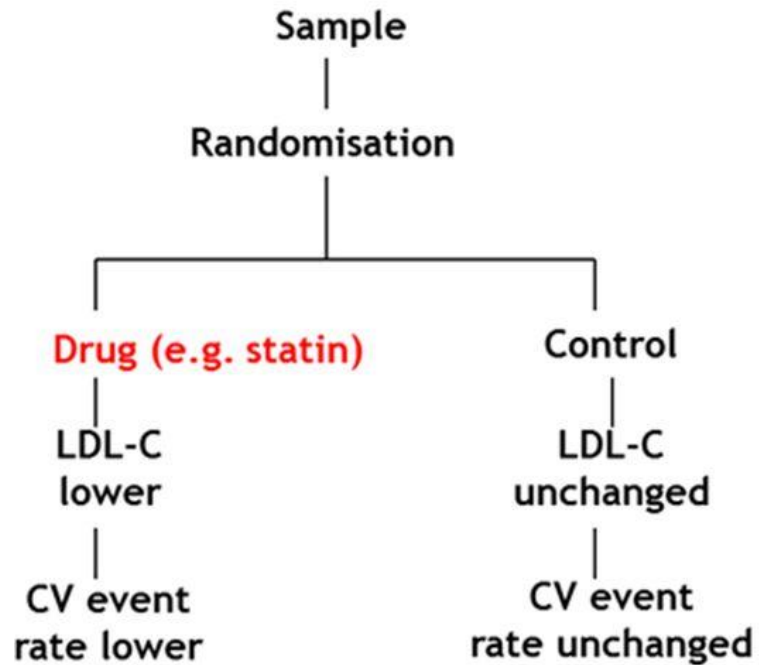


Derrick A Bennett, and Michael V Holmes *Heart* 2017;103:1400-1407



# Comparison of a conventional trial with a Mendelian randomisation study.

## Conventional Trial



Derrick A Bennett, and Michael V Holmes *Heart*  
2017;103:1400-1407



# Measuring sedentary behaviour

Thigh-worn devices have good validity but study sample sizes are relatively small  $n < 10,000$

Wrist-worn devices have less validity, but study sample sizes an order of magnitude larger  $n = \sim 100,000$

Scalar y-axis thresholds struggle to distinguish between sleep/sedentary/light behaviour states.

We need better methods to infer sedentary behaviour from wrist-worn devices.

# Measuring sedentary behaviour

**Table 2.** Minutes of coded sedentary posture from Microsoft's SenseCam by activity category

Image code	Minutes	Percent time in accelerometer cpm <100	Interquartile range of accelerometer cpm	Mean accelerometer cpm
Sports	0	—	1525–2900	2330
Self care	85	60	2–361	284
Manual labor	202	35	41–669	432
Conditioning exercise	230	21	85–1405	1262
Household activity	244	58	10–305	260
Riding in other vehicle	409	82	0–50	90

# Machine learning & sedentary behaviour



Sitting



Walking



Driving

## Wearable camera video

<https://ajpmonline.wordpress.com/2013/04/15/using-wearable-cameras-in-your-research/>

<http://www.sciencedirect.com/science/journal/07493797/44/3>

[https://www.youtube.com/watch?v=\\_D7FhnnKJ2g](https://www.youtube.com/watch?v=_D7FhnnKJ2g)

# Extracting behaviours from camera data



**O** = office/computer work general (11580)      **K**= kitchen activity (5035)  
**E**= eating sitting (13030)

1) Images:      **OOOKOEOKOK** **EEEEER**

2) Split image: **OOOKOEOKOK** **EEEEER**

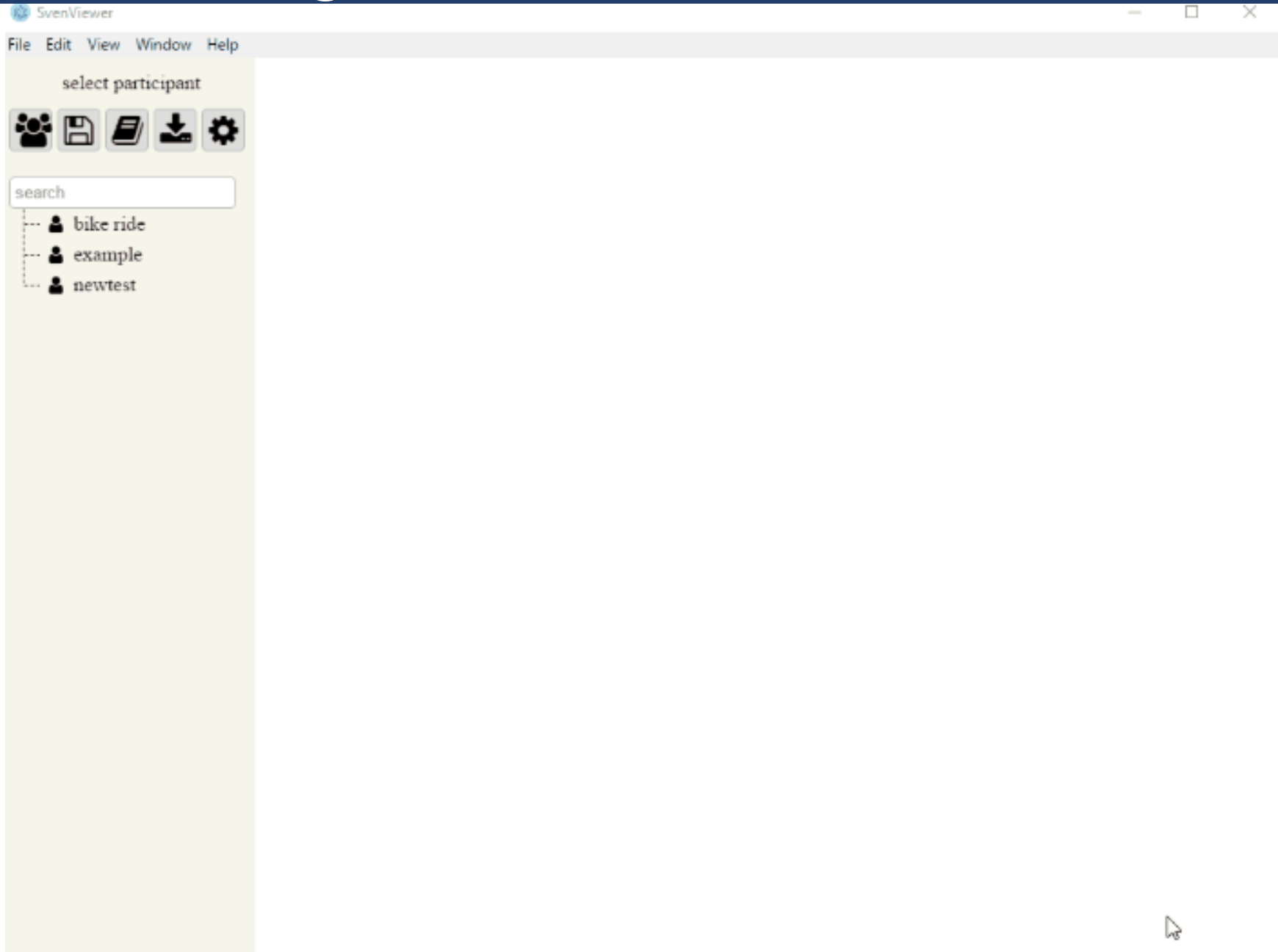
Event 1- Office  
Work

Event 2-  
Eating

The first event, whilst consisting of a variety of actions, is annotated as 'office/computer work general' as this is the dominant activity.



# Extracting behaviours from camera data



<https://github.com/activityMonitoring>

Willetts, M., Hollowell, S., Aslett, L., Holmes, C. & Doherty, A. *Sci. Rep.* 8, 7961 (2018).

