Epidemiology of Sedentary Behaviour: Novel Findings in Health and Measurement

Thesis submitted for the degree of

Doctor of Philosophy

at the University of Leicester

by

Kishan Bakrania, MSc, BSc

Department of Health Sciences

Diabetes Research Centre

University of Leicester

July 2018

Epidemiology of Sedentary Behaviour: Novel Findings in Health and Measurement

Kishan Bakrania

ABSTRACT

The overall aim of this PhD was to further examine the associations between physical activity, sedentary behaviour and health (cardiometabolic health, all-cause mortality, cognitive function), and explore novel approaches for analysing physical activity and sedentary behaviour data.

Key Findings

- In a national survey sample of adults (Health Survey for England), being physically active was associated with better cardiometabolic health, even in those with high sedentary time.
- In a regional sample of high risk of T2DM adults (Walking Away from Type 2 Diabetes), MVPA time was associated with a lower risk of mortality. Conversely, sedentary time showed no association with mortality.
- In a large sample of UK adults (UK Biobank), TV viewing and driving time were inversely associated with cognition. Conversely, computer use time was positively associated with cognition. Further analyses demonstrated that fitness did not modify these associations, and that the number of healthy lifestyle factors was positively associated with cognition.
- Sedentary behaviours can be separated from light activities (except standing still) using intensity-based thresholds derived on experimental raw acceleration data.

In conclusion, this project has helped fill several epidemiological gaps in knowledge via exploiting multifaceted databases, and evaluated innovative measurement techniques. The observational analyses demonstrated the importance of physical activity as a determinant of cardiometabolic health and mortality, but found the role of sedentary behaviour to be relatively equivocal. Additional work with cognitive outcomes showed that some sedentary behaviours, but not all, are associated with poor cognition. These results provide robust data supporting public health policies designed to reduce TV viewing and driving time in adults, and increase healthy behaviours for cognitive well-being. Intervention studies are required to confirm these findings. The experimental analyses showed that researchers can accurately separate sedentary behaviours from light activities using thresholds on raw acceleration data; thus, providing a useful resource for future studies.

ACKNOWLEDGEMENTS

First and foremost, I would like to sincerely thank my supervision team (Dr. Thomas Yates, Dr. Charlotte L. Edwardson, Prof. Kamlesh Khunti, and Prof. Melanie J. Davies) for not only giving me with the opportunity to undertake this project, but also for their exemplary guidance and support over the last three-and-a-half years. It has been a pleasant journey and I am truly privileged to be a part of this wonderful department – thank you. In particular, I would like to express my gratitude towards Dr. Thomas Yates and Dr. Charlotte L. Edwardson. Without their dedication, enthusiasm, knowledge, and patience, this PhD would not have been possible. Many supervision meetings would start off with me confused and hunched over, hands on my head, and knees supporting elbows. However, they would always end with feelings of confidence, excitement, peace of mind, and self-assurance. Thank you very much Tom and Charlotte – I've had a fantastic experience working with you both.

Next, I would like to thank all my colleagues and friends from the Department of Health Sciences and the Diabetes Research Centre. I am honoured to have known and worked with such talented individuals. Notably, I express my sincere thanks to Dr. Alex V. Rowlands for his expertise and support in the work carried out in Chapter Six. I would also like to acknowledge the following epidemiological data resources for making this PhD possible: Health Survey for England, Walking Away from Type 2 Diabetes, and UK Biobank.

Furthermore, I must pay homage to Matthew McCarthy, a fellow PhD student, a prankster, a self-proclaimed emcee with several ongoing underground beefs, a villain – most likely to be a felon in a few years' time, but nevertheless, a real friend. Matt – studying for the PhD and sharing the ups and downs with smiles and frowns in an office with you for the last three-and-a-half years was the most amusing, entertaining and enjoyable experience – thank you – I will keep an eye out for your mugshot in the papers in the years to come, it's inevitable, we both know this. Lastly, I would like to thank my good friend, Thomas Chalk, my grandmother, parents, brother, sister-in-law, family and

friends, my in-laws, and most importantly, my wife, Riddhi, for their continued love, patience, and support – this thesis isn't for me, it's for you.

TABLE OF CONTENTS

ABSTRACT **2**

ACKNOWLEDGEMENTS **3**

TABLE OF CONTENTS **5**

LIST OF TABLES **14**

LIST OF FIGURES **18**

LIST OF ABBREVIATIONS **22**

LIST OF FIRST AUTHOR PUBLICATIONS **24**

- **Published Research Articles** **24**
- **Research Articles Under Review** **25**

LIST OF FIRST AUTHOR CONFERENCE PROCEEDINGS **26**

- **Oral Presentations** **26**
- **Poster Presentations** **27**

LIST OF RELEVANT CO-AUTHOR PUBLICATIONS **28**

- **Published Research Articles** **28**
- **Research Articles Under Review/Preparation** **29**

LIST OF RELEVANT CO-AUTHOR CONFERENCE PROCEEDINGS **30**

- **Oral Presentations** **30**
- **Poster Presentations** **30**

CHAPTER ONE: INTRODUCTION AND RATIONALE FOR THE PROGRAMME OF WORK **32**

- **Chapter Overview** **32**
- **Definitions of Sedentary Behaviour and Physical Activity** **32**
  - **Sedentary Behaviour** **32**

Physical Activity 33

Associations with Health 33

Behavioural Epidemiology Framework 34

Overview of Previous Research and Gaps in Knowledge 37

Cardiometabolic Health (Phase 1 of Behavioural Epidemiology) 37

Mortality (Phase 1 of Behavioural Epidemiology) 38

Cognitive Function (Phase 1 of Behavioural Epidemiology) 38

Measuring Sedentary Behaviour and Physical Activity (Phase 2 of Behavioural Epidemiology) 40

Aim of PhD 41

Key Objectives of PhD 42

Phase 1 of Behavioural Epidemiology: Establish Links between Behaviours and Health 42

Phase 2 of Behavioural Epidemiology: Develop Methods for Measuring the Behaviour 42

Training, Development and Experience 45

CHAPTER TWO: CRITICAL APPRAISAL OF THE EPIDEMIOLOGICAL DATABASES 47

Chapter Overview 47

2008 HSE 48

Background 48

Design and Data Collection 48

Response Rates 50

Strengths and Limitations 50

Walking Away from Type 2 Diabetes 55

Background **55**

Design and Data Collection **55**

Response Rates **56**

Strengths and Limitations **57**

UK Biobank **59**

Background **59**

Design and Data Collection **59**

Response Rates **60**

Strengths and Limitations **61**

CHAPTER THREE: ANALYSIS OF EPIDEMIOLOGICAL DATA: 2008 HSE DATA **65**

Chapter Overview **65**

Associations of Mutually Exclusive Categories of Physical Activity and Sedentary Time with Markers of Cardiometabolic Health in English Adults: A Cross-Sectional Analysis of the 2008 HSE **66**

Abstract **66**

Introduction **68**

Methods **69**

Design and Population **69**

Measuring Physical Activity and Sedentary Time **69**

Derivation of the Behavioural Categories **70**

Markers of Cardiometabolic Health **72**

Confounders **72**

Statistical Analysis **72**

Categorical Measures **73**

Continuous Measures....74
Sensitivity Analysis....74
Statistical Reporting....75
Results....75
Categorical Measures....78
Continuous Measures....81
Sensitivity Analysis....83
Discussion....87
Key Findings....87
Interpretations....87
Strengths and Limitations....89
Conclusion....92
CHAPTER FOUR: ANALYSIS OF EPIDEMIOLOGICAL DATA: WALKING AWAY FROM TYPE 2 DIABETES: A CLUSTER RANDOMIZED CONTROLLED TRIAL: PRIMARY CARE DATA....94
Chapter Overview....94
Associations of Objectively Measured MVPA and Sedentary Time with All-Cause Mortality in a Population of Adults at High Risk of T2DM....95
Abstract....95
Introduction....96
Methods....96
Design and Population....96
Mortality Data....97
Physical Activity and Sedentary Time Data....98
Confounders....98

Statistical Analysis **98**

Sensitivity Analysis **100**

Statistical Reporting **101**

Results **101**

Mortality Analysis **104**

Sensitivity Analysis **106**

Discussion **110**

Key Findings **110**

Interpretations **110**

Strengths and Limitations **111**

Conclusion **112**

CHAPTER FIVE: ANALYSIS OF EPIDEMIOLOGICAL DATA: UK BIOBANK DATA **113**

Chapter Overview **113**

Associations between Sedentary Behaviours and Cognitive Function: Cross-Sectional and Prospective Findings from the UK Biobank **114**

Introduction **115**

Methods **115**

Design and Population **115**

Cognitive Function Tests **119**

Sedentary Behaviours **122**

Confounders **123**

Statistical Analysis **123**

Cross-Sectional Analysis **124**

Prospective Analysis **125**

Sensitivity Analysis **125**

Statistical Reporting **127**

Results **128**

Cross-Sectional Findings **128**

Prospective Findings **151**

Sensitivity Analysis **163**

Discussion **185**

Key Findings **185**

Interpretations **185**

Strengths and Limitations **188**

Conclusion **192**

The Associations between Sedentary Behaviours and Cognitive Function are not Modified by Cardiorespiratory Fitness: A Cross-Sectional Analysis of 51,892 Adults from the UK Biobank **193**

Abstract **193**

Introduction **194**

Methods **195**

Design and Population **195**

Sedentary Behaviours **195**

CRF **195**

Cognitive Function Tests **198**

Confounders **198**

Data Inclusion **198**

Statistical Analysis **200**

Sensitivity Analysis **200**

Statistical Reporting **201**

Results **202**

Cross-Sectional Findings **202**

Sensitivity Analysis **221**

Discussion **237**

Key Findings **237**

Interpretations **237**

Strengths and Limitations **238**

Conclusion **241**

Associations between Lifestyle Factors and Cognitive Function: Cross-Sectional and Prospective Findings from the UK Biobank **242**

Abstract **242**

Introduction **243**

Methods **243**

Design and Population **243**

Cognitive Function Tests **247**

Lifestyle Factors **248**

Confounders **251**

Statistical Analysis **252**

Cross-Sectional Analysis **252**

Prospective Analysis **253**

Sensitivity Analysis **253**

Statistical Reporting **254**

Results **254**

Cross-Sectional Findings **254**

Prospective Findings **271**

Sensitivity Analysis **277**

Discussion **288**

Key Findings **288**

Interpretations **288**

Strengths and Limitations **289**

Conclusion **291**

CHAPTER SIX: ANALYSIS OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR DATA: RAW ACCELERATION DATA **292**

Chapter Overview **292**

Intensity Thresholds on Raw Acceleration Data: ENMO and MAD Approaches **293**

Abstract **293**

Introduction **294**

Methods **297**

Design and Population **297**

Accelerometer Devices **297**

Procedures **298**

Data Reduction and Processing: MAD **300**

Data Reduction and Processing: ENMO **301**

Statistical Analysis **302**

Results **303**

Discussion **314**

Key Findings 314
Interpretations 315
Strengths and Limitations 316
Conclusion 318
CHAPTER SEVEN: DISCUSSION 319
Chapter Overview 319
Thesis Summary 320
Implications and Future Directions 322
Conclusion 328
APPENDICES 330
Appendix One: Author Contribution to Overall Programme of Work 331
Appendix Two: Awards 333
Appendix Three: Supplementary Material 335
Supplementary Data 335
Supplementary Calculations 345
Appendix Four: Main Findings, Strengths, and Limitations 348
BIBLIOGRAPHY 353

LIST OF TABLES

Table 1 - Statistical methods applied in PhD 44

Table 2 - Observational study (2008 Health Survey for England data): Participant characteristics.....76

Table 3 - Observational study (2008 Health Survey for England data): Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health 79

Table 4 - Observational study (2008 Health Survey for England data): Associations of continuous measures of physical activity and sedentary time with markers of cardiometabolic health 82

Table 5 - Observational study (2008 Health Survey for England data): Sensitivity analyses: Weighted mutually exclusive category prevalence 84

Table 6 - Observational study (2008 Health Survey for England data): Sensitivity analyses: Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health 85

Table 7 - Observational study (Walking Away from Type 2 Diabetes data): Participant characteristics.....102

Table 8 - Observational study (Walking Away from Type 2 Diabetes data): Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline with all-cause mortality at follow-up 105

Table 9 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline with all-cause mortality at follow-up whilst further adjusting for other confounders 107

Table 10 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity

(MVPA) and sedentary time at baseline with all-cause mortality at follow-up in the sample of non-smokers 108

Table 11 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline, 12 months, 24 months and 36 months with all-cause mortality at follow-up 109

Table 12 - Observational study (UK Biobank data): Participant characteristics 129

Table 13 - Observational study (UK Biobank data): Cross-sectional associations at baseline between sedentary behaviours and cognitive function 135

Table 14 - Observational study (UK Biobank data): Comparing the characteristics of the baseline sample and the follow-up sample 152

Table 15 - Observational study (UK Biobank data): Prospective associations between sedentary behaviours at baseline and cognitive function at follow-up 157

Table 16 - Observational study (UK Biobank data): Prospective associations between sedentary behaviours at baseline and cognitive function at follow-up using mixed-effects logistic and linear regression models 176

Table 17 - Observational study (UK Biobank data): Cross-sectional associations at baseline between sedentary behaviours and cognitive function using Poisson regression models 180

Table 18 - Observational study (UK Biobank data): Cross-sectional quadratic associations at baseline between computer use time and cognitive function 183

Table 19 - Observational study (UK Biobank data): Participant characteristics 203

Table 20 - Observational study (UK Biobank data): Comparing the characteristics of the included sample and the excluded sample 209

Table 21 - Observational study (UK Biobank data): Dietary data 249

Table 22 - Observational study (UK Biobank data): Participant characteristics 255

Table 23 - Observational study (UK Biobank data): Cross-sectional associations at baseline between each lifestyle factor and fluid intelligence 261

Table 24 - Observational study (UK Biobank data): Comparing the characteristics of the participants with fluid intelligence data at baseline only against those with fluid intelligence data at both baseline and follow-up 272

Table 25 - Experimental study (Laboratory data): Summary of sedentary behaviours and light-intensity physical activities 299

Table 26 - Experimental study (Laboratory data): Mean (standard error) Euclidean Norm Minus One (ENMO) values for each activity stratified by accelerometer brand and monitor placement 305

Table 27 - Experimental study (Laboratory data): Mean (standard error) Mean Amplitude Deviation (MAD) values for each activity stratified by accelerometer brand and monitor placement 307

Table 28 - Experimental study (Laboratory data): Monitor-specific hip Euclidean Norm Minus One (ENMO) thresholds to differentiate between sedentary behaviours and light-intensity physical activities 310

Table 29 - Experimental study (Laboratory data): Monitor-specific wrist Euclidean Norm Minus One (ENMO) thresholds to differentiate between sedentary behaviours and light-intensity physical activities 311

Table 30 - Experimental study (Laboratory data): Monitor-specific hip Mean Amplitude Deviation (MAD) thresholds to differentiate between sedentary behaviours and light-intensity physical activities 312

Table 31 - Experimental study (Laboratory data): Monitor-specific wrist Mean Amplitude Deviation (MAD) thresholds to differentiate between sedentary behaviours and light-intensity physical activities 313

Table S1 - Observational study (UK Biobank data): Correlation coefficients between the different cognitive tests at baseline 342

Table S2 - Main findings, strengths, and limitations of each chapter that involved statistical analysis of study data (Chapters Three, Four, Five, and Six) 348

LIST OF FIGURES

Figure 1 - Behavioural epidemiology framework applied to the sedentary behaviour and physical activity research field 37

Figure 2 - Observational study (2008 Health Survey for England data): Mutually exclusive categories of physical activity and sedentary time 71

Figure 3 - Observational study (UK Biobank data): Flow chart of participants (cross-sectional data) 117

Figure 4 - Observational study (UK Biobank data): Flow chart of participants (prospective data) 118

Figure 5 - Observational study (UK Biobank data): Interactions by age: cross-sectional associations at baseline between sedentary behaviours and cognitive function 139

Figure 6 - Observational study (UK Biobank data): Interactions by sex: cross-sectional associations at baseline between sedentary behaviours and cognitive function 145

Figure 7 - Observational study (UK Biobank data): Interactions by age: prospective associations between sedentary behaviours at baseline and cognitive function at follow-up 161

Figure 8 - Observational study (UK Biobank data): Sensitivity analysis: cross-sectional associations at baseline between sedentary behaviours and cognitive function (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses) 164

Figure 9 - Observational study (UK Biobank data): Sensitivity analysis: prospective associations between sedentary behaviours at baseline and cognitive function at follow-up (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses) 170

Figure 10 - Observational study (UK Biobank data): Flow chart of participants 199

Figure 11 - Observational study (UK Biobank data): Associations of sedentary behaviours and cardiorespiratory fitness with fluid intelligence 214

Figure 12 - Observational study (UK Biobank data): Interactions with cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence 218

Figure 13 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses) 222

Figure 14 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and other cognitive tests (prospective memory and visual-spatial memory) 225

Figure 15 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (analysis executed using age- and sex-specific tertiles for cardiorespiratory fitness) 231

Figure 16 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (analysis executed using a continuous cardiorespiratory fitness variable) 234

Figure 17 - Observational study (UK Biobank data): Flow chart of participants (cross-sectional data) 245

Figure 18 - Observational study (UK Biobank data): Flow chart of participants (prospective data) 246

Figure 19 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the lifestyle factors and fluid intelligence 264

Figure 20 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence 267

Figure 21 - Observational study (UK Biobank data): Interactions by age and sex: cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence 269

Figure 22 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and fluid intelligence at follow-up. 276

Figure 23 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses) 278

Figure 24 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and prospective memory.... 279

Figure 25 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and visual-spatial memory (pairs matching - round 1) 280

Figure 26 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and visual-spatial memory (pairs matching - round 2) 281

Figure 27 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and reaction time 282

Figure 28 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and short-term numeric memory 283

Figure 29 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and fluid intelligence at follow-up (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses) 284

Figure 30 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and visual-spatial memory (pairs matching - round 1) at follow-up 285

Figure 31 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and visual-spatial memory (pairs matching - round 2) at follow-up 286

Figure 32 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and short-term numeric memory at follow-up 287

Figure S1 - Observational study (2008 Health Survey for England data): Distributions of the key outcomes and exposures 335

Figure S2 - Observational study (Walking Away from Type 2 Diabetes data): Distributions of the key outcomes and exposures 337

Figure S3 - Observational study (UK Biobank data): Distributions of the key outcomes and exposures 339

Figure S4 - Observational study (UK Biobank data): Interactions with walking pace: associations between sedentary behaviours and fluid intelligence 343

LIST OF ABBREVIATIONS

AUROC	Area Under ROC Curve
BRC	Biomedical Research Centre
β	Beta Coefficient
BPM	Beats Per Minute
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CPM	Counts Per Minute
CVD	Cardiovascular Disease
ECG	Electrocardiography
ENMO	Euclidean Norm Minus One
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoprotein
HES	Hospital Episode Statistics
HR	Hazard Ratio
HSCIC	Health and Social Care Information Centre
HSE	Health Survey for England
Hz	Hertz
ICC	Intraclass Correlation Coefficient
IFG	Impaired Fasting Glycaemia
IGT	Impaired Glucose Tolerance
IRR	Incidence Rate Ratio
LIPA	Light-Intensity Physical Activity/Activities
LOOCV	Leave-One-Out-Cross-Validation
MAD	Mean Amplitude Deviation
MEMS	Micro-Electro-Mechanical Systems
MET	Metabolic Equivalent

MPA	Moderate-Intensity Physical Activity/Activities
MVPA	Moderate-to-Vigorous-Intensity Physical Activity/Activities
N	Number
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OR	Odds Ratio
PC	Personal Computer
ROC	Receiver-Operating-Characteristic
SD	Standard Deviation
SE	Standard Error
SMA	Signal Magnitude Area
T2DM	Type 2 Diabetes Mellitus
TV	Television
UK	United Kingdom
USA	United States of America
VPA	Vigorous-Intensity Physical Activity/Activities

LIST OF FIRST AUTHOR PUBLICATIONS

Published Research Articles

Bakrania K, Yates T, Rowlands AV, Esliger DW, Bunnewell S, Sanders J, et al. Intensity thresholds on raw acceleration data: Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) approaches. *PLOS ONE* 2016; 11(10): e0164045. doi: 10.1371/journal.pone.0164045. PubMed ID: 27706241.

Bakrania K, Edwardson CL, Bodicoat DH, Esliger DW, Gill JMR, Kazi A, et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. *BMC Public Health* 2016; 16:25. doi: 10.1186/s12889-016-2694-9. PubMed ID: 26753523.

Bakrania K, Yates T, Edwardson CL, Bodicoat DH, Esliger DW, Gill JMR, et al. Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England. *BMJ Open* 2017; 7(4): e014456. doi: 10.1136/bmjopen-2016-014456. PubMed ID: 28373255.

Bakrania K, Edwardson CL, Khunti K, Henson J, Stamatakis E, Hamer M, et al. Associations of objectively measured moderate-to-vigorous-intensity physical activity and sedentary time with all-cause mortality in a population of adults at high risk of type 2 diabetes mellitus. *Preventive Medicine Reports* 2017; 5: 285-288. doi: 10.1016/j.pmedr.2017.01.013. PubMed ID: 28149710.

Bakrania K, Edwardson CL, Khunti K, Bandelow S, Davies MJ, Yates T. Associations between sedentary behaviours and cognitive function: cross-sectional and prospective findings from the UK Biobank. *American Journal of Epidemiology* 2018; 187(3): 441-454. doi: 10.1093/aje/kwx273. PubMed ID: 28992036.

Research Articles Under Review

Bakrania K, Edwardson CL, Khunti K, Davies MJ, Celis-Morales CA, Gill JMR, et al. The associations between sedentary behaviours and fluid intelligence are not modified by cardiorespiratory fitness: a cross-sectional analysis of 51,892 adults from the UK Biobank. *Preventive Medicine* 2018; Under Review.

Bakrania K, Khunti K, Edwardson CL, Dhalwani N, Velayudhan L, Davies MJ, et al. Associations between lifestyle factors and fluid intelligence: cross-sectional and prospective findings from the UK Biobank. *American Journal of Public Health* 2018; Under Review.

LIST OF FIRST AUTHOR CONFERENCE PROCEEDINGS

Oral Presentations

Bakrania K, Yates T, Edwardson CL. Novel approaches for analysing accelerometer data. Oral presentation: *Annual Health Sciences Conference*, 26 November 2014, University of Leicester, Leicester, UK.

Bakrania K, Edwardson CL, Bodicoat DH, Esliger DW, Gill JMR, Kazi A, et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. Oral presentation: *Midlands Academy of Medical Sciences Research Festival*, 15 April 2016, University of Leicester, Leicester, UK.

Bakrania K, Yates T, Edwardson CL, Bodicoat DH, Esliger DW, Gill JMR, et al. Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin: a cross-sectional analysis of the Health Survey for England. Oral presentation: *The International Congress on Physical Activity and Public Health: 6th International Society on Physical Activity and Health (ISPAH 2016)*, 16 - 19 November 2016, Queen Sirikit National Convention Center, Bangkok, Thailand.

Bakrania K, Khunti K, Edwardson CL, Davies MJ, Yates T. Lifestyle factors and cognitive function: are associations additive?. Oral presentation: *Second Midlands Academy of Medical Sciences Research Festival*, 31 March 2017, University of Warwick, Coventry, UK.

Poster Presentations

Bakrania K, Yates T, Edwardson CL. Developing and validating generalizable intensity-based thresholds on raw accelerometer data for sedentary behaviour and light activity discrimination - a MAD approach. Poster presentation: *The International Society for the Measurement of Physical Behaviour: 4th International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM 2015)*, 10 - 12 June 2015, University of Limerick, Limerick, Ireland.

Bakrania K, Edwardson CL, Bodicoat DH, Esliger DW, Gill JMR, Kazi A, et al. Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. Poster presentation: *Festival of Postgraduate Research 2016*, 7 July 2016, University of Leicester, Leicester, UK.

LIST OF RELEVANT CO-AUTHOR PUBLICATIONS

The research articles below have arisen from internal and external projects and studies that I substantially contributed to whilst undertaking my PhD.

Published Research Articles

O'Donovan G, **Bakrania K**, Ghouri N, Yates T, Gray LJ, Hamer M, et al. Nonexercise equations to estimate fitness in White European and South Asian men. *Medicine and Science in Sports and Exercise* 2016; 48(5): 854-859. doi: 10.1249/mss.0000000000000836. PubMed ID: 26694847.

Rowlands AV, Olds TS, **Bakrania K**, Stanley RM, Parfitt G, Eston RG, et al. Accelerometer wear-site detection: When one site does not suit all, all of the time. *Journal of Science and Medicine in Sport* 2016; 20(4): 368-372. doi: 10.1016/j.jsams.2016.04.013. PubMed ID: 28117147.

Winkler EA, Bodicoat DH, Healy GN, **Bakrania K**, Yates T, Owen N, et al. Identifying adults' valid waking wear time by automated estimation in activPAL data collected with a 24 h wear protocol. *Physiological Measurement* 2016; 37(10): 1653-1668. doi: 10.1088/0967-3334/37/10/1653. PubMed ID: 27652827.

Edwardson CL, Henson J, Bodicoat DH, **Bakrania K**, Khunti K, Davies MJ, et al. Associations of reallocating sitting time into standing or stepping with glucose, insulin and insulin sensitivity: a cross-sectional analysis of adults at risk of type 2 diabetes. *BMJ Open* 2017; 7(1): e014267. doi: 10.1136/bmjopen-2016-014267. PubMed ID: 28087555.

Yates T, Zaccardi F, Dhalwani N, Davies MJ, **Bakrania K**, Celis-Morales CA, et al. Association of walking pace and handgrip strength with all-cause, cardiovascular and cancer mortality: A UK Biobank observational study. *European Heart Journal* 2017; 38(43): 3232-3240. doi: 10.1093/eurheartj/ehx449. PubMed ID: 29020281.

Henson J, Edwardson CL, Bodicoat DH, **Bakrania K**, Davies MJ, Khunti K, et al. Reallocating sitting time to standing or stepping through isotemporal analysis: associations with markers of chronic low-grade inflammation. *Journal of Sports Sciences* 2018; 36(14): 1586-1593. doi: 10.1080/02640414.2017.1405709. PubMed ID: 29157133.

Yates T, **Bakrania K**, Zaccardi F, Dhalwani N, Hamer M, Davies MJ, et al. Reaction time, cardiorespiratory fitness and mortality in UK Biobank: An observational study. Intelligence 2018; 66(1): 79-83. doi: 10.1016/j.intell.2017.11.006.

Research Articles Under Review/Preparation

Tan MKH, Wong JKL, **Bakrania K**, Abdullahi Y, Harling L, Casula R, et al. Can activity monitors predict outcomes in patients with cardiovascular disease? A systematic review. Open Heart Journal 2018; Under Review.

Collaboration with Omar Jarral (http://www.imperial.ac.uk/people/o.jarral), Imperial College London, Paper Under Preparation.

LIST OF RELEVANT CO-AUTHOR CONFERENCE PROCEEDINGS

The conference proceedings below have arisen from internal and external projects and studies that I substantially contributed to whilst undertaking my PhD.

Oral Presentations

Edwardson CL, **Bakrania K**, Bodicoat DH, Yates T, Healy G, Winkler E. Validation of an automated STATA algorithm developed for isolating waking wear data in activPAL data. Oral presentation: *The International Society for the Measurement of Physical Behaviour: 4th International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM 2015)*, 10 - 12 June 2015, University of Limerick, Limerick, Ireland.

Winkler E, Healy G, Edwardson CL, Bodicoat DH, **Bakrania K**, Yates T, et al. Automated identification of waking wear time in continuously worn activPAL3 data: two algorithms. Oral presentation: *The International Society of Behavioral Nutrition and Physical Activity: 9th International Conference on Diet and Activity Methods (ICDAM 2015)*, 1 - 3 September 2015, Brisbane Convention & Exhibition Centre, Brisbane, Australia.

Poster Presentations

Winkler E, Healy G, Chastin S, Bodicoat DH, Edwardson CL, **Bakrania K**, et al. Automated identification of waking wear time from continuously worn activPAL3 data: a SAS tool. Poster presentation: *The International Society for the Measurement of Physical Behaviour: 4th International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM 2015)*, 10 - 12 June 2015, University of Limerick, Limerick, Ireland.

Rowlands AV, Fraysse F, **Bakrania K**, Yates T, Edwardson CL, Davies MJ, et al. Tapping The Potential Presented By The Gravity Component Of An Accelerometer Signal. Poster presentation: *American College of Sports Medicine (ACSM): 63rd Annual Meeting*, 31 May - 04 June 2016, Hynes Convention Center, Boston, Massachusetts, USA.

