Australian National University

# Planning and implementation of longitudinal cohort studies: opportunities, pitfalls and rewards

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# Outline



- What kind of problem are we trying to solve?
- A tried and tested example
- What can we do with it?
- Design considerations and lessons learnt
- Possible starting point

# The Problem

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Many health-related questions cannot be answered with experiments in humans because:

- Unethical
- Impractical
- Costly

➔Observational research

ME/CFS:

- Epidemiology
- Course of the disease
- Risk factors
- Mechanisms

# PATH Through Life Study

Australian National University

## Goal

“Investigate the epidemiology and course of common mental disorders, cognitive decline and dementia across the lifespan, as well as their social, psychological and genetic risk and protective factors”

## Original and Current Team

Founding CIs: Tony Jorm, Helen Christensen and Bryan Rodgers

Current senior CIs: Kaarin Anstey, Peter Butterworth, Nicolas Cherbuin, Helen Christensen, Simon Easteal, Liana Leach

## Funding & Outputs

Initial funding from ANU, additional grants from NHMRC, ARC, and others (~$10mil)

>300 publications including ~200 peer-reviewed articles

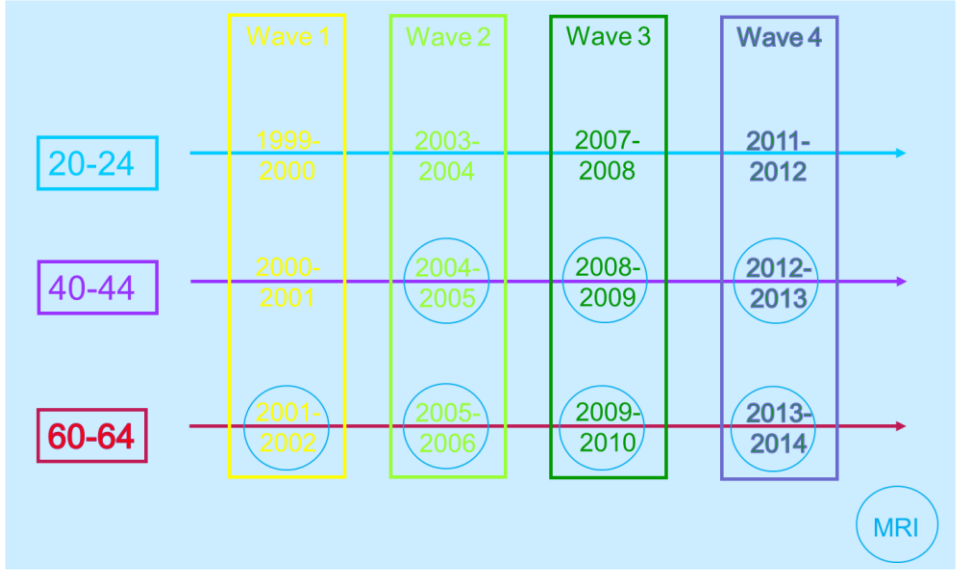
# PATH Through Life Study

Australian National University

- Random sample from the population of Canberra and Queanbeyan (N = 7485)
- Surveys three age groups: 20-24, 40-44, 60-64
- Participants assessed every 4 years

Measures include:

- Socio-demographic
- Lifestyle
- Cognition
- Personality
- Employment
- Health
- Biological
- Genetic




- Linkage to Medicare, PBS, & Death Registry

# A Word of Warning

Epidemiological studies are designed to detect associations

Correlation/Associations ≠ Causation

# Baseline

Individual with type 2 diabetes were more likely to have:

- Poor physical health
- Higher body mass index (BMI)
- Higher depression and anxiety symptomatology
- Greater signs of brain shrinkage
- Poorer cognitive function (visuo-motor skills)

## Association of Type 2 Diabetes With Depression, Brain Atrophy, and Reduced Fine Motor Speed in a 60- to 64-Year-Old Community Sample

*Rajeev Kumar, M.D., F.R.A.N.Z.C.P., Ph.D., Kaarin J. Anstey, Ph.D., Nicolas Cherbuin, Ph.D., Wei Wen, Ph.D., Perminder S. Sachdev, M.D., F.R.A.N.Z.C.P., Ph.D.*

**Objective:** *To examine the relationship of diabetes mellitus to depression, cognition, and structural brain anatomical variables in a 60–64-year-old community-dwelling sample. The authors hypothesized that subjects with Type 2 diabetes are more likely to be depressed, have more brain atrophy, and poorer cognitive function compared with nondiabetic comparison subjects.* **Methods:** *A random sample of 478 subjects aged 60–64 years from a larger community sample were interviewed and underwent physical examinations, assessment of depression, standard cognitive assessments, brain magnetic resonance imaging (MRI) scans, and fasting blood tests. Subjects were considered diabetic if they were on treatment for diabetes or recorded a fasting blood glucose level of greater than 10 mmol/L. The MRI scans were analyzed for brain atrophy, gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), hippocampal, and white matter hyperintensity (WMH) volumes.* **Results:** *MRI data were available for 39 subjects with diabetes and 428 subjects without diabetes. Descriptive analyses showed that subjects with diabetes were more likely to have poor physical health, a higher body mass index, and higher scores of depression and anxiety compared with comparison subjects without diabetes. In multiple regression analyses, diabetes was associated with greater total brain atrophy and larger CSF volume, but did not differ in the WM, GM, and WMH volumes. Diabetes patients performed less well on a task of fine motor dexterity.* **Conclusions:** *Diabetes is related to increased brain atrophy and poor motor function in 60–64 year olds, independent of depression, vascular risk factors, and small vessel disease of the brain.*
(Am J Geriatr Psychiatry 2008; 16:989–998)

**Key Words:** Diabetes mellitus, depression, cognition, brain atrophy

Received December 10, 2007; revised August 8, 2008; accepted August 15, 2008. From the Department of Psychological Medicine, The Canberra Clinical School, Australian National University, Canberra, Australia (RK); Centre for Mental Health Research, Australian National University, Canberra, Australia (RK, KJA, NC); Neuropsychiatric Institute, Prince of Wales Hospital, Sydney NSW, Australia (WW, PSS); and School of Psychiatry, University of New South Wales, Sydney, Australia (WW, PSS). Send correspondence and reprint requests to Rajeev Kumar, M.D., F.R.A.N.Z.C.P., Ph.D., Department of Psychological Medicine, The Canberra Hospital, PO Box-11, Woden, ACT 2606, Australia. e-mail: rajeev.kumar@act.gov.au

# Two Assessments

Individual who developed cognitive impairment over 4 years were more likely to:

- Smoke
- Have a high blood pressure
- Be on depression and anxiety medication
- Be on cholesterol lowering medication
- Have a higher BMI
- Be on medication for type 2 diabetes

Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2009;28:47–55
DOI: 10.1159/000229025

Accepted: May 15, 2009
Published online: July 23, 2009

## Risk Factors of Transition from Normal Cognition to Mild Cognitive Disorder: The PATH through Life Study

Nicolas Cherbuin[a] Chantal Reglade-Meslin[a] Rajeev Kumar[a, b] Patricia Jacomb[a]
Simon Easteal[c] Helen Christensen[a] Perminder Sachdev[d, e] Kaarin J. Anstey[a]

[a]Centre for Mental Health Research, [b]Department of Psychological Medicine, and [c]John Curtin School of Medical Research, Australian National University, Canberra, A.C.T., and [d]School of Psychiatry, University of New South Wales, and [e]Neuropsychiatric Institute, Sydney, N.S.W., Australia

**Key Words**
Mild cognitive impairment · Alcohol · Hypertension · BMI · Depression

**Abstract**
***Aims:*** The aim of this study was to identify physical and mental health and lifestyle predictors of transition from normal cognition to mild cognitive disorder (MCD). ***Methods:*** A total of 2,082 individuals, aged 60–64 years, were assessed at 2 time-points 4 years apart for mild cognitive impairment (MCI) and other MCDs. ***Results:*** The main predictors of conversion to MCI and to other mild cognitive disorders were past alcohol intake, current anxiety and depression medication, increased systolic blood pressure, and past smoking. ***Conclusion:*** Participants with a history of smoking or harmful alcohol consumption, hypertension, or who took medication for anxiety or depression were at increased risk of transitioning to MCI or any MCD. Strategies targeted at managing the above risk factors may have benefits in preventing mild cognitive decline in relatively healthy middle-aged individuals living in the community.


### Introduction

There is considerable evidence for an association between mild cognitive disorders (MCDs) in ageing and Alzheimer's disease (AD) [1], with many studies showing high rates (~30%) of conversion from MCD to AD over relatively short periods of time (2–5 years) [2]. However, few studies have reported on factors predicting transition from normal cognitive ageing to clinically assessed MCD or on factors protecting individuals from such a transition, and those who did generally assessed older individuals [3]. Based on post-mortem studies, Braak et al. [4] have shown that the neurodegenerative processes leading to AD start early in adulthood and progress over decades. It may follow that known risk factors for conversion to dementia are also predictive of conversion to MCD and, therefore, might be amenable to even earlier intervention.

With the aim of identifying these factors in younger individuals, we investigated a community-based cohort of 60–64-year-old participants taking part in a large prospective longitudinal study of ageing. We expected, aside from age, cardiovascular disease [5], diabetes [6], obesity [7], head injury [8], hypercholesterolemia [9], excessive alcohol consumption [10], depression [11], smoking [12],