Doherty, Moulin, Smeaton *Memory* 19(7), 785-795 (2011)

# Examples of sedentary behaviour



Sitting driving car



Sitting riding on a bus



Sitting using computer screen



Sitting eating and watching TV

# Camera defined sedentary behaviour

A sedentary behaviour is one which has a MET energy expenditure score of  $\leq 1.5$  and occurs in a sitting, lying, or reclining posture

As an exception to this rule we also categorised the following as sedentary behaviour:

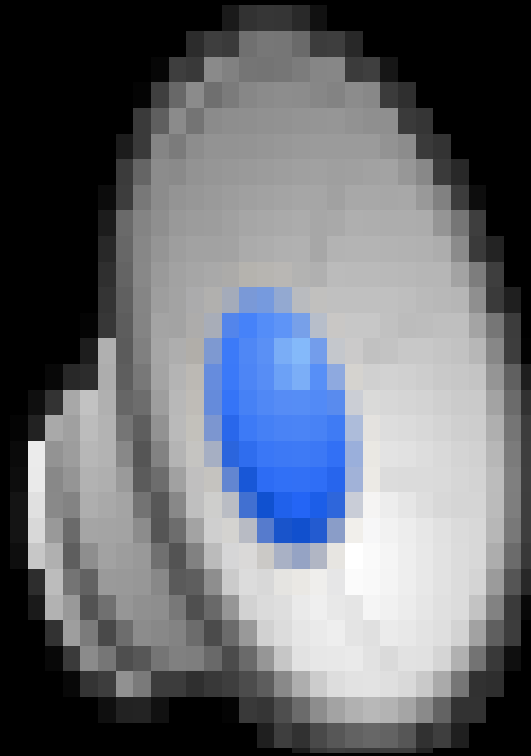
16010 driving automobile or light truck (not a semi) **2.5 METS**

21010 sitting non-desk work (with or without eating at the same time) **2.5 METS**

9065 students/attending seminars or talks **1.8 METS**

9100 retreat/family reunion activities involving sitting eating relaxing talking with more than one person **1.8 METS**

# Machine learning of behaviours from acc data



150 people – activity monitors + cameras

# Behaviour classification – free living groundtruth

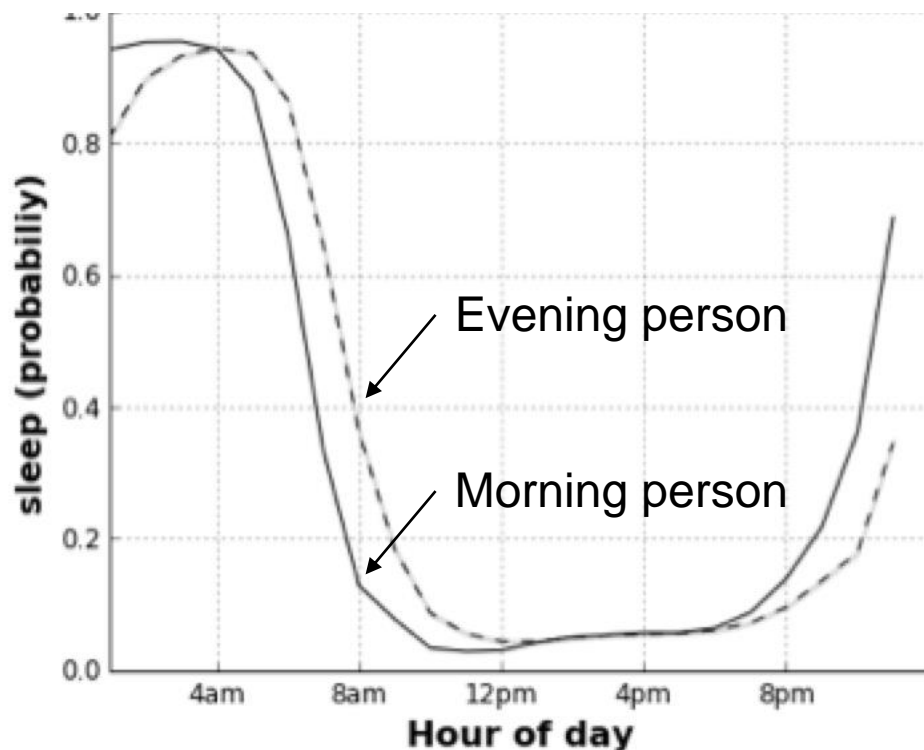
- 188,355 mins annotated behaviour from 153 people
- 230 different behaviours types (57 sedentary)
- Kappa = 0.68 (accuracy = 79%)

Prediction→ Ground truth↓	Sleep	Sedentary	Tasks-light	Walking	Moderate activity
Sleep	91%	8%	<1%	<1%	<1%
Sedentary	6%	81%	5%	3%	6%
Tasks-light	<1%	29%	25%	20%	26%
Walking	<1%	11%	15%	58%	16%
Moderate	<1%	12%	14%	15%	58%

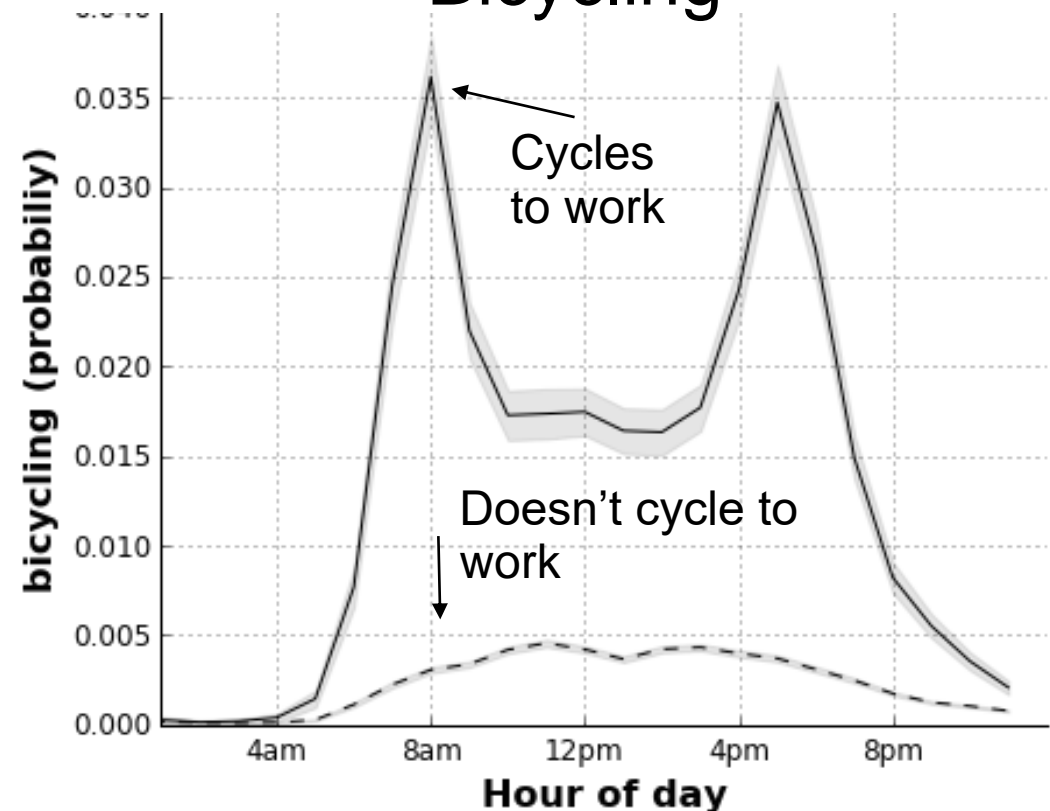
# Behaviour classification – face validity

*Variation in accelerometer-measured behaviour types (2013–2015) across the day by participant characteristics (measured 2007–2010): the UK Biobank study.*

