## Cognitive ageing and dementia: The Whitehall II Study

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## Outline

- Lifecourse approach: relevance for cognitive age & dementia
- Cognitive ageing: our results
- Dementia: our approach & recent results
  - Separate risk from bias (midlife risk)
  - Reverse causation

## Why the lifecourse approach?

- Increasing life expectancy, increase in numbers living with dementia
  - 47 million in 2015, 131 million in the year 2050
  - 1year delay in dementia onset will lead to 9.2 million fewer cases by 2050
- Failure rate of drugs ≈ 100%



• Failure of multi-domain trials (Multidomain Alzheimer Preventive Trial, MAPT)

## Why the lifecourse approach?

 Considerable investment in imaging studies (MRI, CSF), etc. but correlation between brain structure and function far from perfect



Nelson et al., J Neuropathol Exp Neurol 2009

Study	Country	Start	Ν	Age
Iceland Birth Cohort Study	Iceland	1957	3704	61-64
Gothenburg Study	Sweden	1971	1148	70
PAQUID	France	1987	3777	65+
Kungsholmen Project	Sweden	1987	1810	75+
Rotterdam	Netherlands	1990	7983	55+
Cognitive Function & Ageing Study (CFAS)	UK	1991	13004	65+
Etude du Vieillissement Artériel (EVA)	France	1991	1389	60-70
Italian Longitudinal Study on Aging (ILSA)	Italy	1992	5632	65-84
Longitudinal Aging Study Amsterdam (LASA)	Netherlands	1992	3017	55-85
Maastricht Aging Study (MAAS)	Netherlands	1992	2043	24-81
Longitudinal Study of Aging Danish Twins	Denmark	1995	2401	75+
The German Aging Survey	Germany	1996	5000	40-85
In Chianti Study	Italy	1998	1453	20-102
3-City Study	France	1999	9294	65+
The Swedish National study of Aging & Care	Sweden	2001	3089	60+
Newcastle 85+ Study	UK	2006	1042	85+
UK Biobank	UK	2006/2010	500,000	40-69
CONSTANCES	France	2012/2018	200,000	45-69
ΝΑΚΟ	Germany	2014/2019	200,000	20-69

#### Major studies on ageing start data collection at age 65

## **Cognitive function over the lifecourse**



#### **Cognitive function over the lifecourse: WHY?**



## The Whitehall study: unique data to study ageing outcomes



DATA COLLECTION 2018/20

## Our approach: cognitive ageing and dementia



**continuum from function to pathology** 

## No cognitive decline before age 60?

**Results from the Seattle Longitudinal Study** 



Nature Reviews | Neuroscience

Hedden et al. Nat Rev Neurosci. 2004

## No cognitive decline before age 60?



**Results from the Seattle Longitudinal Study** 

**Results from the Whitehall II Study** 



Hedden et al. Nat Rev Neurosci. 2004

Nature Reviews | Neuroscience

#### Singh-Manoux et al. BMJ 2012

haadina	MEN	WOMEN		
paseline	N=5198	N=2192		
45-49 yrs	1113	413		
50-54 yrs	1578	582		
55-59 yrs	1083	497		
60-64 yrs	1049	515		
65-70 yrs	375	185		

#### **Smoking history and cognitive decline**



Sabia,...Singh-Manoux. JAMA Psychiatry 2012

## **Cardiovascular risk & cognitive ageing**



Kaffashian,...Singh-Manoux. Eur Heart J 2011 Kaffashian,...Singh-Manoux. Neurology 2013 Kaffashian,...Singh-Manoux. Alzheimers Dement 2013

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Singh-Manoux et al., Eur Heart J 2017

#### Our approach to research on dementia



### **The Whitehall Study**

## Dementia: our approach & recent results

Separate risk from bias (midlife risk) Reverse causation

#### EHR data for dementia are good enough!



#### **BMI and dementia**



#### Singh-Manoux et al., Alzheimers Dement. 2018

## **BMI and dementia**



#### Singh-Manoux et al., Alzheimers Dement. 2018

## **Hypertension & dementia**

Hypertension: systolic blood pressure threshold



#### Abell,...Singh-Manoux, Eur Heart J. 2018

## Hypertension & dementia: effet of age

	HR (95%CI)			
Hypertension at age 50 Years				
No	1.00			
Yes	1.42 (1.11, 1.82)			
Hypertension at age 60 Years				
No	1.00			
Yes	1.07 (0.81, 1.41)			
Hypertension at age 70 Years				
No	1.00			
Yes	1.13 (0.81, 1.59)			

Analysis adjusted for age, sex, education, ethnicity, marital status, occupational position, health behavours, BMI, diabetes, cardiovascular disease (coronary heart disease, stroke).