# Neuroimaging

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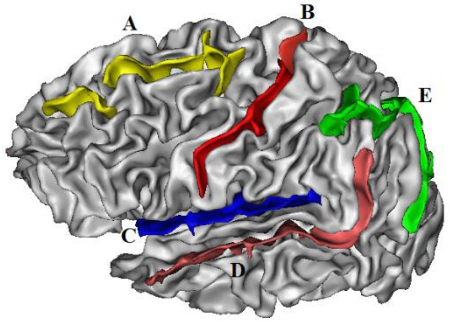
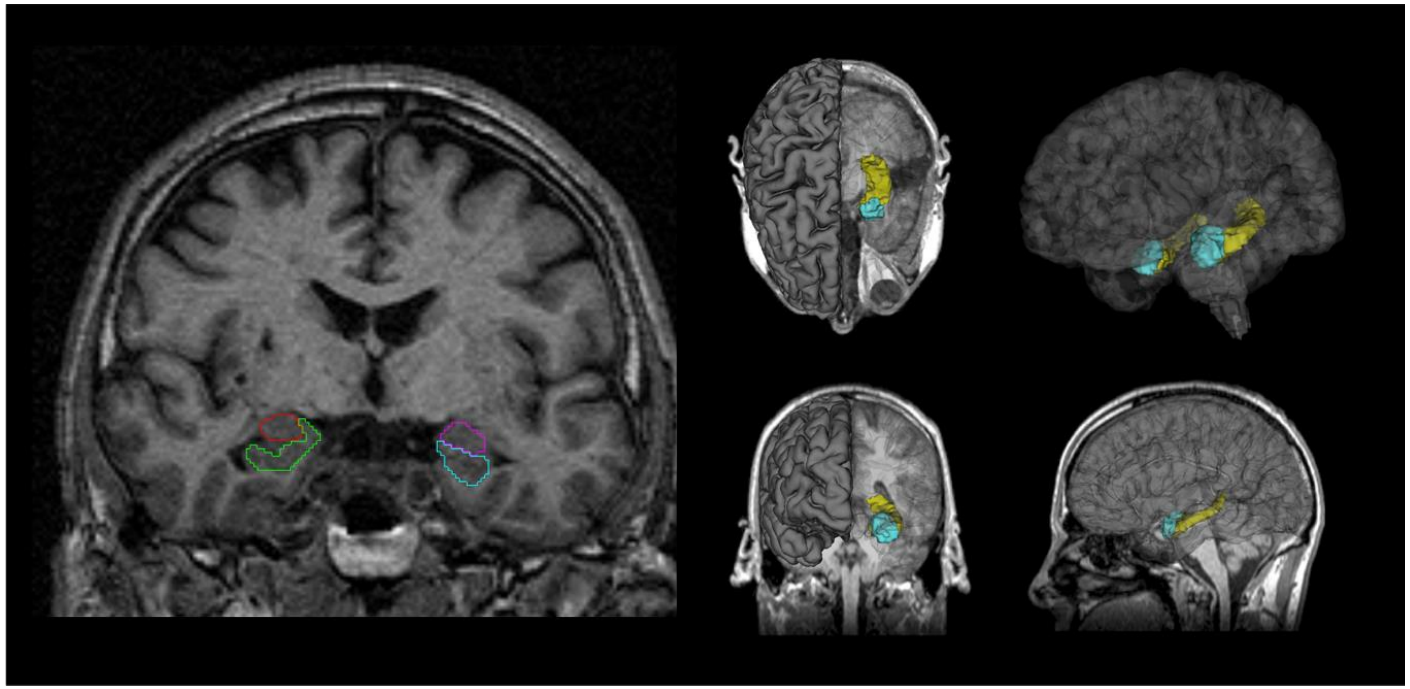
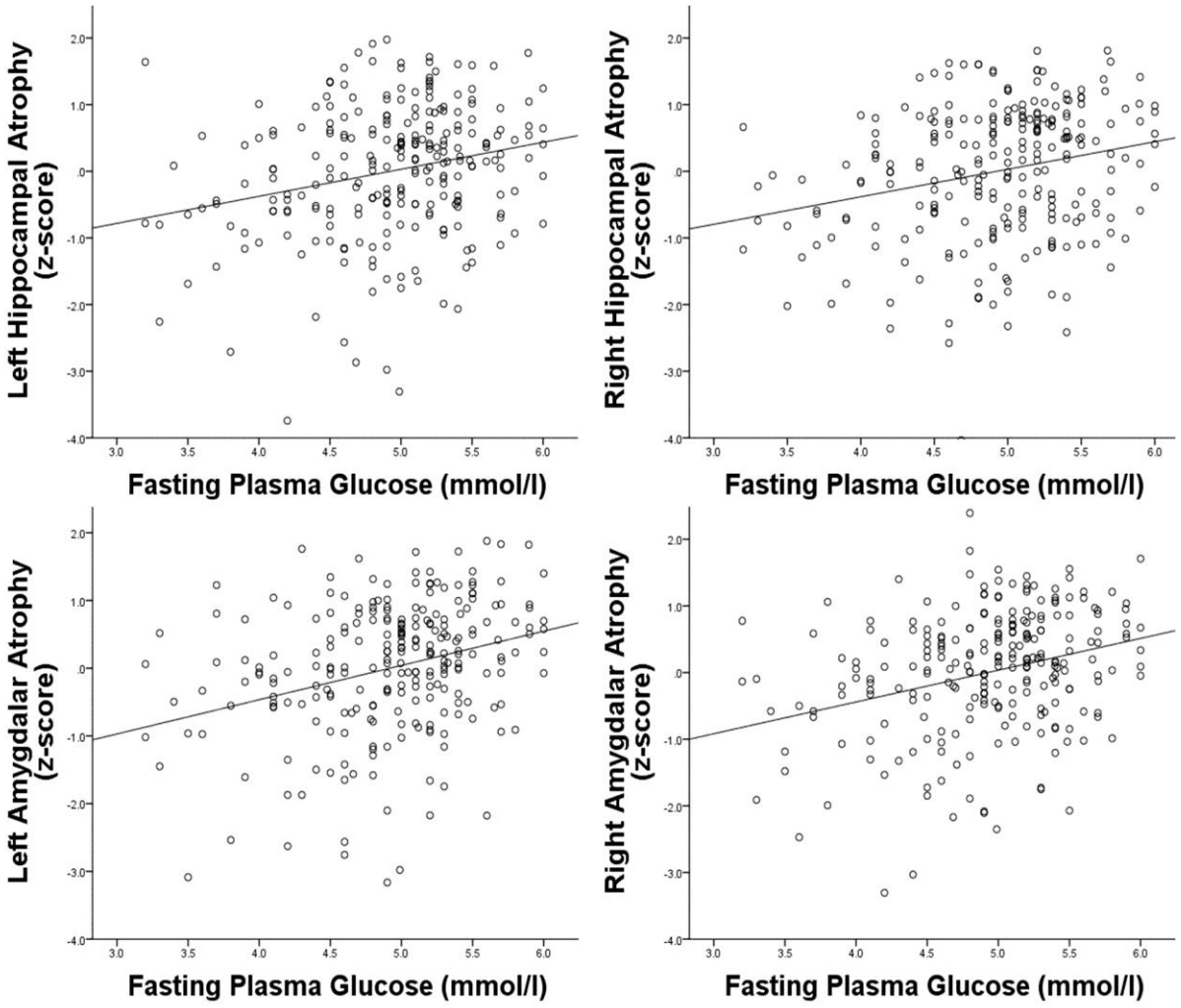
Hippocampus manually traced or automatically segmented on T1-weighted scans with 1mm isotropic resolution



Hippocampus presented in yellow

# Two Assessments




## Higher normal fasting plasma glucose is associated with hippocampal atrophy

### The PATH Study

Nicolas Cherbuin, PhD
Perminder Sachdev, MD, PhD, FRANZCP
Kaarin J. Anstey, PhD

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**ABSTRACT**

**Objectives:** Substantial evidence showing an association between type 2 diabetes (T2D) and cerebral atrophy, cognitive impairment, and dementia is accumulating. However, relatively little is known about the subclinical effects of high plasma glucose levels within the normal range. The aim of this study was to investigate the association between plasma glucose levels and hippocampal and amygdalar atrophy in a sample of 266 cognitively healthy individuals free of T2D, aged 60–64 years, taking part in a longitudinal study of aging.

**Methods:** Fasting plasma glucose was assessed at wave 1. Hippocampal and amygdalar volumes were manually traced on 1.5 T MRI scans collected at wave 1 and at wave 2 4 years later. General linear model analyses were used to assess the relationship between plasma glucose and incident medial temporal lobe atrophy after controlling for a range of sociodemographic and health variables.

**Results:** Plasma glucose levels were found to be significantly associated with hippocampal and amygdalar atrophy and accounted for 6%–10% in volume change after controlling for age, sex, body mass index, hypertension, alcohol, and smoking.

**Conclusions:** High plasma glucose levels within the normal range (<6.1 mmol/L) were associated with greater atrophy of structures relevant to aging and neurodegenerative processes, the hippocampus and amygdala. These findings suggest that even in the subclinical range and in the absence of diabetes, monitoring and management of plasma glucose levels could have an impact on cerebral health. If replicated, this finding may contribute to a reevaluation of the concept of normal blood glucose levels and the definition of diabetes. *Neurology*® 2012;79:1019–1026

**GLOSSARY**

**BMI** = body mass index; **CRP** = C-reactive protein; **FOV** = field of view; **GLM** = general linear model; **HPA** = hypothalamic-pituitary-adrenal; **ICV** = intracranial volume; **IGT** = impaired glucose tolerance; **MetS** = metabolic syndrome; **ROI** = region of interest; **T2D** = type 2 diabetes; **TE** = echo time; **TR** = repetition time.

There is an increasing research focus on type 2 diabetes (T2D) as a risk factor for brain aging, cognitive decline, and dementia.[1,2] Other factors associated with diabetes, such as caloric intake, body weight, and insulin resistance have also been shown to be independently associated with increased risk of age-related cognitive decline.[3–5] However, it is not clear whether high plasma glucose levels in the normal range are also harmful to brain health.

In nondiabetic individuals, experimentally raised plasma glucose levels have been found to be associated with increased systemic inflammation.[6] Because chronic systemic inflammation has been shown to be associated with cerebral atrophy, particularly in the hippocampus, it is possible that consistently higher glucose levels within the normal range may be associated with neurodegeneration. In addition, excessive coagulation function activity, which potentiates inflammatory processes,[7] can also be caused by poorly regulated plasma glucose levels.[8] Higher glucose levels are therefore likely to raise the risk of thrombosis, microemboli, and clinical

Supplemental data at www.neurology.org

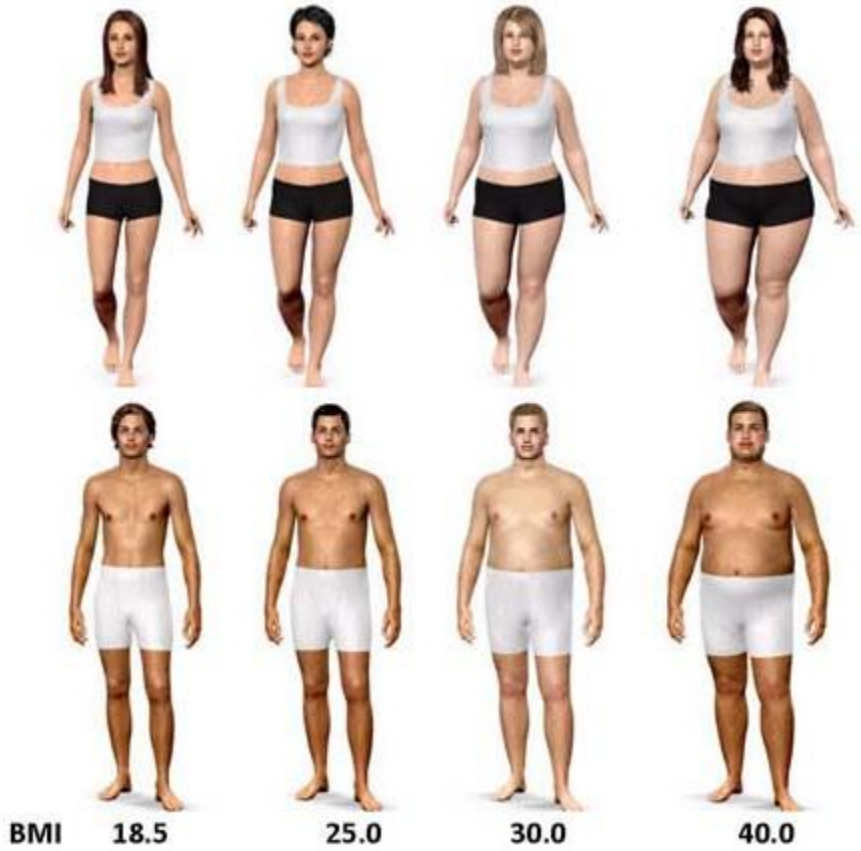
# Body Mass Index (BMI)