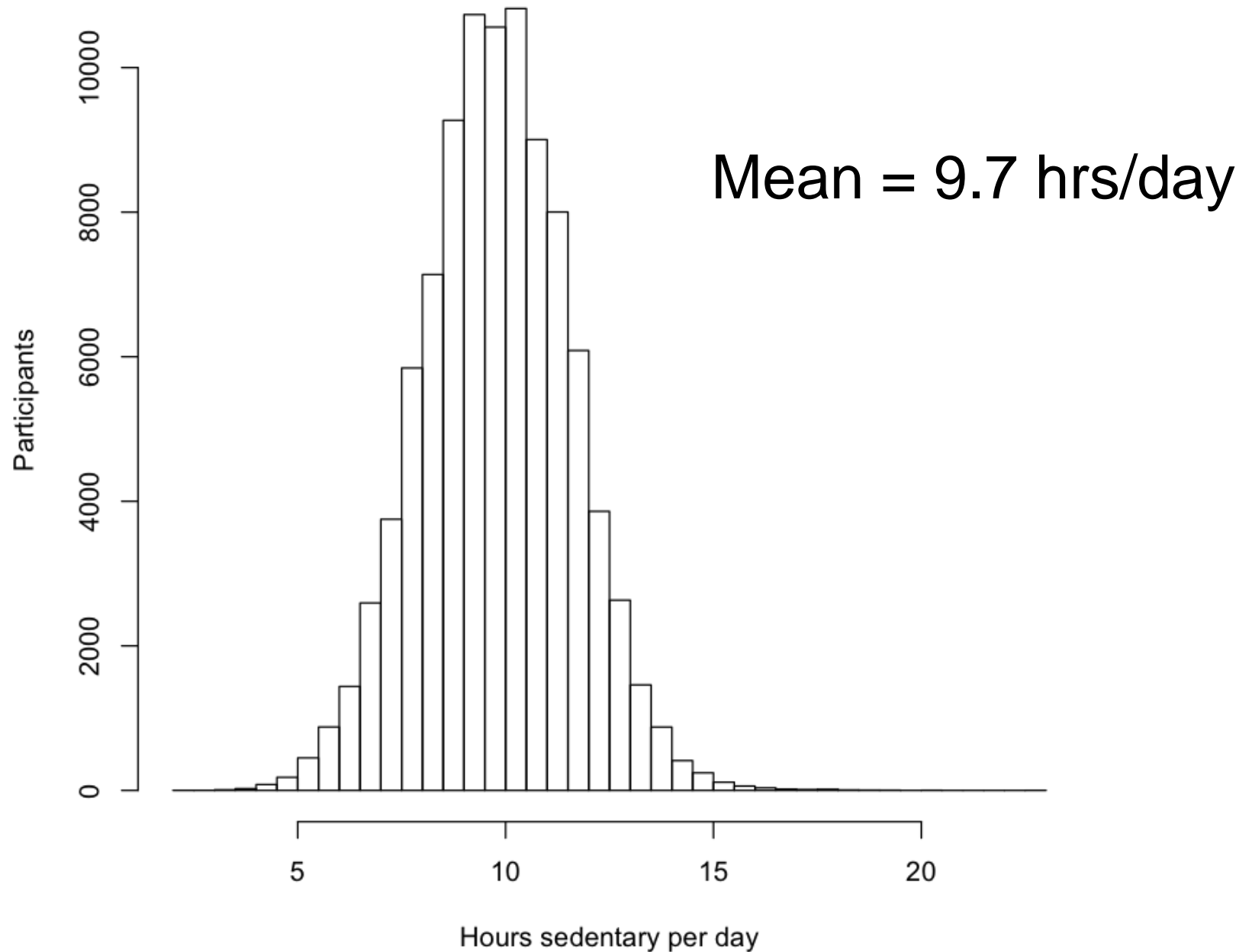
## Sleep



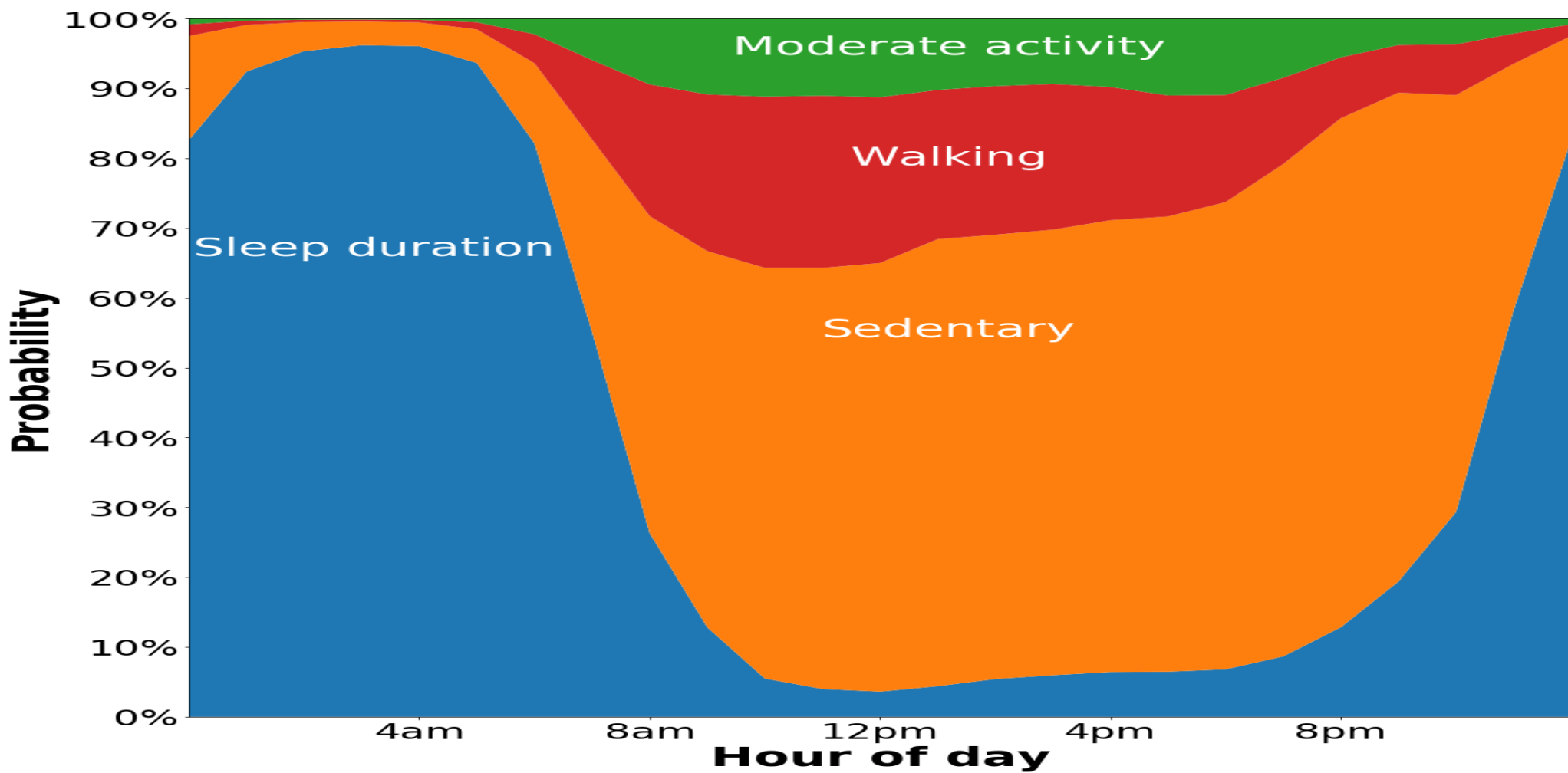
## Bicycling



# Acc inferred sedentary behaviour – UK Biobank (n=96,616)



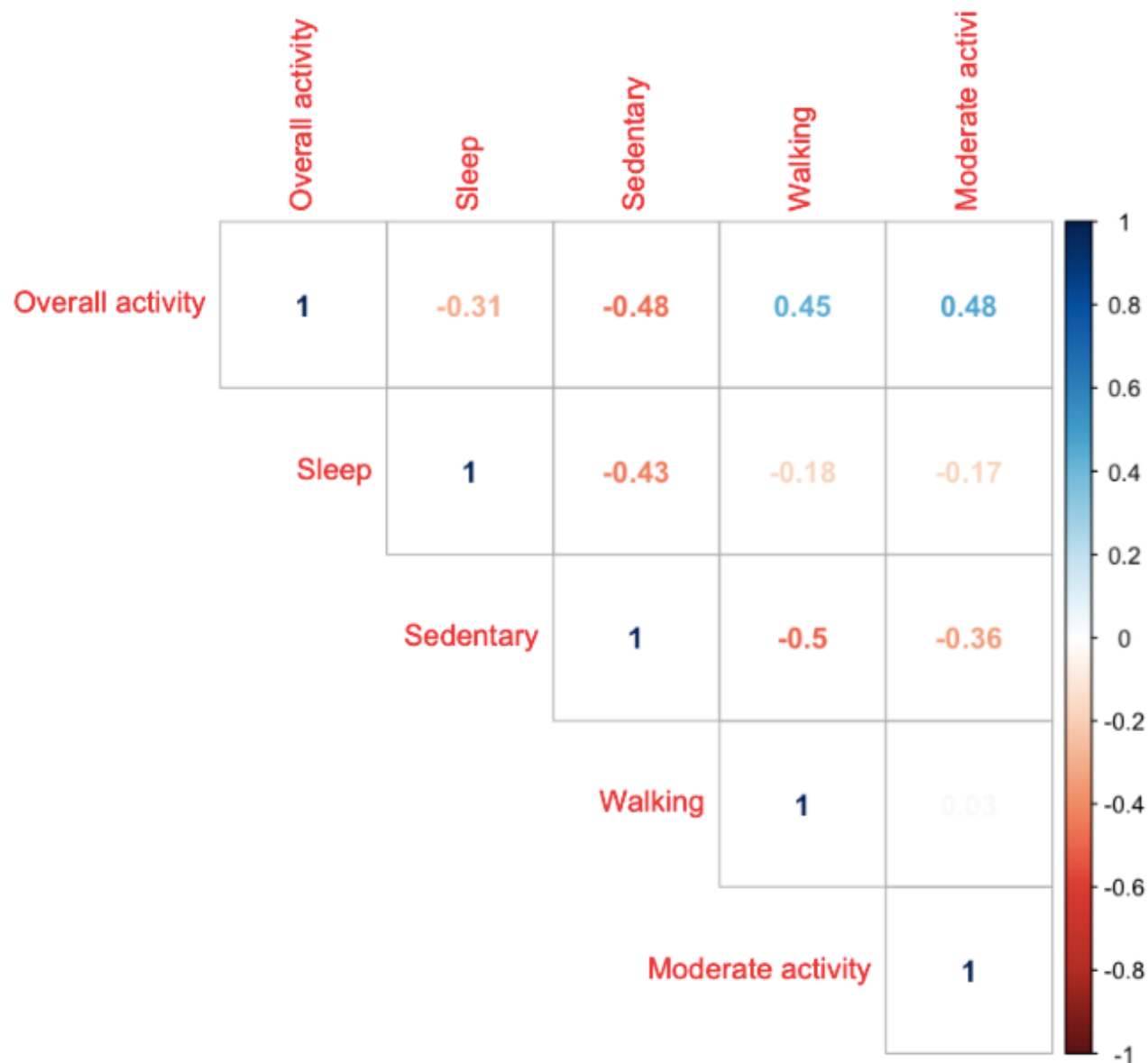
# Behaviour classification in UK Biobank (n=91,105)





