



THE UNIVERSITY  
of EDINBURGH



# Edinburgh OSA research round-up

## SASA Conference 2019

**Dr Lizzie Hill**

Sleep Research Fellow

Centre for Clinical Brain Sciences, The University of Edinburgh  
Specialist Sleep Clinical Physiologist & NRS Career Researcher Fellow, NHS Lothian

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# Overview

- Introduction
- Ongoing studies
  - Brain Changes in Sleep Apnea
  - SOS: Sleep On Side
  - BRAHMS
  - Sleep-disordered breathing & epilepsy
  - SLEEP-EASY
- How to get involved
- Questions



# Introduction

# Sleep Research Unit, University of Edinburgh

## Who are we?

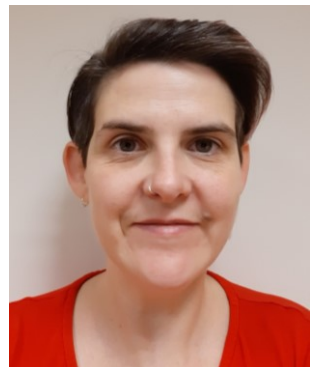
- Dr Renata Riha

- Consultant in Sleep & Respiratory Medicine, Royal Infirmary of Edinburgh
- Honorary Reader, The University of Edinburgh



- Dr Lizzie Hill

- Sleep Research Fellow, The University of Edinburgh
- Specialist Sleep Clinical Physiologist, Royal Hospital for Sick Children
- NHS Research Scotland Career Researcher Fellow



# Sleep Research Unit, University of Edinburgh

## Where are we?

- Based at Edinburgh Bioquarter
  - Royal Infirmary of Edinburgh
  - University of Edinburgh
  
- But collaborate around Scotland, UK and beyond



## What do we do?

- Clinical research in all areas of sleep medicine
  - Sleep-disordered breathing / OSA
  - Narcolepsy / hypersomnias
  - Parasomnias
  - Circadian rhythm disorders
- Predominantly in adults, but also children

# Sleep Research Unit, University of Edinburgh

## What do we do?

- Publications in peer-reviewed journals
- Presentations at international conferences
- Education in sleep medicine
  - Conferences
  - Teaching courses