Measure of weight relative to height

BMI = weight (kg)/ height$^2$ (m$^2$)

Categories:

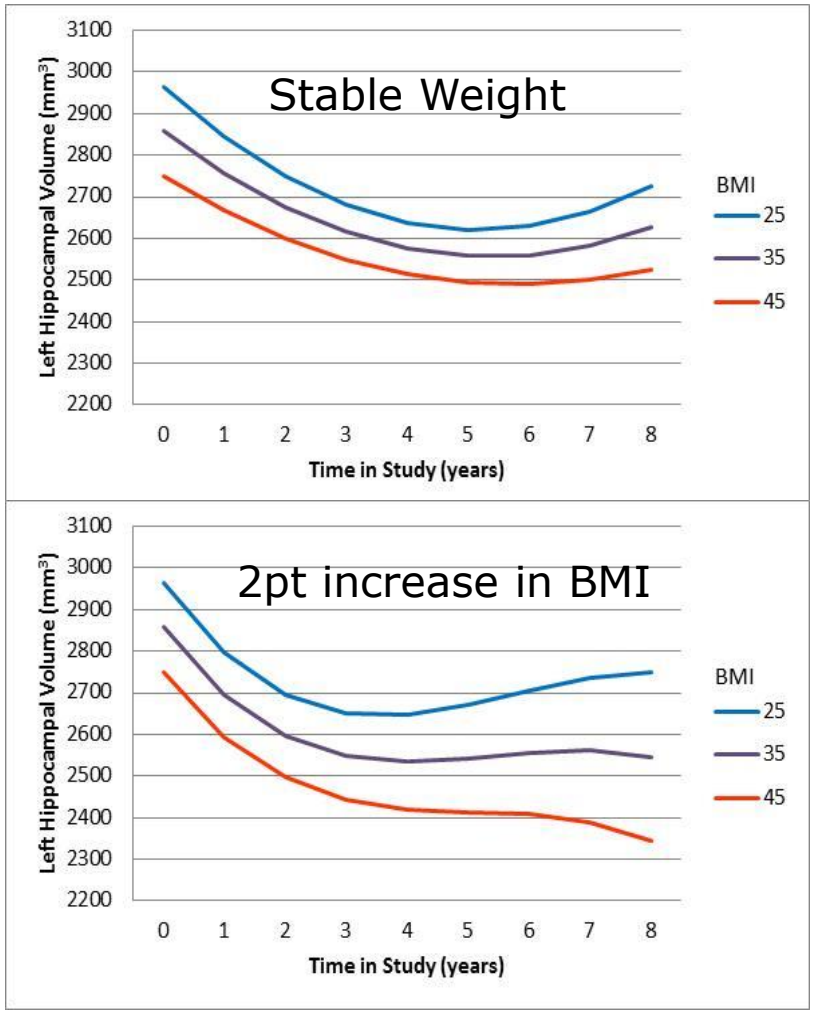
| | |
|---|---|
| normal: | 18.5 – 24.99 |
| overweight: | 25 – 29.99 |
| obese: | ≥ 30 |




What does it mean?

- A person of my height (5’ 6”/170cm) with normal weight (<11.3 stones / <72 kg) ➔ BMI ≤ 25
- A person of my height who is overweight (<13.7 stones / <87 kg) ➔ BMI = 25-30)
- A person of my height who is moderately obese (<15.9 stones /<101 kg) ➔ BMI of ~35

# Three Assessments




International Journal of Obesity (2015), 1–6

www.nature.com/ijo

**ORIGINAL ARTICLE**

## Being overweight is associated with hippocampal atrophy: the PATH Through Life Study

N Cherbuin[1], K Sargent-Cox[1], M Fraser[1], P Sachdev[2] and KJ Anstey[1]

**BACKGROUND:** The prevalence of obesity has increased dramatically in the past two decades, with major implications for individual well-being, population health and the economy. Of particular concern is the risk obesity presents for brain health and its consequences in an ageing population. These associations and their time course are not well understood, particularly after middle age. The aim of this study was to investigate whether being overweight/obese or having an increasing body weight is associated with hippocampal atrophy in early old age.
**METHODS:** Participants were 420 unimpaired (Mini-Mental State Examination >26) individuals aged 60–64 years, living in the community and taking part in a large prospective study of ageing over an 8 year follow-up. Magnetic resonance imaging scans were collected at three assessments and the hippocampus was manually traced by expert neuroscientists. Multi-level analyses assessing the relationship between body mass index (BMI) and hippocampal atrophy over 8 years while controlling for important covariates were conducted.
**RESULTS:** Analyses showed that BMI was negatively associated with left (coefficient: −10.65 mm$^3$; s.e. 4.81; $P=0.027$) and right (coefficient: −8.18 mm$^3$; s.e. 4.91; $P=0.097$) hippocampal volume at the first assessment. Over the follow-up period, those with a higher BMI experienced greater hippocampal atrophy and more so in the left ($P=0.001$) than in the right ($P=0.058$) hippocampus.
**CONCLUSIONS:** The findings from this study provide important evidence indicating that being overweight or obese is associated with poorer brain health. These results are consistent with those of previous animal and human studies and further stress the importance of reducing the rate of obesity through education, population health interventions and policy.

*International Journal of Obesity* advance online publication, 30 June 2015; doi:10.1038/ijo.2015.106

### INTRODUCTION

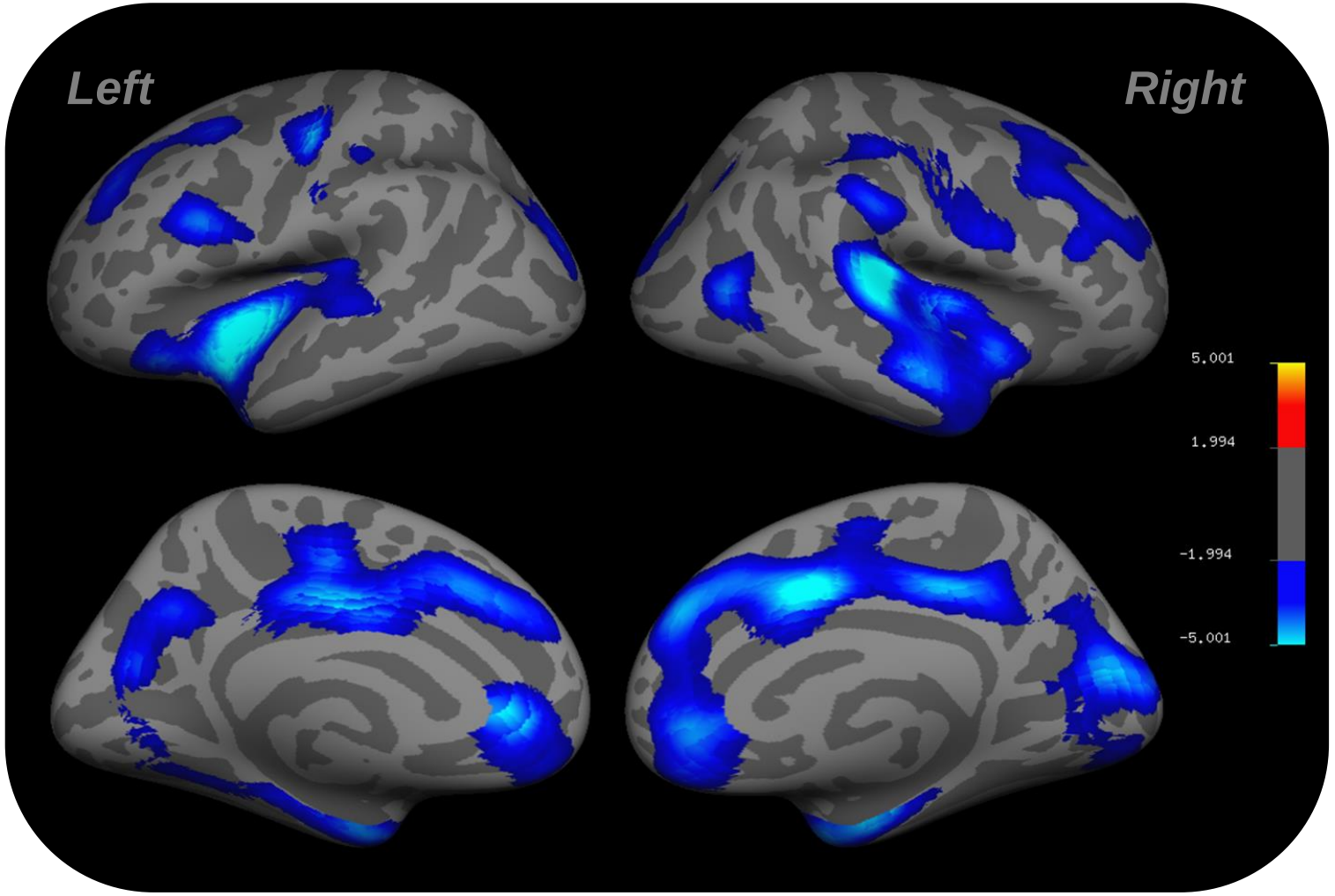
The prevalence of obesity has increased dramatically in the past two decades. In the United States, the adult obesity rate has increased by 50% between 1990 and 2010 (19.4% vs 28.4%),[1] with almost one individual in three being obese. Similar trends have been observed in Australia where the current prevalence rate is 28.3%,[2] and in much of the rest of the world where prevalence rates have typically doubled in the past 30 years. Asia and parts of East, West and Central Africa are exceptions as the obesity prevalence in these regions has remained low.[3] In a globally ageing population, this epidemic presents huge challenges as obesity is associated with an increasing disease burden, social and economic costs, higher morbidity and possibly a greater risk of dementia.[4] It is therefore critical to better understand the mechanisms linking obesity to disease processes and particularly those impacting cerebral health.