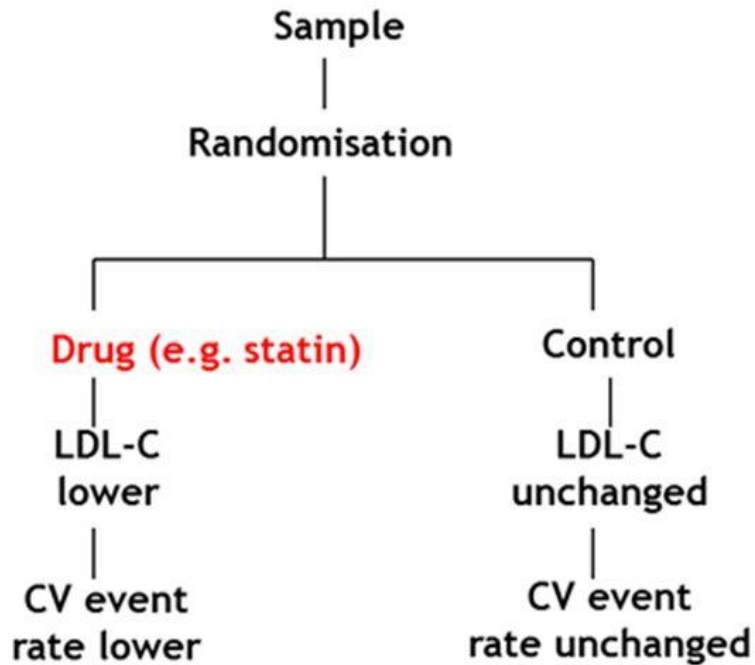
# Behaviour classification in UK Biobank (n=91,105)

## Phenotypic correlations

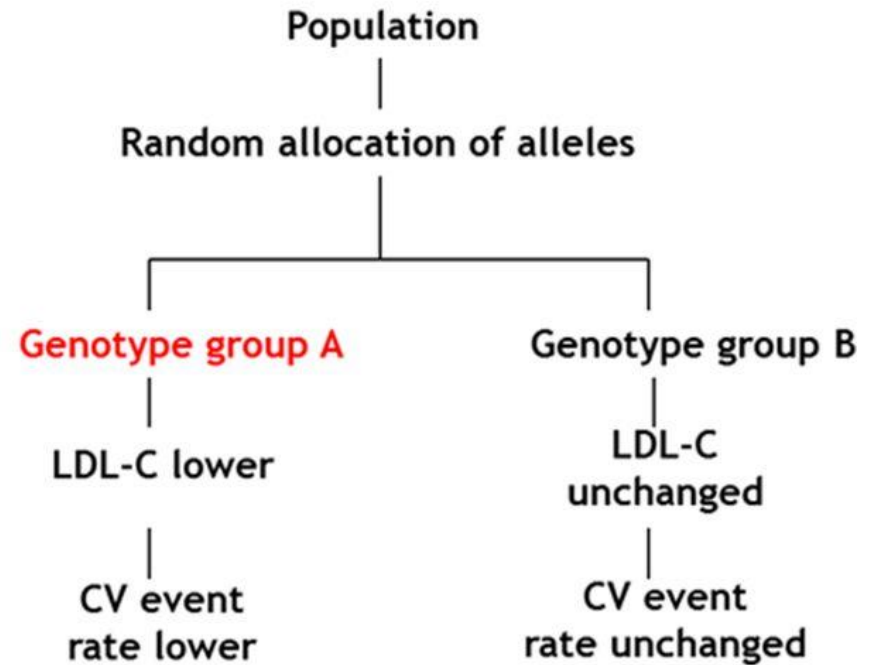


# Comparison of a conventional trial with a Mendelian randomisation study.

## Conventional Trial



## Mendelian randomisation



Derrick A Bennett, and Michael V Holmes Heart  
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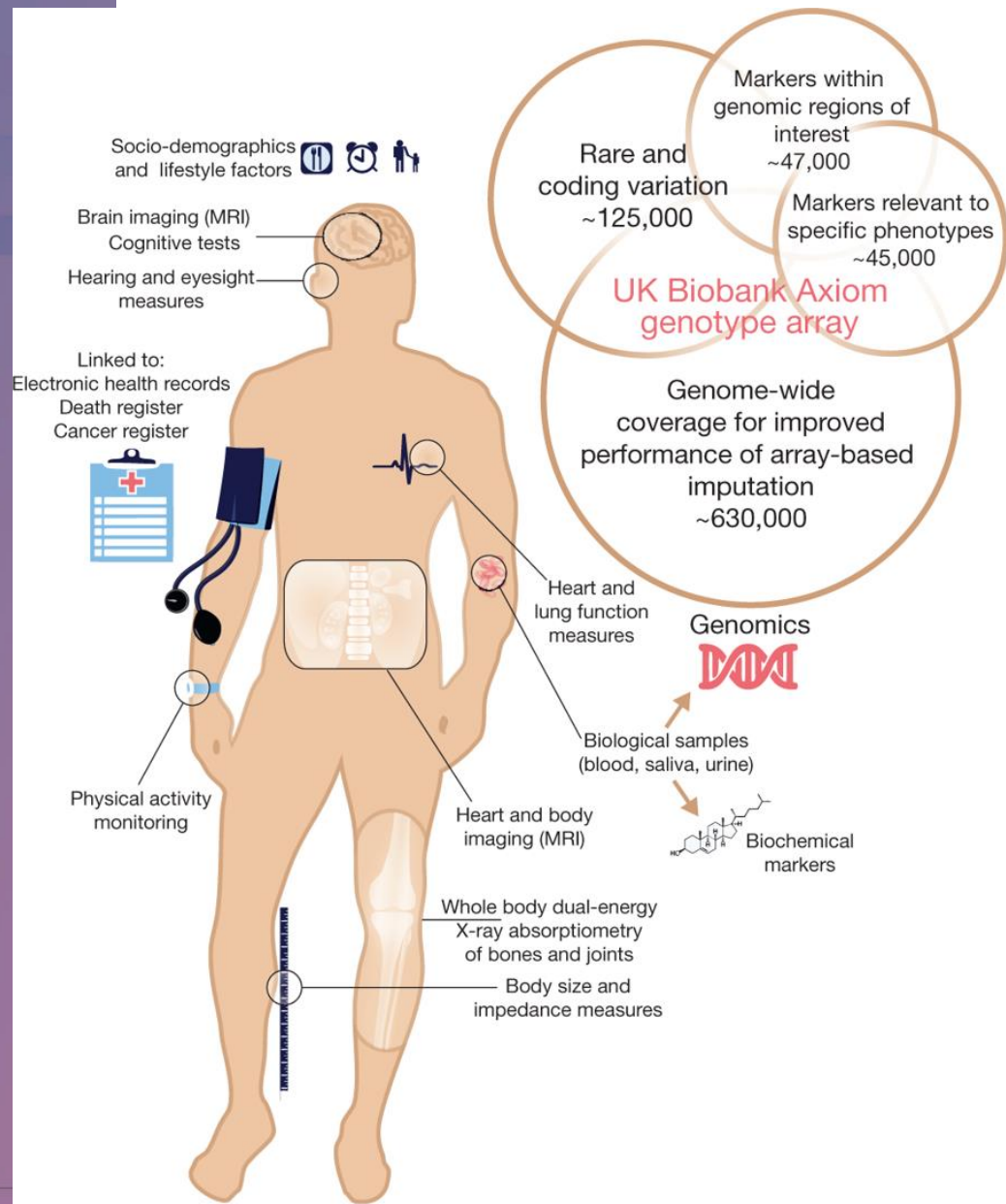