# Ongoing studies

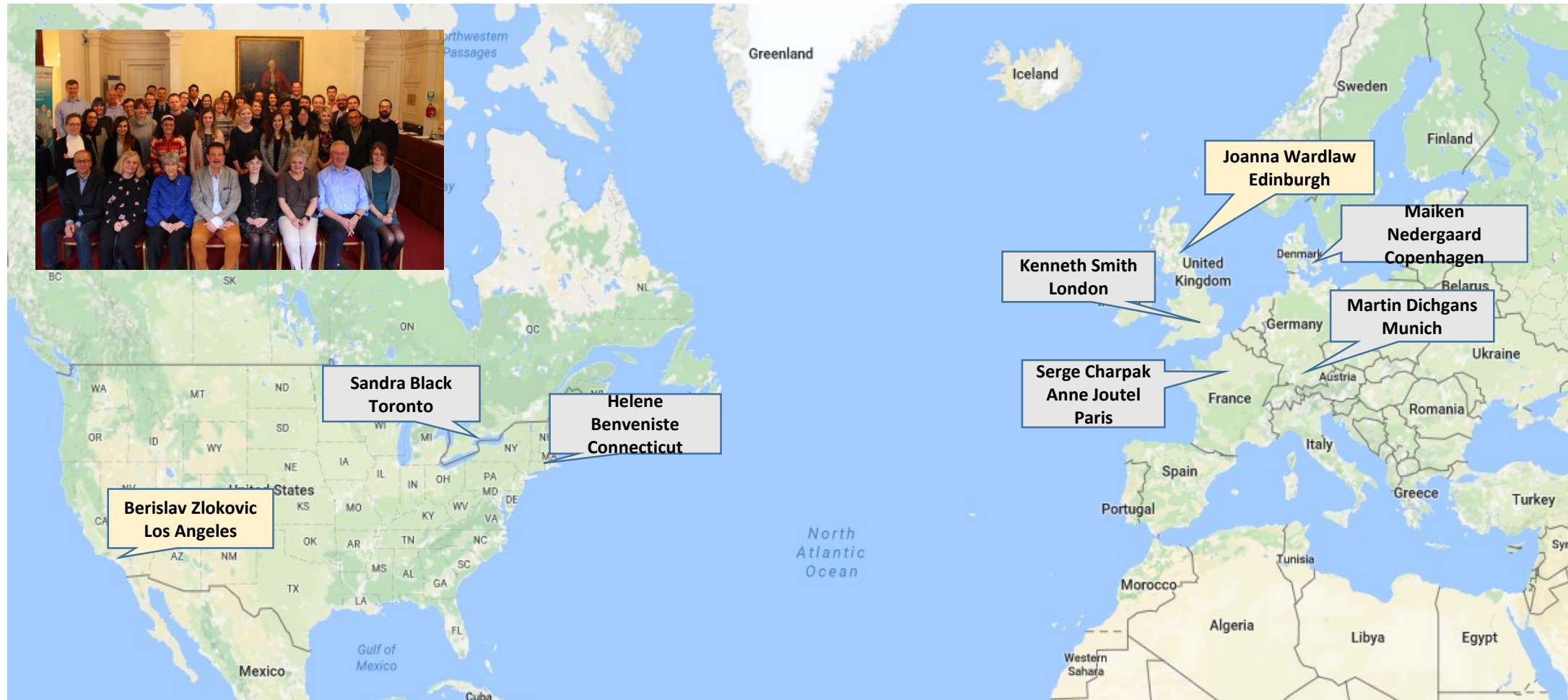
# Brain Changes in Sleep Apnea study

# Brain Changes in Sleep Apnea study

- Multi-site: University of Edinburgh & Sunnybrook Health Sciences, Toronto
- Funders: Fondation Leducq Transatlantic Network of Excellence
- PIs: Joanna Wardlaw / Renata Riha / Fergus Doubal
- Ethics approved – recruitment complete
- n = 80, Edinburgh = 40 (closed recruitment at 44)
- Inclusion:
  - Adults aged  $\geq 18$  years
  - Moderate/severe OSA (AHI  $\geq 15$  on PSG **or**  $\geq 25$  on polygraphy + ODI  $\geq 10$  + ESS  $\geq 11$ )



# Fondation Leducq Transatlantic Network of Excellence



**Understanding the role of the perivascular space in cerebral small vessel disease**

# Cerebral small vessel disease



Wardlaw and Dichgans, 2013

**1 in 5 of all strokes**

**>45% of dementia**

**Gait + Balance  
problems**

**Depression**

**Cognitive  
impairment**

**'Silent'**

**No current specific treatment**

# Brain Changes in Sleep Apnea study

## Aims of this study

- To examine relationship between OSA and SVD features in brain
- To examine relationship between MRI and:
  - Sleep architecture
  - Cognitive function
  - Blood pressure
  - Endothelial function
  - Retinal imaging

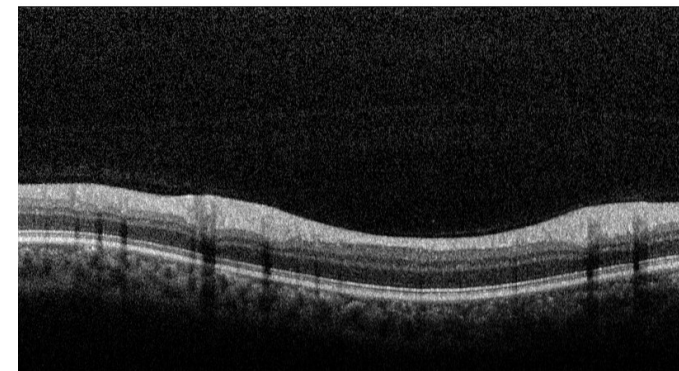
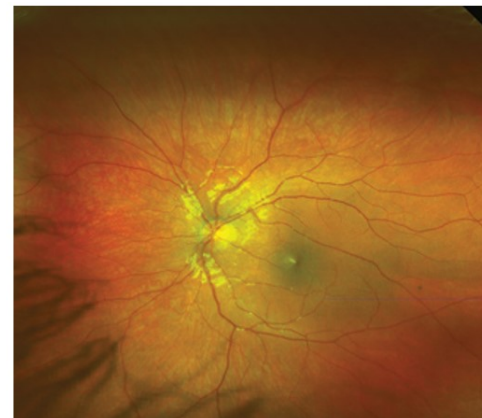
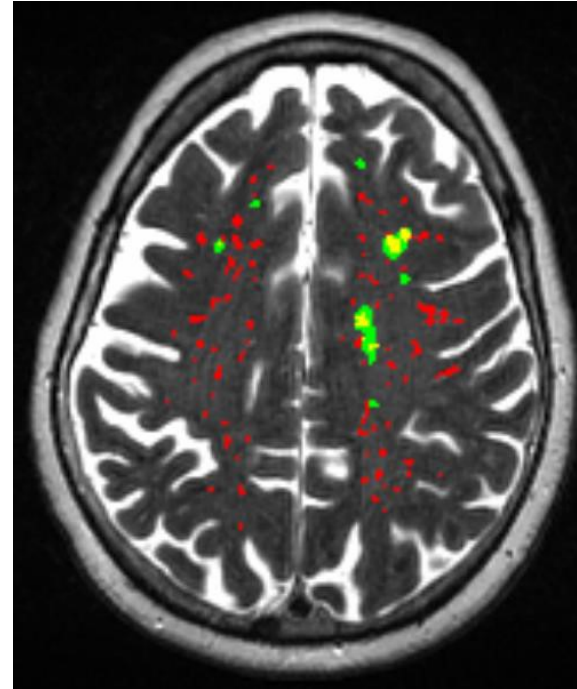
before and after 4 months of CPAP therapy