CHAPTER ONE: INTRODUCTION AND RATIONALE FOR THE PROGRAMME OF WORK

Chapter Overview

This chapter provides the background and overall rationale for the thesis. It introduces the fundamental definitions of sedentary behaviour and physical activity, discusses a behavioural epidemiology framework that this programme of work follows, gives a brief overview of previous research in this field and highlights the gaps in knowledge, and states the key aims and objectives of this PhD.

Definitions of Sedentary Behaviour and Physical Activity

Sedentary Behaviour

Sedentary behaviour is formally defined as "any waking behaviour characterized by an energy expenditure of ≤1.5 metabolic equivalents while in a sitting or reclining posture" (1). Some common examples of sedentary behaviour include watching television (TV), reading, and using a computer (2). Metabolic equivalents (METs) represent the intensity of an activity as a manifold of the basal metabolic rate (3). In other words, the metabolic equivalent is the ratio of the energy consumption rate of a particular activity to the resting energy consumption rate; where one MET is the energy equivalent expended by an individual while at rest. To standardise the definition across individuals, 1 MET has been set as 3.5 $ml \cdot O_2 \cdot kg^{-1} \cdot min^{-1}$; which is equivalent to 1 $kcal \cdot kg^{-1} \cdot hr^{-1}$) (3). An individual who is lying down and watching TV, an action which requires minimal energy, is said to be at full rest in a sedentary state and corresponds with a MET value of 1.0 (4). On the other hand, an individual participating in a high-intensity sport (e.g. boxing) requires more energy; and therefore, corresponds with a much greater MET value of 12.8 (4). In contrast to the definitions of physical activity (see below), there are no approved or recognised guidelines for defining categories of sedentary time. Thus, expressions such as "low sedentary time" and "high sedentary time" can only be used via data-driven definitions (i.e. percentiles).

Physical Activity

The World Health Organisation defines physical activity as "any bodily movement produced by skeletal muscles that requires energy expenditure" (5). The total amount of energy expenditure related with physical activity depends on the duration, frequency and intensity of muscular movement; and the amount of energy expended by an individual is measured as a continuous variable (ranging from low to high). Physical activity can be classified into three intensity groups: light (approximately 1.5 to 3 METs), moderate (approximately 3 to 6 METs) and vigorous (approximately >6 METs) (4); and adults are recommended to engage in ≥150 minutes of moderate-intensity physical activity (MPA) or ≥75 minutes of vigorous-intensity physical activity (VPA) every week (in bouts of ≥10 minutes) (5-7). Universally, those that meet the physical activity guidelines are referred to as 'physically active'. In contrast, 'physically inactive' is commonly used to define individuals who fail to meet the recommendations stated above. Consequently, under these guidelines, it is plausible for an individual to undertake non-sedentary activities (e.g. light walking), while still in principle be classified as 'physically inactive'. Furthermore, although individuals can be both sedentary and physically inactive, it is possible for the status of 'physically active' and high sedentary time to coincide (e.g. an office worker who runs to and from work for 30 minutes every day (thus, meeting the physical activity guidelines), but then remains seated at a desk during working hours and spends majority of the evening watching TV).

Associations with Health

There is increasing evidence that sedentary behaviour is independently associated with several health outcomes including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), depression, and all-cause mortality (8-14). This has important implications given that adults spend most of their waking hours (~55% to ~70%) sedentary (15-18). Furthermore, it is known that higher levels of physical activity, particularly moderate-to-

vigorous-intensity physical activity (MVPA), are associated with improved health, often in a dose-response manner (5-7). Sedentary behaviour and MVPA share a weak inverse relationship and it is possible for an individual, over the course of a day, to have high levels of physical activity and still accumulate large amounts of sedentary time (19-21). Simultaneously, this suggests that high levels of sedentary behaviour and low levels of MVPA symbolise discrete risk factors of poor physical health. Nevertheless, even though the sedentary behaviour and physical activity research area has made substantial developments and progressions over the recent years, explorations in this field are still at an early stage. The following sections will demonstrate that there are still several inconsistencies, limitations and missing gaps in the evidence. However, before these are discussed, a behavioural epidemiology framework proposed by Sallis and colleagues (22), which forms the main motivation for this programme of work, will be presented.

Behavioural Epidemiology Framework

Sallis and colleagues advocated a systematic behavioural epidemiology framework to classify phases of research on health promotion and disease prevention (22). The framework consists of five phases as described below:

Phase 1: Establish links between behaviours and health

Phase 2: Develop methods for measuring the behaviour

Phase 3: Identify factors that influence the behaviour

Phase 4: Evaluate interventions to change the behaviour

Phase 5: Translate research into practice

It is suggested that each phase of the behavioural epidemiology framework builds upon the previous phases. Phases 2 and 3 develop a fundamental understanding of the

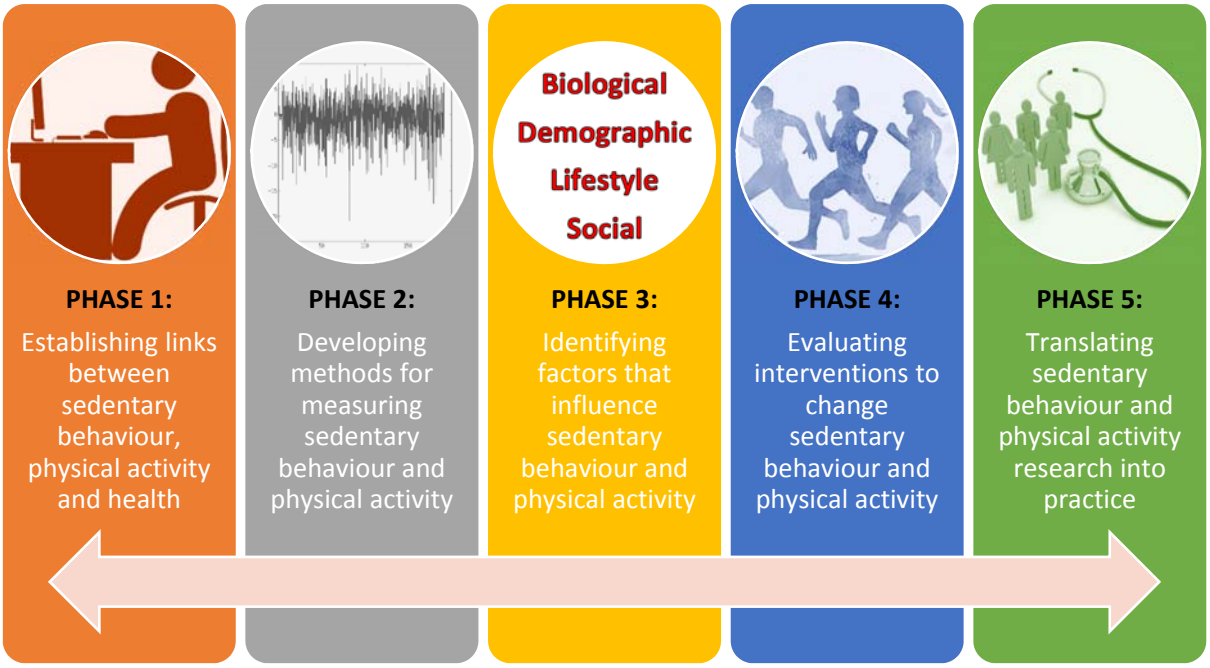
behaviours identified as important to health in Phase 1 by traditional epidemiological research. Based on research in Phase 3, Phase 4 targets groups at risk and assesses theoretically- and empirically-based methods to behaviour change. Phase 5 makes the need to diffuse interventions found to be effective in Phase 4 explicit. However, this seemingly linear sequence also includes several intricate feed-back and feed-forward features. For example, epidemiological evidence from Phase 1 can directly influence public health policies (Phase 5). The availability of valid and reliable measures of the behaviour (Phase 2) can directly affect decisions about the feasibility of field assessments (Phase 4). Furthermore, politically-driven health policy initiatives (Phase 5) can fuel new research at some or all of the preceding phases in the epidemiology framework. Probably the most compelling non-linear element is that as behaviours are better defined and measured (Phase 2), relationships to health outcomes (Phase 1) can be specified more explicitly through analyses using more advanced measures or sub-element of behaviours.

The framework described and proposed by Sallis and colleagues provides an operational definition of behavioural epidemiology, and allows for a more systematic approach to developing, assessing, and disseminating behaviour change interventions to improve public health. Given the central role of behaviours in the aetiology of the chief sources of morbidity and mortality, following a framework such as the one suggested by Sallis and colleagues can help restructure health behaviour research and make a significant contribution to improving the health of the general population.

This framework can be applied to the field of sedentary behaviour and physical activity research (see Figure 1). The aim of my PhD is largely focussed around increasing knowledge in Phase 1 and Phase 2. Phase 1 of the behavioural epidemiology framework is based around establishing associations between behaviours and health. Basic epidemiological studies report relationships between behaviours and health, and such documentation provides a foundation for proceeding to the subsequent phases of behavioural epidemiology research. Beyond simply reporting that a relationship exists, research in Phase 1 also includes dose-response associations between the behaviour and

health outcomes. Evidence from Phase 1 research plays a key role in the derivation of public health guidelines. An example would be formulating guidelines for saturated fat intake based on the dose-response association between the amount of saturated fat in peoples' diets and the risk of coronary heart disease. In Phase 1, this PhD increases knowledge by further examining the associations of physical activity and sedentary behaviour with physical health and mortality, and via investigating novel relationships with cognitive function. Whilst the majority of the evidence has concentrated on cardiometabolic health and mortality, the potential applicability to cognitive health has important public health implications that need probing further. Phase 2 of the behavioural epidemiology framework is based around deriving methods for measuring behaviours. Accurate measures are important for all stages of research and this phase involves establishing the reliability and validity of existing measures, developing new measures, and testing new tools. Using improved behavioural measures to refine results of Phase 1 studies is an example of how various phases can have reciprocal linkages. In Phase 2, this PhD increases knowledge by establishing the reliability and validity of existing open source measurement precision algorithms. This has great utility for future epidemiological studies such as the United Kingdom (UK) Biobank (23). These are covered in greater detail in the next section.

Figure 1 - Behavioural epidemiology framework applied to the sedentary behaviour and physical activity research field



Overview of Previous Research and Gaps in Knowledge

This section gives a brief overview of the previous research conducted in this field and highlights the gaps in knowledge associated with Phase 1 and Phase 2 of the behavioural epidemiology framework that this thesis will address.

Cardiometabolic Health (Phase 1 of Behavioural Epidemiology)

Previous research has largely focused on the independent associations of total physical activity, MVPA, light-intensity physical activity (LIPA) and sedentary time on health (8-14, 19-21, 24-32), rather than the interplay between these constructs. Consequently, the daily equilibrium between physical activity and sedentary behaviour, and the pooled relationship they share with biomarkers of health, is not fully understood. Some studies have suggested that regular MVPA may offset some of the detrimental consequences of a habitually sedentary lifestyle (33-38); and if tested and confirmed in a large national

sample, this would be a clinically important message for a significant proportion of the population who may be concerned about the amount of time they spend sitting.

The Health Survey for England (HSE) database allows for the robust examination of this research topic (17, 39, 40).

Mortality (Phase 1 of Behavioural Epidemiology)

Diabetes prevention has focused on the promotion of established health behaviours, including physical activity, with strong evidence of efficacy (41). However, whilst the effects of promoting physical activity and other lifestyle factors on reducing the risk of T2DM are well-known in those at high risk of T2DM, the strength of association with all-cause mortality is less clear. To my knowledge, only one study has quantified the associations between objectively measured physical activity and mortality/morbidity outcomes in those at high risk of T2DM (42), whilst no studies have examined associations with objectively measured sedentary time. The latter is important given the mounting evidence that sedentary behaviour is associated with poor health and has been advocated as an important behavioural target in the prevention of diabetes (43).

The Walking Away from Type 2 Diabetes database allows for the robust examination of this research topic (44).

Cognitive Function (Phase 1 of Behavioural Epidemiology)

Much of the physical activity and sedentary behaviour research has focused around physical health, with little research carried out around cognitive health. However, cognitive health and function is linked to a range of chronic diseases such as dementia, CVD, and T2DM (45, 46). As populations are now living longer, dementia represents a huge burden on health services worldwide with a current prevalence of nearly 48 million cases (47). It costs the global economy over $600 billion annually and the total number of cases is projected to almost triple by 2050 to 136 million (47). Thus, managing dementia

has become a key health and social priority in adults (47). Cognitive decline throughout adulthood is a recognised consequence of biological ageing, with accelerated cognitive decline resulting in dementia (45). Currently, there are no effective long-term pharmacological therapies for the prevention of cognitive decline or the treatment of dementia. Therefore, identifying potentially modifiable risk factors of cognitive decline is a key priority. Engaging in healthy lifestyle practices, including physical activity, have been associated with a reduced risk of dementia and its symptoms, such as cognitive impairment (48, 49), suggesting a potential role for lifestyle therapies. Indeed, supporting the observational associations, emerging physical activity intervention studies have shown changes to the structure and function of the brain (50-54).

Along with physical activity, engaging in sedentary behaviour could also be an important determinant of poor cognitive function. A recent systematic review summarised the current body of evidence on the associations shared between sedentary behaviour and cognitive function (55). The review suggested that although sedentary behaviour was negatively associated with cognitive function, the relationship between the two is complex, and is likely to be influenced by the type of sedentary behaviour assessed. Therefore, future research should focus on determining how different sedentary behaviours are associated with cognitive function. Limited observational research has indicated that TV viewing is inversely associated with cognitive health (56-59). However, different sedentary behaviours may have different associations, with some evidence of computer/internet use linked to cognitive improvement (57-60). In addition, most of the existing data have emerged from relatively limited cross-sectional findings (58-60); therefore, this warrants investigation in large-scale population-based studies with prospective data. Furthermore, it is unknown whether the associations between sedentary behaviours and cognitive function are modified by the same factors that have been shown to modify the associations with metabolic health (such as cardiorespiratory fitness), or whether sedentary behaviours combined with other lifestyle factors act as determinants of cognitive health.

The UK Biobank database allows for the robust examination of these research topics (23).

Measuring Sedentary Behaviour and Physical Activity (Phase 2 of Behavioural Epidemiology)

Along with MVPA, even engaging in LIPA (e.g. standing and light walking) has been shown to have beneficial effects on health (19, 28, 61). Therefore, accurately identifying and distinguishing between sedentary behaviour and LIPA is important. Conventionally, self-reported methods (e.g. usage of diaries, interviews, questionnaires and surveys) have regularly been employed in sedentary behaviour and physical activity research. These are convenient, come at a low-cost, allow for rapid data collection, have low burden on the participant, and are widely accepted in the academic community. However, although self-reported measures of behaviour are beneficial in some contexts, particularly when wanting to understand the impact of specific types of behaviours on health, they are prone to recall and response bias (with physical activity being often overestimated) (62, 63). Furthermore, due to the recent surge in the development and utilisation of objective measurement tools (e.g. devices such as accelerometers, pedometers, etc.) in this field, self-reported methods are becoming less common. Tri-axial accelerometers, which quantify the acceleration and deceleration in orthogonal directions of three-dimensional space, have gained a reputation as the preferred method of collecting objective measurements of physical activity and sedentary behaviour data in health research (64, 65). These devices are capable of accumulating large amounts of acceleration data (usually over an adjustable sampling frequency range) that can be translated into applicable physical activity and sedentary behaviour parameters (i.e. duration, frequency and intensity) (66).

Accelerometers have historically provided data in some form of ‘counts’ - an aggregate measure of the intensity and magnitude of accelerations over a given time epoch (67-69). Count-based systems are straightforward to operate and do not expend substantial amounts of computational memory. However, counts are produced via proprietary

algorithms which are developed and patented by the manufacturers of these monitors (entailing different amplifiers, filters, frequencies, etc.) (67-72). Therefore, even if the same reference acceleration signal is being measured, different devices can produce diverse outputs (68, 69). This makes it difficult to equate data between different accelerometer brands; and thus, problematic to compare results from studies that have employed different devices. However, due to the significant improvements in technologies over the last few years, raw acceleration data can now be measured and stored at high frequencies, with no need to summarise into proprietary count-based epochs (68-77). Consequently, there is a necessity for the analysis of raw acceleration data using approaches that can be understood and used by all. Furthermore, accelerometers were traditionally worn on the hip; however, wrist-worn accelerometry has recently emerged and is now also being used in large national health surveys (e.g. UK Biobank and National Health and Nutrition Examination Survey (NHANES) series) (23, 78). Therefore, it is essential to also develop analytical methods which are appropriate for use with data from wrist-worn monitors and can be applied to existing methods for processing raw acceleration data.

Experimental data from a laboratory setting allows for the robust examination of this research topic.

Aim of PhD

The overall aim of this project was to harness epidemiology for generating new hypotheses for experimental investigation via further examining the associations between measures of physical activity, sedentary behaviour and health (phase 1 of behavioural epidemiology), and explore novel approaches for analysing physical activity and sedentary behaviour data more effectively (phase 2 of behavioural epidemiology). The specific objectives are presented below.

Key Objectives of PhD

Phase 1 of Behavioural Epidemiology: Establish Links between Behaviours and Health

- To examine the associations of:
    - Objectively measured physical activity and sedentary time with markers of cardiometabolic health (Chapter Three; 2008 HSE data; research article published)
    - Objectively measured physical activity and sedentary time with all-cause mortality (Chapter Four; Walking Away from Type 2 Diabetes data; research article published)
    - Self-reported sedentary behaviours with cognitive function (Chapter Five; UK Biobank data; research article published)
        - assess whether these associations are modified by cardiorespiratory fitness (CRF) (Chapter Five; UK Biobank data; research article under review)
    - Lifestyle factors with cognitive function (Chapter Five; UK Biobank data; research article under review)

Phase 2 of Behavioural Epidemiology: Develop Methods for Measuring the Behaviour

- To examine novel approaches of analysing raw acceleration data from hip- and wrist-worn accelerometers (Chapter Six; experimental data from laboratory; research article published)

In addition, Chapter Two summarised and critically assessed the three epidemiological databases (2008 HSE, Walking Away from Type 2 Diabetes, and UK Biobank) used within this PhD. This thesis was specifically tailored to harness my skills as a statistician and extend my training in the physical activity and sedentary behaviour research area. The objectives above were explicitly chosen to develop the key methodological approaches that a lifestyle researcher needs to gain expertise in the Phases 1 and 2 of the behavioural

epidemiological framework. The range of statistical methods applied in this PhD are shown below (see Table 1).

Table 1 - Statistical methods applied in PhD

PhD Thesis Chapter	Type of Study	Type of Data	Statistical Methods
Chapter Three: Analysis of Epidemiological Data: 2008 HSE Data	Observational	Cross-Sectional (Population-Level Survey Data)	Linear Regression Modelling
Chapter Four: Analysis of Epidemiological Data: Walking Away from Type 2 Diabetes: A Cluster Randomized Controlled Trial: Primary Care Data	Observational	Prospective (Regional-Level Primary Care Data)	Cox Proportional Hazards Regression Modelling Split Cox Proportional Hazards Regression Modelling
Chapter Five: Analysis of Epidemiological Data: UK Biobank Data	Observational	Prospective (Population-Level Cohort Data)	Logistic Regression Modelling Linear Regression Modelling Interaction Regression Modelling Mixed-Effects Logistic and Linear Regression Modelling Poisson Regression Modelling
Chapter Six: Analysis of Physical Activity and Sedentary Behaviour Data: Raw Acceleration Data	Experimental	Cross-Sectional (Laboratory Data)	Logistic Regression Modelling Receiver-Operating-Characteristic Analysis Leave-One-Out-Cross-Validation

Training, Development and Experience

By using multiple different statistical techniques to address the listed objectives above, I believe I have matured and have been trained into a competent and independent researcher specialising in the epidemiology of sedentary behaviour and physical activity. This project has allowed me to identify gaps in knowledge, conceptualise and develop research ideas, apply for datasets from national health governing bodies and resources, derive statistical analysis plans, clean and manage study datasets, execute analyses, interpret and write-up findings in a clear and logical manner, draft and submit abstracts for national and international conferences and meetings, draft and submit research articles for publications in peer-reviewed academic journals, respond to comments from peer-reviewers, liaise with journal editorial teams until the final publication of findings, and present results and disseminate research at local, national and international conferences and meetings. Consequently, through this PhD, I have achieved five research articles in peer-reviewed journals as first author (a further two are currently under review) and seven research articles in peer-reviewed journals as a co-author (a further two are currently under review/preparation). For more details, see Appendix One: Author Contribution to Overall Programme of Work and Appendix Two: Awards. However, more importantly, I have gained substantial and vital experience in conducting epidemiological research, utilising a wide range of statistical methods and tools (e.g. regression analysis, survival analysis, longitudinal analysis, etc.), analysing several large and intricate datasets, developing computer software skills (progressed into a proficient user of Stata: Data Analysis and Statistical Software [Stata Corporation, Texas, United States of America (USA)] and R Statistical Software [R Foundation for Statistical Computing, Vienna, Austria]), and writing and debugging software code. I believe that these skills are indispensable for my future as an epidemiologist in health research. In addition to the academic benefits, the PhD has also provided me the opportunity to train and develop myself. I have had the opportunity to teach statistics and epidemiology to first year medical students, act as a peer reviewer for several academic journals (e.g. British Journal of Sports Medicine, International Journal of Epidemiology, Journal of Sport and Health Science, Medicine,

etc.), and gain substantial collaborative experience via sharing knowledge with both statisticians and non-statisticians.

CHAPTER TWO: CRITICAL APPRAISAL OF THE EPIDEMIOLOGICAL DATABASES

Chapter Overview

This chapter summarises and critically appraises the epidemiological databases (2008 HSE, Walking Away from Type 2 Diabetes, and UK Biobank) used within this PhD. Comprehensively, it discusses the strengths and limitations of each dataset and the consequences of having issues such as a low response rate and missing data.

2008 HSE

Background

Running since 1991, the HSE is a series of cross-sectional national annual epidemiological surveys designed to examine the health and well-being of people living in England (17, 39, 40). Each survey in the series includes primary questions and components such as anthropometric and blood pressure measurements, the analysis of blood and saliva samples, and detailed questions on specific subjects that vary from year-to-year (17, 39, 40). The 2008 HSE was centred on physical activity and fitness. Here, participants were asked to recall their physical activity over recent weeks, and objective measures of physical activity and fitness were also obtained from a subsample of individuals (17, 39). This thesis used data from the 2008 wave including the accelerometer assessed physical activity and sedentary behaviour data. The database is available to researchers via application to the HSE (17, 39, 40).

Design and Data Collection

Similar to previous surveys in the HSE series, the 2008 wave was designed to generate a representative sample of the general population of any age living in private households in England. It adopted a multistage stratified random sampling framework to ensure that households were sampled proportionately across the nine government office regions of England (North East, North West, Yorkshire and the Humber, East Midlands, West Midlands, East of England, London, South East, and South West) (17, 39). Here, a random sample of primary sampling units, based on postcode sectors, was first selected, with probability proportional to the total number of addresses within the primary sampling unit. On average, a postcode sector contains approximately 3,000 addresses, and postcode sectors with less than 500 addresses were pooled with neighbouring sectors to form a primary sampling unit in order to prevent the addresses being too clustered (17, 39). Stratified sampling was then carried out by first ordering the list of primary sampling units by local authority and socioeconomic group, and then sampling at fixed intervals from a random starting point (17, 39). For each

selected primary sampling unit, a random sample of addresses from the postcode address file (a database that contains all known postcodes) was then drawn (17, 39). Using these methods, a random sample of 16,056 addresses were selected from the postcode address file (1,176 postcode sectors were designated, and 13 or 15 addresses were issued in each, depending on whether or not the sample point was in the accelerometry subsample) (17, 39). Each individual within a selected household was eligible for inclusion (up to a maximum of 10 participants), and at the addresses that were eligible for accelerometry (randomly selected), up to two participants were selected and asked to wear an accelerometer for a week to provide an objective measure of physical activity. Further details can be found elsewhere (17, 39). Before a trained interviewer visited, a letter stating the aims and purposes of the survey was sent to each sampled address. At the visit, computer-assisted interviews were carried out. Participants were asked a series of questions on general health, alcohol consumption, smoking, and fruit and vegetable consumption, as well as questions about physical activity. Height and weight measurements were taken at the end of the interview (17, 39). Nurse visits were offered to all participants in the sample. At the nurse visit, questions were asked about prescribed medication, vitamin supplements and use of nicotine replacements. Nurses obtained BP measurements, hip and waist readings, non-fasting blood samples (for the analysis of total and HDL-cholesterol and HbA1c), and saliva samples (for the analysis of cotinine, a derivative of nicotine). Nurses also administered a self-completion booklet about eating behaviours (17, 39). In households selected for the accelerometer subsample, nurses established eligibility (exclusion criteria: aged <4 years, pregnant (self-reported), confined to bed or in a wheelchair, recent abdominal surgery or any health problems that would make a belt round the waist uncomfortable, or latex allergy (the belt on which the accelerometer was worn contained latex)), and guided the participants through the process and conducted a timed step test to assess individual fitness levels (17, 39). Participants provided written informed consent and ethical approval for the 2008 HSE was obtained from the Oxford A Research Ethics Committee (reference number 07/H0604/102). Further details can be found elsewhere (17, 39).

Response Rates

Response to the 2008 HSE can be quantified in two ways; at a household level and at an individual level. Interviews were held in 9,191 households with 22,623 participants (15,102 aged 16 years or over, and 7,521 aged between 2 and 15 years) from the general population with a household response rate of 64% (17, 39). The individual response rate was 58% for participants aged 16 years or over (55% for males, 61% for females), and 63% for participants aged between 2 and 15 years (62% for males, 63% for females) (17, 39). Solely focusing on the participants aged 16 years or over, the individual response rates at various stages of the data collection process were as follows: interview visit (58%), height measured (52%), weight measured (50%), nurse visit (41%), waist and hip measured (40%), blood pressure measured (40%), saliva sample obtained (39%), blood sample obtained (29%) (17, 39). In households that were identified for the accelerometer subsample, 4,507 participants aged 16 years or over (1,998 males and 2,509 females) were selected for accelerometry (17, 39). Of these, 21% of males and 20% of females declined to wear an accelerometer, and 4% of males and 6% of females were ineligible. Even though a substantial proportion of participants agreed to wear the accelerometer, faulty devices meant that there were unusable data for 18% of males and 20% of females. In a small number of cases, some data were recorded but they were of spurious nature. Overall, 53% of men and 51% of women provided eligible data for at least one day, while 49% of men and 46% of women wore the accelerometer for at least 10 hours per day on at least four days. The proportion wearing the accelerometer for the full seven days was 31% in males and 27% in females. Younger participants (aged between 16 and 24 years) were the least likely to wear the accelerometer for seven days. The proportion complying increased with age, with the highest level observed in those aged between 55 and 74 years, although this dropped slightly in those aged 75 years or over. Further details can be found elsewhere (17, 39).

Strengths and Limitations

The HSE study has several strengths. For example, even though it only provides baseline data, the multifaceted stratified random sampling procedure attempts to

draw a nationally representative sample using primary sampling units, clusters and survey weights that adjust for household selection, non-response bias, age, sex and regional profiles (17, 39, 40). These data can be linked to the cancer and mortality registers as well as the Hospital Episode Statistics (HES) database in order to study longitudinal health outcomes. Moreover, via linkage, longitudinal analyses can be conducted in sizeable cohorts by combining the baseline data from the different survey years. These types of analyses have been well documented in the literature (79-82). The HSE database provides abundant information on a broad range of demographic, socioeconomic, and health-related parameters (including the use of interviewer and nurse collected BMI, waist circumference, total cholesterol, HDL-cholesterol and HbA1c data, and specifically in the 2008 cohort, objectively measured physical activity and sedentary behaviour data). This makes it suitable for statistical modelling with different markers of health as outcomes. However, the HSE study also has some limitations. Key restrictions include the cross-sectional design, low response rates, the relatively small sample size for a national survey (relating specifically to the accelerometer cohort i.e. only a small fraction of the total participants was asked to wear an accelerometer), and the ethnically heterogeneous White population (except for survey years 1999 and 2004 where ethnic minority groups were the key focus) (40). Furthermore, the survey does not cover the small proportion of households living at addresses that are not on the postcode address file (<1%) (17, 39, 40). Individuals living in institutes or communal establishments (e.g. nursing and residential homes), who are likely to be older and on average in inferior health than those living in private households, are also not covered by the survey (17, 39, 40). In addition, participants are excluded if they are unable to give consent or understand the survey questions and provide comprehensible answers. This is mainly due to the mental disorders, disabilities, or insufficient knowledge of the English language (17, 39, 40). These factors can add selection bias and misrepresent the population since the cohort generated is more likely to be healthier and English speaking. The latter is particularly important as this could mean that the participants in the database are more educated and possibly in better jobs. The English language element could also explain the predominantly White population in the study. These limitations should be kept in mind

when interpreting any findings from these data, especially when considering the Health Survey's account of the population's health.