## UK BIOBANK

Genetic and health data  
from half a million people  
in the United Kingdom

PAGES 194, 203 & 210



### TECHNOLOGY

#### TIME TO THINK SMALL

Fleets of tiny satellites could  
change space exploration

PAGE 185

### OPTOELECTRONICS

#### TURNING UP THE LIGHT

Boost in performance for  
perovskite LEDs

PAGES 197, 245 & 249

### DEVELOPMENTAL BIOLOGY

#### TWO WAYS TO GROW

A second source for the cells  
that line blood vessels

PAGES 195 & 223

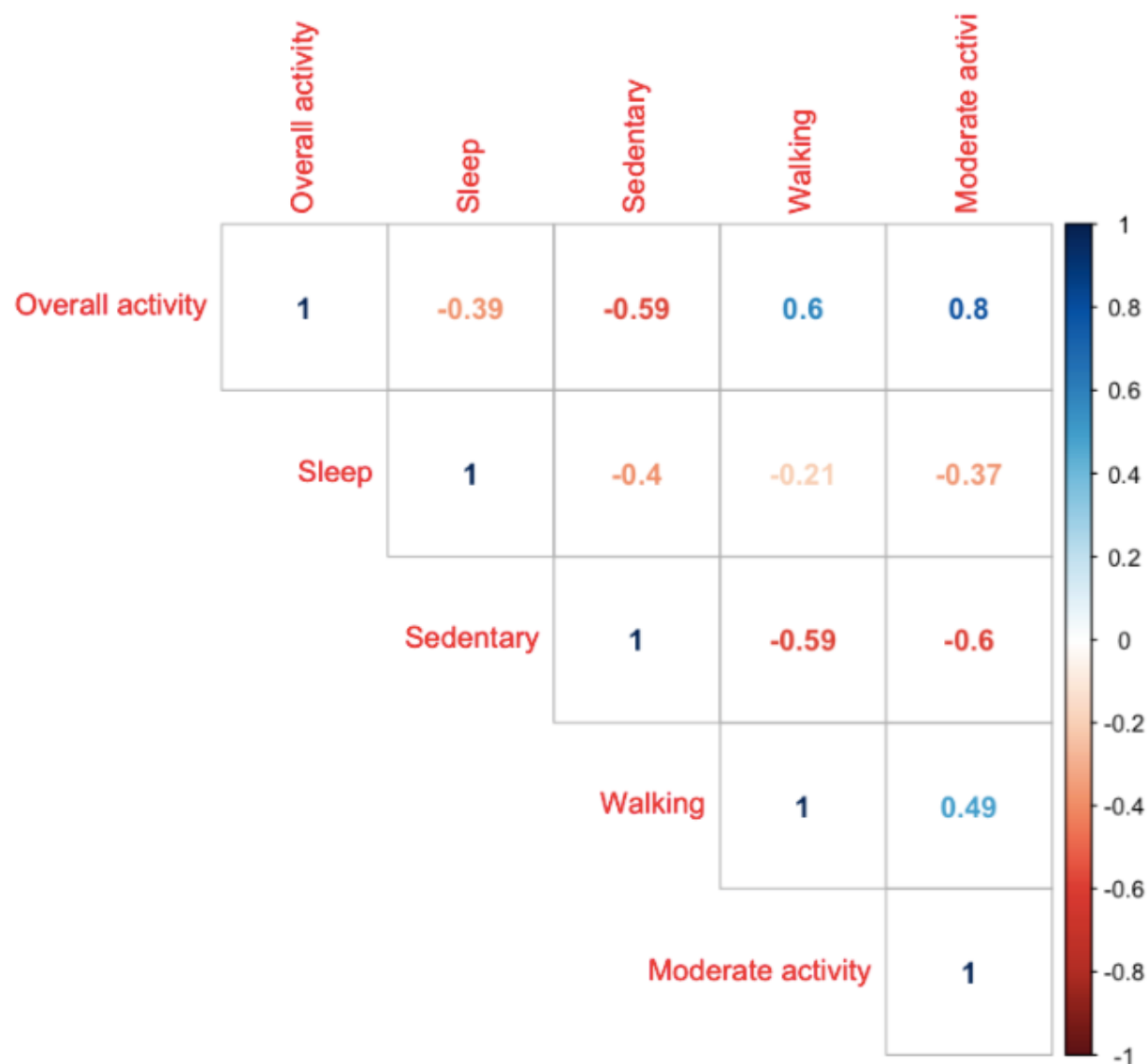
NATURE.COM

11 October 2018