- Validate WatchPAT 200 polygraphy device



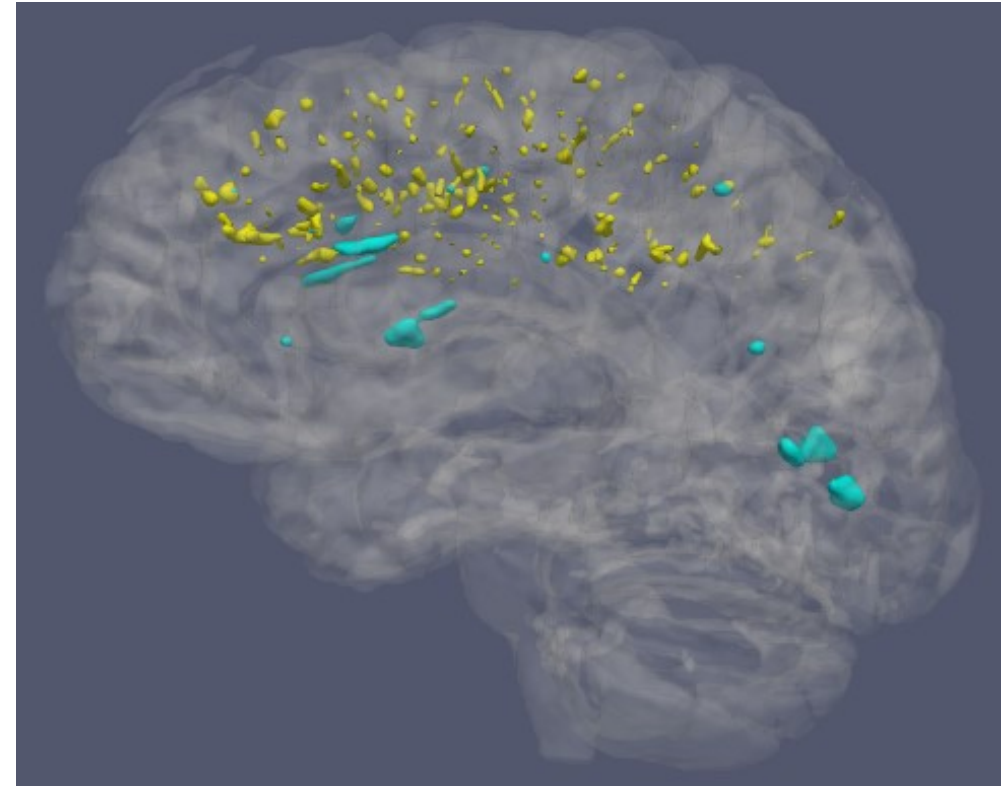
# Brain Changes in Sleep Apnea study

- State-of-the-art MRI scanning techniques
  - Structural scans
  - Cerebrovascular reactivity
  - Contrast imaging
- Retinal imaging
  - Changes in blood vessels in eye reflect changes in brain



# Brain Changes in Sleep Apnea study


Variable	n	Value
Sex (male : female)	44	30 : 14
Age at scan visit (yr)	43	50.1±9.1
Body mass index (kg/m <sup>2</sup> )	43	34.5±6.2
≥1 cardiovascular risk factor	43	29 (67%)
Epworth sleepiness score /24	43	15±3
Apnea/hypopnea index /hr	43	53.6±24.7
≥3% oxygen desaturation index /hr	43	41.1±26.3
SpO <sub>2</sub> nadir %	43	76.3±9.5
WMH volume (ml)	38	0.98(0.53-1.82)
WMH / intracranial volume %	38	0.06(0.04-0.12)
PVS count (total)	33	389±148
PVS volume (ml)	33	5.2±2.4




White matter hyperintensities  
Enlarged perivascular spaces (PVS)

# Brain Changes in Sleep Apnea study


- Presented at World Sleep 2019, Vancouver
- WMH were infrequent in patients with OSA at their pre-treatment scan
- Enlarged perivascular spaces (PVS) were numerous
- No significant associations between AHI or ODI and WMH
- AHI and ODI were significant predictors of PVS count, when controlling for age, sex, BMI, hypertension and smoking
- More results to be presented at BSS 2019, Birmingham



The University of Edinburgh  
Edinburgh Neuroscience



Perivascular spaces  
in small vessel disease  
Foundation Leuven Transatlantic Network of Excellence



CCBS  
Centre for Clinical Brain Sciences

## Magnetic resonance imaging markers of cerebral small vessel disease in adults with moderate/severe obstructive sleep apnea

EA Hill<sup>1</sup>, M Stringer<sup>1</sup>, L Ballerini<sup>1</sup>, M Valdez Hernandez<sup>1</sup>, M Thrippleton<sup>1</sup>, R Brown<sup>1</sup>, D Jaime Garcia<sup>1</sup>, F Chappell<sup>1</sup>, A Lim<sup>2</sup>, B MacIntosh<sup>2</sup>, J Ramirez<sup>2</sup>, S Black<sup>2</sup>, RL Riha<sup>1</sup>, F Doubal<sup>1</sup>, JM Wardlaw<sup>1</sup>

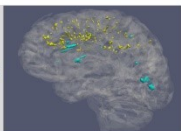
1. Centre for Clinical Brain Sciences, University of Edinburgh, UK    2. Sunnybrook Health Sciences Centre, Toronto, Canada

### Introduction

- Obstructive sleep apnea (OSA) is associated with cardiovascular and cognitive dysfunction.
- Markers of cerebral small vessel disease (SVD), such as white matter hyperintensities (WMH) and enlarged perivascular spaces (PVS), are evident in 20% of strokes and 50% of dementia cases.
- Our systematic literature review (as yet unpublished) demonstrated significant associations between OSA and SVD.
- We tested this hypothesis by assessing MRI markers of SVD and their relationship with objective sleep measures in adults with moderate/severe OSA.