In animal models, obesity in mice fed a high-fat diet has been shown to lead to the upregulation of pro-inflammatory processes,[5] increased production of reactive oxygen species,[6] increased apoptosis and neurodegeneration and decreased neurogenesis,[7] which together lead to decreased brain volumes, particularly of the hippocampus, and impaired memory and other cognitive deficits.[8] Human studies have consistently shown obese individuals to have higher inflammatory markers, lower brain volumes and lower cognitive performance.[7,9]

Obesity has also been linked with the development of Alzheimer's disease pathology in animals[10] while in humans it has been found to be associated with a greater risk of dementia (see Lee[11] for a review). Surprisingly, however, this latter association has only been robustly demonstrated in relation to mid-life obesity, whereas late-life obesity has generally been found not to be associated with cognitive decline or increased dementia risk.[4] This is despite the fact that cross-sectional research in cognitively healthy older adults appears to indicate that obesity remains negatively associated with brain volume later in life[12] and that animal research does not provide any indication that the biological consequences of obesity change in older animals but instead suggest such effects are further compounded by other ageing processes.[13] These inconsistent findings may be due to survivor effects where those obese individuals who live to participate in epidemiological studies of old age are somehow different from those who do not or to the fact that the development of clinical dementia is associated with weight loss and thus may confound the effect of obesity in this age range.[11] Also noteworthy is a recent study, albeit cross-sectional, showing that obesity is associated with lower brain volumes in mild cognitive impairment and Alzheimer's disease.[14]

In order to clarify the effect of obesity on brain health in ageing, it is essential to study associations between obesity and cerebral structure in non-demented individuals using a longitudinal design.

# How about elsewhere in the brain?




Longitudinal associations between BMI and cortical thinning over 12 years in individuals in their 60s (FDR p<0.05).

# Three Assessments

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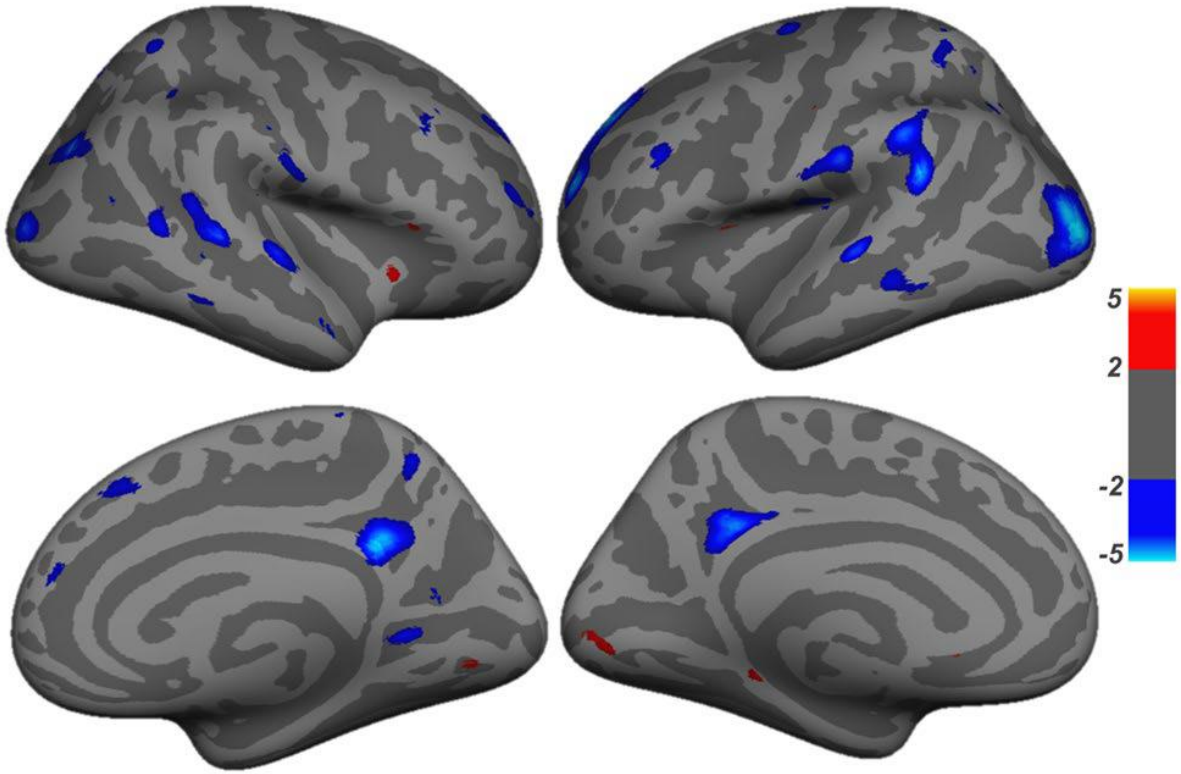
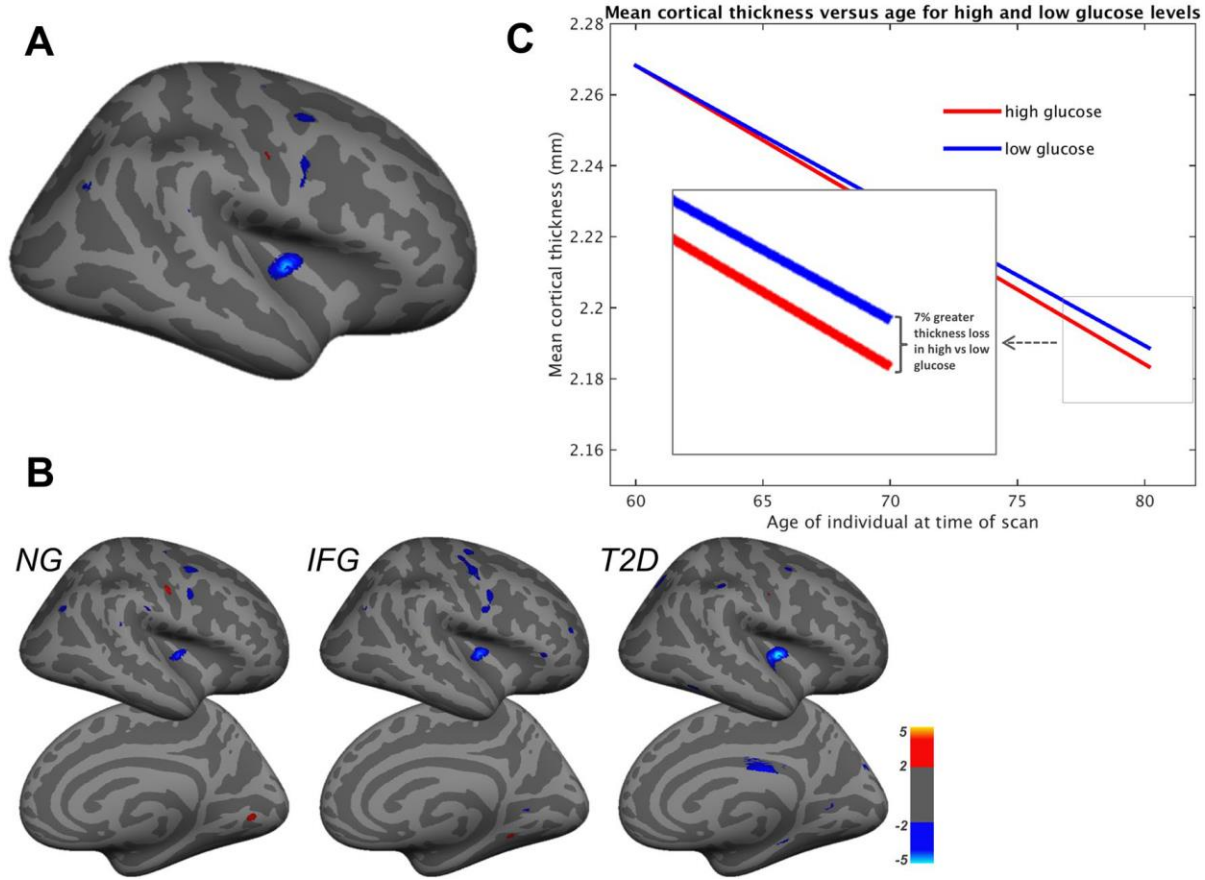
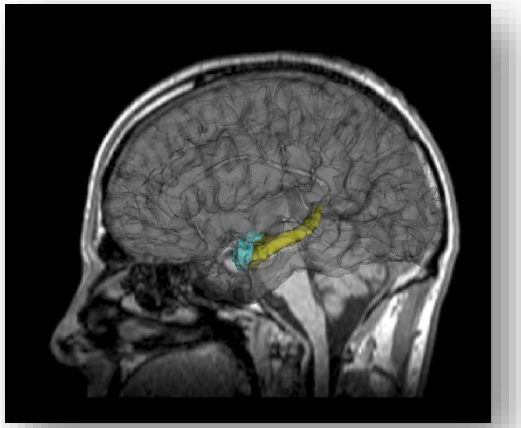
**Cortex is thinner in T2D compared to NFG at baseline**