The two key foundations of bias in surveys arise from a) the selection of the sample and b) non-response (83). The only way to eradicate bias from the selection of the sample is to take a random sample in which every individual has an equal chance of being included (83). Moreover, the only way to make sure that the response is unbiased is to obtain a 100% response rate (83), but this is almost impossible to achieve in practice. Non-response can disintegrate the advantages of a random sample; and the response rate can have a direct impact on the associations observed between the different variables in a study. For example, consider the following hypothetical scenario. Suppose that 50% of the total 'population' of 2,000 children in a school prefer a new lunch menu. A survey that attempts to collect data from all 2,000 children has a response rate of 30% from the 1,000 children who are in favour of it, and a 40% response rate from the 1,000 children who are not in favour of it. The observed result is that 300 out of the 700 children prefer the new menu (43% (95% CI: 39.2%, 46.6%)). Here, not only is the true prevalence of children who prefer the new menu underestimated, but it also lies outside the observed confidence interval. Now, if the response rates were higher, for example, 80% and 75% for the 1,000 children who are in favour and the 1,000 children who are not in favour, respectively; the observed prevalence would equate to 51.6% (95% CI: 49.1%, 54.1%). Here, the estimate is much closer to the true value of 50%; which also falls between the observed confidence interval. This simple example highlights the problems associated with low response rates in studies and how they can produce biased estimates. In addition, associating biased estimates with one another (e.g. a biased prevalence estimate of children who prefer the new menu and a biased prevalence estimate of the number of boys) can further increase the error and lead to inaccurate conclusions. Therefore, data from such studies should be interpreted with care. Note, based on the response rates of the epidemiological studies used within this PhD, not only is this applicable to the data within the 2008 HSE cohort (particularly because of the decreasing response rates over the various stages of the study (i.e. from the individual stages (interview, nurse, etc.) to the accelerometer stage, etc.)), but it is also directly relevant to the data within the

Walking Away from Type 2 Diabetes and UK Biobank cohorts (see later sections in this Chapter).

In the 2008 HSE database, the household response rate was 64% (17, 39). This can be considered low given that the HSE is a nationally representative survey of the general population. The response rate was highest amongst households living in detached houses (68%), and lowest amongst households living in flats on the fourth floor or above (54%) (17, 39), suggesting that affluent households may have been overrepresented here. Furthermore, the household response ranged from 54% (London) to 78% (North East) (17, 39), which meant households from the capital city were underrepresented here. Similarly, the individual response rates at the different data collection stages can also be considered low [interview visit (58%), height measured (52%), weight measured (50%), nurse visit (41%), waist and hip measured (40%), BP measured (40%), provided saliva sample obtained (39%), blood sample obtained (29%)] (17, 39). There were several reasons for missing data. For example, the inability or refusal to answer specific questions, the refusal to cooperate in an entire section of the survey (such as the nurse visit (thus, no waist, hip, BP, saliva, or blood data) or a self-completion questionnaire), and situations where the question was not valid for the participant (17, 39). Missing data are associated with numerous issues; for example, low statistical power, low representation of the population, and biased estimated parameters. Each of these could affect the cogency of the data; and therefore, lead to biased inferences. In order to minimise the effects of non-response and reduce any systematic bias from the missing data, weighting the data is an option; however, this method can still be problematic because it assumes that the participants who responded were similar to those that did not respond. This might not always be the case; and therefore, this assumption could again lead to erroneous findings. Moreover, since only a small proportion of these participants took part in the accelerometry study, the generalizability of the cohort was further reduced, and the data analysed might not truly represent the national population. Even though the complex survey strategy was controlled for, this is a relevant point when considering analyses that examined the associations between accelerometer assessed physical activity and sedentary behaviour data (e.g. the smaller cohort) and outcomes with

large numbers of missing data (e.g. blood data (HDL-cholesterol, total cholesterol, and HbA1c)); and therefore, these models need to be interpreted with caution.

Consequently, all of these factors together (in particular, the low response rates, the participant exclusion criteria, and the small accelerometer cohort) can introduce bias and have implications for the interpretation of the observed associations between physical activity, sedentary behaviour and cardiometabolic health (Chapter Three). Accordingly, these limitations should be kept in mind when interpreting any findings from these data.

Walking Away from Type 2 Diabetes

Background

The Walking Away from Type 2 Diabetes study was a trial that examined whether a lifestyle intervention programme, based on a brief pragmatic structured education programme with minimal ongoing support, could promote continued long-term increases in physical activity in those identified with a high risk of T2DM in a primary care setting (44, 84). Compared with control conditions, the trial found modest increases in objectively measured ambulatory activity after 12 months; however, the results were not sustained over 36 months (84). Mortality data were obtained for participants who consented to have their records followed-up. This thesis used the trial and mortality data as a secondary epidemiological analysis of the study.

Design and Data Collection

The Walking Away from Type 2 Diabetes trial was a cluster randomized controlled trial running for 36 months undertaken at the general practice level (44, 84). In order to detect a difference in change in ambulatory activity of 2,000 steps/day at the end of the trial between the control arm (usual care) and intervention arm (three-hour Walking Away structured education programme with ongoing annual support), sample size calculations indicated that eight general practice clusters, with 90 individuals in each cluster, would be required (44, 84). However, after taking into account any potential dropouts, 10 clusters would be appropriate. Between 2009 and 2010, after assessing eligibility, 10 general practices from urban and rural locations across Leicestershire, UK were recruited via dissemination at local diabetes training events, presentations at general practice meetings, and email invitations (84). Of these, 5 were randomized to the control arm and 5 were randomized to the intervention arm (84). Individuals at an increased risk of non-diabetic hyperglycaemia or undiagnosed T2DM were identified for recruitment within each practice using the Leicester Practice Risk Score (44, 84-86), and those scoring above the 90th percentile of calculated risk were sent an invitation letter and a patient information sheet by a member of their general

practice (44, 84). Individuals who could not walk, had a terminal illness, or were on any steroid medications (due to any potential confounding endocrinological effects) were not invited to take part in the trial (84). Between 2010 and 2011, eligible individuals wishing to participate were recruited over an appointment (44, 84). At baseline, participants provided detailed data on anthropometrics, biochemical markers, dietary, demographics, health-related quality of life, physical activity (self-reported and objectively measured using an accelerometer), anxiety and depression, and perceptions and perceived knowledge of diabetes risk (44, 84). Participants were followed-up at 12, 24 and 36 months. Mortality data were obtained from ONS via application to HSCIC for those who consented at baseline to have their records followed-up in the future. All participants provided written informed consent and the trial was approved by the Nottingham Research Ethics Committee, UK. Further details are available elsewhere (44, 84).

Response Rates

Overall, 3,769 individuals (control arm: n = 1,558; intervention arm: n = 2,211) scored above the 90th percentile of calculated risk and were invited to take part (84, 86). Of these, 833 (22.1%) eligible individuals responded, consented and were recruited; however, 25 were excluded because they were diagnosed with T2DM at baseline, leaving 808 (21.4%) participants in the trial (control arm: n = 385 (24.7%); intervention arm: n = 423 (19.1%)) (84, 86). After 12, 24, and 36 months, 696 (137 (16.4%) missing since baseline), 645 (188 (22.6%) missing since baseline), and 624 (209 (25.1%) missing since baseline) participants attended, respectively (84). In the control arm, after 12, 24, and 36 months, 339 (46 (11.9%) missing since baseline), 319 (66 (17.1%) missing since baseline), and 316 (69 (17.9%) missing since baseline) participants attended, respectively (84). In the intervention arm, after 12, 24, and 36 months, 357 (66 (15.6%) missing since baseline), 326 (97 (22.9%) missing since baseline), and 308 (115 (27.2%) missing since baseline) participants attended, respectively (84). Here, missing data occurred if participants died, withdrew from the trial, or were lost to follow-up. Of the 833 participants that were recruited at baseline, 712 (85.5% (18.9% of those invited)) consented to have their records followed-up for mortality status, and 683 (82.0%

(18.1% of those invited)) also provided valid accelerometer data. Further details can be found elsewhere (84).

Strengths and Limitations

The Walking Away from Type 2 Diabetes database has several strengths, notably the randomized trial design, primary care feature, high risk population, objectively measured physical activity data, annual follow-up of participants over three years, and linkage to mortality status. However, there are some limitations. A response rate of 22.1% can be considered low; and as discussed in detail earlier in the chapter, this can significantly affect the representativeness of the data (i.e. the findings are only characteristic of the individuals who take part - making it difficult to generalise the results to the wider population), reduce statistical power, introduce unwanted bias, and produce unreliable findings that must be interpreted with caution. There are several reasons that could explain the low response rate. For example, due to the heavy burden involved in taking part in this clinical trial (repeat visits, blood tests, accelerometer wear, etc.) it is possible that many individuals decided to not participate on this basis. Moreover, the trial was only conducted in Leicestershire, UK, where there is a high prevalence of ethnic minority groups, in particular, South Asians (86, 87). This community has previously been reported to have low awareness and interest in T2DM screening (88, 89); and therefore, they are less likely to participate, even though the increased risk of T2DM is well-known within this group (89). Furthermore, potential participants were only told that they were at a higher risk of T2DM (86), they were not informed of their absolute risk or the prospective benefits of early diagnosis and intervention, factors which could have increased the response rate had they been mentioned. Lastly, only those scoring in the top 10% of calculated risk were invited to take part; whereas the National Institute for Health and Care Excellence (NICE) recommend that the top 50% should be invited for further analysis (90). However, although this would have increased the sample size of the trial, it is likely that this would not have affected or improved the low response rate.

Other limitations include the cluster design at the practice level, which means that there is a higher chance of observing variations between groups at the participant

level. The sample is further limited since only patients registered with these 10 general practices in Leicestershire had a chance of being selected. By design, individuals who were not registered with a practice (e.g. private patients, etc.) or were registered with a practice outside Leicestershire region were missed. This selection bias restricts the sample drawn (in comparison to uninvited individuals, those invited could have different levels of physical activity, etc.), which can affect the observed associations between the measured exposures and outcomes. Moreover, of the 833 participants recruited at baseline, only 712 consented to have their records linked to mortality, and this was carried out after approximately 6 years, with only 26 deaths occurring (see Chapter Four for more details). Although statistical techniques to appropriately handle a low number of events in a Cox proportional hazards regression model exist (91), the missing mortality data on the 121 individuals who did not provide consent for linkage restricted the power of the analysis, which could have consequences on the observed associations. For example, hypothetically, had these participants consented for linkage, then there is a possibility that there would be a higher number of deaths in the data, and consequently, the analysis would be stronger with more robust observed associations. In addition to the low response rate and low number of events, the missing data in the objectively measured physical activity data could further reduce the generalizability and produce biased estimated parameters.

Hence, all of these features together (in particular, the low response rate, the selection bias of the sample, the missing accelerometer data, and the low number of events) can have implications for the interpretation of the observed associations of objectively measured physical activity and sedentary time with all-cause mortality (Chapter Four). For that reason, these limitations should be kept in mind when interpreting any findings from these data.

UK Biobank

Background

The UK Biobank is a large long-term epidemiological study of the middle-aged population living in England, Scotland, and Wales (92-94). The main aim of the study is to advance the prevention, diagnosis and treatment of a wide range of diseases and medical conditions (92-94). Around 0.5 million participants were recruited between 2006 and 2010 and provided detailed health data at baseline (92-94). Around 20,000 adults also provided detailed repeat assessment data between 2012 and 2013, and subsets of participants (all of a different size) also provided additional exposure data (online questionnaires and/or accelerometer assessed physical activity data) between 2011 and 2016 (depending on the exposure data) (95, 96). Furthermore, the UK Biobank data were linked to mortality status (97). This thesis used the baseline data including the exercise test data and the web-based questionnaire data for the follow-up of cognitive function. The database is available to researchers via application to the UK Biobank (23).

Design and Data Collection

At baseline, participants were recruited between 2006 and 2010 via mailing out invitations to those registered with the NHS and living within 25 miles of one of the 22 assessment centres across England, Scotland, and Wales (Edinburgh, Glasgow, Newcastle-upon-Tyne, Middlesbrough, Leeds, Bury, Manchester, Altrincham, Liverpool, Sheffield, Nottingham, Stoke-on-Trent, Birmingham, Oxford, Bristol, Reading, central London, Hounslow, Croydon, Cardiff, Swansea and Wrexham) (92-94, 98). Volunteers who attended an assessment centre completed questionnaires on their lifestyle, environment and medical history, had a wide range of physical measures performed (including an exercise test) and had samples of blood, urine and saliva collected (92-94). The process was replicated between 2012 and 2013 at the repeat assessment centre (Manchester) (95). The additional exposure data included: online 24-hour dietary recall questionnaire (between 2011 and 2012), physical activity data

collected from a wrist-worn accelerometer (between 2013 and 2016), online cognitive function questionnaire (between 2014 and 2015), online 'healthy work' questionnaire (2015), and online mental health questionnaire (2016) (96). All of these data were collected remotely except for the accelerometer data, which were collected via post (96, 99). For the follow-up of mortality, the date and cause of death were acquired from the NHS Information Centre for participants from England and Wales, and from the NHS Central Register, Scotland for participants from Scotland (97). All participants provided written informed consent and the study was approved by the NHS National Research Ethics Service (Ref: 11/NW/0382). Further details can be found elsewhere (92-94).

Response Rates

Around 9.2 million adults were invited to take part in the UK Biobank study (92, 100). Of these, there were approximately 6.5 million non-responders and approximately 2 million responders (100). Around 0.5 million invitations outcomes were unknown and around 0.2 million invitations were undelivered (100). Of the 2 million responders, approximately 0.6 million agreed to take part, but only around 0.5 million attended the assessment centre and gave consent (100). Therefore, overall, this resulted in a low response rate of 5.5% (92, 100). The participation rate was higher in females (6.4% and 5.1% in females and males, respectively), in older individuals (9% and 3% in adults aged ≥60 years and adults aged <44 years, respectively), and in those from better socioeconomic areas (8.3% and 3.1% in adults from the least deprived areas and from the most deprived areas, respectively) (100). The participation rates also showed regional differences; it was lowest in West Scotland (4.3%), followed by London (4.7%), West Midlands (4.7%), North West England (4.7%), East Scotland (8.2%), and then highest in South West England (9.6%) (100). Similarly, the repeat assessment centre data, collected at one centre (Manchester) in around 20,000 participants, were also associated with a low response rate (21%) (95). Furthermore, of the 0.5 million UK Biobank participants at baseline, around 0.3 million individuals provided an email address to allow for the remote follow-up of cognitive function in the future, and of these, approximately 0.125 million complied (101).

Strengths and Limitations

The UK Biobank study has several strengths, notably the large sample size and the broad range of detailed baseline and follow-up data covering various aspects of physical and mental health, which allows for the robust examination of associations between different exposures and outcomes. These data can be broadly grouped into the following areas of interest: cognitive function, early life exposures, family history of illness, general health, lifestyle exposures (including diet, physical activity and smoking), medical history, occupation and sociodemographics, and psychological state (94). In the UK Biobank, in order to develop and identify suitable questions to quantify the exposures in these areas, a review examining the questionnaires previously used in observational studies, clinical trials and population surveys was first implemented (94). In addition, extensive consultations with international experts in each subject area also took place (94). In some cases, validated questionnaires for the topics of interest were too broad to be fully included, or the questions were unsuitable for a general population sample (94). In adapting questionnaires where short scales were unavailable, consideration was given to those questions likely to be reliably reported, straightforward to answer and with a comprehensive range of responses (and this was evaluated in the pilot studies) (94). For most subject areas, the questions selected for inclusion in the UK Biobank questionnaires were explicit and non-contentious (94). Questions about disability, early life exposures, family history, general health, smoking, and sociodemographic factors have previously been utilised in many population studies, and there was little difficulty in selecting validated and important sets of questions that could be readily answered by participants (e.g. leisure time physical activity, sleep duration, walking pace, etc.) (94). For example, dietary data were reported using a food frequency questionnaire (94); and these data have also recently been shown to have good reliability and repeatability (102, 103). The inclusion and exclusion of baseline physical measurements (height, weight, handgrip strength, etc.) at the assessment for UK Biobank were considered with respect to relevance, reliability and resources. With respect to reliability, methods were chosen within a quality assurance framework that involved calibration, maintenance, ease of use,

training, monitoring and data transfer to IT systems. Further details are available elsewhere (94). However, the UK Biobank study also comes with some limitations. For example, even though the sample of 0.5 million participants were recruited efficiently, this was achieved with a response rate of 5.5%, which can be considered low and is subject to selection bias (92, 100, 104). This selection bias arises from the "healthy volunteer" effect (100). For example, based on a number of health-related, lifestyle, physical, and socioeconomic characteristics, the literature reports that the UK Biobank cohort does not represent the general population (100). Overall, UK Biobank participants have better socioeconomic status; are less likely to be obese, to smoke, and to drink alcohol every day; and have fewer self-reported health conditions (100). All-cause mortality and cancer incidence rates are also lower in the UK Biobank data compared to the general population (100). Therefore, on average, the UK Biobank cohort is made up of more health-conscious and healthy volunteers. However, even though the database is not appropriate for examining disease prevalence and incidence rates (although some features, such as the prevalence of pain, have been shown to be similar to levels reported in the general population (105)), it is suitable for investigating the associations between exposures and outcomes due to the large and varied base population. Nevertheless, as mentioned earlier in the chapter, the response rate of a study is important to the credibility of the findings. A low response rate may reduce the statistical power of the data collected, produce biased estimates, and thus, weaken the reliability of any observed associations since the study is only representative of those who replied.

There are also other important limitations. For example, only those living within 25 miles of one of the 22 assessment centres across England, Scotland, and Wales and registered with the NHS were invited to take part (92-94). Hence, the study would automatically miss out on any individuals that are not invited i.e. those that are living outside the radius of an assessment centre (e.g. possible areas include city outskirts and rural locations) and/or those are not registered with the NHS (e.g. private patients, immigrants, refugees, etc.). This again forms a type of selection bias and limits the sample drawn. Similarly, the repeat assessment centre data were collected via only inviting NHS registered individuals living within 25 miles of the Stockport assessment

centre (Manchester) (95); thus, limiting the generalizability of these 20,000 participants. Furthermore, in comparison to the baseline measurements, the additional exposure data were collected at various different time points. For example, the objective measures of physical activity in the subsample of 0.1 million participants were collected between 2013 and 2016; thus, not coinciding at all with the collection of the baseline data (96, 99). Although physical activity levels have been shown to remain stable over time (106, 107), this time lag is still an issue here since some studies have shown that there tends to be a decline in physical activity with age (108, 109). Nevertheless, a 100,000 subsample with accelerometer data would allow for powerful analyses.

Focusing on the key measures used in this thesis (see Chapter Five for more details), there are several reasons for the missing data observed in the cognitive function, sedentary behaviour, exercise test, and online follow-up cognitive function variables. At baseline, there were differences in the numbers of individuals who completed each cognitive assessment due to the tests being abandoned or skipped by participants (particular tests or the whole section), incorporated towards the end of recruitment (e.g. fluid intelligence test), and/or phased out during the early stages of recruitment (e.g. short-term numeric memory test) (110). This resulted in some tests having nearly full data (e.g. visual-spatial memory test (n ~485,000)) or mostly missing data (e.g. short-term numeric memory test (n ~50,000)). In contrast, the sedentary behaviour variables had very low missing data (TV viewing time (n ~495,000), driving time (n ~490,000), and computer use time (n ~490,000). This could be due to the fact that these data were collected using distinct, simple and straightforward questions, which were not too difficult or time-consuming for the participant to answer, so they were less likely to not answer it. Similar to some of the cognitive tests, the exercise test used to derive CRF data was also introduced into the study towards the end of the recruitment; accordingly, these data were only available in a subsample of individuals (n ~68,000); and thus, this variable has a lot of missing data, further limiting the generalizability. As mentioned earlier, the UK Biobank aimed to remotely follow-up on cognitive function in all individuals that provided an email address at baseline (n ~300,000) (101). However, these data were only available in a small proportion of

individuals (n ~ 125,000; note, this was significantly larger than the cognitive data available at the repeat assessment centre and allowed for more powerful analyses), and the method of contact implies that the participants who responded and took part were likely to be those with computer access, internet access, and general computer knowledge; and thus, potentially more computer literate than those who did not respond or provide an email address. Consequently, interpreting any findings using these cognitive data should be done with caution. It is interesting to note that some tests carried out at baseline (e.g. prospective memory test here) were not repeated at the online follow-up (preventing any prospective analysis); however, new tests (e.g. trail making test) were introduced (101, 110). Another important point to note is that in the UK Biobank, majority of the characteristics data were collected using touchscreen questionnaires (111), without any interactions from staff. Thus, anything not understood by the participant would be skipped and result in missing data. In comparison, the majority of the data in the HSE, for example, were collected by the interviewer (17, 39), who could explain and probe the participants for further information, etc.

Therefore, all of these issues together (in particular, the low response rate, the selection bias arising from the "healthy volunteer" effect, and the missing data in the baseline cognitive, CRF and online follow-up cognitive variables) can have implications for the interpretation of the observed associations between different sedentary behaviours, lifestyle factors and cognitive function (Chapter Five). For that reason, these limitations should be kept in mind when interpreting any findings from these data.

CHAPTER THREE: ANALYSIS OF EPIDEMIOLOGICAL DATA: 2008 HSE DATA

Chapter Overview

This chapter is based on the analysis of epidemiological data and uses the 2008 HSE dataset. In brief, this project exploited a nationally representative sample of English adults with accelerometer data. Here, I investigated the relationships between mutually exclusive categories of objectively measured physical activity and sedentary time with markers of cardiometabolic health. The results of this study were presented as an oral talk at the Midlands Academy of Medical Sciences Research Festival (April 2016, University of Leicester, Leicester, UK), and as a poster at the Festival of Postgraduate Research 2016 (July 2016, University of Leicester, Leicester, UK). The findings of this original piece of work were published as a Research Article in BMC Public Health (currently over 35 citations), and gained substantial media coverage. I also used these data to investigate the relationships between MVPA time and body mass index (BMI) with glycated haemoglobin (HbA1c); however, this analysis is not a part of this thesis. Nevertheless, the results of this study were presented as an oral presentation at the International Congress on Physical Activity and Public Health: 6th International Society on Physical Activity and Health (ISPAH 2016) (November 2016, Queen Sirikit National Convention Center, Bangkok, Thailand). The findings of this original piece of work were published as a Research Article in BMJ Open.

Associations of Mutually Exclusive Categories of Physical Activity and Sedentary Time with Markers of Cardiometabolic Health in English Adults: A Cross-Sectional Analysis of the 2008 HSE

Abstract

Background: Both physical activity and sedentary behaviour have been individually associated with health; however, the extent to which the combination of these behaviours influence health is less well-known. The aim of this study was to examine the associations of four mutually exclusive categories of objectively measured physical activity and sedentary time on markers of cardiometabolic health in a nationally representative sample of English adults.

Methods: Using the 2008 HSE dataset, 2,131 participants aged ≥18 years, who provided valid accelerometry data, were included for analysis and grouped into one of four behavioural categories: (1) 'Busy Bees': physically active & low sedentary, (2) 'Sedentary Exercisers': physically active & high sedentary, (3) 'Light Movers': physically inactive & low sedentary, and (4) 'Couch Potatoes': physically inactive & high sedentary. 'Physically active' was defined as accumulating ≥150 minutes/week of MVPA. 'Low sedentary' was defined as residing in the lowest quartile of the ratio between the average sedentary time and the average LIPA time. Weighted multiple linear regression models, adjusting for measured confounders, investigated the differences in markers of health across the derived behavioural categories. The associations between continuous measures of physical activity and sedentary levels with markers of health were also explored, as well as several sensitivity analyses.

Results: In comparison to 'Couch Potatoes', 'Busy Bees' [BMI: -1.67 kg/m^2 (p-value<0.001); waist circumference: -1.17 cm (p-value=0.007); HbA1c: -0.12% (p-value=0.003); high-density lipoprotein (HDL)-cholesterol: 0.09 mmol/L (p-value=0.001)], 'Sedentary Exercisers' [BMI: -1.64 kg/m^2 (p-value<0.001); HbA1c: -0.11% (p-value=0.009); HDL-cholesterol: 0.07 mmol/L (p-value<0.001)] and 'Light Movers' [HDL-cholesterol: 0.11 mmol/L (p-value=0.004)] had more favourable health

markers. The continuous analyses showed consistency with the categorical analyses and the sensitivity analyses indicated robustness and stability.

Conclusions: In this national sample of English adults, being physically active was associated with a better health profile, even in those with concomitant high sedentary time. Low sedentary time independent of physical activity had a positive association with HDL-cholesterol.

Introduction

There is increasing evidence that sedentary behaviour is strongly associated with several health outcomes (8-14). These studies have shown that high levels of sedentary behaviour are associated with a greater risk of morbidity and mortality, which is potentially concerning given that most adults spend the majority of their waking hours (~55% to ~70%) sedentary (15-18). In contrast, it is known that high levels of physical activity, particularly MVPA, are associated with improved health, often in a dose-response manner (5-7). Sedentary behaviour and MVPA share a weak inverse relationship and it is possible for an individual, over the course of a day, to have high levels of physical activity and still accumulate large amounts of sedentary time (19-21).

Previous research has largely focused on the independent associations of total physical activity, MVPA, LIPA and sedentary time on health (8-14, 19-21, 24-32), rather than the interplay between these constructs. Consequently, the mutual relationship they share with biomarkers of health, is not fully understood. Although some studies have started to explore different techniques for quantifying combined connections and patterns of MVPA and sedentary behaviour (36, 68, 112-117), to my knowledge, only one study based in the USA has investigated the associations between categories of physical activity and sedentary time with markers of health (35). Loprinzi and colleagues found that in comparison to adults who engaged in <150 minutes/week of MVPA with high sedentary time (sedentary time > LIPA time), participants engaging in ≥150 minutes/week of MVPA had a more favourable cardiometabolic health profile regardless of their sedentary status (35), suggesting that regular MVPA may counterbalance some of the harmful consequences of a habitually sedentary lifestyle. If verified, this would be a clinically important message for a large proportion of the population who may be concerned about the amount of time they spend sitting.

The aim of this chapter was to use the 2008 HSE (17, 39) dataset to examine and quantify the combined categories of objectively measured physical activity and sedentary time amongst English adults and associate these factors to clinically relevant anthropometric and biochemical markers of cardiometabolic health.

Methods

Design and Population

The HSE is a series of national annual surveys designed to examine the health and well-being of people living in England (17, 39, 40). To obtain a population-based sample, these cross-sectional surveys employ a multistage stratified random sampling procedure with postcode regions acting as the primary sampling unit. The 2008 wave was centred on physical activity and fitness and sampled 22,623 participants [aged ≥2 years]. Six thousand two hundred and fourteen individuals [aged ≥4 years] were randomly selected and approached to wear an accelerometer. Adults [aged ≥18 years] who had accelerometry data available were included in the present study (N = 2,313). Note, the 2008 HSE defined adults as participants aged 16 years or over, whereas in my study, I used the widely accepted classification of 18 years or over. Participants provided written informed consent. Ethical approval for the 2008 HSE survey was obtained from the Oxford A Research Ethics Committee (reference number 07/H0604/102). Further details regarding this sample can be found elsewhere (17, 39). Please see Chapter Two for a critical assessment of the HSE database (response rates, strengths and limitations, etc.).

Measuring Physical Activity and Sedentary Time

Physical activity and sedentary time were measured using an ActiGraph GT1M accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) worn on the right hip for seven consecutive days during waking hours (except water-based activities) (17). The ActiGraph GT1M device was initialised to collect data using one minute epochs. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, UK). Accelerometer counts were used to calculate the time spent in each intensity band: sedentary behaviour (<100 counts per minute (CPM)), LIPA (100 - 1951 CPM) and MVPA (≥1952 CPM) (118). In addition, MVPA time accumulated in bouts of ≥10 minutes, allowing for a two-minute exception in the intensity threshold, was also derived. Non-wear time was defined as any periods of continuous zero counts for ≥60

consecutive minutes (119). A valid day was defined as ≥10 hours (i.e. ≥600 minutes) of wear-time. Adults who provided ≥4 days of valid accelerometer data were included.