### Figure 1:

3D image reconstructed from T2 MRI, showing white matter hyperintensities (blue) and enlarged perivascular spaces (yellow) in a single study participant.



### Participants

- Treatment-naïve adult patients aged ≥18yr
- Moderate/severe OSA (AHI≥15/hr + ODI≥10/hr)
- Recruited from sleep clinic at Royal Infirmary of Edinburgh, UK as part of a larger multicenter trial

### Results

- One male participant withdrew prior to MRI. Analysis of PVS completed in 33 and WMH in 38 participants.
- Multiple linear regression modeling showed no significant associations between AHI/ODI and WMH.
- AHI and ODI were significant predictors of PVS count, when controlling for age, sex, BMI, hypertension and smoking (presented as beta coefficient(95% CI)):  
AHI:  $\beta$  5.877(0.682-11.073),  $p=0.027$   
ODI:  $\beta$  -5.985(-10.987- -0.982),  $p=0.019$

### Measures

- Anthropometric and demographic data, including vascular risk factors
- Apnea/hypopnea index (AHI) and ≥3% oxygen desaturation index (ODI) as measured by level IV home sleep study (WatchPAT200, Itamar Medical Ltd, Caesera, Israel)
- 3T MRI (3D, ~1mm isotropic) scanning sequences: T1, T2, FLAIR, proton density

### Table 1: Summary of baseline demographic, sleep and MRI data. Presented as mean±SD or median(IQR25-75).

Variable	n	Value
Sex (male : female)	44	30 : 14
Age at scan visit (yr)	43	50.1±9.1
Body mass index (kg/m <sup>2</sup> )	43	34.5±6.2
≥1 cardiovascular risk factor	43	29 (67%)
Epworth sleepiness score /24	43	15±3
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WMH volume (ml)	38	0.98(0.53-1.82)
WMH / intracranial volume %	38	0.06(0.04-0.12)
PVS count (total)	33	389±148
PVS volume (ml)	33	5.2±2.4

### Analysis

- MRI analysis using previously published methods<sup>1,2</sup>
- Standard statistical analyses undertaken using IBM SPSS Statistics for Windows Version 25 (IBM Corp., Armonk, NY, USA)

### Conclusions

White matter hyperintensities were infrequent in patients with OSA, though enlarged perivascular spaces were numerous and related to AHI and ODI. This study is ongoing in Edinburgh and Toronto.

References: 1. Ballerini L, et al. *Scientific Reports* (2018). 8:2132. 2. Valdés Hernández M, et al. *Brain and Behavior* (2015). 5(12):e00415.

This work is funded by a Fondation Leducq Transatlantic Network of Excellence grant (16 CVD 05)  
The University of Edinburgh is a charitable body, registered in Scotland, with registration number SC005336

# **BRAHMS study**

# BRAHMS study

- *All-night sound recording via smartphone of subjects during multi-channel home sleep apnoea testing to generate data for the development of algorithms capable of classifying sleep disordered breathing from phone audio data alone*
- Single-site collaboration: Edinburgh/Sheffield
- Funders: Innovate UK via Passion For Life Healthcare/University of Sheffield
- PIs: Guy Brown, Lizzie Hill



The  
University  
Of  
Sheffield.