Vol. 562, No. 7726

# Behaviour classification in UK Biobank (n=91,105)

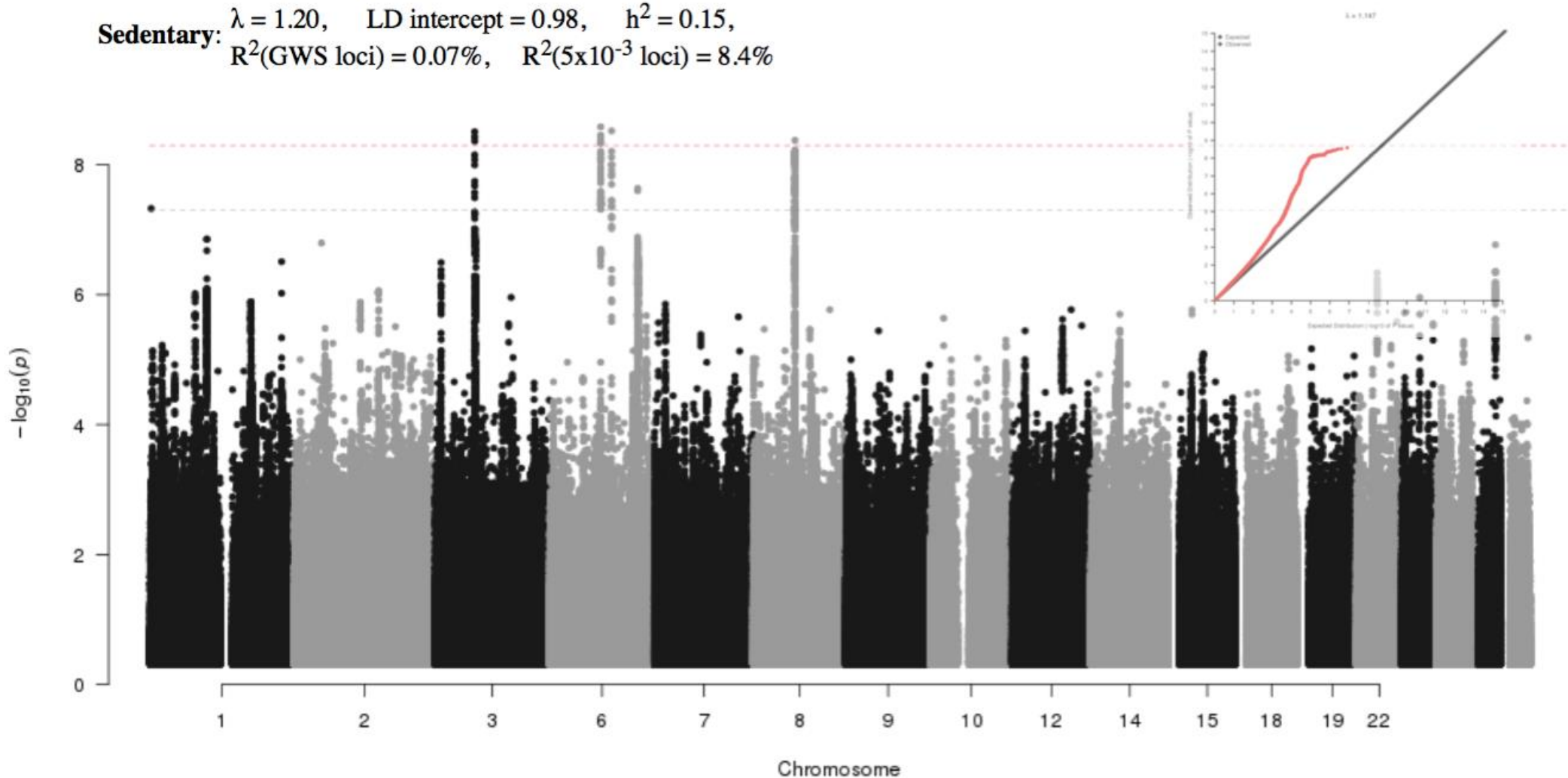
## Genetic correlations



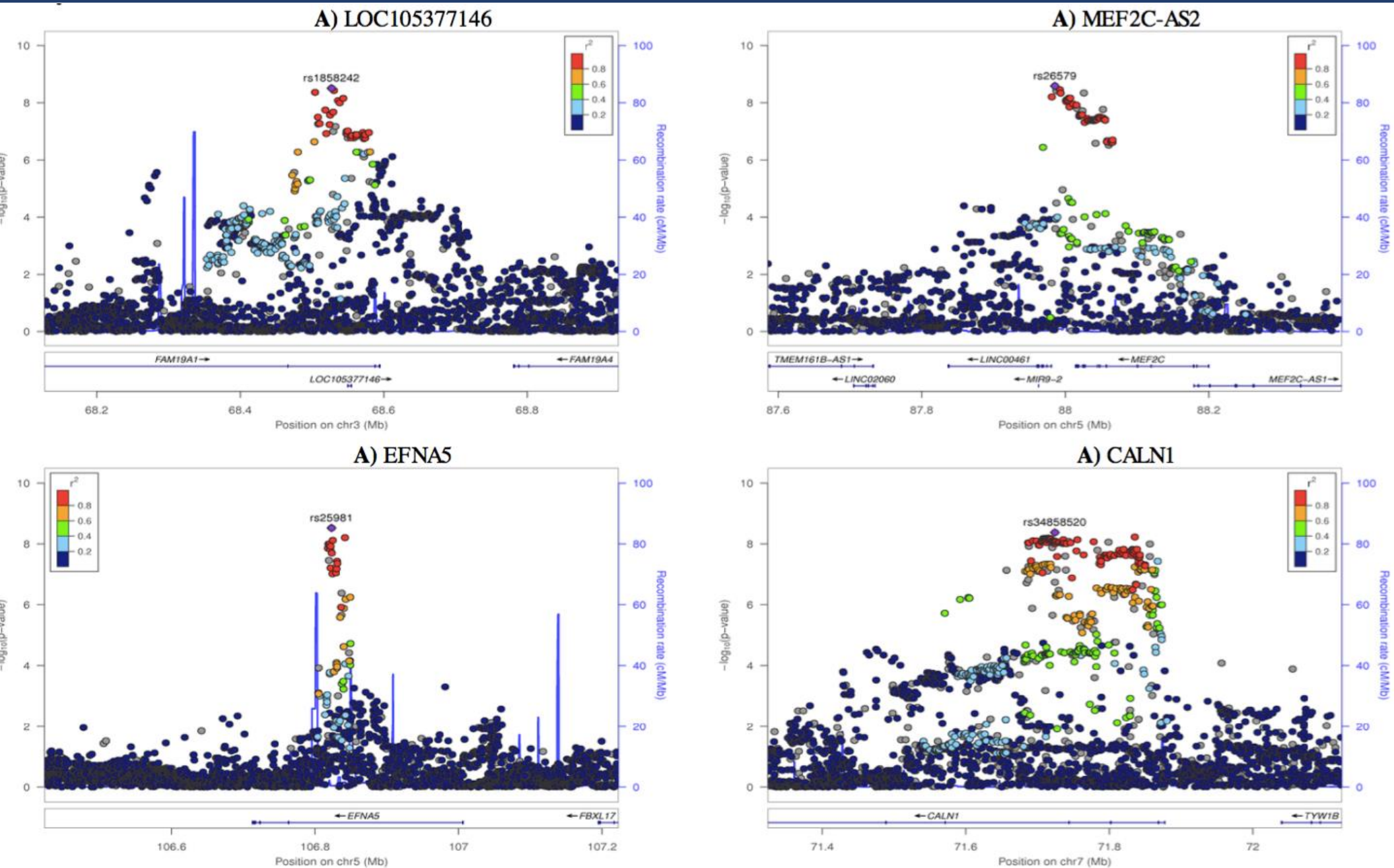
# Genetic variants associated with sedentary behaviour

*GWAS of accelerometer measured sedentary behaviour (via machine learning) in 91,105 UK Biobank participants*

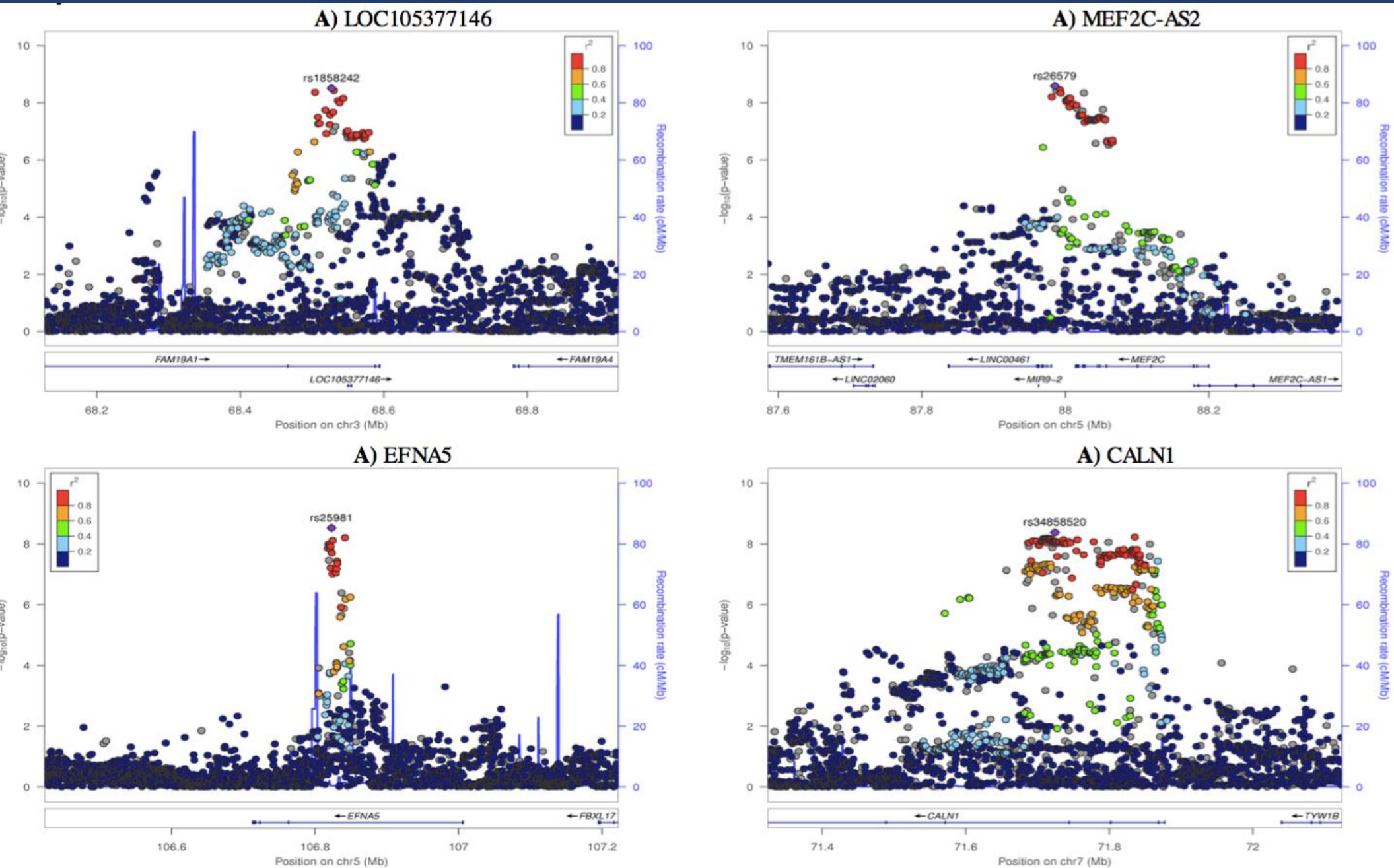
**Sedentary:**  $\lambda = 1.20$ , LD intercept = 0.98,  $h^2 = 0.15$ ,  
 $R^2(\text{GWS loci}) = 0.07\%$ ,  $R^2(5 \times 10^{-3} \text{ loci}) = 8.4\%$