Derivation of the Behavioural Categories

For each individual, the average number of minutes/valid day spent in MVPA, LIPA and sedentary behaviour were calculated. Based upon other studies (35, 120), the sedentary behaviour-to-LIPA ratio (average sedentary time ÷ average LIPA time) was used for the classification of sedentary status. Participants were then split into quartiles based on this ratio. Given that the levels of sedentary behaviour in the general population are predominantly high (15-18), a conservative, data-driven approach was undertaken and individuals were classified as 'low sedentary' if they resided in quartile 1 and 'high sedentary' if they resided in quartiles 2, 3 or 4. MVPA status was classified as 'physically active' or 'physically inactive' on the basis of whether or not participants accumulated ≥150 minutes/week of MVPA. This allowed the formation of four mutually exclusive categories (see Figure 2), which are provided with communicative names to aid interpretability: (1) 'Busy Bees': physically active & low sedentary, (2) 'Sedentary Exercisers': physically active & high sedentary, (3) 'Light Movers': physically inactive & low sedentary, and (4) 'Couch Potatoes': physically inactive & high sedentary.

Figure 2 - Observational study (2008 Health Survey for England data): Mutually exclusive categories of physical activity and sedentary time

Mutually Exclusive Categories		Sedentary Status	
		Low [a]	High [b]
Physical Activity Status	Physically Active [c]	'Busy Bees' [d]	'Sedentary Exercisers' [e]
	Physically Inactive [f]	'Light Movers' [g]	'Couch Potatoes' [h]

[a] *Quartile 1 of the ratio between the average sedentary time and the average light-intensity physical activity time*
[b] *Quartiles 2, 3 or 4 of the ratio between the average sedentary time and the average light-intensity physical activity time*
[c] *≥150 minutes/week of moderate-to-vigorous-intensity physical activity*
[d] *Physically active and low sedentary*
[e] *Physically active and high sedentary*
[f] *<150 minutes/week of moderate-to-vigorous-intensity physical activity*
[g] *Physically inactive and low sedentary*
[h] *Physically inactive and high sedentary*

Markers of Cardiometabolic Health

A trained interviewer recorded height (measured to the nearest 0.1 cm using a portable stadiometer) and weight (measured to the nearest 0.1 kilogram using an electronic scale) readings (39). BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres). Waist circumference was defined as the midpoint between the lower rib and the upper boundary of the iliac crest. A nurse measured this twice to the nearest 0.1 cm using a tape and the mean of the two readings was used (39). Non-fasting blood samples were collected by the nurse for the analysis of HDL-cholesterol, total cholesterol and HbA1c. Blood analytes were assayed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, England. Further details regarding these variables can be found elsewhere (39).

Confounders

The following factors, collected by a trained interviewer (39), were also utilised: age (continuous: years), CVD index (categorical: no CVD, one or more CVD), fruit and vegetable consumption (categorical: 0, 1-3, 4-6, 7+ portions/day), ethnicity (categorical: white, non-white), sex (categorical: male, female), smoking status (categorical: never smoked, ex-smoker, current smoker), socioeconomic status (categorical: national statistics socioeconomic classification: high, high-intermediate, intermediate, low-intermediate, low), blood pressure (BP) medication (categorical: no, yes), cholesterol medication (categorical: no, yes), and any other prescribed medication (categorical: no, yes). The 'CVD index' variable was based on the following physician diagnosed cardiovascular conditions/events: abnormal heart rhythm, angina, atrial fibrillation, congenital heart disease, heart attack, heart transplant, heart valve disease, intermittent claudication, stroke, and transient ischaemic attack.

Statistical Analysis

All statistical analyses were conducted using Stata/IC V13.1 (Stata Corporation, College Station, Texas, USA) and controlled for the complex survey strategy employed in the 2008 HSE (primary sampling units, clustering and survey weights) (17, 39) (Stata

commands: ‘svyset’ and ‘svy’). Interview weights, which adjusted for: household selection, non-response bias, age, sex and regional profiles, were applied to produce estimates representing the national population. Nurse weights (generated from interview weights) were utilised to further reduce non-response bias arising from individuals who were interviewed but did not have a nurse visit. Blood weights (generated from nurse weights) were utilised to analyse the blood related variables. To maximise the use of the data, pairwise deletion was used throughout the study for handling any missing data. The weighted prevalence (N; %) of the English adults in each mutually exclusive category were computed. Participant characteristics of the full sample, stratified by each category, were tabulated. Categorical variables were presented as proportions (N; %), whereas the continuous variables were summarised via their means and standard errors (SEs).

The analyses carried out in this chapter involved modelling the associations of objectively measured physical activity and sedentary time with markers of health. The markers of health (outcomes) were all of a continuous nature. All other data (exposures and confounders) were either treated as categorical variables or as continuous variables. Hence, after studying the distributions of all of these data, linear regression analysis was deemed to be the most suitable method to examine the associations between the exposure and outcome variables (Stata commands: ‘svyset’ and ‘svy: regress’) (121). For more details on the distributions of the key outcomes and exposures used in this analysis, see Figure S1 in Appendix Three: Supplementary Material: Supplementary Data. The assumptions of linear regression were assessed (linearity, normality, independence, homoscedasticity, multicollinearity) (121).

Categorical Measures

Univariate linear regression models (Model 1), with ‘behavioural category’ as the independent variable, were fitted for the following assessed health markers: BMI, waist circumference, HDL-cholesterol, total cholesterol, and HbA1c. The ‘Couch Potatoes’ category, representing physically inactive adults with high sedentary time (i.e. the least desirable group), was selected as the reference category. Subsequently,

multiple linear regression models (Model 2) were also fitted for each dependent variable with the following covariates: age, BMI (except in the model with BMI as the dependent variable), CVD index, ethnicity, fruit and vegetable consumption, sex, smoking status, socioeconomic status, and accelerometer wear-time. Models with HDL-cholesterol and total cholesterol as the dependent variable were also controlled for both BP medication and cholesterol medication. Similarly, the model with HbA1c as the dependent variable was controlled for any prescribed medication.

Continuous Measures

The associations between continuous measures of physical activity and sedentary levels with markers of health were also investigated. Multiple linear regression models (Model 2) were fitted for each health marker whilst controlling for the appropriate corresponding confounders as well as both continuous MVPA time and sedentary status (sedentary-behaviour-to-LIPA ratio).

Sensitivity Analysis

The following sensitivity analyses, examining the robustness of the main categorical analyses (Model 2), were also investigated: (1) missing data in the covariates were imputed using the behavioural category means (continuous variables: BMI) and modes (categorical variables: smoking status and socioeconomic status), (2) participants with a CVD index of 'one or more CVD' were excluded, (3) 'Low Sedentary' was defined as residing in the lowest tertile of the ratio between the average sedentary time and the average LIPA time, and (4) participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes. The reasons for selecting these particular sensitivity analyses are as follows. Missing data can introduce bias; and therefore, (1) was implemented to assess whether the missing values in the confounders were having any influence on the observed associations. Furthermore, (2) was carried out to examine the confounding impact of individuals with CVD. After removing these 'unhealthy' participants, the remaining sample of 'healthier' individuals would potentially provide more reliable and unbiased

estimates. Moreover, based on quartiles, the main categorical analysis used a data-driven approach to classify sedentary status. Consequently, in (3), it was important to change this threshold and investigate whether a different cut-off had any effect on the associations. Lastly, it is recommended that the 150 minutes or more per week of MVPA should be carried out in bouts of at least 10 minutes; and hence, (4) was implemented to fully meet these physical activity guidelines.

For each sensitivity analysis, the weighted behavioural category prevalence and health associations were reported.

Statistical Reporting

For each variable of interest, the beta coefficient (β) with 99% confidence intervals (99% CIs) and p-values are reported. All reported p-values are two-sided. To account for multiple comparisons, p-value<0.01 was considered to be statistically significant.

Results

A total of 2,131 adults were available for analysis after retaining only those individuals who provided ≥4 valid days of accelerometer data. The four groups were comprised as follows: (1) 'Busy Bees': N = 385; 18.6%, (2) 'Sedentary Exercisers': N = 743; 36.7%, (3) 'Light Movers': N = 147; 6.8%, and (4) 'Couch Potatoes': N = 856; 37.9%. Table 2 presents the characteristics of the participants.

Table 2 - Observational study (2008 Health Survey for England data): Participant characteristics

Participant characteristics	Sample N = 2,131	'Busy Bees' [a] N = 385; 18.6%	'Sedentary Exercisers' [b] N = 743; 36.7%	'Light Movers' [c] N = 147; 6.8%	'Couch Potatoes' [d] N = 856; 37.9%
Age (years) [e]	50.8 (0.47)	44.8 (0.72)	45.6 (0.72)	49.8 (1.27)	58.9 (0.74)
Cardiovascular disease index [f]					
No cardiovascular disease	2,030 (95.6)	374 (97.4)	707 (95.7)	141 (96.2)	808 (94.6)
One or more cardiovascular diseases	101 (4.4)	11 (2.6)	36 (4.3)	6 (3.8)	48 (5.4)
Ethnicity [f]					
White	2,008 (93.2)	364 (93.6)	691 (92.1)	141 (95.1)	812 (93.8)
Non-white	123 (6.8)	21 (6.4)	52 (7.9)	6 (4.9)	44 (6.2)
Fruit & vegetable consumption (portions/day) [f]					
0	95 (4.5)	25 (6.1)	29 (3.9)	8 (5.5)	33 (4.0)
1 - 3	680 (32.4)	128 (34.8)	221 (30.6)	46 (30.9)	285 (33.4)
4 - 6	968 (45.3)	152 (39.0)	359 (48.0)	69 (48.4)	388 (45.3)
7+	388 (17.8)	80 (20.1)	134 (17.5)	24 (15.2)	150 (17.3)
Sex [f]					
Male	981 (49.3)	172 (48.8)	414 (59.0)	36 (28.8)	359 (43.8)
Female	1,150 (50.7)	213 (51.2)	329 (41.0)	111 (71.2)	497 (56.2)
Smoking status [f]					
Never smoked	993 (47.1)	171 (44.5)	393 (53.7)	57 (37.8)	372 (43.6)
Ex-smoker	726 (32.7)	113 (28.6)	232 (29.5)	51 (34.0)	330 (37.5)
Current smoker	410 (20.1)	101 (26.9)	116 (16.4)	39 (28.2)	154 (18.9)
Missing [g]	2 (0.1)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)
Socioeconomic status [f]					
High	769 (36.7)	80 (20.5)	358 (49.0)	34 (22.5)	297 (35.1)
High-intermediate	276 (12.4)	41 (9.6)	100 (13.2)	22 (13.4)	113 (12.8)
Intermediate	203 (9.5)	48 (12.4)	48 (6.2)	18 (13.7)	89 (10.5)
Low-intermediate	191 (9.3)	52 (15.0)	44 (5.8)	14 (11.4)	81 (9.6)
Low	646 (29.8)	154 (40.1)	177 (23.3)	58 (38.5)	257 (29.5)
Missing [g]	46 (2.3)	10 (2.4)	16 (2.5)	1 (0.5)	19 (2.5)
Blood pressure medication [f]					
No	1,629 (78.7)	349 (91.1)	636 (87.6)	119 (82.5)	525 (63.4)
Yes	502 (21.3)	36 (8.9)	107 (12.4)	28 (17.5)	331 (36.6)
Cholesterol medication [f]					
No	1,797 (85.8)	366 (95.7)	669 (91.3)	129 (88.5)	633 (75.2)
Yes	334 (14.2)	19 (4.3)	74 (8.7)	18 (11.5)	223 (24.8)
Any prescribed medication [f]					
No	1,031 (51.2)	238 (63.2)	426 (60.1)	80 (57.4)	287 (35.5)
Yes	1,100 (48.8)	147 (36.8)	317 (39.9)	67 (42.6)	569 (64.5)
Moderate-to-vigorous-intensity physical activity time [e] (minutes/day)	30.3 (0.59)	51.3 (1.46)	44.0 (0.80)	13.2 (0.39)	9.7 (0.22)
Sedentary time [e] (minutes/day)	540.2 (2.29)	417.2 (3.62)	564.5 (2.68)	435.5 (3.84)	595.7 (2.39)
Light-intensity physical activity time [e] (minutes/day)	289.1 (2.06)	394.9 (3.16)	260.5 (1.88)	396.2 (4.35)	245.9 (2.47)
Accelerometer wear-time [e] (minutes/day)	859.7 (1.72)	863.5 (4.53)	869.1 (2.69)	844.9 (5.65)	851.4 (2.78)
Sedentary-to-light-intensity physical activity time ratio [e]	2.2 (0.03)	1.1 (0.01)	2.3 (0.03)	1.1 (0.01)	2.8 (0.05)

Number of valid days [f]					
4	99 (4.9)	18 (4.7)	35 (5.1)	8 (5.7)	38 (4.8)
5	185 (9.1)	36 (9.7)	55 (8.1)	21 (14.6)	73 (8.8)
6	414 (20.4)	80 (21.0)	139 (20.1)	32 (23.5)	163 (20.0)
7	1,433 (65.6)	251 (64.6)	514 (66.7)	86 (56.2)	582 (66.4)
Body mass index (kg/m^2) [e]	27.5 (0.12)	26.6 (0.24)	26.8 (0.17)	27.6 (0.43)	28.7 (0.21)
Missing [g]	185 (8.7)	30 (7.8)	44 (5.9)	8 (5.4)	103 (12.0)
Waist circumference (cm) [e]	93.4 (0.36)	90.1 (0.70)	91.7 (0.57)	91.5 (1.18)	97.0 (0.55)
Missing [g]	242 (11.4)	44 (11.4)	80 (10.8)	17 (11.6)	101 (11.8)
HDL-cholesterol (mmol/L) [e]	1.49 (0.01)	1.53 (0.02)	1.49 (0.02)	1.58 (0.04)	1.44 (0.01)
Missing [g]	728 (34.2)	120 (31.2)	245 (33.0)	51 (34.7)	312 (36.4)
Total cholesterol (mmol/L) [e]	5.42 (0.03)	5.37 (0.06)	5.49 (0.05)	5.48 (0.12)	5.37 (0.05)
Missing [g]	728 (34.2)	120 (31.2)	245 (33.0)	51 (34.7)	312 (36.4)
Glycated haemoglobin (%) [e]	5.64 (0.02)	5.47 (0.02)	5.51 (0.02)	5.89 (0.14)	5.82 (0.04)
Missing [g]	746 (35.0)	127 (33.0)	250 (33.6)	52 (35.4)	317 (37.0)

[a] *Physically active and low sedentary*
[b] *Physically active and high sedentary*
[c] *Physically inactive and low sedentary*
[d] *Physically inactive and high sedentary*
[e] *Continuous variable: mean (standard error)*
[f] *Categorical variable: number (%)*
[g] *Number (%)*
All analyses accounted for primary sampling units, clustering and survey weights.

Categorical Measures

The unadjusted (Model 1) and adjusted (Model 2) categorical analyses are displayed in Table 3. The adjusted (Model 2) analyses showed that in comparison to 'Couch Potatoes', 'Busy Bees' had significantly lower BMI (p-value<0.001), waist circumference (p-value=0.007) and HbA1c (p-value=0.003) levels, and higher HDL-cholesterol (p-value=0.001) levels. Similarly, 'Sedentary Exercisers' had significantly lower BMI (p-value<0.001) and HbA1c (p-value=0.009) levels, and higher HDL-cholesterol (p-value<0.001) levels. 'Light Movers' had significantly higher HDL-cholesterol (p-value=0.004) levels. Model assumptions were satisfied.

Table 3 - Observational study (2008 Health Survey for England data): Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health

Cardiometabolic health marker	Linear regression model	'Busy Bees' [a]		'Sedentary Exercisers' [b]		'Light Movers' [c]		'Couch Potatoes' [d]
		β (99% CI) [e]	p-value	β (99% CI) [e]	p-value	β (99% CI) [e]	p-value	
Body mass index (kg/m^2)	Model 1 [f]	**-2.06 (-2.86, -1.26)**	**<0.001**	**-1.93 (-2.61, -1.25)**	**<0.001**	-1.04 (-2.26, 0.18)	0.027	Reference
	Model 2 [g]	**-1.67 (-2.57, -0.77)**	**<0.001**	**-1.64 (-2.43, -0.85)**	**<0.001**	-0.66 (-1.92, 0.60)	0.175	Reference
Waist circumference (cm)	Model 1 [f]	**-6.92 (-9.17, -4.68)**	**<0.001**	**-5.31 (-7.33, -3.30)**	**<0.001**	**-5.53 (-8.89, -2.16)**	**<0.001**	Reference
	Model 2 [g]	**-1.17 (-2.28, -0.06)**	**0.007**	-0.71 (-1.56, 0.14)	0.032	-0.07 (-1.61, 1.47)	0.908	Reference
HDL-cholesterol (mmol/L)	Model 1 [f]	**0.09 (0.02, 0.17)**	**0.001**	0.05 (-0.01, 0.11)	0.021	**0.14 (0.04, 0.24)**	**<0.001**	Reference
	Model 2 [g]	**0.09 (0.02, 0.16)**	**0.001**	**0.07 (0.02, 0.13)**	**<0.001**	**0.11 (0.01, 0.21)**	**0.004**	Reference
Total cholesterol (mmol/L)	Model 1 [f]	-0.00 (-0.21, 0.21)	0.981	0.12 (-0.06, 0.29)	0.081	0.11 (-0.23, 0.45)	0.408	Reference
	Model 2 [g]	0.02 (-0.17, 0.22)	0.761	0.17 (-0.01, 0.35)	0.014	0.08 (-0.22, 0.38)	0.490	Reference
Glycated haemoglobin (%)	Model 1 [f]	**-0.35 (-0.47, -0.24)**	**<0.001**	**-0.32 (-0.43, -0.20)**	**<0.001**	0.07 (-0.32, 0.46)	0.656	Reference
	Model 2 [g]	**-0.12 (-0.22, -0.01)**	**0.003**	**-0.11 (-0.23, -0.01)**	**0.009**	0.26 (-0.11, 0.63)	0.072	Reference

[a] *Physically active and low sedentary*
[b] *Physically active and high sedentary*
[c] *Physically inactive and low sedentary*
[d] *Physically inactive and high sedentary (reference group)*
[e] *Beta coefficient (99% confidence interval)*
[f] *Model 1 was not adjusted for any confounders*

[g] *Model 2 was adjusted for age, body mass index (except in the model with body mass index as the dependent variable), cardiovascular disease index, ethnicity, fruit and vegetable consumption, sex, smoking status, socioeconomic status, and accelerometer wear-time. Models with HDL-cholesterol and total cholesterol as the dependent variable were also adjusted for both blood pressure medication and cholesterol medication. Similarly, the model with glycated haemoglobin as the dependent variable was adjusted for any prescribed medication*
All analyses accounted for primary sampling units, clustering and survey weights.
***Bold** indicates statistical significance (i.e. p-value<0.01).*

Continuous Measures

The adjusted (Model 2) continuous analyses are displayed in Table 4 and showed consistency with the categorical analyses. These models, which controlled for relevant confounders as well as both MVPA time and sedentary status, revealed that MVPA time was significantly associated with lower BMI (p-value<0.001), waist circumference (p-value<0.001) and HbA1c (p-value=0.002) levels, and higher HDL-cholesterol (p-value<0.001) levels. In contrast, sedentary status was significantly associated with lower HDL-cholesterol (p-value=0.004) levels. Model assumptions were satisfied.

Table 4 - Observational study (2008 Health Survey for England data): Associations of continuous measures of physical activity and sedentary time with markers of cardiometabolic health

Cardiometabolic health marker	Linear regression model	Moderate-to-vigorous-intensity physical activity time [a]		Sedentary behaviour-to-light-intensity physical activity ratio [b]	
		β (99% CI) [c]	p-value	β (99% CI) [c]	p-value
Body mass index (kg/m^2)	Model 2 [d]	**-0.0393 (-0.0505, -0.0282)**	**<0.001**	-0.1109 (-0.3918, 0.1700)	0.305
Waist circumference (cm)	Model 2 [d]	**-0.0315 (-0.0442, -0.0188)**	**<0.001**	0.1380 (-0.2502, 0.5261)	0.355
HDL-cholesterol (mmol/L)	Model 2 [d]	**0.0019 (0.0009, 0.0029)**	**<0.001**	**-0.0253 (-0.0476, -0.0030)**	**0.004**
Total cholesterol (mmol/L)	Model 2 [d]	0.0006 (-0.0024, 0.0036)	0.606	-0.0480 (-0.1335, 0.0376)	0.146
Glycated haemoglobin (%)	Model 2 [d]	**-0.0021 (-0.0037, -0.0004)**	**0.002**	-0.0079 (-0.0564, 0.0407)	0.673

[a] *Continuous measure of moderate-to-vigorous-intensity physical activity time (minutes/day)*
[b] *Continuous measure of the sedentary behaviour-to-light-intensity physical activity ratio*
[c] *Beta coefficient (99% confidence interval)*
[d] *Model 2 was adjusted for age, body mass index (except in the model with body mass index as the dependent variable), cardiovascular disease index, ethnicity, fruit and vegetable consumption, sex, smoking status, socioeconomic status, and accelerometer wear-time. Models with HDL-cholesterol and total cholesterol as the dependent variable were also adjusted for both blood pressure medication and cholesterol medication. Similarly, the model with glycated haemoglobin as the dependent variable was adjusted for any prescribed medication*
All analyses accounted for primary sampling units, clustering and survey weights.
***Bold** indicates statistical significance (i.e. p-value<0.01).*

Sensitivity Analysis

The sensitivity analyses, including an alternative less conservative method for classifying sedentary status, indicated robustness and stability. Although the prevalence in each category varied across the different methods used (see Table 5), the main results from the primary multiple linear regression models were largely unaffected (see Table 6). These data suggested that: (1) the missing values in the confounders were not influencing the observed associations, (2) the inclusion of individuals with CVD in the main analyses was having minimal confounding impact, (3) using a different threshold to classify sedentary status was not having any major effects on the associations, and (4) similar associations are observed when using bouted MVPA data.

Table 5 - Observational study (2008 Health Survey for England data): Sensitivity analyses: Weighted mutually exclusive category prevalence

		Weighted prevalence (N; %)			
Method [a]	N	'Busy Bees' [b]	'Sedentary Exercisers' [c]	'Light Movers' [d]	'Couch Potatoes' [e]
0	2,131	385; 18.6%	743; 36.7%	147; 6.8%	856; 37.9%
1	2,131	385; 18.6%	743; 36.7%	147; 6.8%	856; 37.9%
2	2,030	374; 18.9%	707; 36.7%	141; 6.8%	808; 37.6%
3	2,131	495; 23.9%	633; 31.4%	215; 9.8%	788; 34.9%
4	2,131	96; 4.6%	241; 12.0%	436; 20.8%	1,358; 62.6%

[a] *Method 0 = mutually exclusive categories derived and utilised in the main analysis. Method 1 = missing data in the covariates were imputed using the mutually exclusive category means (continuous variables: body mass index) and modes (categorical variables: smoking status and socioeconomic status). Method 2 = participants with a cardiovascular disease index of 'one or more cardiovascular diseases' were excluded. Method 3 = 'low Sedentary' was defined as residing in the lowest tertile of the ratio between the average sedentary time and the average light-intensity physical activity time. Method 4 = participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of moderate-to-vigorous-intensity physical activity in bouts of ≥10 minutes*

[b] *Physically active and low sedentary*

[c] *Physically active and high sedentary*

[d] *Physically inactive and low sedentary*

[e] *Physically inactive and high sedentary*

All analyses accounted for primary sampling units, clustering and survey weights.

Table 6 - Observational study (2008 Health Survey for England data): Sensitivity analyses: Associations of mutually exclusive categories of physical activity and sedentary time with markers of cardiometabolic health

Cardiometabolic health marker	Method [a b]	'Busy Bees' [c] β (99% CI) [g]	'Sedentary Exercisers' [d] β (99% CI) [g]	'Light Movers' [e] β (99% CI) [g]	'Couch Potatoes' [f]
Body mass index (kg/m^2)	0	**-1.67 (-2.57, -0.77)**	**-1.64 (-2.43, -0.85)**	-0.66 (-1.92, 0.60)	Reference
	1	**-1.61 (-2.51, -0.71)**	**-1.55 (-2.33, -0.78)**	-0.61 (-1.85, 0.64)	Reference
	2	**-1.71 (-2.59, -0.84)**	**-1.67 (-2.48, -0.85)**	-0.62 (-1.93, 0.69)	Reference
	3	**-1.70 (-2.63, -0.77)**	**-1.62 (-2.53, -0.71)**	-0.48 (-1.67, 0.71)	Reference
	4	**-2.83 (-4.05, -1.62)**	**-2.00 (-1.20, 0.32)**	-0.44 (-1.20, 0.32)	Reference
Waist circumference (cm)	0	**-1.17 (-2.28, -0.06)**	-0.71 (-1.56, 0.14)	-0.07 (-1.61, 1.47)	Reference
	1	**-1.50 (-2.85, -0.15)**	-0.89 (-1.97, 0.20)	-0.67 (-2.42, 1.08)	Reference
	2	**-1.19 (-2.32, -0.05)**	-0.66 (-1.55, 0.23)	-0.11 (-1.71, 1.50)	Reference
	3	**-1.29 (-2.45, -0.14)**	-0.64 (-1.65, 0.38)	-0.29 (-1.74, 1.16)	Reference
	4	**-1.83 (-3.61, -0.05)**	**-1.08 (-2.11, -0.05)**	-0.40 (-1.37, 0.56)	Reference
HDL-cholesterol (mmol/L)	0	**0.09 (0.02, 0.16)**	**0.07 (0.02, 0.13)**	**0.11 (0.01, 0.21)**	Reference
	1	**0.10 (0.04, 0.17)**	**0.08 (0.03, 0.14)**	**0.12 (0.02, 0.21)**	Reference
	2	**0.09 (0.02, 0.17)**	**0.08 (0.02, 0.13)**	**0.10 (0.01, 0.20)**	Reference
	3	**0.09 (0.02, 0.17)**	**0.08 (0.02, 0.15)**	**0.11 (0.03, 0.20)**	Reference
	4	**0.20 (0.09, 0.31)**	0.07 (-0.01, 0.15)	0.04 (-0.02, 0.10)	Reference
Total cholesterol (mmol/L)	0	0.02 (-0.17, 0.22)	0.17 (-0.01, 0.35)	0.08 (-0.22, 0.38)	Reference
	1	0.02 (-0.17, 0.21)	0.21 (-0.04, 0.37)	0.09 (-0.20, 0.39)	Reference
	2	0.01 (-0.18, 0.21)	0.18 (-0.01, 0.35)	0.05 (-0.25, 0.35)	Reference
	3	0.02 (-0.19, 0.23)	0.22 (-0.01, 0.45)	0.11 (-0.19, 0.40)	Reference
	4	-0.28 (-0.59, 0.02)	0.04 (-0.19, 0.28)	0.01 (-0.18, 0.19)	Reference
Glycated haemoglobin (%)	0	**-0.12 (-0.22, -0.01)**	**-0.11 (-0.23, -0.01)**	0.26 (-0.11, 0.63)	Reference
	1	**-0.13 (-0.23, -0.03)**	**-0.13 (-0.24, -0.02)**	0.23 (-0.14, 0.59)	Reference
	2	**-0.11 (-0.21, -0.01)**	-0.10 (-0.22, 0.02)	0.28 (-0.11, 0.66)	Reference
	3	**-0.11 (-0.23, -0.01)**	**-0.12 (-0.26, -0.02)**	0.19 (-0.14, 0.52)	Reference
	4	-0.07 (-0.18, 0.03)	**-0.12 (-0.23, -0.01)**	0.05 (-0.07, 0.18)	Reference

[a] *Method 0 = mutually exclusive categories derived and utilised in the main analysis. Method 1 = missing data in the covariates were imputed using the mutually exclusive category means (continuous variables: body mass index) and modes (categorical*

variables: smoking status and socioeconomic status). Method 2 = participants with a cardiovascular disease index of 'one or more cardiovascular diseases' were excluded. Method 3 = 'low Sedentary' was defined as residing in the lowest tertile of the ratio between the average sedentary time and the average light-intensity physical activity time. Method 4 = participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of moderate-to-vigorous-intensity physical activity in bouts of ≥10 minutes

[b] *Models were adjusted for age, body mass index (except in the model with body mass index as the dependent variable), cardiovascular disease index, ethnicity, fruit and vegetable consumption, sex, smoking status, socioeconomic status, and accelerometer wear-time. Models with HDL-cholesterol and total cholesterol as the dependent variable were also adjusted for both blood pressure medication and cholesterol medication. Similarly, the model with glycated haemoglobin as the dependent variable was adjusted for any prescribed medication*

[c] *Physically active and low sedentary*

[d] *Physically active and high sedentary*

[e] *Physically inactive and low sedentary*

[f] *Physically inactive and high sedentary (reference group)*

[g] *Beta coefficient (99% confidence interval)*

All analyses accounted for primary sampling units, clustering and survey weights.