Innovate UK



# BRAHMS study

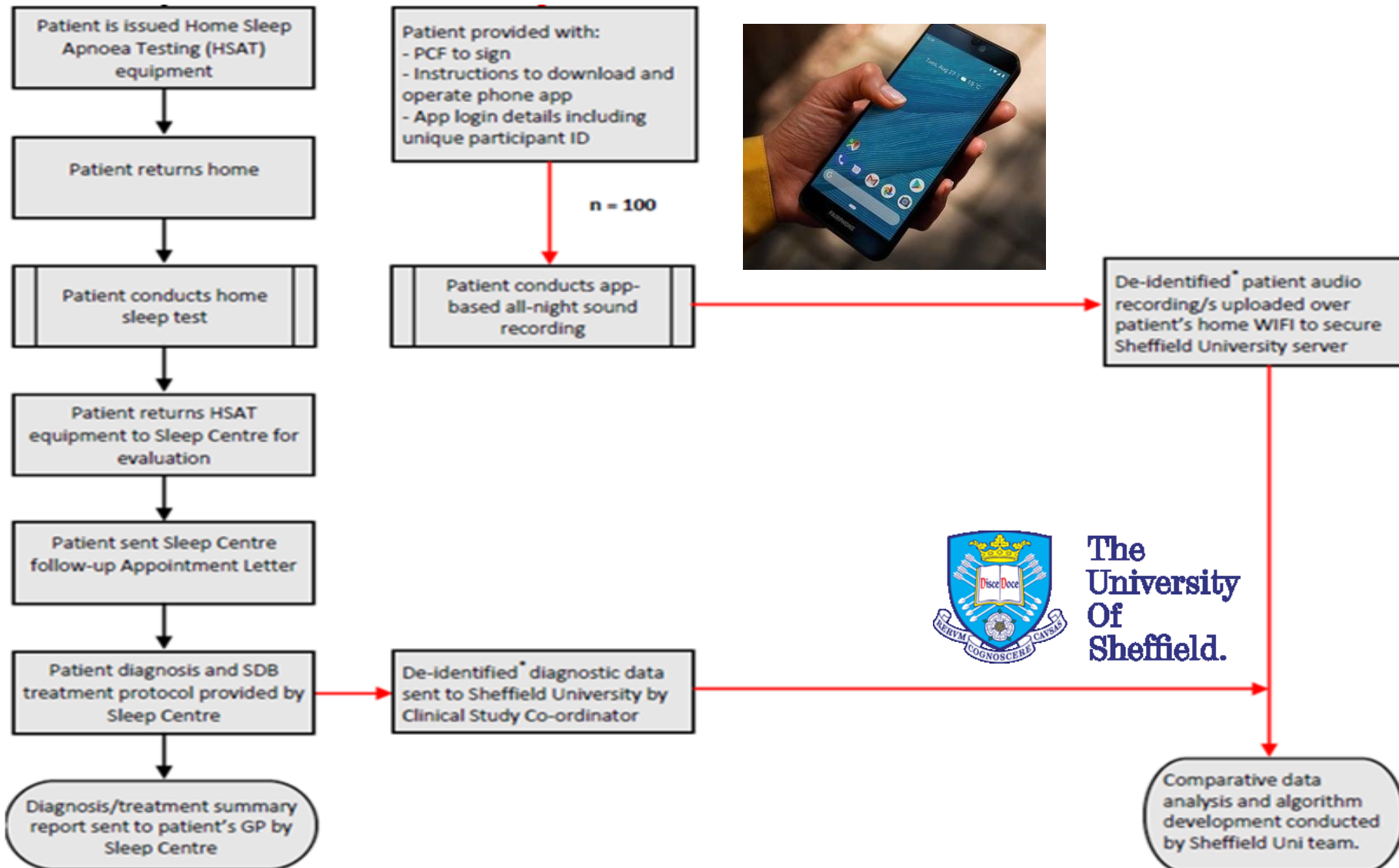
- Ethics approved – recruitment not yet commenced
- n = 100
- Inclusion:
  - Adults aged  $\geq 18$  years
  - Referred for assessment of ?SDB/OSA clinically
  - Attending department for planned home polygraphy using SomnoTouch



# BRAHMS study

- Snoring and breathing sounds can give an indication of SDB
- App on patient's own smartphone to record audio
- Analysed by computer scientists and compared to home polygraphy data
- Use data to “train” and improve existing algorithm
- Hope to produce a commercial app which consumers can use to screen for SDB at home

# BRAHMS study



\* De-identified but including participant ID and date of recording to permit correlation of SDB diagnostic data with audio recording.

**SOS: Sleep On Side**

# SOS: Sleep on Side study

- *A Multi-center, Prospective, Randomized Crossover Study with the NightBalance Lunoa SPT Compared to Positive Airway Pressure (PAP) for the Treatment of Positional Obstructive Sleep Apnea (POSA)*
- Multi-site: Across Europe
- Funders: Philips Respironics
- PI: Renata Riha

**PHILIPS**



# SOS: Sleep on Side study

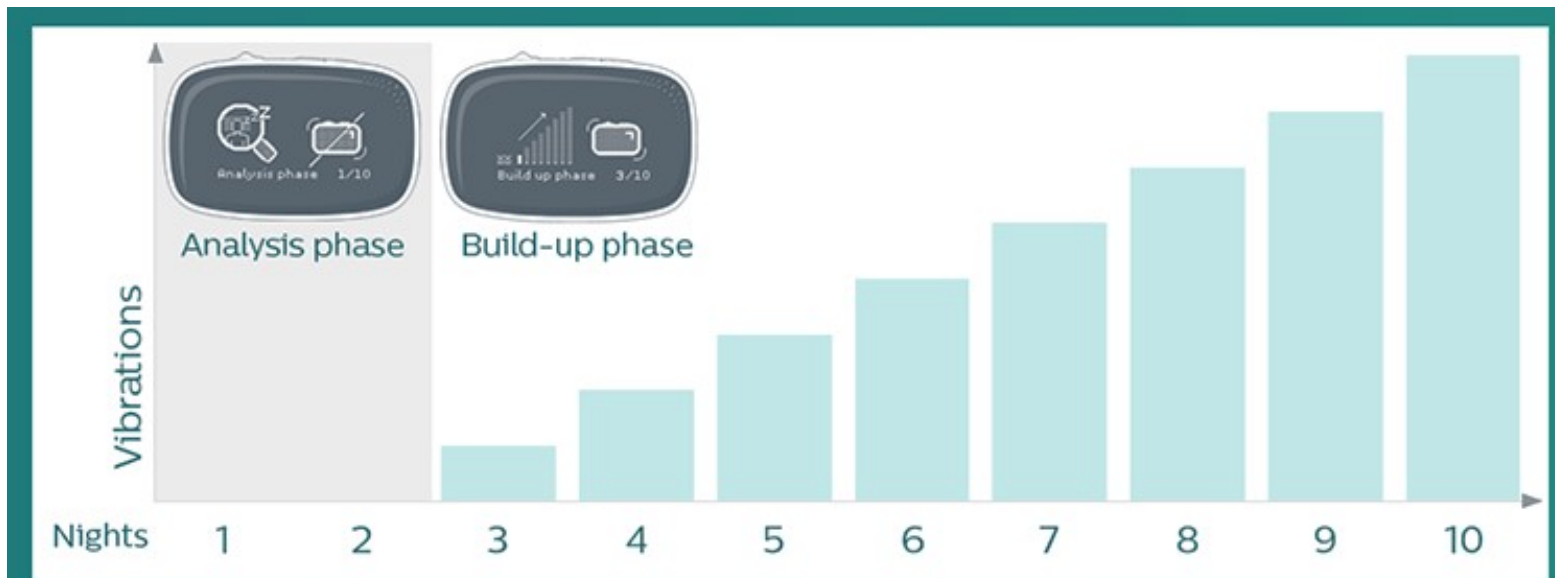
- Ethics approved – recruitment not yet commenced
- n = 150, Edinburgh = as many as possible (competitive recruitment)
- Inclusion:
  - Adults aged  $\geq 18$  years
  - CPAP-naïve or non-complier
  - AHI > 15 on PSG **or**  
polygraphy + supine AHI at least twice the lateral AHI + supine time 30-70%