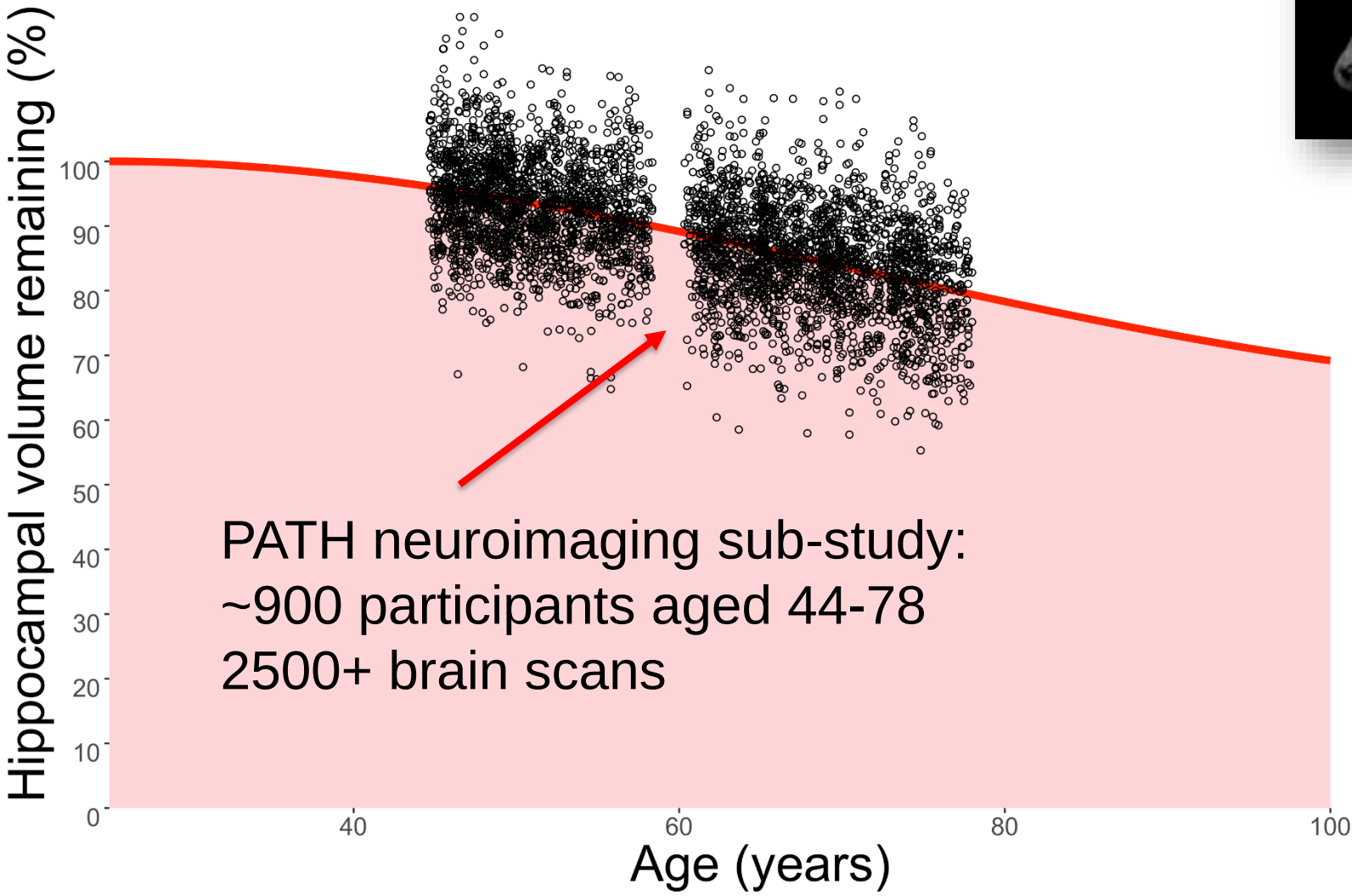


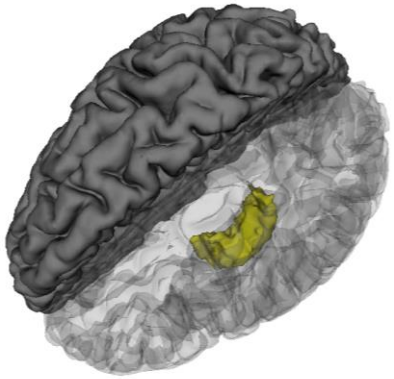

**Plasma glucose affects cortical thinning rate, dependent on age**




Shaw et al. (2017)




Hippocampal volume remaining (%)
100
90
80
70
60
50
40
30
20
10
0
40
60
80
100
Age (years)
PATH neuroimaging sub-study:
~900 participants aged 44-78
2500+ brain scans



Large cross-sectional dataset (Potvins et al. 2016):
- 2790 participants
- aged 18-94 years

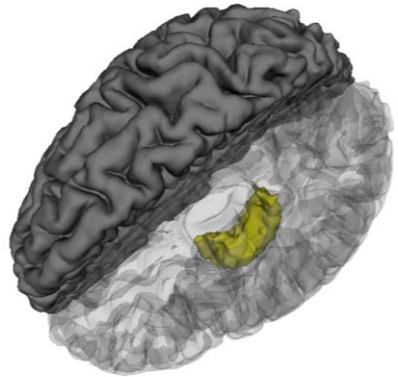
Estimates based on meta-analysis (Fraser et al. 2015):
- 3429 participants
- aged 20-90 years

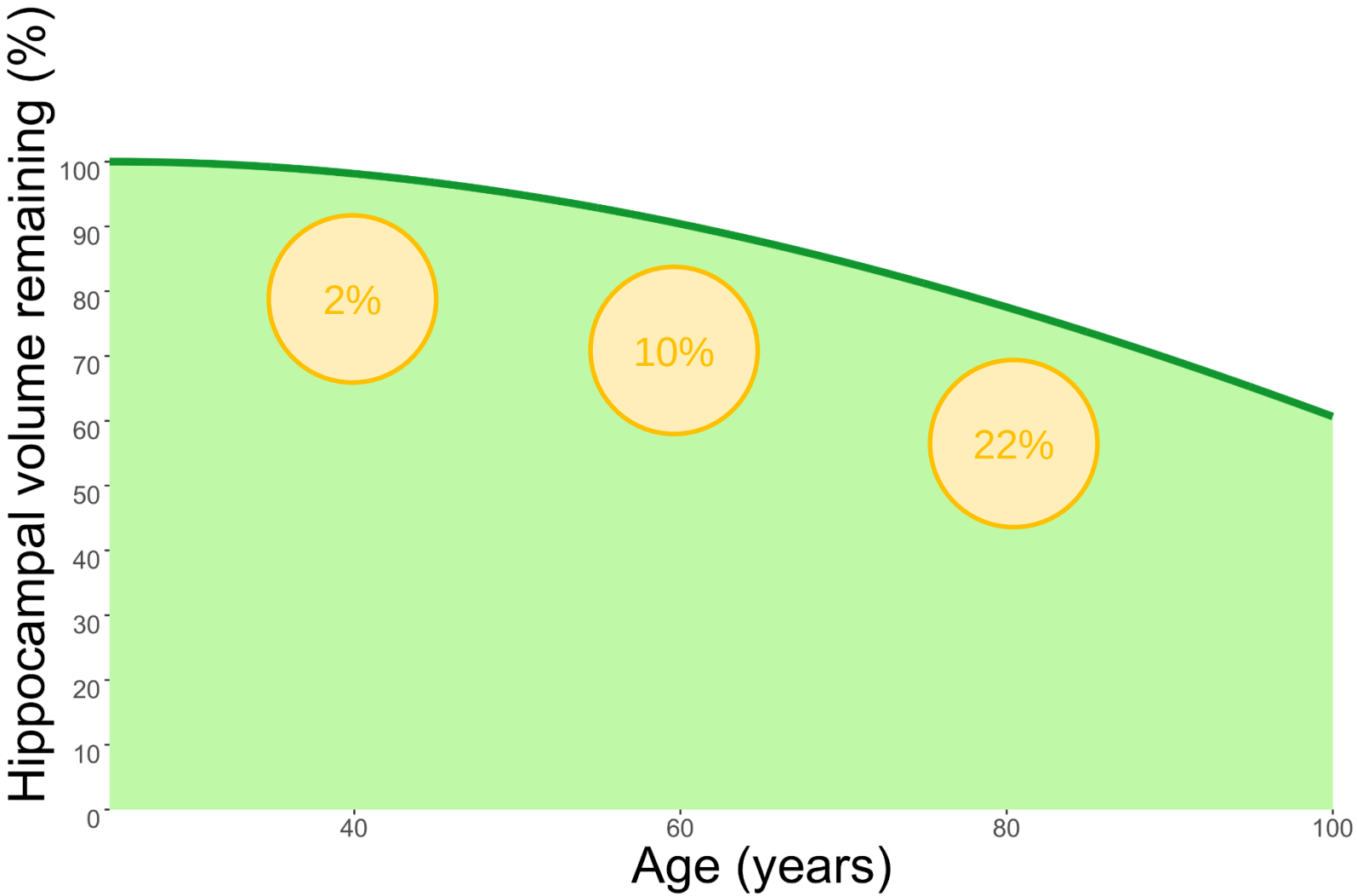
Hippocampal volume remaining (%)

100
90
80
70
60
50
40
30
20
10
0

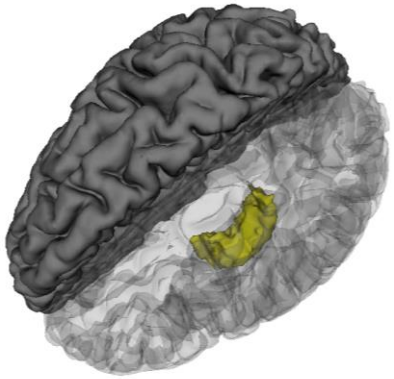
40
60
80
100

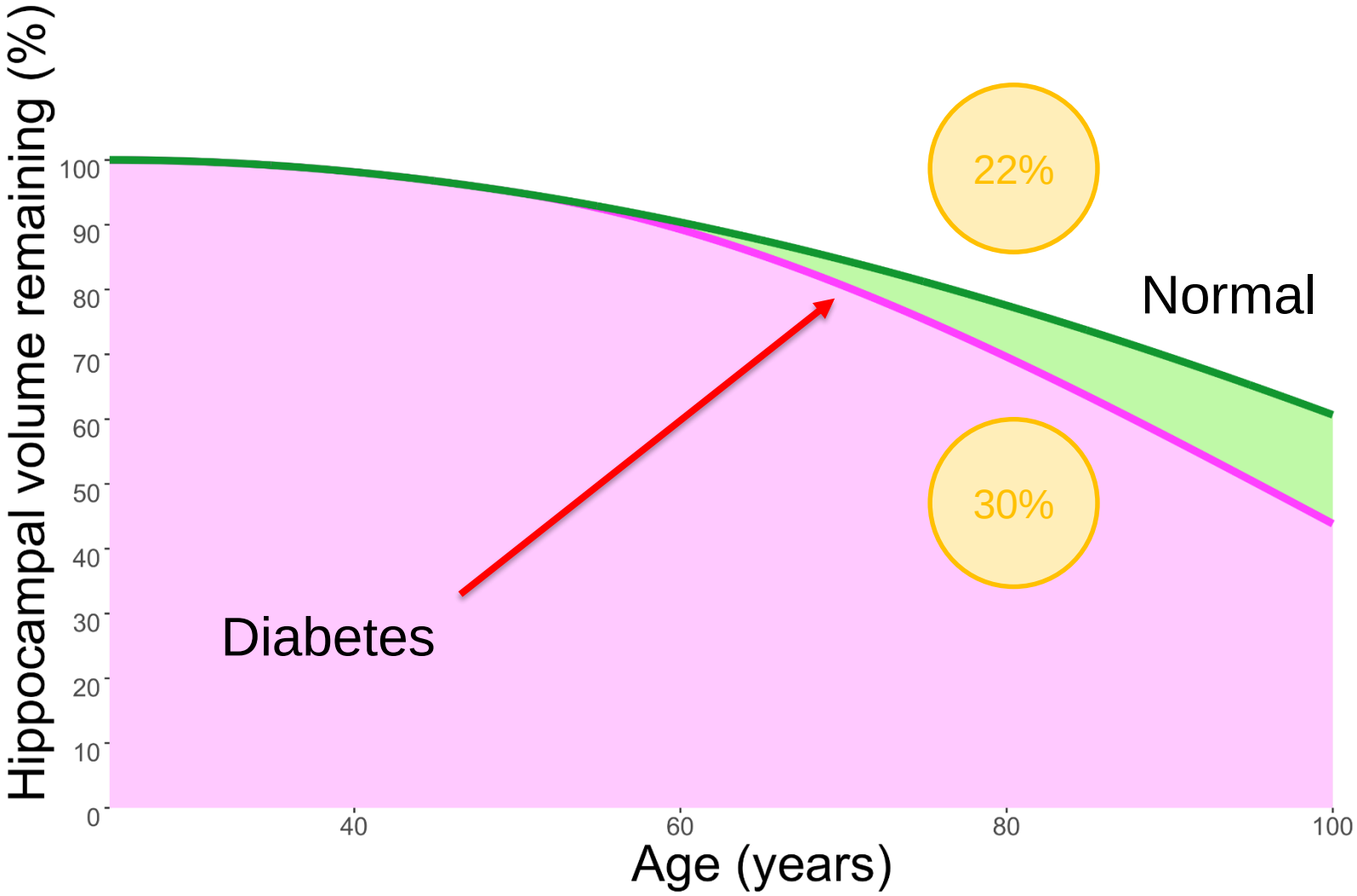
Age (years)