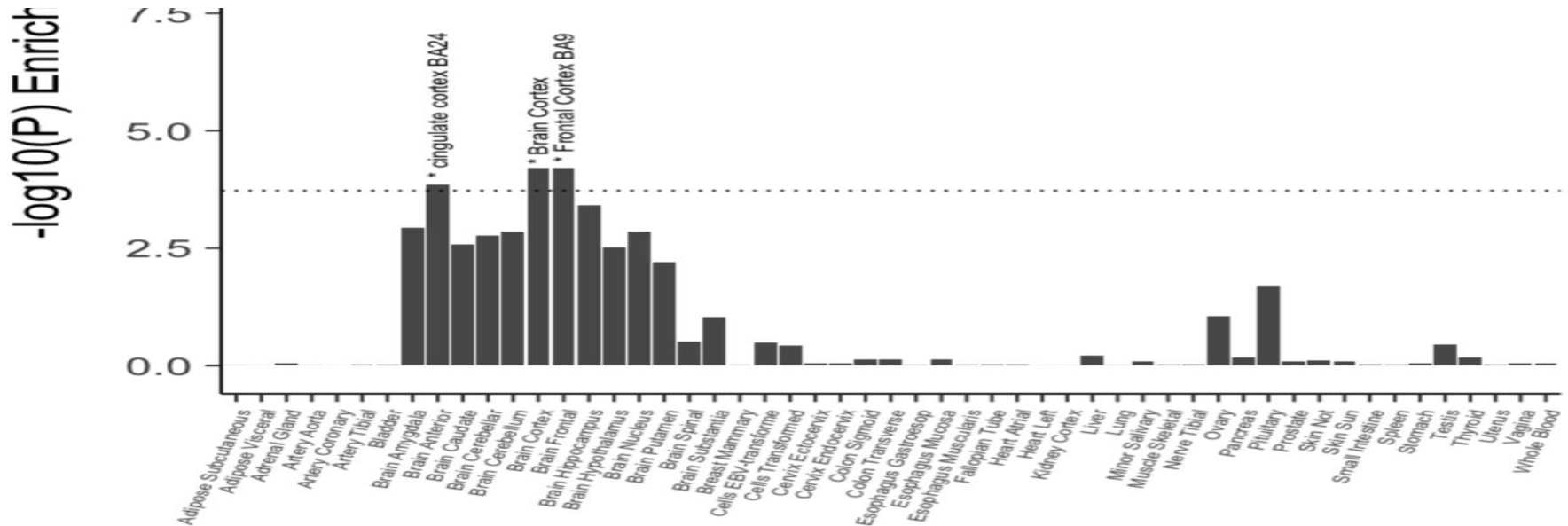
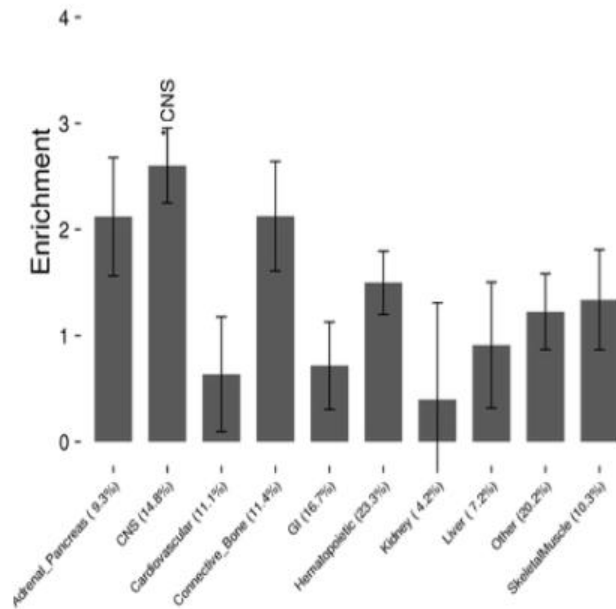
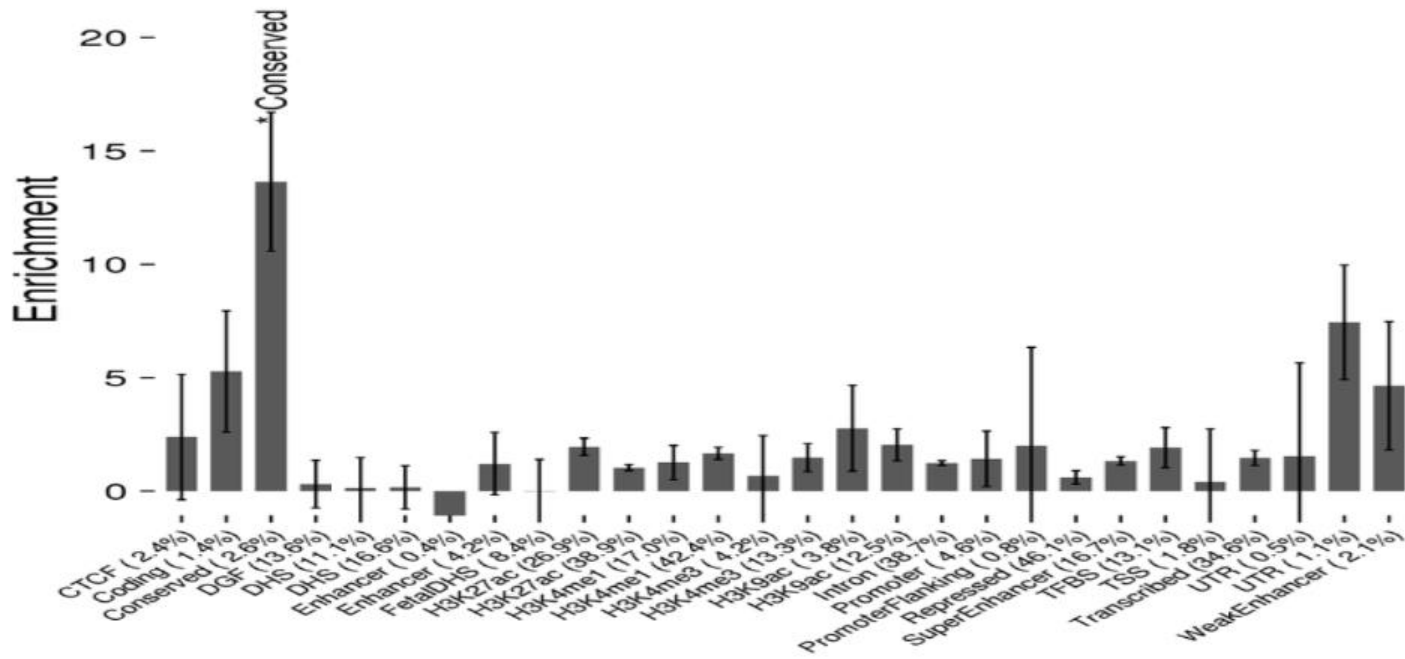
# Genetic variants associated with sedentary behaviour



# Genetic variants associated with sedentary behaviour



# Sedentary behaviour - heritability & shared genetics





# Sedentary behaviour – genetic correlations with other traits

After adjusting for multiple testing ( $p < 1.2 \times 10^{-5}$ , 4160 tests), we found correlations with 72 traits:

34x anthropometric

15x exercise & work

7x education & intelligence

Increases in sedentary time were genetically correlated with:

Improved fluid intelligence score  
( $r_g = 0.35$ ,  $p = 5.1 \times 10^{-22}$ )

Decreased health status  
(e.g. for body fat percentage  $r_g = 0.26$ ,  $p = 2.1 \times 10^{-20}$ )

## Other genetic correlations of note:

- Time spent using computer ( $r_g=0.47$ ,  $p=8.3 \times 10^{-42}$ )
- HDL cholesterol ( $r_g=-0.20$ ,  $p=2.3 \times 10^{-7}$ )
- Diabetes diagnosed by doctor ( $r_g=0.23$ ,  $p=6.1 \times 10^{-9}$ )
- Body mass index ( $r_g=0.26$ ,  $p=3.5 \times 10^{-15}$ )

# Sedentary behaviour - Mendelian randomisation results

After adjusting for multiple testing ( $p < 4.7 \times 10^{-4}$ , 21 diseases, 105 tests) ... **we found no significant associations.**