# SOS: Sleep On Side study

- Validation of NightBalance Lunoa positional trainer device
- Treatment for positional OSA (POSA)
  - Majority of events when sleeping on back
  - 35% of patients with OSA
- Commercially available
- Randomised crossover trial of Lunoa v. APAP



# SOS: Sleep on Side study



## Ongoing treatment



Patient can fall asleep in any position. After 15 minutes, the device activates and begins monitoring.



NightBalance detects when the patient is on their back. It prompts the patient to move off their back without disturbing their sleep.<sup>3,4</sup>



Vibrations will stop when patient is on their side.

# **Sleep-disordered breathing & epilepsy**

# SDB & Epilepsy study

- Investigation of sleep quality and prevalence of obstructive sleep apnoea in children and young people with epilepsy
- Single-site: Royal Hospital for Sick Children
- Funders: Action Medical Research / RS MacDonald Trust
- PI: Don Urquhart



# SDB & Epilepsy study

- Ethics approved – recruitment in progress
- n = 90
- Inclusion:
  - Children 5-18 years
  - Known diagnosis of epilepsy or non-epileptic control
  - No prior diagnosis or high clinical suspicion of SDB

# SDB & Epilepsy study

- Epilepsy and OSA are common conditions
  - 0.5% and 6% of children respectively
- Pilot data using PSQ-SRBD questionnaire
  - high risk of OSA in 55% of CWE v 7% of controls
- Further investigate OSA prevalence using polysomnography (PSG)
- 1 night of PSG in sleep lab at RHSC





## Observational pilot study of reported symptoms of obstructive sleep apnoea in children with epilepsy

DON S URQUHART<sup>1,2</sup> | OLANIYI O KEHINDE<sup>3</sup> | AILSA E MCLELLAN<sup>2,3</sup>



# SDB & Epilepsy study

- Results presented at World Sleep 2019
- Prevalence of OSA was higher than expected in CWE (18%) and controls (12%)
- No significant differences in AHI or SpO<sub>2</sub> nadir
- ODI was statistically, but not clinically, significantly higher in CWE
- CWE were subjectively sleepier than controls
  - 15% reporting EDS
- More results to be presented at BSS 2019

## Polysomnographic assessment of the prevalence of obstructive sleep apnea (OSA) in children and young people with epilepsy (CWE) living in Scotland

Hill EA<sup>1,2</sup>, Hill L<sup>1</sup>, Carruthers E<sup>1</sup>, Shetty J<sup>3,4</sup>, McLellan A<sup>3</sup>, Chin R<sup>3,5</sup>, Urquhart DS<sup>5,6</sup>

1. Paediatric Sleep Physiology, NHS Lothian, UK  
 2. Sleep Research Unit, University of Edinburgh, UK  
 3. Paediatric Neurosciences, NHS Lothian, UK  
 4. Centre for Reproductive Health, University of Edinburgh, UK  
 5. Child Life & Health, University of Edinburgh, UK  
 6. Paediatric Respiratory & Sleep Medicine, NHS Lothian, UK

### Introduction

- Epilepsy and OSA are common conditions, affecting 0.5% and 6% of children respectively.
- Pilot data utilising the PSQ-SRBD<sup>1</sup> reported a high risk of OSA in 55% of CWE versus 7% of controls<sup>2</sup>.
- This study (currently ongoing) aimed to further test this association and assess whether objective OSA prevalence, as measured by polysomnography (PSG) is higher in CWE than controls.

### Results

- Fifty-five children underwent PSG: 38 CWE, 17 controls
- Groups did not differ significantly in age, sex or BMI.
- A diagnosis of OSA (oAHI≥1) was evident in 18% of CWE and 12% controls (p=0.426).
- No controls reported excessive daytime sleepiness (cESS>10), in contrast to 15% of CWE (p=0.040).