#### Abell,...Singh-Manoux, Eur Heart J. 2018

## Hypertension & dementia: role of CVD



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#### Abell,...Singh-Manoux, Eur Heart J. 2018

## **Reverse causation**

#### **Physical activity**

- Meta-analysis of observational studies suggest an association
   Blondel et al. BMC Public Health 2014
- Intervention studies: null findings
  Sink et al. JAMA 2015
  Andrieu et al. Lancet Neurol 2017

#### **Depressive symptoms**

 Meta-analysis of observational studies suggest an association
 Ownby et al. Arch Gen Psychiatry. 2006

For both exposures, evidence of stronger associations in studies with a short follow-up

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BMJ 2017;357:j2709 doi: 10.1136/bmj.j2709 (Published 22 June 2017)



#### RESEARCH

## Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study

Séverine Sabia *research associate*<sup>1,2</sup>, Aline Dugravot *statistician*<sup>1</sup>, Jean-François Dartigues *professor*<sup>3</sup>, Jessica Abell *research associate*<sup>1,2</sup>, Alexis Elbaz *research professor*<sup>1</sup>, Mika Kivimäki *professor*<sup>2</sup>, Archana Singh-Manoux *research professor*<sup>1,2</sup>

<sup>1</sup>Centre for Research in Epidemiology and Population Health, INSERM U1018, Université Paris-Saclay, Hôpital Paul Brousse, Paris, France; <sup>2</sup>Department of Epidemiology and Public Health, University College London, London, UK; <sup>3</sup>INSERM U1219, University of Bordeaux, Bordeaux, France

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#### For both exposures, evidence of stronger associations in studies with a short follow-up

Research

JAMA Psychiatry | Original Investigation

### Trajectories of Depressive Symptoms Before Diagnosis of Dementia A 28-Year Follow-up Study

Archana Singh-Manoux, PhD; Aline Dugravot, MSc; Agnes Fournier, PhD; Jessica Abell, PhD; Klaus Ebmeier, MD, PhD; Mika Kivimäki, PhD; Séverine Sabia, PhD

# Trajectories of total physical activity (hours/week) prior to dementia



#### Number of observations in the analysis

Years	-28 to	-24 to	-20 to	-16 to	-12 to	-8 to	-4 to
	-24	-20	-16	-12	-8	-4	0
Dementia free	10893	7856	6958	2456	5237	6937	6756
(N=9979)							
Dementia cases	256	200	105	160	160	107	110
(N=329)	250	298	195	103	108	137	118

#### Sabia,...Singh-Manoux BMJ 2017

### **Trajectories of physical activity prior to dementia**



Mixed models adjusted for 5y birth cohort, age at time 0, sex, ethnicity, education, dementia, time, time<sup>2</sup>, time<sup>3</sup>, their interactions with time, time<sup>2</sup>, time<sup>3</sup>, time-dependent covariates socio-economic and behavioural variables

#### Sabia,...Singh-Manoux BMJ 2017

## **Trajectories of depressive syndromes prior to dementia**



Singh-Manoux et al. JAMA Psychiatry 2017

## **Conclusions**

#### **Risk factors for dementia**

Which ones? Age of exposure (timing & duration) Threshold of risk

#### Prevention

Failure of drug trials How do risk factors work together? When does prevention begin?



"the vascular system is a <u>phenomenal</u> <u>target</u> because we have in our brains about 400 miles of blood vessels and these have to do their primary job of bringing food and oxygen to the brain and taking toxins out of the brain."

Zlokovic, JAMA 2017



## Thank you!





Whitehall II

Dementia



Alzheimer's disease Multimorbidity Epidemiology of ageing & neurodegenerative dis



Accelerometers



Cognitive & motor decline



lnserm