***Bold** indicates statistical significance (i.e. p-value<0.01).*

Discussion

Key Findings

This is the first study to quantify associations of mutually exclusive categories of objectively measured physical activity and sedentary time with markers of cardiometabolic health in a nationally representative sample of English adults. Overall, adults who engaged in ≥150 minutes/week of MVPA, including those with concomitant high sedentary time ('Sedentary Exercisers'), had more favourable health profiles compared to physically inactive individuals with high sedentary time ('Couch Potatoes'). Low sedentary time independent of physical activity ('Light Movers') had positive associations with HDL-cholesterol. These findings were consistent with the continuous and sensitivity analyses.

Interpretations

The approach to categorising the population into one of four mutually exclusive categories extends previous research using HSE. For example, previous analysis of HSE has reported associations between both self-reported and objectively assessed sedentary time with markers of health in working age and older adults and between MVPA and markers of health (30-32). The wider evidence has increasingly demonstrated that objectively measured sedentary time is independently associated with markers of cardiometabolic health (19-21, 24, 25, 33, 122), although not all studies have demonstrated this link (123). Whilst these previous analyses have adjusted for MVPA, the associations of sedentary time with health across physical activity levels are less well understood. Therefore, this study adds to the evidence by investigating associations of sedentary status with health across categories of physical activity.

These findings are in broad agreement with the only other study to have used a similar methodology (35). Using national survey data from the USA, Loprinzi and colleagues found that in comparison to individuals (aged ≥20 years) who engaged in <150 minutes/week of MVPA with high sedentary time (sedentary time > LIPA time), individuals engaging in ≥150 minutes/week of MVPA had a more favourable

cardiometabolic profile (BMI, waist circumference, C-reactive protein, white blood cells and neutrophils) regardless of their sedentary status.(35) Participants in the most desirable group (≥150 minutes/week of MVPA with low sedentary time) also had better HDL-cholesterol, triglyceride and insulin levels. Similar to my study, participants in the physically inactive group with low sedentary time had fewer beneficial associations, although more favourable profiles for triglycerides and insulin levels were still observed.

My findings, alongside those of Loprinzi and colleagues (35), are also consistent with the emerging evidence that levels of fitness or physical activity may modify the associations between sedentary time and markers of health in adults (33, 34, 36, 37), with sedentary behaviour only emerging as a determinant of health in those that are inactive or unfit. Together, these studies suggest that being physically active may confer some protection from the potentially deleterious impact of high sedentary behaviour.

In this study, low sedentary time in the absence of being physically active ('Light Movers') was associated with higher levels of HDL-cholesterol (+0.11 mmol/L), suggesting that physical inactivity in a combination with low sedentary time may have some positive relationships with health. However, the potential benefits appeared to be less numerous and consistent than those observed for physically active categories ('Busy Bees' and 'Sedentary Exercisers'). One reason for this could be in the assessed markers of cardiometabolic health. Although a measure of glycaemia (HbA1c) was included in this study, more sensitive measures of insulin resistance, which have shown stronger associations with sedentary time (13, 24, 25, 124), were not available.

Although sedentary behaviour and MVPA have been hypothesised to be distinctive health behaviours, it is unclear to what extent the underlying mechanisms act through the same or independent pathways. This reflects a limitation in the evidence more generally where mechanisms underpinning the benefits of sedentary behaviour have not been adequately elucidated. To date, the only evidence-based independent mechanism for sedentary behaviour has been through the activation of lipoprotein lipase which has been shown to change by a factor of 10 in animal models following

hind limb suspension (125). This supports the observation in this study where low sedentary time was associated with higher HDL-cholesterol levels, even in those who were physically inactive ('Light Movers'). In contrast to sedentary behaviour, acute and chronic physiological adaptions have been well established linking higher levels of physical activity to cardiometabolic health (126-128).

Strengths and Limitations

This analysis has several strengths and some limitations. Strengths include exploitation of a well-characterised national survey which employs a multifaceted stratified random sampling procedure, utilising objectively measured physical activity and sedentary behaviour data, and a wide range of sensitivity analyses to test the robustness of these findings. The method used for deriving sedentary status has both strengths and limitations in itself. In contrast to Loprinzi and colleagues (35), who used a pre-defined method for classifying high/low sedentary time, I took a conservative, data-driven approach. Differences between accelerometer characteristics, such as wear-time, across populations can have a significant effect on the average sedentary time, artificially inflating or deflating the number of participants falling within a fixed threshold. For example, based on the method used by Loprinzi and colleagues (35), less than 8% of the participants in this sample would be classified as 'Low Sedentary', and only 1.6% of the population would be categorised as physically inactive with low sedentary time i.e. 'Light Movers'. Therefore, the approach used in this study ensures that the categories are determined in relation to the population characteristics and not influenced by measurement artefact. However, the corresponding limitation is that specific targets for intervention are difficult to define. Additional pertinent limitations that are applicable to this analysis include the cross-sectional design which prohibits the possibility of establishing causality (reverse-causality remains open) or that unmeasured variables were confounding observed associations. Furthermore, only the general population weights (interview, nurse, blood) were available for this analysis; the weights further calibrated for the accelerometer sample were not accessible and this limitation reduces the generalizability of the findings. Other factors which may also restrict the generalizability include: the relatively small sample size for a national

survey, the ethnically heterogeneous White population, non-fasting measures of HDL-cholesterol and total cholesterol, and moderately high proportions of missing data in the blood analytes, particularly for HbA1c. Furthermore, a larger sample would have allowed for more dose-response categories. Lastly, the accelerometer data in this study were based on classifying horizontal movement intensity; and cannot distinguish between different postures (i.e. sitting and standing).

This next section particularly focuses on the reliability and validity of the data. As previously stated in this chapter, BMI was calculated using the height and weight data (weight/height^2), which were recorded to the nearest 0.1 cm using a portable stadiometer and to the nearest 0.1 kilogram using an electronic scale, respectively (39). Waist circumference was defined as the centre point between the lower rib and the upper boundary of the iliac crest, and a nurse measured this twice to the nearest 0.1 cm using a tape and the mean of the two readings was used (39). In relation to these, in order to collect logical and rational data in the 2008 HSE, a large number of quality control measures were incorporated into the survey at both data collection and subsequent stages to check on the quality of the data (e.g. BMI, waist circumference, etc.) (39). For instance, the computer software used for data collection carried out automatic checks that queried improbable or unusual answers as well as responses that were outside the standard range. Furthermore, the biological samples from the 2008 HSE have also been shown to be reliable and valid (39). It has previously been reported that the methods and equipment used for the measurement of three blood analytes (HDL-cholesterol, total cholesterol, and HbA1c) produced internal quality control and external quality assessment results within the expected boundaries, and were deemed to be acceptable (39). These three blood analytes have also been reported in the literature to be robust markers of cardiometabolic health and are widely-used in clinical practice (129-131).

Recall that the data on the time spent in physical activity and sedentary behaviour were collected using an ActiGraph GT1M accelerometer (17, 39). The feasibility of using this accelerometer in the 2008 HSE was assessed as a part of a pilot study where it performed well in testing (17). The ActiGraph GT1M is a digital uni-axial accelerometer that records movement on the vertical axis and provides a measure of

the frequency, intensity and duration of physical activity, allowing for the classification of activity levels as sedentary, light, moderate and vigorous (17, 39). Specifically, the accelerometer records the intensity and magnitude of accelerations over a given time period and transforms the raw data into the form of proprietary 'counts' (based on different filters, frequencies, etc.) (69). To give biological meaning to the output, thresholds have been developed to calibrate accelerometer output, typically using regression or receiver-operating-characteristic (ROC) curves to convert accelerometer counts to estimates of time spent in a given physical activity intensity band, e.g. time spent in MVPA (132, 133). This is an easy and efficient way for end users to convert accelerometer counts into more meaningful units as the amount of time spent in a given activity intensity, e.g. MVPA, is simply the time accumulated with accelerometer counts per epoch greater than the MVPA threshold. In my study, I applied the widely used thresholds proposed by Freedson and colleagues (118). However, it should be noted that the approach to developing thresholds impacts on the estimates of intensity (134), with thresholds based on ambulatory activities being higher than those based on lifestyle activities. It is also important to highlight that the application of specific thresholds reflect absolute intensity rather than relative light, moderate and vigorous intensities, and accelerometer output for a given activity intensity will vary from person to person and from population to population. In addition, the use of intensity thresholds based on movement to define sedentary time is limited by the fact that it cannot be used to define posture, indeed the method for measuring sedentary time in this study has been shown to only explain 39% of the variation in sitting time when assessed by direct observation (135). Using mechanical shakers, Silva and colleagues conducted a study to assess the reliability of the ActiGraph GT1M activity count function (136). They demonstrated that this accelerometer was reliable for measuring counts (mean coefficient of variation (intra): 2.9% (low within variability); and mean coefficient of variation (inter): 3.5% (low between variability)) (136). Furthermore, other studies have shown the validity of this device using measures estimated through indirect calorimetry under laboratory conditions (137-139); for example, Kelly and colleagues reported a correlation coefficient of 0.88 for the relationship between counts and oxygen consumption (138). Conversely, for the

validity of the direct acceleration measure, a mechanical shaker analysis would be required. Both mechanical shaker and human laboratory studies have shown that ActiGraph counts are linearly associated with intensity up to a certain point, but at higher intensities, the association becomes non-linear (71, 72, 140-142). Brage and colleagues commented on the frequency-based filtering that occurs in this accelerometer causing this non-linear response (70). Studies have previously demonstrated that the filtering process trims the signal at high intensities/speeds (72, 141). Therefore, vigorous exercise may be underestimated using this device. In fact, Brage and colleagues were one of the first to report this phenomena in 2003 and showed that converting counts into raw accelerations provided more precise estimates of intensity (71, 72). This was reiterated by Rowlands and colleagues who showed that the counts generated from activities such as intense running could be the same or very similar to the counts generated from activities such as walking due to a combination of the frequency-dependent filtering and the examination of acceleration signals in the vertical axis only (running predominantly has constant vertical acceleration in the vertical plane) (142). As a consequence, these results must be interpreted with caution since a misrepresentation of the time spent in the different physical activity intensity bands could have important implications and lead to biased and erroneous findings.

A more detailed discussion on the strengths and limitations of the HSE database is provided in Chapter Two.

Conclusion

In conclusion, this analysis demonstrates that in comparison to adults who are physically inactive with high sedentary time, those who are physically active have a more desirable health profile across multiple cardiometabolic markers even when combined with high sedentary time. In contrast, low sedentary time in the absence of physical activity is associated with higher HDL-cholesterol levels. By suggesting that being physically active may offset some of the deleterious consequences of a routinely sedentary lifestyle, this study further emphasises the importance of physical activity in the promotion and maintenance of health. However, given the observational design, the interaction and relative magnitude of effect of physical activity and sedentary

behaviour on health needs further elucidation through experimental research to better inform public health policy and guidance.

CHAPTER FOUR: ANALYSIS OF EPIDEMIOLOGICAL DATA: WALKING AWAY FROM TYPE 2 DIABETES: A CLUSTER RANDOMIZED CONTROLLED TRIAL: PRIMARY CARE DATA

Chapter Overview

This chapter is based on the analysis of epidemiological data and uses the Walking Away from Type 2 Diabetes: A Cluster Randomized Controlled Trial dataset. In brief, this project exploited a population of adults at high risk of T2DM recruited from primary care with mortality and accelerometer assessed physical activity and sedentary behaviour data. Using these data, I examined the associations of objectively measured MVPA and sedentary time with all-cause mortality. The findings of this original piece of work were published as a Research Article in Preventive Medicine Reports.

Associations of Objectively Measured MVPA and Sedentary Time with All-Cause Mortality in a Population of Adults at High Risk of T2DM

Abstract

The relationships of physical activity and sedentary time with all-cause mortality in those at high risk of T2DM are unexplored. To address this gap in knowledge, I examined the associations of objectively measured MVPA and sedentary time with all-cause mortality in a population of adults at high risk of T2DM. In 2010-2011, 712 adults (Leicestershire, UK), identified as being at high risk of T2DM, consented to be followed-up for mortality. MVPA and sedentary time were assessed by accelerometer; those with valid data (≥10 hours of wear-time/day with ≥4 days of data) were included. Cox proportional hazards regression models, adjusted for potential confounders, were used to investigate the independent associations of MVPA and sedentary time with all-cause mortality. 683 participants (250 females (36.6%)) were included and during a mean follow-up period of 5.7 years, 26 deaths were registered. Every 10% increase in MVPA time/day was associated with a 5% lower risk of all-cause mortality [Hazard Ratio (HR): 0.95 (95% CI: 0.91, 0.98); p-value=0.004]; indicating that for the average adult in this cohort undertaking approximately 27.5 minutes of MVPA/day, this benefit would be associated with only 2.75 additional minutes of MVPA/day. Conversely, sedentary time showed no association with all-cause mortality [HR (every 10-minute increase in sedentary time/day): 0.99 (95% CI: 0.95, 1.03); p-value=0.589]. These data support the importance of MVPA in adults at high risk of T2DM. The association between sedentary time and mortality in this population needs further investigation.

Introduction

Diabetes is a leading health care burden nationally and internationally (143). Therefore, the prevention of diabetes, particularly T2DM, is an identified health care priority. Diabetes prevention has focused on the promotion of established health behaviours, including physical activity, with strong evidence of efficacy (41). However, whilst the effects of promoting physical activity and other lifestyle factors on reducing the risk of T2DM are well-known in those at high risk of T2DM (defined as non-diabetic hyperglycaemia), the strength of association with all-cause mortality is less clear. To my knowledge, only one study has quantified the associations between objectively measured physical activity and mortality/morbidity outcomes in those at high risk of T2DM (42), whilst no studies have examined associations with objectively measured sedentary time. The latter is important given the mounting evidence that sedentary behaviour, defined as sitting or reclining with low energy expenditure, is associated with poor health and has been advocated as an important behavioural target in the prevention of diabetes (43).

This chapter quantifies the associations of objectively measured MVPA and sedentary time with all-cause mortality in a population of adults at high risk of T2DM recruited from primary care.

Methods

Design and Population

Participants for this study were part of the Walking Away from Type 2 Diabetes trial (44). The trial consisted of adults at an increased risk of T2DM who were recruited in 2010 - 2011 through 10 primary care practices in Leicestershire, UK. Individuals (N = 833) with an increased risk of non-diabetic hyperglycaemia (defined as: impaired glucose tolerance (IGT) and/or impaired fasting glycaemia (IFG)) or undiagnosed T2DM were identified for recruitment using the Leicester Practice Risk Score (44, 84-86). The score was developed using logistic regression analysis with the data coming from the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION)-Leicester study (144), and the data included

anthropometric measurements and self-reported questionnaires (age, BMI, ethnicity, family history of T2DM, sex and antihypertensive medication). The score was externally validated using the 'Screening Those At Risk' (STAR) database (85, 88). The Walking Away from Type 2 Diabetes trial recruited those above the 90th percentile of calculated risk. Accordingly, it would not be appropriate to use the score as a confounder since only those at the highest level of risk were included. At baseline, participants were randomized to usual care or the three-hour Walking Away structured education programme with ongoing annual support (44). Participants were followed-up at 12, 24 and 36 months. Over the 36 months, no overall difference was observed in levels of physical activity or sedentary behaviour between the two arms (84). This analysis uses the baseline data and includes the 712 adults within the cohort who consented to have their records followed-up for health status (a sensitivity analysis also makes use of the repeated measures of physical activity and sedentary time data). All participants provided written informed consent and the study was approved by the Nottingham Research Ethics Committee, UK. Please see Chapter Two for a critical assessment of the Walking Away from Type 2 Diabetes database (response rates, strengths and limitations, etc.).

Mortality Data

Mortality data were obtained from the Office for National Statistics (ONS) via an application to the Health and Social Care Information Centre (HSCIC). All-cause mortality was defined as any death recorded between baseline and end of data linkage on 6 April 2016. All-cause mortality was coded as a binary variable representing censoring or death. For censored data, survival time (in days) was defined as the difference between the follow-up date (6 April 2016) and the date of baseline visit. For event data, survival time was defined as the difference between the date of death and baseline visit.

Physical Activity and Sedentary Time Data

MVPA and sedentary time were measured using an ActiGraph GT3X accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) which was worn on the right hip for seven consecutive days during waking hours. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, UK). The ActiGraph GT3X device was initialised to collect data using 15 seconds epochs, and files were reintegrated into one minute epochs. Accelerometer counts derived from the vertical axis were used to calculate the amount of time spent in sedentary behaviour (<100 CPM) and in MVPA (≥1952 CPM) (118). Non-wear time was defined as any periods of continuous zero counts for ≥60 consecutive minutes (119). Valid accelerometer data were defined as ≥10 hours of wear-time/day with ≥4 days of data. Participants who provided valid accelerometer data were retained for analysis. The average number of minutes/valid day spent sedentary and in MVPA were calculated.

Confounders

The following covariate data were also utilised: age (continuous: years), BMI (continuous: kg/m^2), ethnicity (categorical: white, non-white), sex (categorical: male, female), smoking status (categorical: non-smoker, smoker), medical history of CVD (categorical: no, yes (myocardial infarction, heart failure, angina and/or stroke)), BP and/or cholesterol medication (categorical: no, yes (ACE-inhibitors, alpha-blockers, angiotensin-II receptor antagonists, beta-blockers, calcium channel blockers, lipid lowering statins and/or lipid lowering fibrates)), aspirin medication (categorical: no, yes), and accelerometer wear-time (continuous: minutes/day). Body weight (Tanita TBE 611; Tanita, West Drayton, UK) and height were measured to the nearest 0.1 kg and 0.5 cm, respectively. BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres).

Statistical Analysis

Statistical analyses were conducted using Stata/MP V14.0 (Stata Corporation, College Station, Texas, USA). Participant characteristics, stratified by mortality status, were

tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations (SDs). A series of Cox proportional hazards regression models (with survival time in days) were used to investigate the independent associations of MVPA and sedentary time with all-cause mortality (Stata commands: 'stset' and 'stcox') (145). This analytical technique is useful for exploring the relationships between exposures and survival time (time-to-event) outcomes. Here, all-cause mortality was the time-to-event, and MVPA and sedentary time were the key exposures. MVPA time indicated a non-normal distribution; therefore, it was log-transformed to reduce the influence of skewed data (Figure S2 in Appendix Three: Supplementary Material: Supplementary Data shows how effective the log-transformation was in this case). To ensure that the HRs represented a 10% increase in MVPA time/day, a log base of 1.1 (i.e. $\log_{1.1}$(MVPA time)) was used. This log-transformed MVPA time variable was calculated as follows. The log of 0 is undefined; and therefore, taking the log of a variable containing 0 values would result in the loss of data. In order to prevent this from happening, a value of 1 was first added to the MVPA time variable to offset any 0 values (note, this is a commonly used procedure in such situations, and this approach simply shifts the distribution without changing the attributes or the nature of the data):

$$(MVPA\ time) + 1 = x$$

The log (base 10) of this variable was then generated:

$$\log_{10}(x) = y$$

Next, to be certain that the HRs represent a 10% increase in MVPA time/day, the log (base 10) of 1.1 was calculated:

$$\log_{10}(1.1) = 0.041392685158$$

Then, y was divided by $\log_{10}(1.1)$ to derive the desired variable of interest:

$$\frac{y}{\log_{10}(1.1)} = \frac{\log_{10}(x)}{\log_{10}(1.1)} = \log_{1.1}(x) = \log_{1.1}((MVPA\ time) + 1)$$

In the analysis, this is simply referred to and used as:

$$\log_{1.1}(MVPA\ time)$$

Sedentary behaviour was presented as a 10-minute increase in sedentary time/day. Model 1 adjusted for: age, sex and smoking status. Model 2 further adjusted for sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis). Model 3 further adjusted for BMI. Ethnicity, accelerometer wear-time, medical history of CVD, BP and/or cholesterol medication, and aspirin medication were also individually considered as covariates in the minimally adjusted model (Model 1). However, their inclusion did not affect the HRs, direction of association or interpretation (significance/non-significance) of the models. Therefore, in order to maintain an adequate ratio between the number of events and covariates in the model (91), the more parsimonious model was used.

The proportional hazards assumption of each model was assessed via: a) plotting the Schoenfeld residuals against time; and b) executing a formal post-hoc proportional hazards global test (Stata command: 'estat phtest').

Sensitivity Analysis

Since smokers are generally more likely to be physically inactive in comparison to non-smokers, they could potentially modify the associations with all-cause mortality. Therefore, in order to assess the robustness and replicability of the findings, the main analysis (Models 1, 2 and 3) was repeated in the sample of non-smokers. Furthermore, data on accelerometer-assessed MVPA and sedentary time were available across a total of 4 time points (0 months (baseline), 12 months, 24 months, and 36 months). Accordingly, as an additional analysis, I examined whether the associations of MVPA and sedentary time with all-cause mortality remained the same after taking into

account this extra follow-up information. Split Cox proportional hazards regression models with continuous time-varying MVPA and sedentary time variables (Stata commands: 'stset', 'stsplit' and 'stcox') were fitted to investigate the independent associations of MVPA and sedentary time with all-cause mortality (146). Here again, MVPA time indicated a non-normal distribution; consequently, it was log-transformed using the same methods described earlier before it was entered into the models (Models 1, 2 and 3) (see Figure S2 in Appendix Three: Supplementary Material: Supplementary Data).

Note, for more details on the distributions of the key outcomes and exposures, see Figure S2 in Appendix Three: Supplementary Material: Supplementary Data.

Statistical Reporting

For each variable of interest, the HRs with 95% CIs and p-values are reported. All reported p-values are two-sided with p-value<0.05 considered to be statistically significant.

Results

Of the 712 individuals who consented for data linkage, 683 participants [mean age (SD) = 63.6 (7.8) years; mean BMI (SD) = 32.0 (5.3) kg/m^2; 250 females (36.6%)] provided valid accelerometer data and were included for analysis. During a mean follow-up period of 5.7 years, 26 deaths were registered. In relation to the split Cox proportional hazards regression analysis that utilised the repeated measures of MVPA and sedentary time, some missing MVPA and sedentary time values were observed at 12, 24 and 36 months. Table 7 displays the characteristics of the included participants further stratified by mortality status.

Table 7 - Observational study (Walking Away from Type 2 Diabetes data): Participant characteristics

Participant characteristics	Sample N = 683	Censored N = 657	Deaths N = 26
Age (years) [a]	63.6 (7.8)	63.6 (7.8)	64.4 (8.0)
Body mass index (kg/m^2) [a]	32.0 (5.3)	32.0 (5.3)	33.2 (6.8)
Ethnicity [b]			
White	608 (89.0)	584 (88.9)	24 (92.3)
Non-white	75 (11.0)	73 (11.1)	2 (7.7)
Sex [b]			
Male	433 (63.4)	412 (62.7)	21 (80.8)
Female	250 (36.6)	245 (37.3)	5 (19.2)
Smoking status [b]			
Non-smoker	630 (92.2)	609 (92.7)	21 (80.8)
Smoker	53 (7.8)	48 (7.3)	5 (19.2)
Medical history of cardiovascular disease [b]			
No	609 (87.2)	589 (89.7)	20 (76.9)
Yes	74 (10.8)	68 (10.3)	6 (23.1)
Blood pressure and/or cholesterol medication [b]			
No	295 (43.2)	285 (43.4)	10 (38.5)
Yes	388 (56.8)	372 (56.6)	16 (61.5)
Aspirin medication [b]			
No	577 (84.5)	559 (85.1)	18 (69.2)
Yes	106 (15.5)	98 (14.9)	8 (30.8)
Accelerometer wear-time (minutes/day): 0 months [a]	855.5 (79.2)	856.3 (79.0)	834.6 (81.7)
Moderate-to-vigorous-intensity physical activity time (minutes/day): 0 months [a]	27.5 (24.4)	27.8 (24.5)	19.0 (19.5)
Sedentary time (minutes/day): 0 months [a]	538.0 (92.1)	537.5 (91.1)	551.5 (116.5)
Accelerometer wear-time (minutes/day):			
12 months [a]	856.5 (80.1)	856.6 (80.0)	854.8 (83.2)
Missing [c]	128 (18.7)	120 (18.3)	8 (30.8)
Moderate-to-vigorous-intensity physical activity time (minutes/day): 12 months [a]	27.5 (24.0)	27.5 (23.8)	27.3 (30.1)
Missing [c]	128 (18.7)	120 (18.3)	8 (30.8)
Sedentary time (minutes/day):			
12 months [a]	548.1 (96.1)	547.3 (96.5)	572.4 (81.2)
Missing [c]	128 (18.7)	120 (18.3)	8 (30.8)
Accelerometer wear-time (minutes/day):			
24 months [a]	851.8 (77.3)	851.8 (76.9)	851.7 (90.6)
Missing [c]	134 (19.6)	124 (18.9)	10 (38.5)
Moderate-to-vigorous-intensity physical activity time (minutes/day): 24 months [a]	24.1 (22.5)	23.9 (22.4)	28.4 (25.7)
Missing [c]	134 (19.6)	124 (18.9)	10 (38.5)
Sedentary time (minutes/day):			
24 months [a]	557.6 (87.9)	556.7 (87.0)	585.9 (113.9)
Missing [c]	134 (19.6)	124 (18.9)	10 (38.5)
Accelerometer wear-time (minutes/day):			
36 months [a]	861.3 (78.0)	860.8 (78.1)	881.8 (74.1)

Missing [c]	153 (22.4)	139 (21.2)	14 (53.8)
Moderate-to-vigorous-intensity physical activity time (minutes/day): 36 months [a]	23.7 (22.7)	23.5 (22.2)	33.8 (38.8)
Missing [c]	153 (22.4)	139 (21.2)	14 (53.8)
Sedentary time (minutes/day): 36 months [a]	561.1 (93.6)	559.9 (92.1)	612.4 (139.9)
Missing [c]	153 (22.4)	139 (21.2)	14 (53.8)
Survival time (years) [a]	5.6 (0.5)	5.7 (0.2)	3.9 (1.4)

[a] *Continuous variable: mean (standard deviation)*
[b] *Categorical variable: number (%)*
[c] *Number (%)*

Mortality Analysis

In the maximally adjusted model (Model 3), every 10% increase in MVPA time/day was associated with a 5% lower risk of all-cause mortality [HR: 0.95 (95% CI: 0.91, 0.98); p-value=0.004]. Conversely, sedentary time showed no association with all-cause mortality [HR (every 10-minute increase in sedentary time/day): 0.99 (95% CI: 0.95, 1.03); p-value=0.589]. The proportional hazards assumption of each model was satisfied with the Schoenfeld residuals showing no trend with time and all global tests reporting p-value>0.05. Table 8 displays the results from the Cox proportional hazards regression analyses.

Table 8 - Observational study (Walking Away from Type 2 Diabetes data): Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline with all-cause mortality at follow-up

Cox proportional hazards regression model	$\log_{1.1}$ (MVPA time (minutes/day))		Sedentary time (10 minutes/day)	
	HR (95% CI) [a]	p-value	HR (95% CI) [b]	p-value
Model 1 [c]	**0.94 (0.91, 0.98)**	**0.001**	1.01 (0.97, 1.06)	0.538
Model 2 [d]	**0.94 (0.91, 0.97)**	**0.001**	0.99 (0.95, 1.03)	0.604
Model 3 [e]	**0.95 (0.91, 0.98)**	**0.004**	0.99 (0.95, 1.03)	0.589

[a] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every $\log_{1.1}$-unit increase in MVPA time/day (i.e. for every 10% increase in MVPA time/day)*
[b] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every 10-unit increase in sedentary time/day (i.e. for every 10-minute increase in sedentary time/day)*
[c] *Model 1 adjusted for age, sex and smoking status*
[d] *Model 2 further adjusted for sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis)*
[e] *Model 3 further adjusted for body mass index*
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Sensitivity Analysis

Table 9 displays the findings of the minimally adjusted model (Model 1) that individually considered all other confounders (ethnicity, accelerometer wear-time, CVD, BP and/or cholesterol medication, and aspirin medication). Table 10 displays the findings of the sensitivity analysis where the main analysis (Models 1, 2 and 3) was repeated in the sample of non-smokers (N = 630; mean follow-up period of 5.6 years; 21 deaths). Table 11 shows the results from the Split Cox proportional hazards regression analysis (Models 1, 2 and 3) where continuous time-varying MVPA and sedentary time variables across 4 time points (0 months (baseline), 12 months, 24 months, and 36 months) were used. All findings were robust and generalizable. In all models, similar to the main analyses, an increase in MVPA time was associated a lower risk of all-cause mortality, whereas sedentary time showed no association with mortality.