Table 1: Summary data for children with epilepsy (CWE) and non-epileptic control children. Groups compared using Student's t-test or chi-square test. Results presented as number (%), mean±SD or median(IQR25-75%) as appropriate. AHI: Apnea/hypopnoea index; ODI: Oxygen desaturation index.

Variable	CWE n=38	Controls n=17	p
Age (years)	11±3	11±3	0.910
Sex (Male : Female)	22 : 16 (58% : 42%)	10 : 7 (59% : 41%)	0.594
Body mass index (kg/m <sup>2</sup> )	21.1±5.7	19.0±3.8	0.161
cESS (/24)	5(2-9)	3(1-5)	0.007
Obstructive AHI (/hr)	0.0(0.0-0.5)	0.1(0.0-0.4)	0.725
Central AHI (/hr)	0.2(0.0-0.8)	0.3(0.0-0.4)	0.240
ODI (/hr)	0.6(0.2-1.3)	0.2(0.0-0.7)	0.023
SpO <sub>2</sub> nadir (%)	92±3	93±3	0.555

### Participants

- CWE aged 5-18 years and age/sex-matched controls
- Recruited from an NHS epilepsy clinic in Edinburgh, UK between March 2017 and August 2019
- Children with unstable epilepsy or significant comorbidities were excluded

### Measurements & analysis

- Anthropometric data & medical history
- Children's Epworth Sleepiness Scale (cESS)<sup>3</sup>
- Single night of attended level I polysomnography (SOMNOscreen plus™, SOMNOMedics, Randersacker, Germany)
- PSG run and scored using AASM v2.3 (2016) guidelines by Registered PSG Technologists (RPSGT)
- Standard statistical analyses (SPSS Statistics 25, IBM Corp, Armonk, USA), with significance set at p<0.05

### Conclusions

- Prevalence of OSA was higher than expected population norms in both CWE (18%) and controls (12%). However, no significant differences in AHI or SpO<sub>2</sub> nadir were observed.
- ODI was statistically, but not clinically, significantly higher in children with epilepsy.
- CWE were subjectively sleepier than non-epileptic controls, with 15% reporting excessive daytime sleepiness.

**References**

1. Chenin R, et al. *Sleep Med* 2000; 1: 21-32. 2. Urquhart DS, et al. *Dev Med Child Neurol*. 2016; 58: 1063-1068. 3. Marcus CL, et al. *Pediatrics* 2012; 130: e714-e755.

This work is funded by Action Medical Research and the RS Macdonald Charitable Trust.  
Dr J. Shetty, Dr E. Hill and Dr D. Urquhart acknowledge the financial support of NHS Research Scotland (NRS), through NHS Lothian.

**SLEEP-EASY**

# SLEEP-EASY study

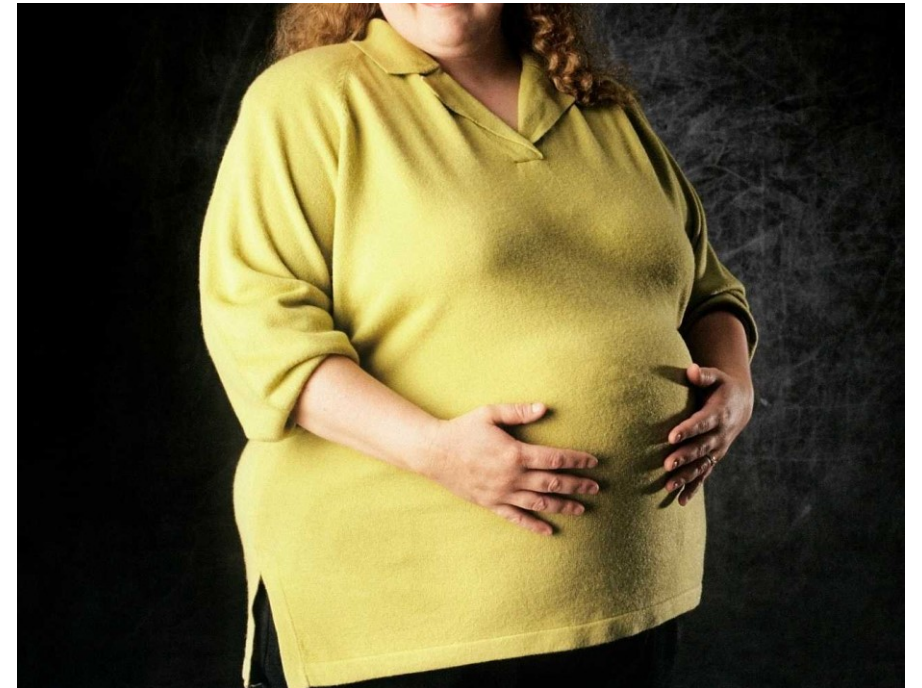
- *Sleep disordered breathing in pregnancy: an observational study examining prevalence and potential mechanisms influencing maternal and offspring outcomes*
- Single-site: University of Edinburgh
- Funders: Tommy's
- PI: Rebecca Reynolds