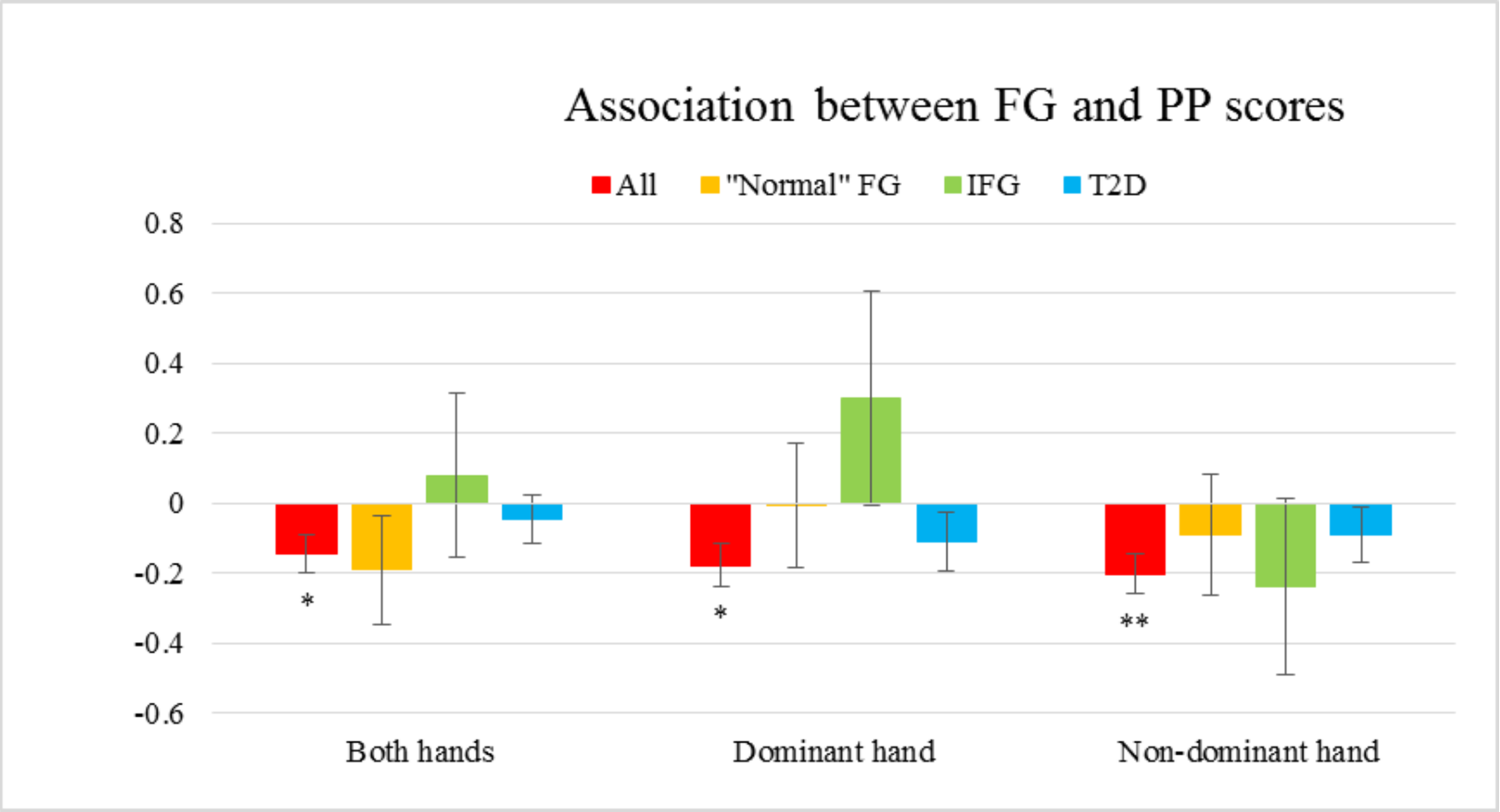

Hippocampal volume remaining (%)
100
90
80
70
60
50
40
30
20
10
0
2%
10%
22%
40
60
80
100
Age (years)

# Type 2 Diabetes

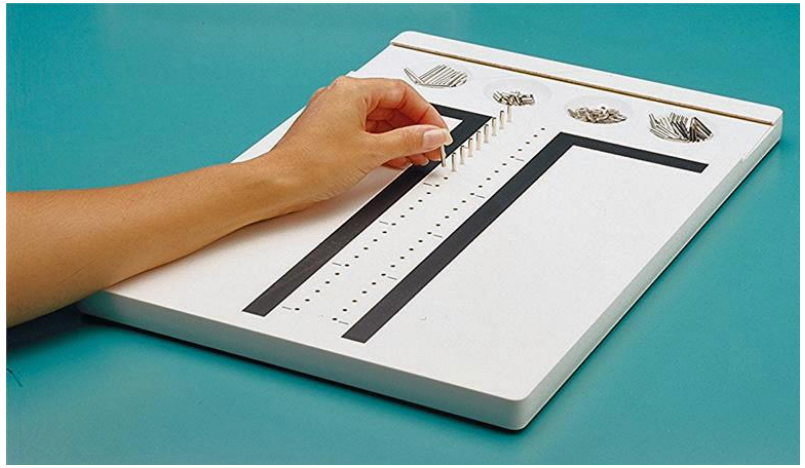




# Blood Sugar – Diabetes - Cognition




Controlling for Age, Sex and Intracranial Volume. *: $p < 0.017$ **: $p < 0.001$



- > 6.9mmol/l or self-report: **Type 2 Diabetes**
- 5.6mmol/l - 6.9mmol/l: **Impaired Fasting Glucose (IFG)**
- < 5.6 mmol/l: **“Normal”**

Zhang et al. (2018)

# ...and more

Diabetes & Metabolism xxx (2017) xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Research letter

**Brain atrophy in ageing: Estimating effects of blood glucose levels vs. other type 2 diabetes effects**

OPEN ACCESS Freely available online

PLOS ONE

## High ''Normal'' Blood Glucose Is Associated with Decreased Brain Volume and Cognitive Performance in the 60s: The PATH through Life Study

**Moyra E. Mortby[1]*, Andrew L. Janke[2], Kaarin J. Anstey[1], Perminder S. Sachdev[3], Nicolas Cherbuin[1]**

1 Centre for Research on Ageing, Health and Wellbeing, The Australian National University, Canberra, Australia, 2 Centre for Advanced Imaging, The University of Queensland, Brisbane, Australia, 3 Neuropsychiatric Institute, University of New South Wales, Sydney, Australia

**Abstract**

***Context:*** Type 2 diabetes is associated with cerebral atrophy, cognitive impairment and dementia. We recently showed higher glucose levels in the normal range not to be free of adverse effects and to be associated with greater hippocampal and amygdalar atrophy in older community-dwelling individuals free of diabetes.

***Objective:*** This study aimed to determine whether blood glucose levels in the normal range (<6.1 mmol/L) were assoc with cerebral volumes in structures other than the hippocampus and amygdale, and whether these glucose-related reg volumes were associated with cognitive performance.

***Design, Setting and Participants:*** 210 cognitively healthy individuals (68–73 years) without diabetes, glucose intoleran metabolic syndrome were assessed in the large, community-based Personality and Total Health Through Life (PATH) s

***Main Outcome Measure:*** Baseline blood glucose levels in the normal range (3.2–6.1 mmol/l) were used to deter regional brain volumes and associated cognitive function at wave 3.

***Results:*** Higher blood glucose levels in the normal range were associated with lower grey/white matter regional volun the frontal cortices (middle frontal gyrus, inferior frontal gyrus precentral gyrus). Moreover, identified cerebral regions associated with poorer cognitive performance and the structure-function associations were gender specific to men.

***Conclusion:*** These findings stress the need to re-evaluate what is considered as healthy blood glucose levels, and cor the role of higher normal blood glucose as a risk factor for cerebral health, cognitive function and dementia. A b lifetime management of blood glucose levels may contribute to improved cerebral and cognitive health in later life possibly protect against dementia.

**Citation:** Mortby ME, Janke AL, Anstey KJ, Sachdev PS, Cherbuin N (2013) High "Normal" Blood Glucose Is Associated with Decreased Brain Volume and Co Performance in the 60s: The PATH through Life Study. PLoS ONE 8(9): e73697. doi:10.1371/journal.pone.0073697

**Editor:** Friedemann Paul, Charité University Medicine Berlin, Germany

**Received** March 26, 2013; **Accepted** July 29, 2013; **Published** September 4, 2013



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**Competing Interests:** The authors have declared that no competing interests exist.

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### Introduction

It is well established that type 2 diabetes is associated with 'accelerated brain ageing' [1], white matter lesions [2], atrophy [3,4] and the presence of infarcts [5], which in turn relate to reduced cognitive functioning [1,4], an increased risk of Alzheimer's disease [6,7] and vascular damage [8]. A review by Awad et al. [9] of the relationship between impaired glucose tolerance, type 2 diabetes and cognitive function highlighted research linking sub-clinical levels of glucose in the high-normal range for glucose tolerance or impaired glucose tolerance (fasting glucose levels <7 mmol/L) with cognitive function, smaller hippocampal volumes and poor glucose regulation [10]. Notably, research has shown a decrement in cognitive function associated with impaired glucose tolerance in men, while women appear to demonstrate virtually identical scores to normoglycaem [11].

We have recently shown that higher glucose levels in th range (<6.1 mmol/L) are not necessarily free of adver and are associated with greater hippocampal and a atrophy in older community-dwelling individuals free o [12]. These findings are in accordance with anim demonstrating higher plasma glucose levels in rats to be with hippocampal neuronal loss, decreased neurogenesis, spatial learning, reduced hippocampal dendritic spine de reduced long-term potentiation [13–15]. Furthermore diabetics, experimentally raised plasma glucose levels l associated with increased systemic inflammation [16,17 mal coagulation function [18], chronic stress and activat

ed that ageing is associated with brain ite adulthood [1,2]. From age 60 on- ain atrophies ≈ 0.5%/yr for the whole natter and ≈ 0.62–0.68%/yr for white n small, but cumulatively adds up to over decades: between the ages of mL (5%) of total brain volume is lost, a upled with cumulative atrophy across etes mellitus (T2D) is associated with tural brain abnormalities, including over time [2]. Individuals with T2D total brain volume (0.1–1.5%), grey WMV (< 1%) than those with normal esponding to between one and three

(aged 60–64 years at baseline) with MRI scans taken on four occasions four years apart (M = 4.36, *SD* = 1.58), and fasting blood glucose measurements on three occasions. After exclusions, due to missing data and history of neurological disorders, there were *n* = 279 participants. They did not differ from the wider PATH sample except for a slightly higher education level (M = 14.46 vs. M = 13.71; *t* (294) = 4.284, *P* = < 0.01). See supplementary material for additional information on sample selection and inclusion criterion. This study was approved by the Australian National University Ethics Committee. All participants provided written, informed consent.