Table 9 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline with all-cause mortality at follow-up whilst further adjusting for other confounders

Cox proportional hazards regression model	$\log_{1.1}$ (MVPA time (minutes/day))		Sedentary time (10 minutes/day)	
	HR (95% CI) [a]	p-value	HR (95% CI) [b]	p-value
Model 1a [c]	**0.94 (0.91, 0.97)**	**<0.001**	1.01 (0.97, 1.06)	0.536
Model 1b [d]	**0.95 (0.91, 0.98)**	**0.002**	1.04 (0.99, 1.10)	0.106
Model 1c [e]	**0.95 (0.91, 0.98)**	**0.002**	1.01 (0.97, 1.05)	0.633
Model 1d [f]	**0.94 (0.91, 0.98)**	**0.001**	1.01 (0.97, 1.06)	0.546
Model 1e [g]	**0.95 (0.91, 0.98)**	**0.001**	1.01 (0.97, 1.05)	0.587

[a] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every $\log_{1.1}$-unit increase in MVPA time/day (i.e. for every 10% increase in MVPA time/day)*
[b] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every 10-unit increase in sedentary time/day (i.e. for every 10-minute increase in sedentary time/day)*
[c] *Model 1a adjusted for age, sex, smoking status and ethnicity*
[d] *Model 1b adjusted for age, sex, smoking status and accelerometer wear-time*
[e] *Model 1c adjusted for age, sex, smoking status and cardiovascular disease*
[f] *Model 1d adjusted for age, sex, smoking status and blood pressure and/or cholesterol medication*
[g] *Model 1e adjusted for age, sex, smoking status and aspirin medication*
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Table 10 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline with all-cause mortality at follow-up in the sample of non-smokers

Cox proportional hazards regression model	$\log_{1.1}$ (MVPA time (minutes/day))		Sedentary time (10 minutes/day)	
	HR (95% CI) [a]	p-value	HR (95% CI) [b]	p-value
Model 1 [c]	**0.95 (0.91, 0.98)**	**0.003**	0.99 (0.95, 1.04)	0.693
Model 2 [d]	**0.94 (0.90, 0.97)**	**0.001**	0.97 (0.92, 1.01)	0.136
Model 3 [e]	**0.94 (0.90, 0.98)**	**0.002**	0.96 (0.92, 1.01)	0.133

[a] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every $\log_{1.1}$-unit increase in MVPA time/day (i.e. for every 10% increase in MVPA time/day)*
[b] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every 10-unit increase in sedentary time/day (i.e. for every 10-minute increase in sedentary time/day)*
[c] *Model 1 adjusted for age and sex*
[d] *Model 2 further adjusted for sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis)*
[e] *Model 3 further adjusted for body mass index*
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Table 11 - Observational study (Walking Away from Type 2 Diabetes data): Sensitivity analyses: Prospective associations of moderate-to-vigorous-intensity physical activity (MVPA) and sedentary time at baseline, 12 months, 24 months and 36 months with all-cause mortality at follow-up

Split Cox proportional hazards regression model	$\log_{1.1}$ (MVPA time (minutes/day))		Sedentary time (10 minutes/day)	
	HR (95% CI) [a]	p-value	HR (95% CI) [b]	p-value
Model 1 [c]	**0.95 (0.92, 0.98)**	**0.002**	1.00 (1.00, 1.00)	0.718
Model 2 [d]	**0.94 (0.91, 0.98)**	**0.001**	1.00 (0.99, 1.00)	0.496
Model 3 [e]	**0.95 (0.91, 0.99)**	**0.009**	1.00 (0.99, 1.00)	0.490

[a] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every $\log_{1.1}$-unit increase in MVPA time/day (i.e. for every 10% increase in MVPA time/day)*
[b] *Hazard ratios (95% confidence intervals) represent the risk of all-cause mortality for every 10-unit increase in sedentary time/day (i.e. for every 10-minute increase in sedentary time/day)*
[c] *Model 1 adjusted for age, sex and smoking status*
[d] *Model 2 further adjusted for sedentary time (for MVPA time analysis) and MVPA time (for sedentary time analysis)*
[e] *Model 3 further adjusted for body mass index*
Last observed values were carried forward for any missing MVPA and sedentary time data at 12, 24 or 36 months.
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Discussion

Key Findings

These findings demonstrate that the risk of death was reduced by 5% for every 10% increase in MVPA time in adults at high risk of T2DM. This indicates that for the average adult in this cohort undertaking approximately 27.5 minutes of MVPA/day, this benefit would be associated with only 2.75 additional minutes of MVPA/day. In contrast, sedentary time was not associated with all-cause mortality. The sensitivity analyses indicated that these findings were robust.

Interpretations

Previous research has consistently shown that both MVPA and sedentary behaviour are associated with all-cause mortality (8, 13, 147, 148). However, the majority of the studies in this research area have been limited by self-reported measures, which rely on recall and suffer from response bias; hence, they tend to have low validity and high levels of measurement error. Few studies have examined the associations of MVPA and sedentary time with mortality using objective measurements. In a national sample of US adults with objectively measured data, Schmid and colleagues observed that both low levels of MVPA and high levels of sedentary behaviour were independently associated with early all-cause mortality (117). Other studies have reported similar findings (149, 150). In contrast, a recent study in a subset of participants with diabetes from this national survey showed no associations between sedentary time and all-cause mortality after adjusting for total physical activity (151). However, all of these studies utilised the same survey dataset; thus, the relationships need testing in other populations including those at a high risk of T2DM.

The results for MVPA are consistent with other studies that have looked at the associations of pedometer assessed physical activity or CRF with mortality in similar cohorts. An international study reported that the risk of CVD morbidity and mortality was reduced by 8% for every 2000 steps/day increase in walking activity (corresponds to approximately 20 minutes/day of MVPA based on a cadence of 100 steps/minute) in those at high risk of T2DM (42), with another study showing that the risk of mortality

was reduced with higher fitness in those with IGT or undiagnosed T2DM (152). Since the completion and publication of this study, a similar analysis by Lee and colleagues examined the associations of accelerometer-assessed total volume of physical activity (total accelerometer counts), MVPA, LIPA, and sedentary behaviour with all-cause mortality in a large population of women (153). Their results were consistent with my findings. After adjusting for potential confounders, the authors observed that MVPA was inversely associated with all-cause mortality (p-value for trend = 0.0002). In contrast, sedentary behaviour showed no association (p-value for trend = 0.99) (153).

Strengths and Limitations

This study has strengths and limitations. Strengths include the utilisation of objectively measured MVPA and sedentary behaviour data, a high risk sample, and a robust statistical analysis plan. Furthermore, in relation to the quality of the primary outcome and exposure data used in this analysis, the mortality data came from ONS, and based on the internal validation checks that ONS carry out, these data are known to be dependable and robust (154, 155). Moreover, similar to the 2008 HSE study, the time spent in MVPA and sedentary behaviour were collected using an ActiGraph accelerometer. Here, the tri-axial ActiGraph GT3X device was used. This accelerometer has previously been shown to be reliable for measuring counts using vibration testing (for frequencies common to most types of daily human activities, the coefficient of variation (intra) was generally ≤2.5% (low within variability), and the coefficient of variation (inter) was generally ≤9.0% (low between variability)) (156), and valid using indirect calorimetry (e.g. a correlation coefficient of 0.81 for the relationship between counts and oxygen consumption) (138). However, as mentioned earlier in this chapter, only the outputs from the vertical axis were used; and therefore, the strengths and limitations of these data are consistent with those highlighted for the 2008 HSE accelerometer data (see Discussion section of Chapter Three). The key limitation of this study was the low number of events. Nonetheless, it has previously been shown that Cox proportional hazards regression analysis can potentially be considered as a robust estimation method even with a low number of events. A ratio of the number of events to the number of predictor variables of approximately 5 or more has been

shown to produce accurate estimates in Cox proportional hazards models (91). In this analysis, the principles of parsimony were followed and only a small number of key covariates were adjusted for - this also prevented any overfitting of the models. However, although the findings were unaffected after additionally adjusting for other potential confounders (ethnicity, accelerometer wear-time, medical history of CVD, BP and/or cholesterol medication, and aspirin medication) it is possible that other factors were confounding the associations or that reverse causation was contributing to the observed association between MVPA and all-cause mortality. In addition to the ratio of events per predictor variable, large regression coefficients and high correlations between predictor variables can cause issues in the approximation process (157). Here, all of the model coefficients were small and there were low correlations between the predictors in the models. Nevertheless, these results should be interpreted with caution; in particular, the non-significant association with sedentary time could be due to a type II error arising from a lack of statistical power.

A fuller discussion on the strengths and limitations of the Walking Away from Type 2 Diabetes database is provided in Chapter Two.

Conclusion

In conclusion, these data support the importance of MVPA in adults at high risk of T2DM. However, more research is required to assess whether objectively measured sedentary time is associated with health outcomes in those at high risk of T2DM independently of MVPA.

CHAPTER FIVE: ANALYSIS OF EPIDEMIOLOGICAL DATA: UK BIOBANK DATA

Chapter Overview

This chapter is based on the analysis of epidemiological data and uses the UK Biobank dataset. In brief, this project exploited a large nationally representative sample of adults living in the UK with comprehensive data on a broad range of outcomes (e.g. cognitive function, demographic, health, lifestyle, mental, social, etc.). In the first part of this project, I investigated the relationships between domains of sedentary behaviour and cognitive function. The findings of this original piece of work were published as a Research Article in American Journal of Epidemiology. In the second part of this project, I examined whether these relationships were modified by CRF. The findings of this original piece of work are currently under review in Preventive Medicine. Finally, in the third part of this project, I explored the associations between lifestyle factors and cognitive function. The findings of this original piece of work are currently under review in American Journal of Public Health.

Associations between Sedentary Behaviours and Cognitive Function: Cross-Sectional and Prospective Findings from the UK Biobank

Abstract

Here, I investigate the cross-sectional and prospective associations between different sedentary behaviours and cognitive function in a large sample of UK Biobank adults. Baseline data were available on 502,643 participants (years 2006 to 2010). Cognitive tests included prospective memory [N = 171,585 (baseline only)], visual-spatial memory [round 1 (N = 483,832); round 2 (N = 482,762)], fluid intelligence [N = 165,492], and short-term numeric memory [N = 50,370]. After a mean period of 5.3-years, between 12,091 and 114,373 participants also provided follow-up cognitive data. Sedentary behaviours [TV viewing, driving, and non-occupational computer use time] were measured at baseline. At baseline, both TV viewing and driving time were inversely associated with cognitive function across all outcomes [e.g. for each additional hour spent watching TV, the total number of correct answers in the fluid intelligence test was 0.15 (99% CI: 0.14, 0.16) lower]. Computer use time was positively associated with cognitive function across all outcomes. Both TV viewing and driving time at baseline were positively associated with the odds of having cognitive decline at follow-up across most outcomes. Conversely, computer use time at baseline was inversely associated with the odds of having cognitive decline at follow-up across most outcomes. This study supports health policies designed to reduce TV viewing and driving in adults.

Introduction

Currently, there are no effective long-term pharmacological therapies for the treatment or prevention of dementia. Therefore, identifying potentially modifiable risk factors of cognitive decline, a major characteristic of dementia, is a key priority. Engaging in healthy lifestyle practices, including physical activity, has been associated with a reduced risk of dementia and its symptoms, such as cognitive impairment (48, 49); suggesting a potential role for lifestyle therapies. Indeed, physical activity intervention studies have shown changes to the structure and function of the brain (50-54), supporting the observational associations.

Along with physical activity, engaging in sedentary behaviour could also be an important determinant of poor cognitive function. A recent systematic review suggested that sedentary behaviour is negatively associated with cognitive function; although the relationship between the two is complex, and recommend that future studies should focus on determining how different sedentary behaviours are associated with cognitive function (55). Limited observational research has indicated that TV viewing is inversely associated with cognition (56-59). However, different sedentary behaviours may have different associations, with some evidence of computer/internet use linked to cognitive improvement (57-60). Furthermore, most of the existing data have emerged from relatively limited cross-sectional findings (58-60). Therefore, this warrants investigation in large-scale studies with prospective data.

The aim of the first part of this chapter was to use the UK Biobank cohort to examine the cross-sectional and prospective associations between domains of sedentary behaviour (TV viewing, driving, and computer use) and cognitive function (prospective memory, visual-spatial memory, fluid intelligence and short-term numeric memory).

Methods

Design and Population

The primary aim of the UK Biobank, which is a large prospective study of the middle-aged population, is to improve the prevention, diagnosis and treatment of a wide range of medical conditions (92-94). Approximately 500,000 adults (aged 37-73 years)

were recruited between 2006-2010 via mailing out invitations to those registered with the National Health Service (NHS) and living within 25 miles of one of the 22 study assessment centres across England, Scotland, and Wales. Participants provided comprehensive baseline data on a broad range of biological, cognition, demographic, health, lifestyle, mental, social, and well-being outcomes. Approximately 300,000 participants also provided an email address to allow for the remote follow-up of cognitive function in the future. From 2014 to 2015, around 125,000 participants provided some online follow-up cognitive function data. For the present study, baseline data were available on 502,643 individuals. Of these, depending on the cognitive test, between 50,370 and 483,832 participants provided baseline cognitive function data (see Figure 3). Of these, after a mean period of 5.3 years and depending on the cognitive test, between 12,091 and 114,373 participants also provided online follow-up cognitive function data (see Figure 4). All participants provided written informed consent and the study was approved by the NHS National Research Ethics Service (Ref: 11/NW/0382). Further details are available elsewhere (92-94). Please see Chapter Two for a critical assessment of the UK Biobank database (response rates, strengths and limitations, etc.).

Figure 3 - Observational study (UK Biobank data): Flow chart of participants (cross-sectional data)

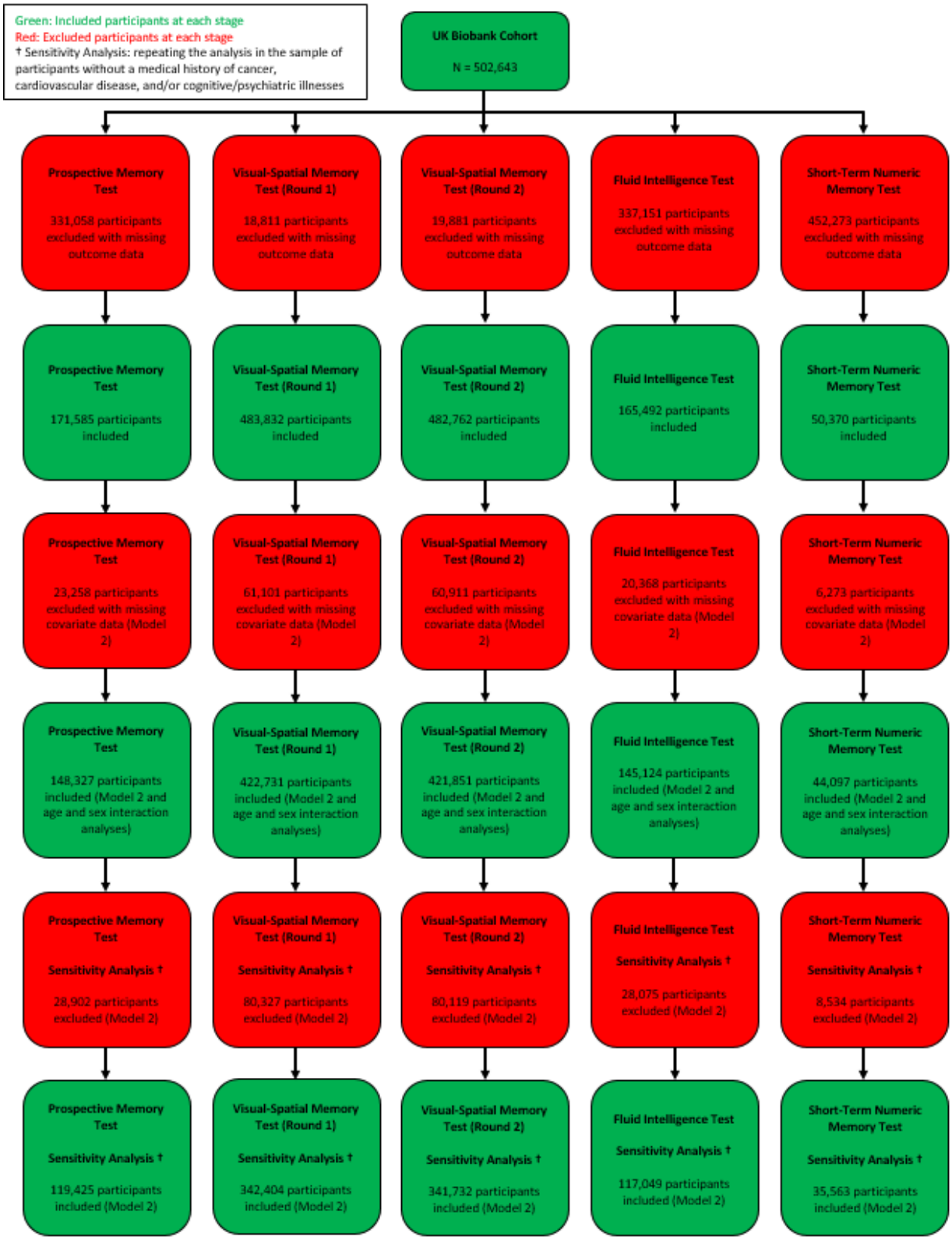


Figure 4 - Observational study (UK Biobank data): Flow chart of participants (prospective data)

Cognitive Function Tests

Questionnaires administered through a computerised touchscreen interface assessed cognitive function at baseline (110). Using the same methodology minus the touchscreen ability, follow-up measurements were obtained via online questionnaires that were completed remotely (101). To ensure effortless application on a large scale and wide response distributions, the cognitive function tests, which were refined over piloting, were designed comprehensively and specifically for UK Biobank. Prospective memory (available at baseline only), visual-spatial memory, fluid intelligence, and short-term numeric memory tests were included in this analysis. At baseline, there were variations between the numbers of individuals who completed each cognitive assessment due to tests being: abandoned or skipped by participants, incorporated towards the end of recruitment (e.g. fluid intelligence), and/or phased out during the early stages of recruitment (e.g. short-term numeric memory) (110).

Prospective memory (available at baseline only): This assessment measured prospective memory, which is the ability to remember and execute a definite instruction at a specific time or event in the future. This test was implemented at the baseline assessment centre as follows: before any of the other cognitive tests were performed, participants were shown the following text on the touchscreen: *"At the end of the games we will show you four coloured shapes and ask you to touch the Blue Square. However, to test your memory, we want you to actually touch the Orange Circle instead"*. This was followed by the other cognitive tests. After the course of these, the following text appeared: *"Please touch the Blue Square then touch the 'Next' button"*. For the cross-sectional analyses, the prospective memory result at baseline was categorised and used as a binary outcome variable: good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. The reason for this is as follows. In the UK Biobank, majority of the data points for this test lied in the 'correct recall on first attempt' category (~80%). The combined prevalence of the other categories (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect) was low (~20%). Therefore, merging these 'poor' results together

and defining them as ‘incorrect recall on first attempt’ was justified. For more details, see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data.

Visual-spatial memory (available at baseline and follow-up): This assessment measured visual-spatial memory, which is the aptitude to understand and recall the spatial associations among objects. This test involved playing two rounds of matching pairs using symbol cards [round 1: 3 pairs (6 cards), round 2: 6 pairs (12 cards)]. The test was implemented at the baseline assessment centre as follows: Cards were displayed on the touchscreen and the participants were asked to memorise the position of as many matching pairs as possible [round 1: cards shown for 3 seconds, round 2: cards shown for 5 seconds]. The cards were then turned face down and the participants were asked to select as many matching pairs as possible in the fewest tries. The test was reimplemented as an online questionnaire for the follow-up of visual-spatial memory. Data were only retained for those who matched all cards in each round (i.e. round 1: matched all 6 cards; round 2: matched all 12 cards). For the cross-sectional analyses, the pairs matching result i.e. the ‘number of incorrect matches’ in the two rounds at baseline were categorised and used as binary outcome variables. Round 1: good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. Round 2: good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. Similar to the prospective memory test, the reasons for these categorisations here are based on the distributions of the data. In the UK Biobank, majority of the individuals who took round 1 of this test had 0 incorrect matches (~70%). Therefore, combining those with ≥1 incorrect matches (~30%) was justified. In contrast, in attempt to differentiate those who performed well whilst simultaneously taking into account the greater scope of error, a less conservative categorisation was used in the round 2. For more details, see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data. Similarly, for the prospective analyses, the pairs matching result i.e. ‘number of incorrect matches’ in the two rounds at follow-up were categorised and used as binary outcome variables. Round 1: good outcome at follow-up [(reference) <1 incorrect matches at follow-up]; or poor outcome at follow-up [≥1 incorrect matches at follow-up]. Round 2: good outcome at follow-up [(reference) <2 incorrect matches at follow-up]; or poor outcome at follow-up [≥2 incorrect matches at follow-up].

Fluid intelligence (available at baseline and follow-up): This assessment measured fluid intelligence, which is the capacity to solve numeric and verbal problems that require logic and reasoning ability, discrete of any acquired knowledge. The test was implemented at the baseline assessment centre as follows: participants were asked to solve as many of the 13 fluid intelligence problems as possible within a two-minute time limit [0 points for each incorrect answer, 1 point for each correct answer (minimum score = 0, maximum score = 13)]. In comparison to the other cognitive tests at baseline, a lower number of participants had data for this assessment as it was incorporated into the touchscreen towards the end of recruitment. The test was reimplemented as an online questionnaire for the follow-up of fluid intelligence. For the cross-sectional analyses, the fluid intelligence score at baseline, quantified as the 'total number of correct answers', indicated a normal distribution (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data) and was therefore used as a continuous outcome variable. For the prospective analyses, the fluid intelligence score at follow-up was used to derive a binary fluid intelligence outcome variable: good outcome at follow-up [(reference) baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score].

Short-term numeric memory (available at baseline and follow-up): This assessment measured short-term memory via examining the ability to recall strings of numeric digits by increasing length. The test was implemented at the baseline assessment centre as follows: commencing with a 2-digit number, the number of digits to recall increased in length by 1 digit if it was remembered correctly by the participant (up to a maximum of 12 digits). In comparison to the other cognitive tests at baseline, a significantly lower number of participants had data for this assessment as it was phased out during the early stages of recruitment. The test was reimplemented as an online questionnaire for the follow-up of short-term memory. For the cross-sectional analyses, the numeric memory score at baseline, quantified as the 'maximum digits remembered correctly', indicated a normal distribution (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data) and was therefore used as a continuous outcome variable. For the prospective analyses, the numeric memory score

at follow-up was used to derive a binary numeric memory outcome variable: good outcome at follow-up [(reference) baseline numeric memory score ≤ follow-up numeric memory score]; or poor outcome at follow-up [baseline numeric memory score > follow-up numeric memory score].

Sedentary Behaviours

Data on sedentary behaviours were self-reported and collected at baseline using a questionnaire that was administered through a computerised touchscreen interface. Domains of sedentary behaviour included: TV viewing time (<1, 1, 2, 3, ≥4 hours/day), driving time (<1, 1, 2, ≥3 hours/day), and non-occupational computer use time (<1, 1, 2, ≥3 hours/day). Time spent watching TV: Participants were asked the following question: *"In a typical day, how many hours do you spend watching TV?"*. Enabled responses were: *"less than an hour a day"* or any integer value between 0 and 24 inclusive. The question was asked twice to those who reported >8 hours/day. For the present analyses, 'TV viewing time' was classified into an ordinal categorical variable: <1, 1, 2, 3, ≥4 hours/day. Time spent driving: Participants were asked the following question: *"In a typical day, how many hours do you spend driving?"*. Enabled responses were: *"less than an hour a day"* or any integer value between 0 and 24 inclusive. The question was asked twice to those who reported >6 hours/day. For the present analyses, 'Driving time' was classified into an ordinal categorical variable: <1, 1, 2, ≥3 hours/day. Time spent using computer: Participants were asked the following question: *"In a typical day, how many hours do you spend using the computer? (Do not include using a computer at work)"*. Enabled responses were: *"less than an hour a day"* or any integer value between 0 and 24 inclusive. The question was asked twice to those who reported >6 hours/day. For the present analyses, 'Computer use time' was classified into an ordinal categorical variable: <1, 1, 2, ≥3 hours/day. The reasons for these particular categorisations are based on the distributions of the data. For each sedentary behaviour, even though the enabled responses were *"less than an hour a day"* or any integer value between 0 and 24 inclusive, majority of the data were observed to be lying in the lower categories (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data). These groupings also approximated

the widely-used categories for these sedentary behaviours in this field. Therefore, overall, this justified the categorisations made above.

Confounders

Covariate data included: anthropometric (BMI), demographic (age, sex, ethnicity, social deprivation index, employment status, education level), health (number of cancers, number of non-cancer illnesses, number of medications/treatments), and lifestyle (smoking status, alcohol drinking status, sleep duration, fruit and vegetable consumption, physical activity) variables. These data were used as follows: age (continuous: years), BMI (continuous: kg/m^2), ethnicity (categorical: White British, other), sex (categorical: female, male), social deprivation index (continuous: Townsend deprivation index), employment status (categorical: in paid employment or self-employed, not in paid employment or self-employed), education level (categorical: college or university degree, no college or university degree), smoking status (categorical: never, previous, current), alcohol drinking status (categorical: never, previous, current), fruit and vegetable consumption (categorical: <5 portions/day, ≥5 portions/day), sleep duration (continuous: hours/day), physical activity [frequency of ≥10 minutes of walking (categorical: 0, 1, 2, 3, 4, 5, 6, 7 days/week), frequency of ≥10 minutes of MPA (categorical: 0, 1, 2, 3, 4, 5, 6, 7 days/week), frequency of ≥10 minutes of VPA (categorical: 0, 1, 2, 3, 4, 5, 6, 7 days/week)], number of cancers (categorical: 0, ≥1), number of non-cancer illnesses (categorical: 0, 1, 2, 3, ≥4), and number of medications/treatments (categorical: 0, 1, 2, 3, 4, 5, ≥6). The Townsend deprivation index is a measure of socioeconomic deprivation and status. By combining the census and postcode data of a population, this material deprivation score (with higher values representing greater deficiency) merges social class, car availability, employment and housing data.

Statistical Analysis

Statistical analyses were executed using Stata/MP V14.0 (Stata Corporation, College Station, Texas, USA). With the intention of maximising the use of the data, pairwise

deletion was used to handle missing data (see Figure 3 and 4). Participant characteristics were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and SDs; and presented with their minimum and maximum values.

Cross-Sectional Analysis

Regression analysis was used to examine the cross-sectional associations between the three domains of sedentary behaviour and cognitive function at baseline (Stata commands: 'logit' and 'regress') (121). Multiple logistic regression models were fitted for each binary cognitive outcome variable (prospective memory, visual-spatial memory (round 1), and visual-spatial memory (round 2)) (Stata command: 'logit') (121). Multiple linear regression models were fitted for each continuous cognitive outcome variable (fluid intelligence and short-term numeric memory) (Stata command: 'regress') (121). Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex. Model 2 was further adjusted for BMI, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, physical activity (frequency of ≥10 minutes of walking (days/week), frequency of ≥10 minutes of MPA (days/week), frequency of ≥10 minutes of VPA (days/week)), number of cancers, number of non-cancer illnesses, and number of medications/treatments. For each sedentary behaviour, the '<1 hour/day' category was selected as the reference group. Linear trends (linear terms) across the categories of each sedentary behaviour were reported. Interaction terms were separately added to the fully adjusted model (Model 2) to observe whether the associations between the sedentary behaviours and cognitive function were modified by age or sex. Significant results for age were stratified at 60 years. The assumptions of linear and logistic regression were assessed (121).

Prospective Analysis

Multiple logistic regression models investigated the prospective associations between the three domains of sedentary behaviour at baseline and cognitive function at follow-up (Stata command: 'logit') (121). These models estimated the odds of having cognitive decline (i.e. a poor outcome) at follow-up. Cognitive outcomes included: visual-spatial memory (round 1), visual-spatial memory (round 2), fluid intelligence, and short-term numeric memory. As well as controlling for the baseline result/score of the cognitive test under consideration, models were adjusted for all of the covariates mentioned previously (see list of confounders in Models 1 and 2 of the cross-sectional analyses). Linear trends across the categories of each sedentary behaviour were reported. Interactions by age and sex were also investigated. The assumptions of logistic regression were assessed (121).