**Tommy's**  
Funding research  
Saving babies' lives

# SLEEP-EASY study

- Led by Dr Emma Johns
- Ethics approved – recruitment in progress
- n = 60
  - 30 obese, 30 lean
- Inclusion:
  - Pregnant women aged 16-50 years
  - 10 to 22 weeks gestation
  - Booking BMI normal or obese



# SLEEP-EASY study

- Growing evidence to suggest sleep has an important role in pregnancy health
- SDB linked to an increased risk of serious pregnancy complications
  - Gestational diabetes (1.5-3 fold ↑)
  - Gestational hypertension/pre-eclampsia (2 fold ↑)
  - Pre-term birth (1.6-2 fold ↑)
  - Caesarean section (40-80% ↑)
  - Low birthweight (54% ↑)
  - Stillbirth/perinatal death (2 fold ↑)
  - Neonatal intensive care/special care admission (28-90% ↑)

# SLEEP-EASY study

- Home polygraphy using Cidelec
  - 1<sup>st</sup> trimester
  - 3<sup>rd</sup> trimester
- Analysis of blood and placental samples post-partum



# SLEEP-EASY study

	<b>Obese (n=26)</b>	<b>Lean (n=17)</b>
<b>A+H/hour, second trimester</b>		
≥5 (n, %)	6 (24%)	0
Mild SDB (n, %)	5 (19.2%)	0
Moderate SDB (n, %)	1 (3.9%)	0
<b>A+H/hour, third trimester</b>	<b>n=16</b>	<b>n=9</b>
≥5 (n, %)	5 (31.25%)	0
Mild SDB (n, %)	4 (25%)	0
Moderate SDB (n, %)	1 (6.3%)	0

# How to get involved

# How to get involved

## SHARE

- Sign up to SHARE: [www.registerforshare.org](http://www.registerforshare.org)

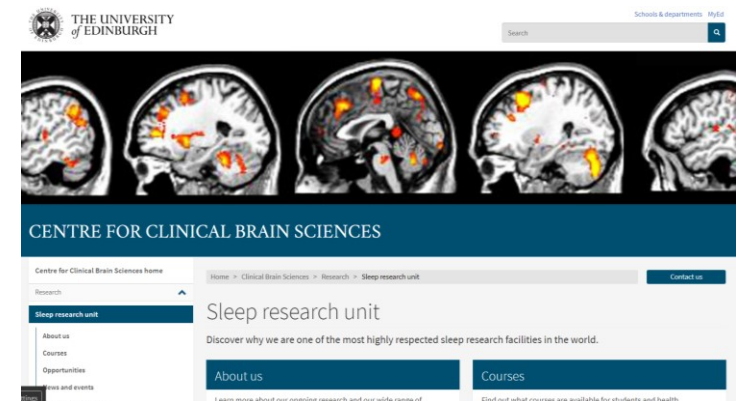
## SASA

- SASA will email you when researchers are looking for participants with SDB/OSA

## Sleep Research Unit

- Visit our website or drop us a line:

[www.ed.ac.uk/clinical-brain-sciences/research/sleep-research-unit](http://www.ed.ac.uk/clinical-brain-sciences/research/sleep-research-unit)



# SVD Research Group, CCBS

## Joanna Wardlaw

### Physics

Michael Stringer  
Michael Thrippleton  
Ian Marshall  
Mark Bastin

### Image Analysis

Lucia Ballerini  
Maria Valdes-Hernandez  
Eleni Sakka  
Susana Munoz-Maniega

### Physicians

Fergus Doubal (stroke)  
Renata Riha (sleep)  
Anna Williams (neurology)  
Thomas Gattlinger (neurology)  
Vera Cvorovic (stroke)

### Neuroradiologist

Gerry Thompson

### Radiographers

Iona Hamilton  
Charlotte Jardine  
Gayle Barclay  
Sean Denham  
Lucy Kessler  
Donna McIntyre  
Elaine Sandeman

### Clinical Research Fellows

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Yulu Shi  
Carol Di Perri  
Una Clancy

### Non-clinical PhD students

Michelle Haglund  
Olivia Hamilton  
Sophie Quick

### Administration

Moira Henderson  
Rosalind Brown

### Postdocs

Rozanna Meijboom  
Stewart Wiseman  
Lizzie Hill  
Caroline McHutchison  
Ellen Backhouse

### Statistician

Francesca Chappell

### Data managers

Dominic Job  
David Rodriguez



# Collaborators

## **RHSC**

- Don Urquhart
- Ailsa McLellan
- Jay Shetty
- Richard Chin
- Laura Hill
- Emma Carruthers
- David Fynn

## **Reproductive Health**

- Emma Johns
- Rebecca Reynolds
- Fiona Denison

**And all at the Dept. of  
Sleep Medicine, RIE**

## **BRAHMS**

- Iain Spray
- Guy Brown
- Stelios Giannoulis
- Richard Wiffen
- Ning Ma
- Hector Romero Ramirez



British Sleep Society

UK Multidisciplinary Sleep Professionals

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British Sleep Society Biennial Scientific Conference

[www.sleepsociety.org.uk](http://www.sleepsociety.org.uk)



**Any questions?**

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