*Plasma glucose and brain measures*

Venous blood was collected following an overnight fast of at least 10 hours. Plasma glucose was measured on a Beckman LX20 Analyser by an oxygen rate method (Fullerton, California). Diabetic grouping was defined by non-overlapping categories of T2D (self-reported, or two or more fasting blood glucose measures > 7 mmol/L), IFG (not T2D and two or more blood glucose measures > = 5.6 mmol/L), or NFG (not T2D or IFG, two or more blood glucose measures < 5.6), following American Diabetes Association guide-

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## Trajectories of BMI change impact glucose and insulin metabolism

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**KEYWORDS**
Weight change;
Insulin;
HOMA;
Glucose;
Body Mass Index

**Abstract** *Background and aims:* The aim of this study was to examine, in a community setting, whether trajectory of weight change over twelve years is associated with glucose and insulin metabolism at twelve years.
*Methods and results:* Participants were 532 community-living middle-aged and elderly adults from the Personality and Total Health (PATH) Through Life study. They spanned the full weight range (underweight/normal/overweight/obese). Latent class analysis and multivariate generalised linear models were used to investigate the association of Body Mass Index (BMI, kg/m$^2$) trajectory over twelve years with plasma insulin (μIU/ml), plasma glucose (mmol/L), and HOMA2 insulin resistance and beta cell function at follow-up. All models were adjusted for age, gender, hypertension, pre-clinical diabetes status (normal fasting glucose or impaired fasting glucose) and physical activity. Four weight trajectories were extracted; constant normal (mean baseline BMI = 25; follow-up BMI = 25), constant high (mean baseline BMI = 36; follow-up BMI = 37), increase (mean baseline BMI = 26; follow-up BMI = 32) and decrease (mean baseline BMI = 34; follow-up BMI = 28). At any given current BMI, individuals in the constant high and increase trajectories had significantly higher plasma insulin, greater insulin resistance, and higher beta cell function than those in the constant normal trajectory. Individuals in the decrease

RESEARCH ARTICLE Open Access

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## Western diet is associated with a smaller hippocampus: a longitudinal investigation

Felice N. Jacka[1,2,3,4*], Nicolas Cherbuin[5], Kaarin J. Anstey[5], Perminder Sachdev[6] and Peter Butterworth[5]

**Abstract**

**Background:** Recent meta-analyses confirm a relationship between diet quality and both depression and cognitive health in adults. While the biological pathways that underpin these relationships are likely multitudinous, extensive evidence from animal studies points to the involvement of the hippocampus. The aim of this study was to examine the association between dietary patterns and hippocampal volume in humans, and to assess whether diet was ential rates of hippocampal atrophy over time.

drawn from the Personality and Total Health Through Life Study and focused on a subsample 5) who were aged 60–64 years at baseline in 2001, completed a food frequency questionnaire, nagnetic resonance imaging scans approximately 4 years apart. Longitudinal generalized inear regression models were used to assess the association between dietary factors and left al volumes over time.

andard deviation increase in healthy "prudent" dietary pattern was associated with a 45.7 mm$^3$ m$^3$) larger left hippocampal volume, while higher consumption of an unhealthy "Western" ndependently) associated with a 52.6 mm$^3$ (SE 26.6 mm$^3$) smaller left hippocampal volume. vere independent of covariates including age, gender, education, labour-force status, and medication, physical activity, smoking, hypertension and diabetes. While hippocampal time, there was no evidence that dietary patterns influenced this decline. No relationships were etary patterns and right hippocampal volume.

ntakes of nutrient-dense foods and higher intakes of unhealthy foods are each independently r left hippocampal volume. To our knowledge, this is the first human study to demonstrate diet and hippocampal volume concordant with data previously observed in animal models.

ived neurotrophic factor, Hippocampus, Diet, Magnetic resonance imaging, Neurogenesis,

its are recognised as major con- the common noncommunicable rdiovascular disease, cancer and has been a global shift toward fast foods and sugar-sweetened is increasingly "obesogenic" en- nuch of the development of the sity epidemic [2].

Emerging evidence also supports a role for poor diet in promoting mental disorders, including depression and dementia [4, 5] and there are now extensive data showing that a healthy diet is inversely related to the risk for both depression and cognitive decline [6, 7]. We have previously shown that dietary patterns characterized by higher intakes of nutrient-dense foods, such as vegetables, fruit, whole grains and fish, are associated with a reduced prevalence and risk for depressive symptoms and disorders, whereas dietary patterns higher in saturated fats and refined carbohydrates—a Western-style dietary pattern—are independently associated with increased depression and depressive symptoms, both

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# Systems Approach

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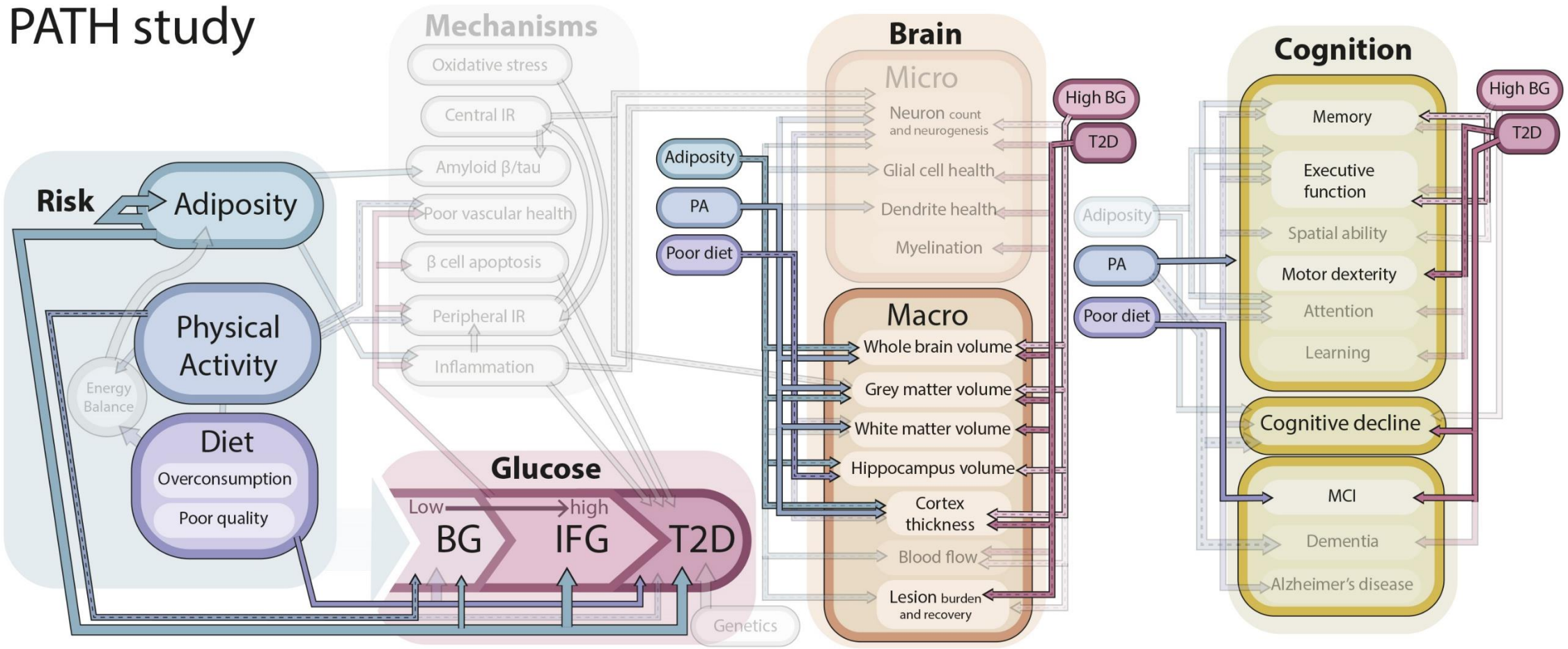
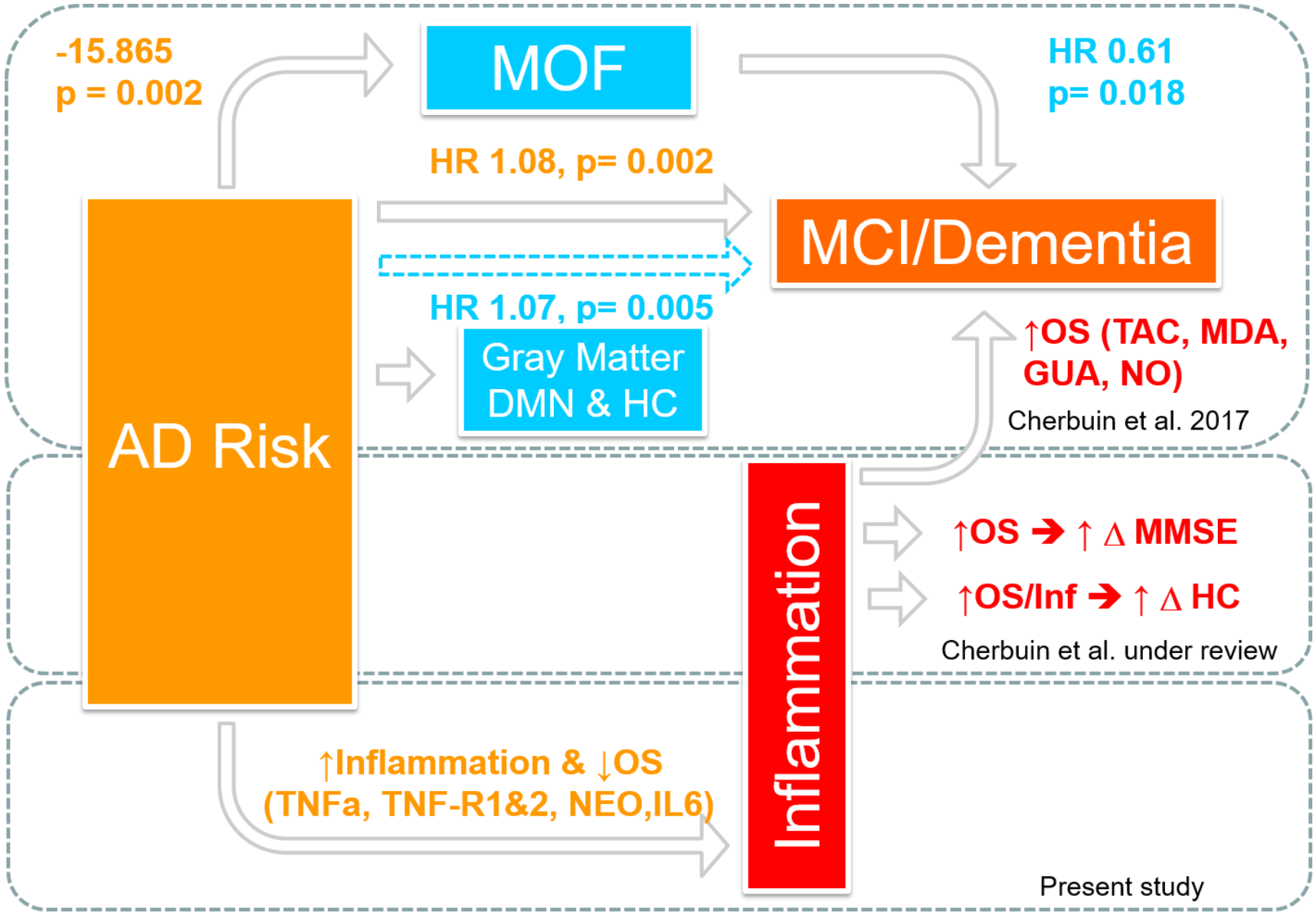