Sensitivity Analysis

To assess the generalizability of the findings, the cross-sectional and prospective analyses investigating the associations between sedentary behaviours and cognitive function (Model 1 and Model 2) were repeated across the sample of participants without a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses as sensitivity analyses. For this sensitivity analysis, participants with cancer were removed from the analysis using the "Number of cancers" variable, where all participants with ≥1 cancers were excluded. Participants with CVD (angina, heart attack/myocardial infarction, and/or stroke) and/or cognitive/psychiatric illnesses (neurological injury/trauma, psychological/psychiatric problem, chronic/degenerative neurological problem, motor neurone disease, multiple sclerosis, Parkinson's disease, dementia/Alzheimer's disease/cognitive impairment, depression, anxiety/panic attacks, nervous breakdown, schizophrenia, deliberate self-harm/suicide attempt, and/or mania/bipolar disorder/manic depression) were identified and removed from the analysis using the "Non-cancer illness code" variable in the data showcase (158). This sensitivity analysis allows for the examination of the confounding impact of participants with a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses on the associations. After removing these 'unhealthy' individuals, who could

directly affect cognitive function via introducing bias through causal pathways or reverse causality, the remaining sample of 'healthier' participants would potentially provide more reliable and unbiased estimates of the associations between the different sedentary behaviours and cognitive function.

The analytical techniques described in this section (linear (continuous outcome data) and logistic (binary outcome data) regression analyses) were selected after studying the distributions of all of the key outcomes and exposures used in this analysis (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data). However, the prospective associations between the three sedentary behaviours at baseline and cognitive function at follow-up were also analysed using generalized regression modelling techniques, specifically mixed-effects logistic and linear regression models (with both fixed and random effects) (Stata commands: 'melogit' and 'mixed') (121). Multiple mixed-effects logistic regression models were fitted for each binary cognitive outcome variable (visual-spatial memory (round 1) and visual-spatial memory (round 2)) (Stata command: 'melogit'); and multiple mixed-effects linear regression models were fitted for each continuous cognitive outcome variable (fluid intelligence and short-term numeric memory) (Stata command: 'mixed'). All of the covariates mentioned previously (see list of confounders in Models 1 and 2 of the cross-sectional analyses), as well as time (years), were entered as fixed effects. Participant identification was entered as a random effect. Using all available data from baseline to follow-up, these models yielded estimates of the associations between the three sedentary behaviours at baseline and cognitive function at follow-up.

Furthermore, as opposed to continuous outcome data which is typically modelled using linear regression analysis, some of cognitive outcomes in the UK Biobank could be considered and modelled as count data (i.e. non-negative integer values: 0, 1, 2, etc.) using Poisson regression analysis (121). Therefore, to demonstrate this, using Poisson regression, I also examined the cross-sectional associations at baseline (Model 1 and Model 2) between the sedentary behaviours and the cognitive count data outcomes that were previously only intended to be modelled using linear regression (fluid intelligence test and short-term numeric memory test) (Stata command: 'poisson') (see Figure S3 in Appendix Three: Supplementary Material: Supplementary

Data). Note, the prospective data were analysed as binary categories; therefore, these additional Poisson regression models were only implemented in the cross-sectional data at baseline.

Statistical Reporting

For each variable of interest (sedentary behaviours), β (linear regression or mixed-effects linear regression), odds ratio (OR) (logistic regression or mixed-effects logistic regression), or incidence rate ratio (IRR) with 99% CIs and p-values are reported. For binary cognitive outcome variables (prospective memory and visual-spatial memory) in the cross-sectional analysis, an OR of less than 1 indicates lower odds of a poor result; and an OR of greater than 1 indicates higher odds of a poor result. For continuous cognitive outcome variables (fluid intelligence and short-term numeric memory) in the cross-sectional analysis, a β of greater than 0 indicates a higher score; and a β of less than 0 indicates a lower score. As mentioned previously, these two cognitive outcomes could also be modelled as counts. Accordingly, for count cognitive outcome variables (fluid intelligence and short-term numeric memory) in the cross-sectional analysis, an IRR of greater than 1 indicates a higher rate of a high score; and an IRR of less than 1 indicates a lower rate of a high score. For all cognitive outcome variables in the prospective analysis (all binary variables), an OR of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an OR of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up). All analyses employed robust SEs and all reported p-values are two-sided. To account for multiple comparisons, p-value<0.01 was considered to be statistically significant for the main analyses. For the interaction analyses, p-value<0.05 was considered to be statistically significant.

Results

Cross-Sectional Findings

Table 12 presents the characteristics of the 502,643 participants with baseline data. The mean (SD) age of these individuals was 56.5 (8.1) years and 273,467 (54.4%) were female.

Table 12 - Observational study (UK Biobank data): Participant characteristics

Participant characteristics	N = 502,643
Anthropometric	
Body mass index (kg/m^2) [a]	27.4 (4.8); 12.1 - 74.7
Missing [b]	3,105 (0.6)
Demographic	
Age (years) [a]	56.5 (8.1); 37.0 - 73.0
Missing [b]	0 (0.0)
Ethnicity [c]	
White British	442,699 (88.1)
Other	57,166 (11.4)
Missing [b]	2,778 (0.5)
Sex [c]	
Female	273,467 (54.4)
Male	229,176 (45.6)
Missing [b]	0 (0.0)
Social deprivation index [a]	-1.3 (3.1); -6.3 - 11.0
Missing [b]	627 (0.1)
Employment status [c]	
In paid employment or self-employed	287,234 (57.1)
Not in paid employment or self-employed	212,451 (42.3)
Missing [b]	2,958 (0.6)
Education level [c]	
College or university degree	161,210 (32.1)
No college or university degree	331,291 (65.9)
Missing [b]	10,142 (2.0)
Lifestyle	
Smoking status [c]	
Never	273,603 (54.4)
Previous	173,099 (34.4)
Current	52,989 (10.6)
Missing [b]	2,952 (0.6)
Alcohol drinking status [c]	
Never	22,547 (4.5)
Previous	18,114 (3.6)
Current	460,479 (91.6)
Missing [b]	1,503 (0.3)

Fruit and vegetable consumption (portions/day) [c]	
<5	300,352 (59.8)
≥5	189,979 (37.8)
Missing [b]	12,312 (2.4)
Sleep duration (hours/day) [a]	7.2 (1.1); 1.0 - 23.0
Missing [b]	4,218 (0.8)
Frequency of ≥10 minutes of walking (days/week) [c]	
0	12,455 (2.5)
1	13,459 (2.7)
2	29,991 (6.0)
3	39,339 (7.8)
4	40,036 (8.0)
5	80,039 (15.9)
6	50,082 (9.9)
7	228,697 (45.5)
Missing [b]	8,545 (1.7)
Frequency of ≥10 minutes of moderate-intensity physical activity (days/week) [c]	
0	61,178 (12.2)
1	38,290 (7.6)
2	69,799 (13.9)
3	71,507 (14.2)
4	47,201 (9.4)
5	71,441 (14.2)
6	26,436 (5.3)
7	89,506 (17.8)
Missing [b]	27,285 (5.4)
Frequency of ≥10 minutes of vigorous-intensity physical activity (days/week) [c]	
0	178,275 (35.5)
1	66,853 (13.3)
2	75,055 (14.9)
3	65,276 (13.0)
4	30,705 (6.1)
5	32,452 (6.5)
6	9,430 (1.9)
7	17,005 (3.4)
Missing [b]	27,592 (5.5)
Health	
Number of cancers [c]	
0	460,075 (91.5)
≥1	41,706 (8.3)
Missing [b]	862 (0.2)

Number of non-cancer illnesses [c]	
0	126,639 (25.2)
1	134,113 (26.7)
2	98,825 (19.6)
3	62,828 (12.5)
≥4	79,376 (15.8)
Missing [b]	862 (0.2)
Number of medications/treatments [c]	
0	137,704 (27.4)
1	94,776 (18.8)
2	77,673 (15.4)
3	57,819 (11.5)
4	42,211 (8.4)
5	29,937 (6.0)
≥6	61,661 (12.3)
Missing [b]	862 (0.2)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [c]	
No	402,897 (80.2)
Yes	99,746 (19.8)
Missing [b]	0 (0.0)
Sedentary behaviour	
TV viewing time (hours/day) [c]	
<1	39,456 (7.8)
1	62,503 (12.4)
2	132,780 (26.4)
3	116,940 (23.3)
≥4	145,546 (29.0)
Missing [b]	5,418 (1.1)
Driving time (hours/day) [c]	
<1	259,920 (51.7)
1	140,144 (27.9)
2	60,977 (12.1)
≥3	31,663 (6.3)
Missing [b]	9,939 (2.0)
Computer use time (hours/day) [c]	
<1	240,648 (47.9)
1	140,821 (28.0)
2	62,859 (12.5)
≥3	48,939 (9.7)
Missing [b]	9,376 (1.9)
Cognitive function at baseline	

Prospective memory test [c]		
Good result (correct recall on first attempt)		130,910 (26.0)
Poor result (incorrect recall on first attempt)		40,675 (8.1)
Missing [b]		331,058 (65.9)
Visual-spatial memory test (round 1) [c]		
Good result (<1 incorrect matches)		345,685 (68.8)
Poor result (≥1 incorrect matches)		138,147 (27.5)
Missing [b]		18,811 (3.7)
Visual-spatial memory test (round 2) [c]		
Good result (<2 incorrect matches)		82,130 (16.3)
Poor result (≥2 incorrect matches)		400,632 (79.7)
Missing [b]		19,881 (4.0)
Fluid intelligence test [a]		
Total number of correct answers		6.0 (2.2); 0.0 - 13.0
Missing [b]		337,151 (67.1)
Short-term numeric memory test [a]		
Maximum digits remembered		6.7 (1.3); 2.0 - 12.0
Missing [b]		452,273 (90.0)
Cognitive function at follow-up [d]	N (range) = 12,091 to 114,373	
	Baseline	Follow-up
Visual-spatial memory test (round 1) (N = 114,373) [c]		
Good result (<1 incorrect matches)	89,137 (77.9)	70,761 (61.9)
Poor result (≥1 incorrect matches)	25,236 (22.1)	43,612 (38.1)
Good outcome at follow-up		70,761 (61.9)
Poor outcome at follow-up		43,612 (38.1)
Visual-spatial memory test (round 2) (N = 113,479) [c]		
Good result (<2 incorrect matches)	23,262 (20.5)	14,886 (13.1)
Poor result (≥2 incorrect matches)	90,217 (79.5)	98,593 (86.9)
Good outcome at follow-up		14,886 (13.1)
Poor outcome at follow-up		98,593 (86.9)
Fluid intelligence test (N = 46,704) [a]		
Total number of correct answers	6.7 (2.1); 0.0 - 13.0	5.5 (2.0); 0.0 - 13.0
Good outcome at follow-up		15,384 (32.9)
Poor outcome at follow-up		31,320 (67.1)
Short-term numeric memory test (N = 12,091) [a]		
Maximum digits remembered	7.0 (1.2); 2.0 - 12.0	6.9 (1.5); 2.0 - 11.0

Good outcome at follow-up	7,791 (64.4)
Poor outcome at follow-up	4,300 (35.6)

[a] *Continuous variable: mean (standard deviation); minimum - maximum*
[b] *Number (%)*
[c] *Categorical variable: number (%)*
[d] *Participants with cognitive function data at both baseline and follow-up*

Table 13 presents the associations between the sedentary behaviours and cognitive function. In the fully adjusted models (Model 2), the cross-sectional data showed that TV viewing time was inversely associated with cognitive function across all outcomes apart from visual-spatial memory (round 2). For example, for each additional hour spent watching TV up to ≥4 hours/day, the fluid intelligence and short-term numeric memory scores were 0.15 (99% CI: 0.14, 0.16) and 0.09 (99% CI: 0.07, 0.10) units lower, respectively. Correspondingly, the odds of a poor result in the prospective memory and visual-spatial memory (round 1) tests were 2% (0%, 3%) and 3% (2%, 4%) higher, respectively. Driving time was inversely associated with cognitive function across all outcomes. In contrast, computer use time was positively associated with cognitive function across all outcomes. Model assumptions were satisfied.

Table 13 - Observational study (UK Biobank data): Cross-sectional associations at baseline between sedentary behaviours and cognitive function

Sedentary behaviours and cognitive function (Model 1 and Model 2) [a b]	Prospective memory test [c]	Visual-spatial memory test (round 1) [d]	Visual-spatial memory test (round 2) [e]	Fluid intelligence test [f]	Short-term numeric memory test [g]
	Good result or Poor result	Good result or Poor result	Good result or Poor result	Total number of correct answers	Maximum digits remembered correctly
Model 1 [a]	N = 166,401	N = 471,474	N = 470,433	N = 161,348	N = 49,035
	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	β (99% CI) [i]; p-value	β (99% CI) [i]; p-value
TV viewing time (hours/day)					
<1 (reference)	-	-	-	-	-
1	0.99 (0.93, 1.07); 0.838	**1.05 (1.01, 1.09); 0.002**	1.01 (0.96, 1.05); 0.712	**-0.13 (-0.19, -0.07); <0.001**	**-0.15 (-0.22, -0.08); <0.001**
2	0.94 (0.88, 1.00); 0.012	**1.07 (1.03, 1.11); <0.001**	1.02 (0.98, 1.06); 0.303	**-0.30 (-0.36, -0.24); <0.001**	**-0.25 (-0.31, -0.19); <0.001**
3	0.97 (0.91, 1.04); 0.303	**1.14 (1.10, 1.18); <0.001**	1.03 (0.99, 1.08); 0.036	**-0.54 (-0.60, -0.49); <0.001**	**-0.35 (-0.41, -0.29); <0.001**
≥4	**1.23 (1.15, 1.30); <0.001**	**1.26 (1.22, 1.31); <0.001**	**1.08 (1.03, 1.12); <0.001**	**-0.99 (-1.04, -0.93); <0.001**	**-0.55 (-0.61, -0.48); <0.001**
Linear trend	**1.07 (1.05, 1.08); <0.001**	**1.06 (1.06, 1.07); <0.001**	**1.02 (1.01, 1.03); <0.001**	**-0.26 (-0.27, -0.25); <0.001**	**-0.13 (-0.15, -0.12); <0.001**
Driving time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**1.05 (1.02, 1.09); <0.001**	0.99 (0.97, 1.01); 0.270	1.01 (0.98, 1.03); 0.569	**-0.19 (-0.22, -0.16); <0.001**	-0.02 (-0.06, 0.01); 0.139
2	**1.12 (1.07, 1.18); <0.001**	**1.05 (1.02, 1.08); <0.001**	1.03 (1.00, 1.06); 0.024	**-0.37 (-0.41, -0.33); <0.001**	**-0.13 (-0.18, -0.08); <0.001**
≥3	**1.50 (1.41, 1.60); <0.001**	**1.26 (1.22, 1.31); <0.001**	**1.12 (1.07, 1.17); <0.001**	**-0.88 (-0.94, -0.82); <0.001**	**-0.28 (-0.34, -0.21); <0.001**
Linear trend	**1.11 (1.09, 1.12); <0.001**	**1.05 (1.04, 1.06); <0.001**	**1.03 (1.01, 1.04); <0.001**	**-0.24 (-0.26, -0.23); <0.001**	**-0.08 (-0.09, -0.06); <0.001**
Computer use time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**0.68 (0.66, 0.71); <0.001**	**0.79 (0.77, 0.80); <0.001**	**0.85 (0.83, 0.87); <0.001**	**0.52 (0.49, 0.55); <0.001**	**0.21 (0.17, 0.25); <0.001**
2	**0.69 (0.66, 0.72); <0.001**	**0.77 (0.75, 0.79); <0.001**	**0.80 (0.78, 0.83); <0.001**	**0.58 (0.53, 0.62); <0.001**	**0.21 (0.16, 0.26); <0.001**
≥3	**0.86 (0.82, 0.90); <0.001**	**0.81 (0.79, 0.84); <0.001**	**0.82 (0.79, 0.85); <0.001**	**0.40 (0.35, 0.44); <0.001**	**0.16 (0.11, 0.22); <0.001**

Linear trend	**0.91 (0.89, 0.92); <0.001**	**0.91 (0.90, 0.92); <0.001**	**0.92 (0.91, 0.93); <0.001**	**0.18 (0.17, 0.20); <0.001**	**0.07 (0.06, 0.09); <0.001**

Model 2 [b]	N = 148,327 OR (99% CI) [h]; p-value	N = 422,731 OR (99% CI) [h]; p-value	N = 421,851 OR (99% CI) [h]; p-value	N = 145,124 β (99% CI) [i]; p-value	N = 44,097 β (99% CI) [i]; p-value
TV viewing time (hours/day)					
<1 (reference)	-	-	-	-	-
1	1.04 (0.96, 1.12); 0.232	**1.07 (1.03, 1.12); <0.001**	1.01 (0.97, 1.06); 0.403	**-0.12 (-0.18, -0.06); <0.001**	**-0.13 (-0.20, -0.06); <0.001**
2	0.96 (0.90, 1.03); 0.142	**1.07 (1.03, 1.11); <0.001**	1.02 (0.98, 1.07); 0.128	**-0.21 (-0.27, -0.16); <0.001**	**-0.20 (-0.26, -0.13); <0.001**
3	0.96 (0.89, 1.03); 0.159	**1.09 (1.05, 1.14); <0.001**	1.03 (0.98, 1.07); 0.136	**-0.33 (-0.39, -0.28); <0.001**	**-0.25 (-0.32, -0.19); <0.001**
≥4	**1.09 (1.01, 1.17); 0.003**	**1.14 (1.10, 1.19); <0.001**	1.03 (0.99, 1.08); 0.053	**-0.58 (-0.64, -0.53); <0.001**	**-0.38 (-0.44, -0.31); <0.001**
Linear trend	**1.02 (1.00, 1.03); 0.001**	**1.03 (1.02, 1.04); <0.001**	1.01 (1.00, 1.02); 0.057	**-0.15 (-0.16, -0.14); <0.001**	**-0.09 (-0.10, -0.07); <0.001**
Driving time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**1.21 (1.17, 1.27); <0.001**	**1.05 (1.03, 1.07); <0.001**	**1.04 (1.02, 1.07); <0.001**	**-0.28 (-0.31, -0.25); <0.001**	**-0.06 (-0.10, -0.03); <0.001**
2	**1.27 (1.20, 1.34); <0.001**	**1.10 (1.06, 1.13); <0.001**	**1.07 (1.03, 1.10); <0.001**	**-0.43 (-0.48, -0.39); <0.001**	**-0.18 (-0.23, -0.13); <0.001**
≥3	**1.54 (1.43, 1.66); <0.001**	**1.23 (1.19, 1.28); <0.001**	**1.11 (1.06, 1.16); <0.001**	**-0.73 (-0.79, -0.68); <0.001**	**-0.27 (-0.34, -0.19); <0.001**
Linear trend	**1.15 (1.13, 1.17); <0.001**	**1.06 (1.05, 1.07); <0.001**	**1.04 (1.02, 1.05); <0.001**	**-0.24 (-0.25, -0.22); <0.001**	**-0.09 (-0.11, -0.07); <0.001**
Computer use time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**0.77 (0.74, 0.81); <0.001**	**0.85 (0.83, 0.87); <0.001**	**0.88 (0.86, 0.90); <0.001**	**0.32 (0.29, 0.35); <0.001**	**0.14 (0.10, 0.17); <0.001**
2	**0.74 (0.70, 0.78); <0.001**	**0.81 (0.79, 0.83); <0.001**	**0.83 (0.80, 0.86); <0.001**	**0.40 (0.36, 0.44); <0.001**	**0.15 (0.10, 0.20); <0.001**
≥3	**0.86 (0.81, 0.91); <0.001**	**0.84 (0.81, 0.86); <0.001**	**0.84 (0.81, 0.88); <0.001**	**0.26 (0.22, 0.31); <0.001**	**0.13 (0.07, 0.18); <0.001**
Linear trend	**0.92 (0.90, 0.94); <0.001**	**0.92 (0.91, 0.93); <0.001**	**0.93 (0.92, 0.94); <0.001**	**0.12 (0.11, 0.14); <0.001**	**0.06 (0.04, 0.07); <0.001**

[a] *Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex*

[b] *Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments*

[c] *Prospective memory result: categorical (binary): good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[d] *Pairs matching result (round 1): categorical (binary): good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[e] *Pairs matching result (round 2): categorical (binary): good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[f] *Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*

[g] *Numeric memory score: continuous: maximum digits remembered correctly. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*

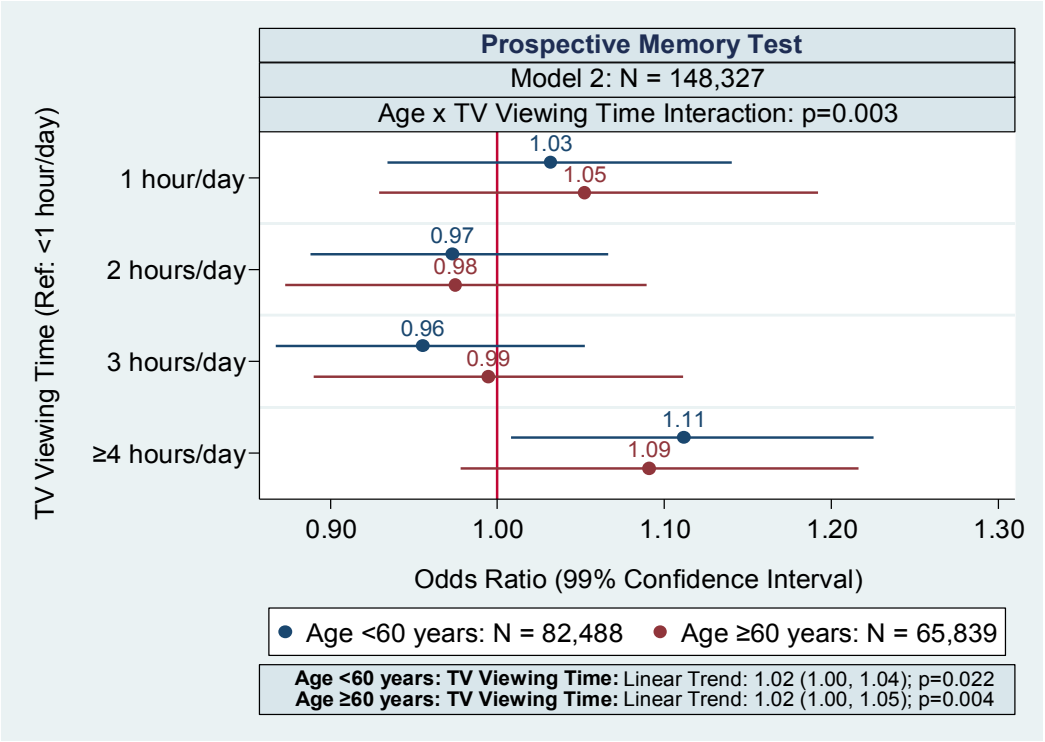
[h] *Odds ratio (99% confidence interval)*

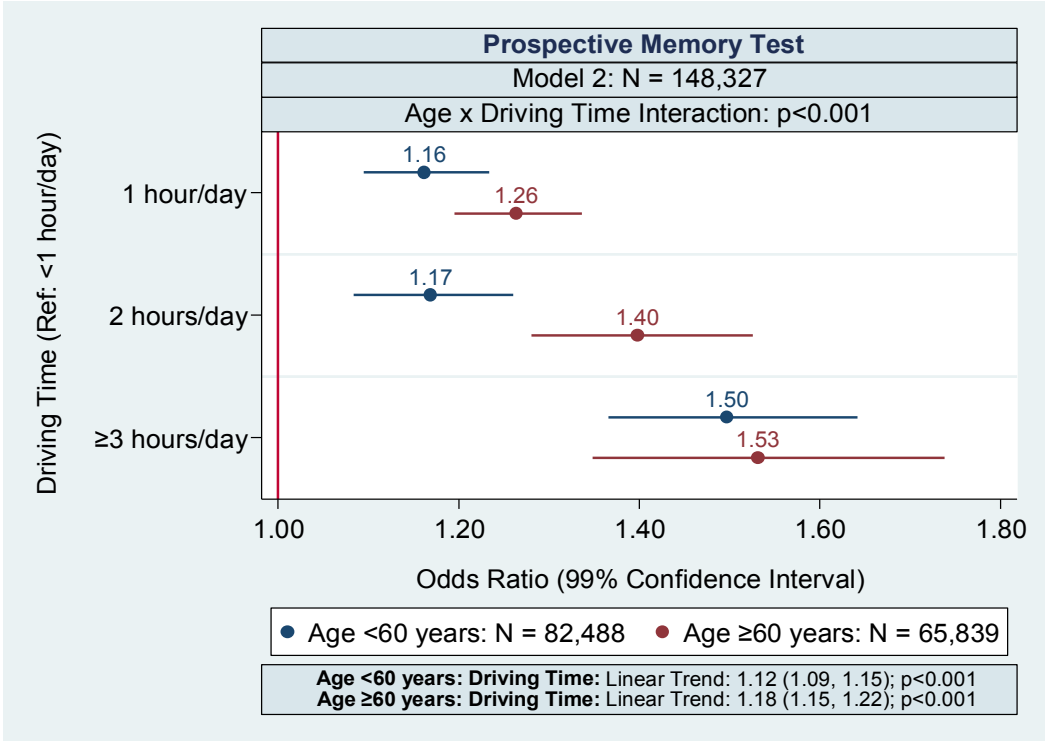
[i] *Beta coefficient (99% confidence interval)*

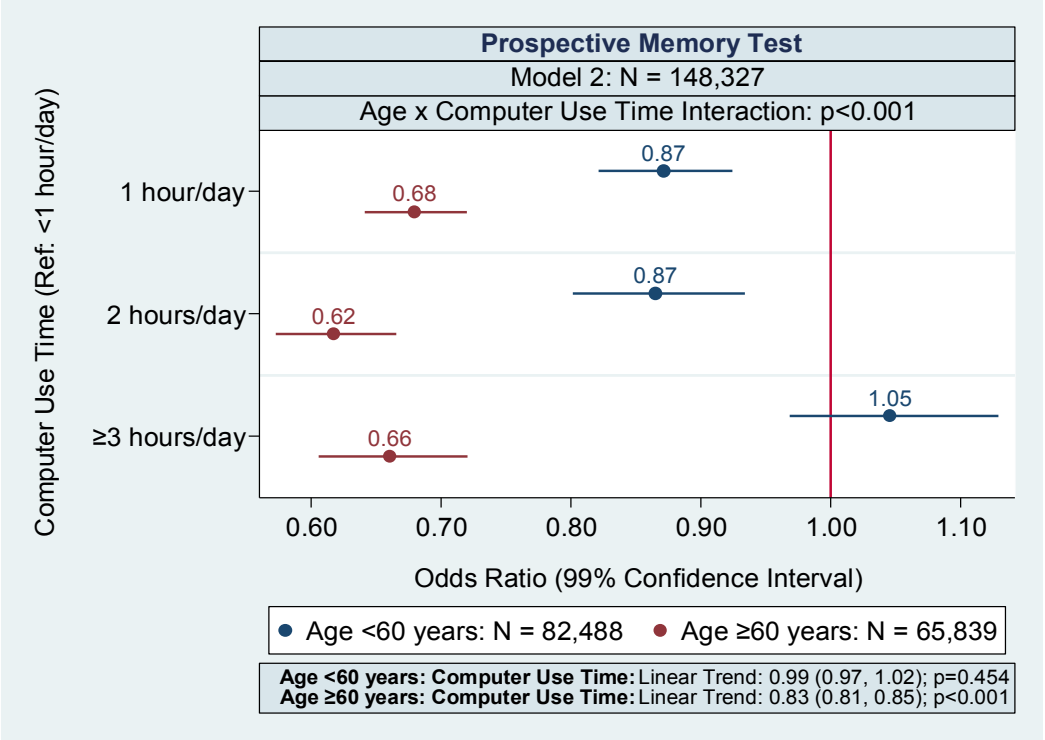
***Bold** indicates statistical significance (i.e. p-value<0.01).*

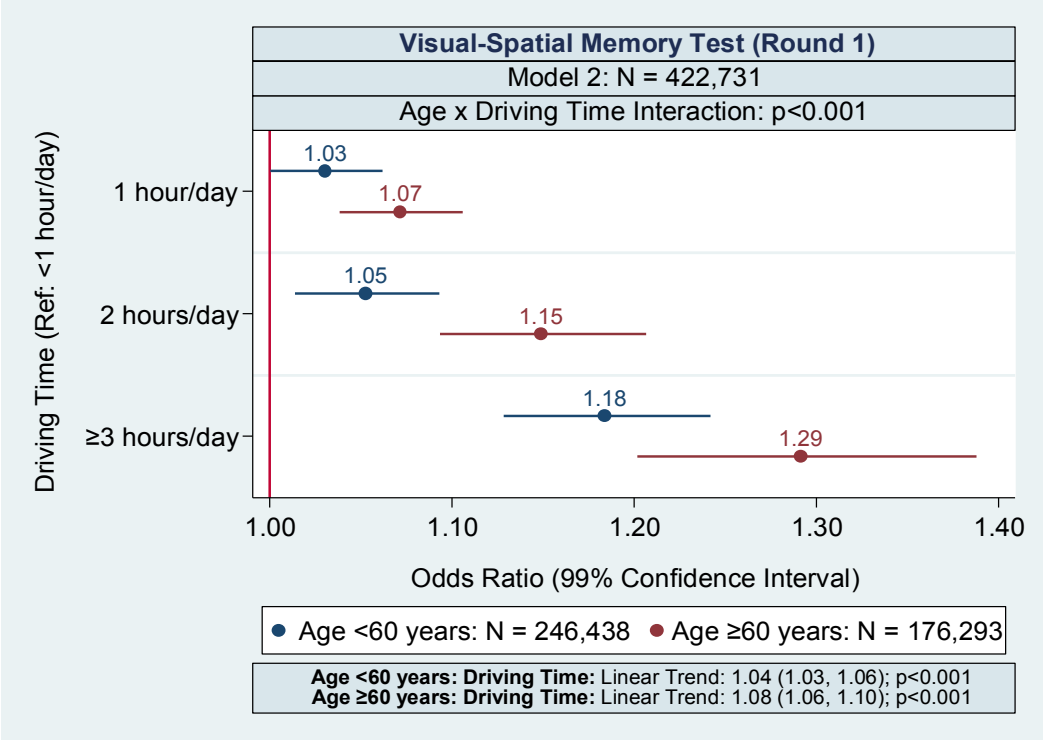
Interaction analyses showed that most findings were modified by age and sex (p-value<0.05). Stratification indicated that the associations were generally stronger in older adults (≥60 years) and in males (see Figures 5 (age) and 6 (sex)). Model assumptions were satisfied.