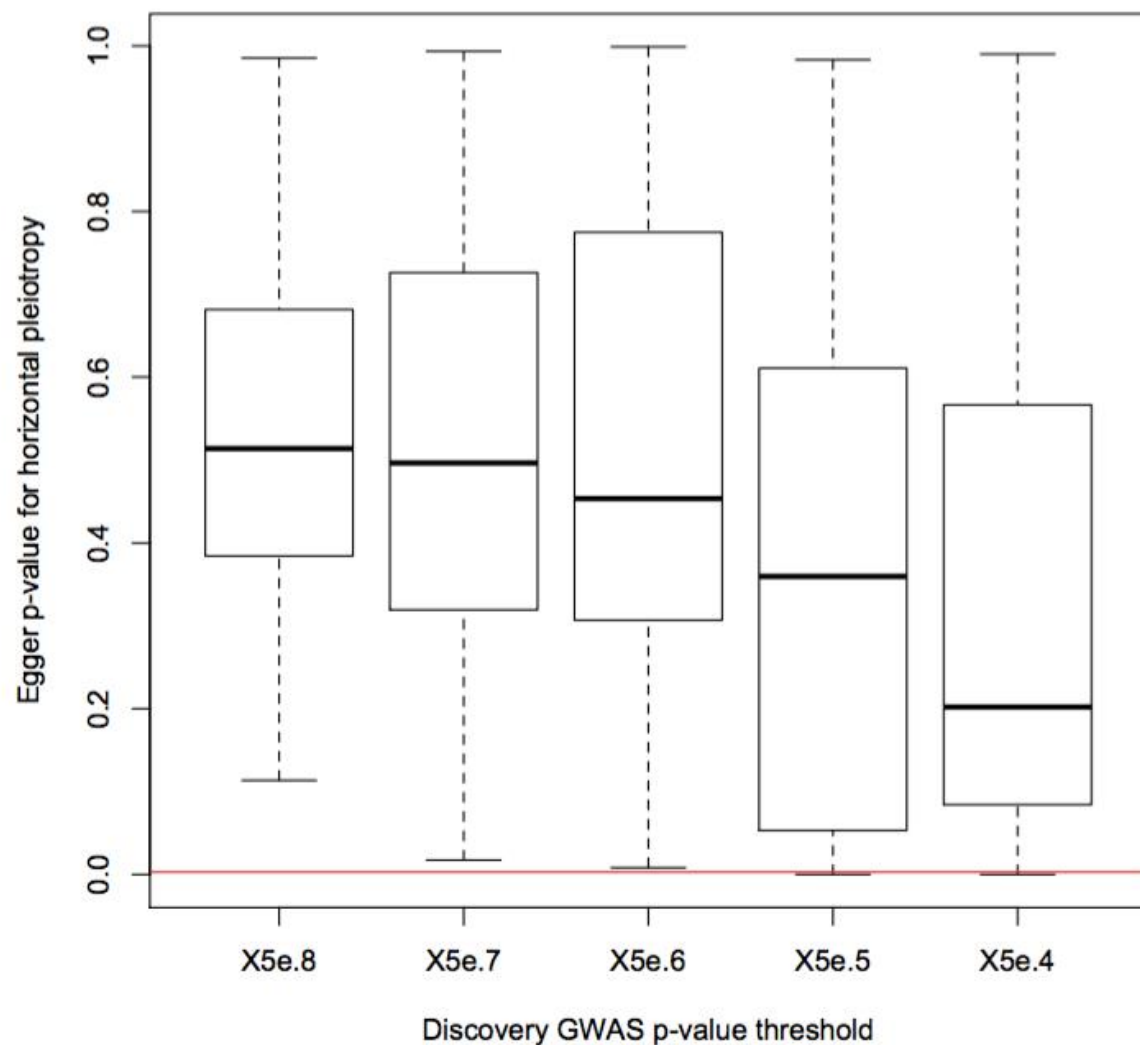
If we wanted to be bad scientists, fish for some hope, and squint \*really\* hard at the results ...

- Body fat % (beta % per SD: 0.81, SE=0.34,  $p=0.017$ )

# Sedentary behaviour - Mendelian randomisation results

**Figure S5 | Effect of p-value threshold for instrument selection on presence of detectable horizontal pleiotropy.** Boxplot represents 90 tests for five accelerometer exposure traits assessed against 18 outcomes in 278,374 UK Biobank participants who were not in the accelerometer discovery GWAS.

**Effect of IV selection on horizontal pleiotropy**



**Large scale studies, ideally with objective measures, provide promise for causal inference**

**Need better measures:**

**Models - semi-supervised learning**

**Devices - inclinometers at scale?**

**Larger sample sizes to detect genetic variants:**

**More cohorts with sensors + genetics**

## **Mendelian randomization of objectively-measured sedentary behaviour in large-scale biobanks**

# Behaviour – machine learning results

- 188,355 mins annotated behaviour from 153 people
- Kappa = 0.68 (accuracy = 79%)

Prediction→ Ground truth↓	Sleep	Sedentary	Tasks-light	Walking	Moderate activity
Sleep	154,099	12,985	652	427	358
Sedentary	6,782	97,899	6,230	3,576	6,938
Tasks-light	95	6,590	5,693	4,469	6,004
Walking	122	3,624	4,731	18,548	4,984
Moderate	94	2,682	3,153	3,311	12,664

# Sedentary behaviour types (1/4)

- home activity;eating;13030 eating sitting alone or with someone
- home activity;household chores;washing/ironing/mending clothes;5080 knitting sewing sitting
- home activity;household chores;washing/ironing/mending clothes;5080 knitting sewing wrapping presents sitting
- home activity;leisure;activities for maintenance of a household;miscellaneous;9100 retreat/family reunion activities involving sitting eating relaxing talking with more than one person
- home activity;leisure;activities for maintenance of a household;9100 retreat/family reunion activities involving sitting eating relaxing talking with more than one person
- home activity;leisure;activities for maintenance of a household;miscellaneous;9100 retreat/family reunion activities involving sitting eating relaxing talking with more than one person
- home activity;miscellaneous;sitting;11580 office work such as writing and typing (with or without eating at the same time)
- home activity;miscellaneous;sitting;11580 office/computer work general
- home activity;miscellaneous;sitting;21010 sitting non-desk work (with or without eating at the same time)
- home activity;miscellaneous;sitting;5080 sitting non-desk work (with or without eating at the same time)
- home activity;miscellaneous;sitting;7010 lying and watching television with TV on as the primary activity
- home activity;miscellaneous;sitting;7010 sitting/lying and watching television with TV on as the primary activity
- home activity;miscellaneous;sitting;7021 sitting without observable activities
- home activity;miscellaneous;sitting;7021 sitting without observable activities
- home activity;miscellaneous;sitting;9030 sitting desk work (with or without eating at the same time)
- home activity;miscellaneous;sitting;9030 sitting desk entertainment/hobby (with or without eating at the same time)



# Sedentary behaviour types (2/4)

- home activity;miscellaneous;sitting;9030 sitting desk work (with or without eating at the same time)
- home activity;miscellaneous;sitting;9045 sitting playing traditional video game computer game
- home activity;miscellaneous;sitting;9055 sitting/lying talking in person/using a mobile phone/smartphone/tablet or talking on the phone/computer (skype chatting)
- home activity;miscellaneous;sitting;9060 sitting reading or using a mobile phone/smartphone/tablet or talking on the phone/computer (skype chatting)
- home activity;miscellaneous;sitting;9060 sitting/lying reading or without observable activities
- home activity;miscellaneous;sitting;9060 sitting/lying reading or without observable/identifiable activities
- home activity;self care;13046 having hair or nails done by someone else sitting
- leisure;eating;13030 eating sitting indoor/outdoor
- leisure;eating;not-social;13030 eating sitting indoor/outdoor
- leisure;eating;social;13030 eating sitting indoor/outdoor
- leisure;miscellaneous;21000 sitting meeting or talking with others
- leisure;miscellaneous;21005 (generic) sitting light office writing typing work
- leisure;miscellaneous;21010 sitting non-desk work (with or without eating at the same time)
- leisure;miscellaneous;sitting;21000 sitting meeting
- leisure;miscellaneous;sitting;21005 (generic) sitting light office writing typing work
- leisure;miscellaneous;sitting;5080 sitting non-desk work (with or without eating at the same time)

# Sedentary behaviour types (3/4)

- leisure;miscellaneous;sitting;9055 sitting talking to person/using the phone
- leisure;miscellaneous;sitting;9060 (generic) sitting/lying reading or without observable activities
- leisure;miscellaneous;sitting;9060 (generic) sitting/lying reading or without observable/identifiable activities
- leisure;religious activities;20000 sitting in church in service attending a ceremony sitting quietly
- leisure;religious activities;20005 sitting in church talking or singing attending a ceremony sitting active
- leisure;sports;water activities;18012 boating power passenger
- occupation;interruption;11585 sitting meeting/talking to colleagues with or without eating
- occupation;interruption;11585 sitting meeting/talking to colleagues with or without eating
- occupation;interruption;13030 eating sitting
- occupation;interruption;9055 sitting using a mobile phone/smartphone/tablet or talking on the phone/computer (skype meeting etc.)
- occupation;interruption;9060 (generic) sitting without observable activities
- occupation;interruption;9060 (generic) sitting without observable/identifiable activities
- occupation;interruption;9060 sitting using a mobile phone/smartphone/tablet or talking on the phone/computer (skype meeting etc.)
- occupation;interruption;sitting;11585 sitting meeting/talking to colleagues with or without eating
- occupation;interruption;sitting;13030 eating sitting
- occupation;interruption;sitting;9055 sitting using a mobile phone/smartphone/tablet or talking on the phone/computer (skype meeting etc.)

# Sedentary behaviour types (4/4)

- occupation;interruption;sitting;9060 sitting without observable/identifiable activities
- occupation;office and administrative support;11580 office wok/computer work general
- occupation;office and administrative support;11580 office work/computer work general
- occupation;office and administrative support;11580 office/computer work general
- occupation;public admin/education/health;education;9065 students/attending seminars or talks
- transportation;private transportation;16010 driving automobile or light truck (not a semi)
- transportation;private transportation;16015 riding in a car or truck
- transportation;public transportation;16016 riding in a bus or train
- transportation;waiting;7021 sitting