# Inflammation & Cognitive Decline



# Experience from Randomised Controlled Trials

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Open Access Protocol

BMJ Open

## Protocol for a pragmatic randomised controlled trial of Body Brain Life—General Practice and a Lifestyle Modification Programme to decrease dementia risk exposure in a primary care setting

Sarang Kim,[1] Mitchell McMaster,[1] Susan Torres,[2] Kay L Cox,[3] Nicola Lautenschlager,[4] George W Rebo
Ian McRae,[1] Nicolas Cherbuin,[1] Kaarin J

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**ABSTRACT**

**Introduction** It has been estimated that a 10%–25% reduction in seven key risk factors could potentially prevent 1.1–3.0 million Alzheimer's disease cases globally. In addition, as dementia is preceded by more subtle cognitive deficits which have substantial social and economic impact, effective preventative interventions would likely have more extensive benefits. The current study evaluates in primary care a multidomain risk-reduction intervention targeting adults with high risk of developing dementia.

**Methods and analysis** A randomised controlled trial (RCT) is being conducted to evaluate three intervention programmes using a pragmatic approach suitable to the clinic: (1) a 12-week online and face-to-face dementia risk-reduction intervention (Body Brain Life—General Practice (BBL-GP)); (2) a 6-week face-to-face group lifestyle modification programme (LMP); and (3) a 12-week email-only programme providing general health information. We aim to recruit 240 participants, aged 18 and over, to undergo a comprehensive cognitive and physical assessment at baseline and follow-ups (postintervention, 18, 36 and 62 weeks). The primary

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Alzheimer's & Dementia: Translational Research & Clinical Interventions 1 (2015) 72-80

## Body brain life: A randomized controlled trial of an online dementia risk reduction intervention in middle-aged adults at risk of Alzheimer's disease

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[b]*Center on Aging and Health, Johns Hopkins University, Baltimore, MD, USA*

**Abstract**

**Objective:** To examine the efficacy of body brain life (BBL), a 12-week online dementia risk reduction intervention.

**Methods:** BBL was evaluated in a randomized controlled trial in 176 middle-aged adults with >2 risk factors and <2 protective factors for Alzheimer's disease (AD) assessed on a brief screening instrument. Participants were randomized to BBL, BBL plus face-to-face group sessions (BBL + FF) or active control (control). Score on the Australian National University-Alzheimer's disease risk index (ANU-ADRI), a validated index of AD risk, was the primary outcome measure assessed at baseline, 12, and 26 weeks.

**Results:** A group by time interaction at 26 weeks showed a significant reduction in ANU-ADRI score for BBL compared with control. Planned contrasts showed the BBL and BBL + FF groups had improvement in ANU-ADRI scores at 12 weeks (BBL + FF: $z = -0.25$; $P = .021$; BBL:

## Tailored and Adaptive Computerized Cognitive Training in Older Adults at Risk for Dementia: A Randomized Controlled Trial

**Article type:** Research Article

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Alzheimer's & Dementia

...gnitive Training (CCT) has been shown to improve cognitive ...itive impairment (MCI) or mood-related neuropsychiatric ...s remain unresolved. Objective:To evaluate the extent to which ...l and MrNPS, and its effects on meta-cognitive and non- ...whether adapting difficulty levels and tailoring to individuals' ...ethods:Older adults with MCI (n=9), MrNPS (n=11), or both ...ome-based individually-tailored and adaptive CCT (n=21) or an ... double-blind design. Interventions lasted 8–12 weeks and ...vention, and at a 3-month follow-up. Results:Participants in ...ction with their everyday memory following intervention and ...e CCT condition showed greater improvement on composite ...al cognition at follow-up. Participants with MrNPS in the CCT ...oved mood at 3-month follow-up and reported using fewer ...tion and follow-up assessments. There was no evidence that ...ged relative to the other diagnostic conditions. Finally, ...ed at follow-up assessment in the CCT condition relative to the ... CCT with adaptive difficulty and personal tailoring appears ...to both cognitive and non-cognitive outcomes. Mechanisms of ...re discussed.

..., cognitive training, mild cognitive impairment, randomized

... vol. 60, no. 3, pp. 889-911, 2017

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# Lessons Learnt & Experiences to Share

# Goals

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May seem obvious but study aims need to be clearly identified as they will influence every aspect of the study including:

- Sample size
- Length of follow-up
- Types of measures used
- Budget
- Management structures and data curation

For longitudinal investigations lasting years need to ensure short and long-term goals are identified

# Governance

Good governance is key to conducting a successful longitudinal study and requires:

- Specifying governance structures and mechanisms
- Developing a data management plan
- Setting-up a steering committee
- Planning for disagreement, it will occur!

# Collaboration & Consortia

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Who is doing similar research?

Might collaboration benefit research outcomes?

- Learn from previous experience
- Produce more generalizable findings
- Decrease costs
- Use of more comparable measures

# Target Population

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- Who will be recruited
  - Age group
  - Disease stage (recent vs long history)

- How will participants be recruited?
  - Population?
  - Clinic?
  - Interest group?

- How will the recruitment strategy impact:
  - Representativeness?
  - Specificity/precision?
  - Staging?
  - Research outcomes?
  - Feasibility

# Consumer/Stakeholder-Informed Research

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Involving consumers/stakeholders in study design can be very helpful

- Help identify problem
- Ensure feasibility
- Test methodology before going in the field
- Build links in the community which may facilitate recruitment
- Increasingly a requirement from funding agencies

But…..

➔ in order to be most effective needs to be implemented from start

# Design

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- Cross-sectional vs longitudinal
- Prospective vs retrospective
- Case-control vs population
- Assessment frequency
  - Short-bursts (moment to moment change)
  - Frequent assessments (seasonal changes, recall reliability)
  - More widely spaced assessment
- Narrow-age cohort vs lifespan

# Ethics, Approvals and Processes

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- Benefit to Participants
  - Interest/contribution to science
  - Feedback (performance, test results, research findings)
- Participants' burden
  - How much is too much?
  - Risk of drop-out
- Risk to participants
  - physical/psychological
- Participants' consent
  - Informed & written
  - Third party contact
  - Allow re-contact
  - Duty of care (provide clinicians with abnormal results)
  - Linkage with external databases (MBS, PBS, Death registry)

# Recruitment Strategy

Failure to recruit is a key risk to study success

- Are there enough target participants in the catchment area?
- Are there adequate channels to identify them?
- Is the design of the study optimal to attract participants?
- What is the worse case scenario?
- Is there a plan B?

# Controls

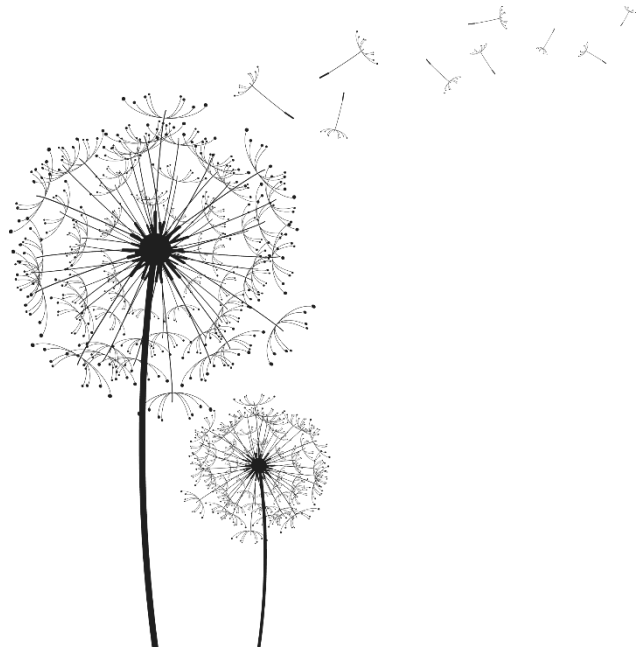
- Sourced from same/different population
- Matched
  - 1/1 ratio
  - Sex
  - Age
  - Education

- Meaningful involvement
  - What's in it for me?
  - Feedback
  - Compensation for time and travel

# Attrition

- Most studies suffer from significant attrition due to:
  - Drop out
  - Loss to follow-up
  - Death

- Attrition presents significant challenges for:
  - Representativeness of sample
  - Mis-match in sex ratio between groups
  - Decreased capacity to detect effects/differences (decreased statistical power)



# Participants Engagement

- Regular contact
- Share progress and knowledge
- Newsletters / Christmas card / Birthday email

# Participants' Consent

Careful consideration of participants consent is crucial

- Compliance with Ethics/Privacy
- Minimise loss to follow-up
- Allow re-contact
- Enable new data collection
- Data linkage
- Duty of care

# Measures

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- Quality vs quantity
- Continuity (ability to detect change)
- Quantitative / qualitative
- Objective (measurements) / subjective (self-report)
- Domains (biological, psychological, genetic, neuroimaging, cognitive, health, QoL, lifestyle, employment)
- Binary vs categorical vs continuous (e.g. Education: finished high school: yes/no; primary/secondary/higherEd)
- Learning effects

# Analyses

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Why consider analyses at the study design stage?

- Ensure match between goals and methods
- Statistical power
- Covariates
- Measure quality

# Data Curation & Archiving

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- Where will the data be saved?
- Who will have access?
- How will the data be shared?
  - Processes
  - Guidelines
  - Privacy
  - Ethics
- How will the data be organised & formatted?
  - Data structures
  - File names
  - Naming conventions
- How will the study be documented?
  - History
  - Processes
  - Decisions & rationales
  - Data dictionary

# A Place to Start

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- Longitudinal cohort study with a planned follow-up of 10 years
- 500 Participants (half controls: sex, age matched)
- Mixed recruitment strategy (clinic, population)
- Well-defined selection criteria (age range, time from onset, diagnosis)
- Controls recruited from partners/friends of ME/CFS participants
- Survey
  - Online three times per year ➔ efficient, seasonal effects
  - Face-to-face once a year ➔ functional, biological, MRI assessment
- Measures
  - Health, biological, neuroimaging, genetics, cognition, psychological, socio-demographic, lifestyle, social, work participation
- Sample collection
- Data linkage
  - MBS
  - PBS
  - My Health Record?
  - Clinical data collection platform
- Costs?

But…..

➔Prevalence? Geospatial effects?

National Health Survey? other population studies?


thank you!