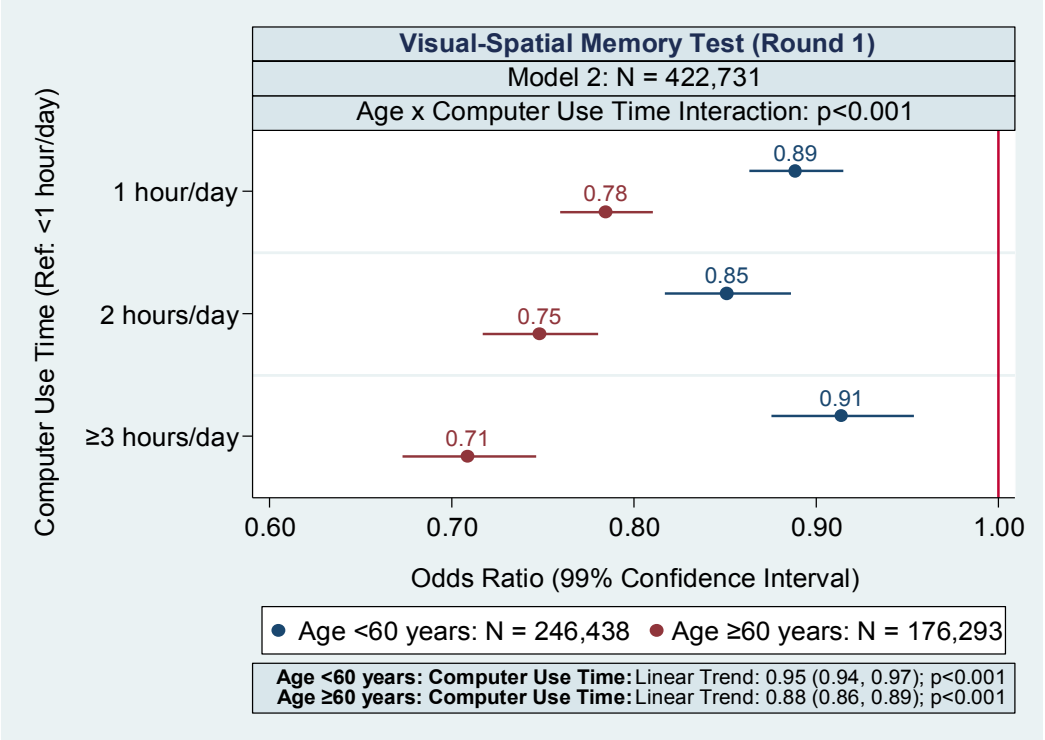
Figure 5 - Observational study (UK Biobank data): Interactions by age: cross-sectional associations at baseline between sedentary behaviours and cognitive function

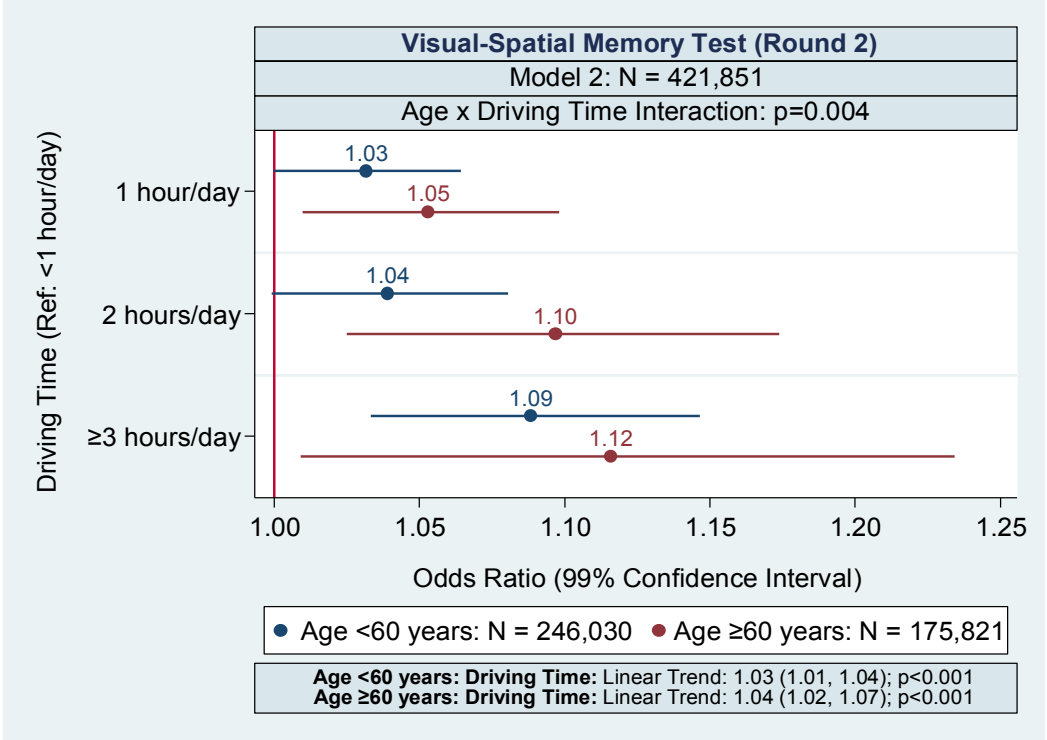


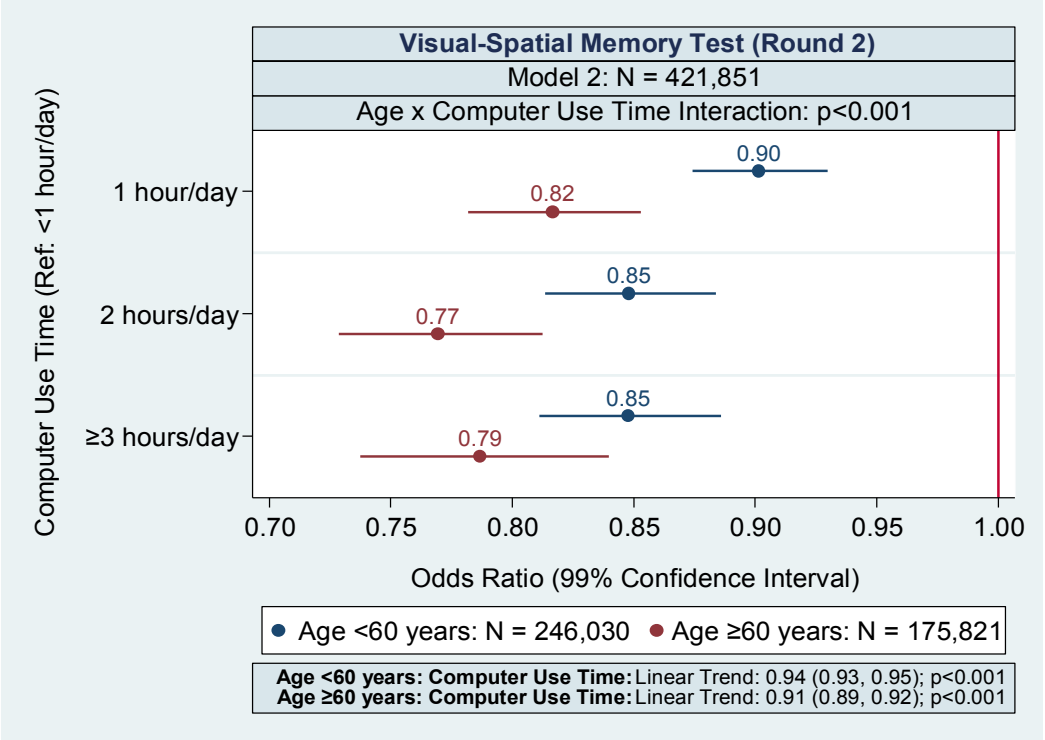


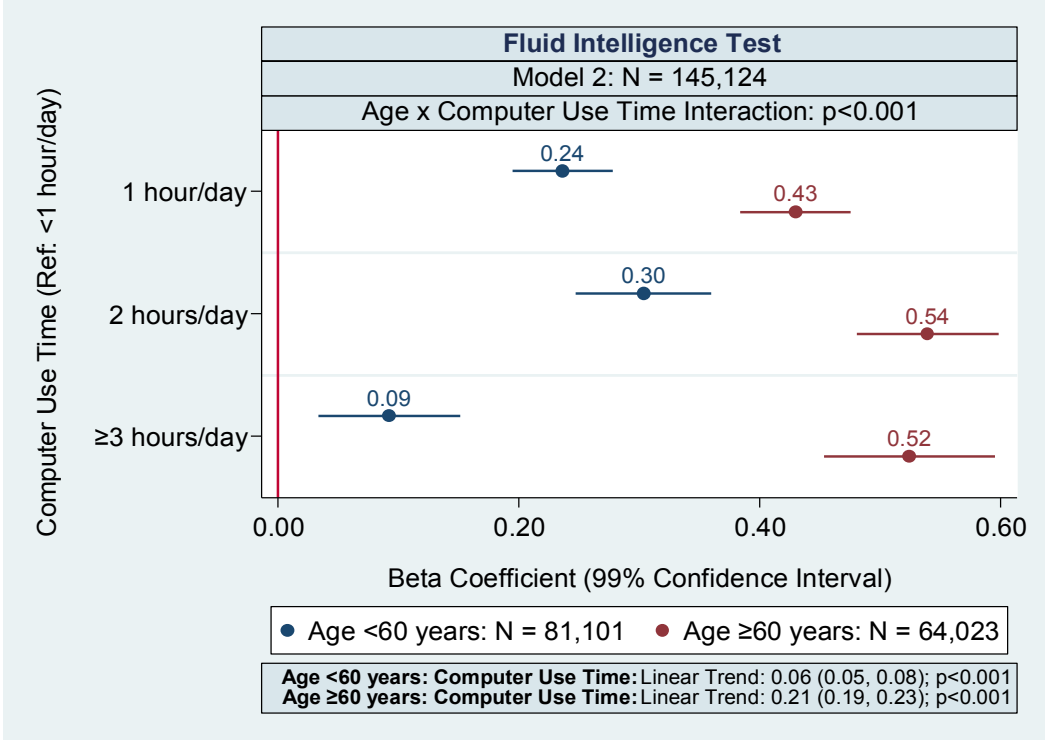

Prospective Memory Test
Model 2: N = 148,327
Age x Computer Use Time Interaction: p<0.001
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.87
0.68
0.87
0.62
1.05
0.66
0.60
0.70
0.80
0.90
1.00
1.10
Odds Ratio (99% Confidence Interval)
Age <60 years: N = 82,488
Age ≥60 years: N = 65,839
Age <60 years: Computer Use Time: Linear Trend: 0.99 (0.97, 1.02); p=0.454
Age ≥60 years: Computer Use Time: Linear Trend: 0.83 (0.81, 0.85); p<0.001

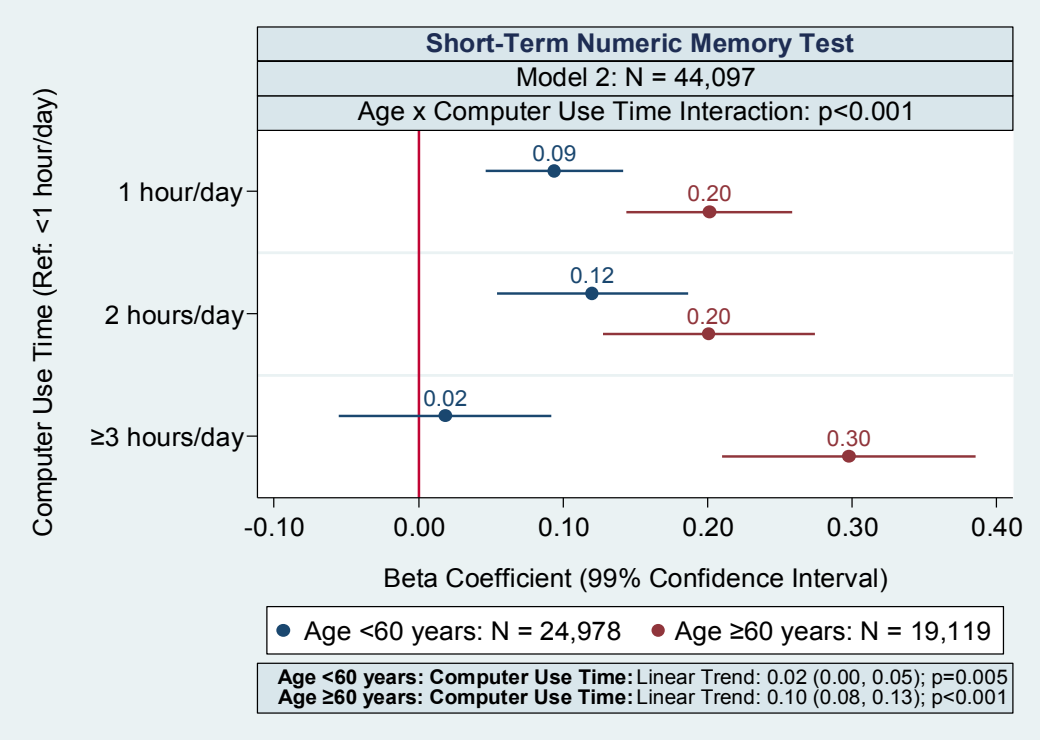

Visual-Spatial Memory Test (Round 1)
Model 2: N = 422,731
Age x Driving Time Interaction: p<0.001
Driving Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
1.03
1.07
1.05
1.15
1.18
1.29
1.00
1.10
1.20
1.30
1.40
Odds Ratio (99% Confidence Interval)
Age <60 years: N = 246,438
Age ≥60 years: N = 176,293
Age <60 years: Driving Time: Linear Trend: 1.04 (1.03, 1.06); p<0.001
Age ≥60 years: Driving Time: Linear Trend: 1.08 (1.06, 1.10); p<0.001


Visual-Spatial Memory Test (Round 1)
Model 2: N = 422,731
Age x Computer Use Time Interaction: p<0.001
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.89
0.78
0.85
0.75
0.91
0.71
0.60
0.70
0.80
0.90
1.00
Odds Ratio (99% Confidence Interval)
Age <60 years: N = 246,438
Age ≥60 years: N = 176,293
Age <60 years: Computer Use Time: Linear Trend: 0.95 (0.94, 0.97); p<0.001
Age ≥60 years: Computer Use Time: Linear Trend: 0.88 (0.86, 0.89); p<0.001


Visual-Spatial Memory Test (Round 2)
Model 2: N = 421,851
Age x Driving Time Interaction: p=0.004
Driving Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
1.03
1.05
1.04
1.10
1.09
1.12
1.00
1.05
1.10
1.15
1.20
1.25
Odds Ratio (99% Confidence Interval)
Age <60 years: N = 246,030
Age ≥60 years: N = 175,821
Age <60 years: Driving Time: Linear Trend: 1.03 (1.01, 1.04); p<0.001
Age ≥60 years: Driving Time: Linear Trend: 1.04 (1.02, 1.07); p<0.001


Visual-Spatial Memory Test (Round 2)
Model 2: N = 421,851
Age x Computer Use Time Interaction: p<0.001
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.90
0.82
0.85
0.77
0.85
0.79
0.70
0.75
0.80
0.85
0.90
0.95
1.00
Odds Ratio (99% Confidence Interval)
Age <60 years: N = 246,030
Age ≥60 years: N = 175,821
Age <60 years: Computer Use Time: Linear Trend: 0.94 (0.93, 0.95); p<0.001
Age ≥60 years: Computer Use Time: Linear Trend: 0.91 (0.89, 0.92); p<0.001


Fluid Intelligence Test
Model 2: N = 145,124
Age x Computer Use Time Interaction: p<0.001
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.24
0.43
0.30
0.54
0.09
0.52
0.00
0.20
0.40
0.60
Beta Coefficient (99% Confidence Interval)
Age <60 years: N = 81,101
Age ≥60 years: N = 64,023
Age <60 years: Computer Use Time: Linear Trend: 0.06 (0.05, 0.08); p<0.001
Age ≥60 years: Computer Use Time: Linear Trend: 0.21 (0.19, 0.23); p<0.001



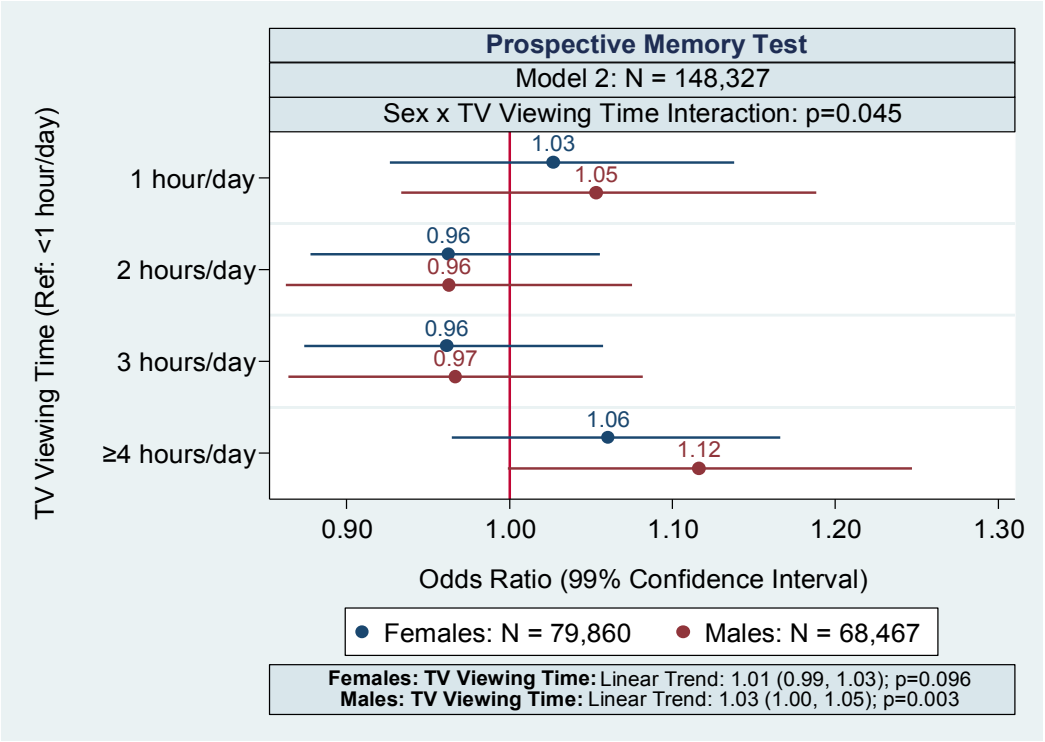
Prospective memory result: categorical (binary): good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 1): categorical (binary): good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 2): categorical (binary): good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.
Numeric memory score: continuous: maximum digits remembered correctly. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

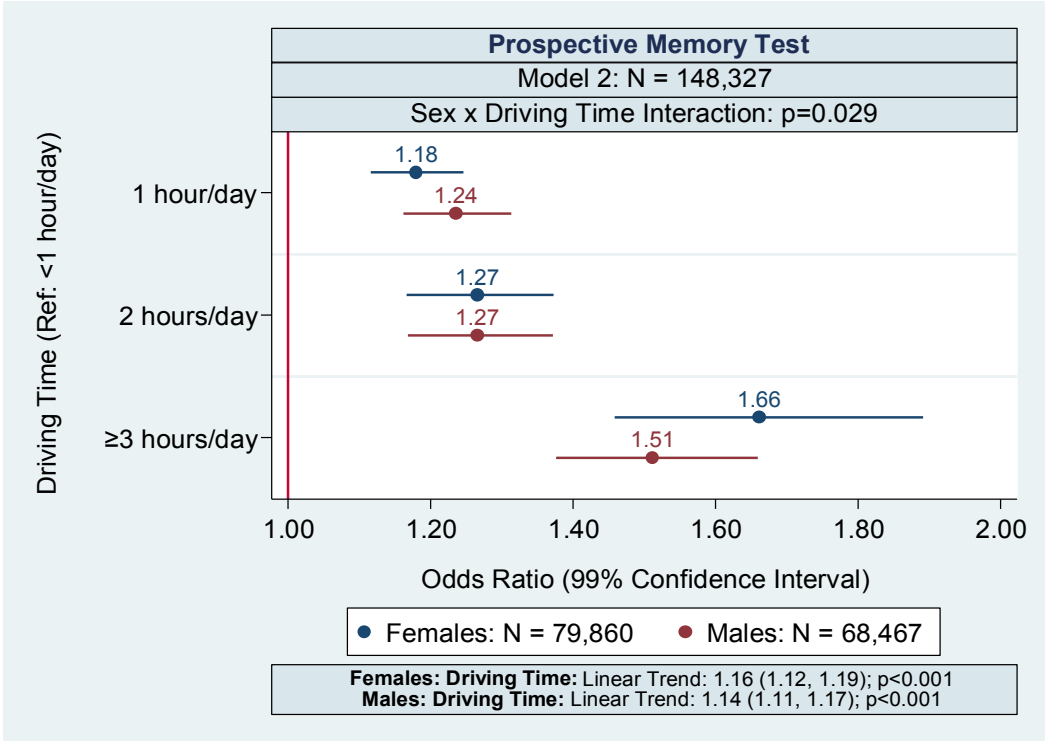
Interaction between age and TV viewing time (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were adjusted for body mass index, ethnicity, sex, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, driving time, and computer use time.

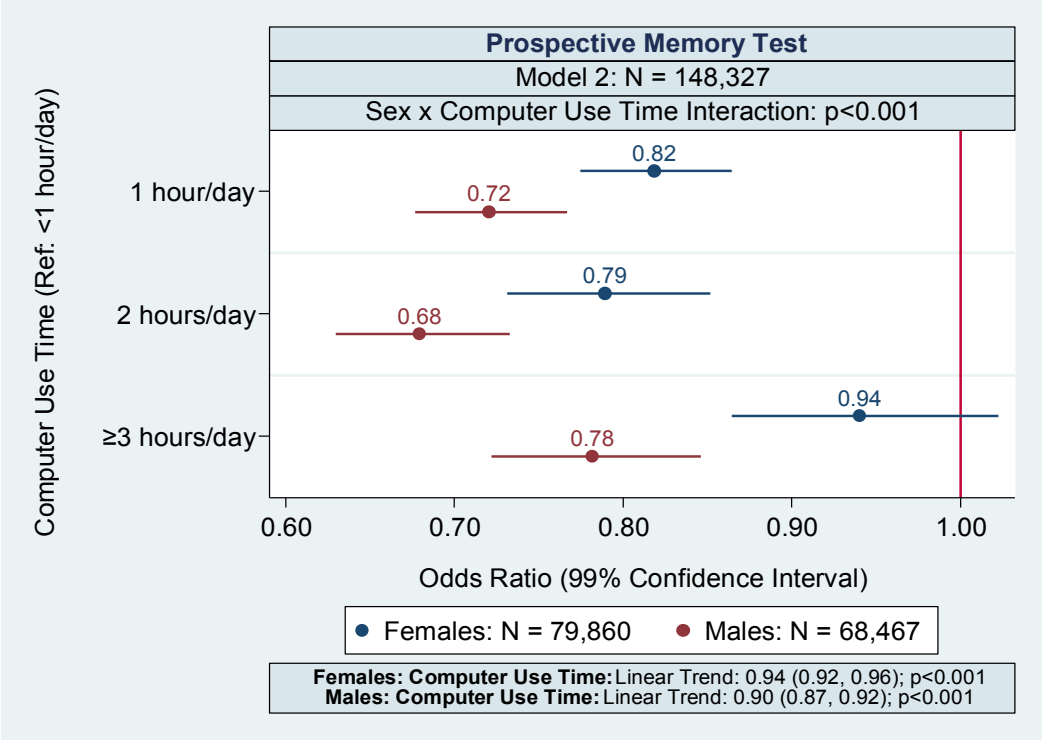
Interaction between age and driving time (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were adjusted for body mass index, ethnicity, sex, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, TV viewing time, and computer use time.

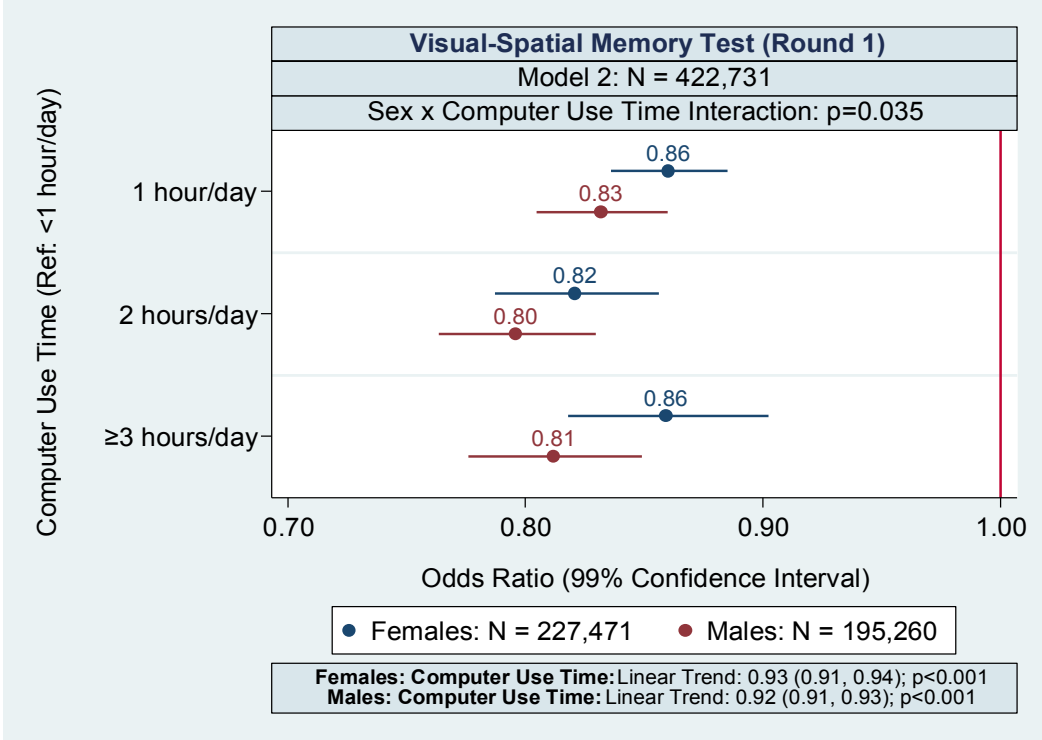
Interaction between age and computer use time (statistical significance was established at p-value<0.05): stratified model (statistical significance was established at p-value<0.01) were adjusted for body mass index, ethnicity, sex, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, TV viewing time, and driving time.

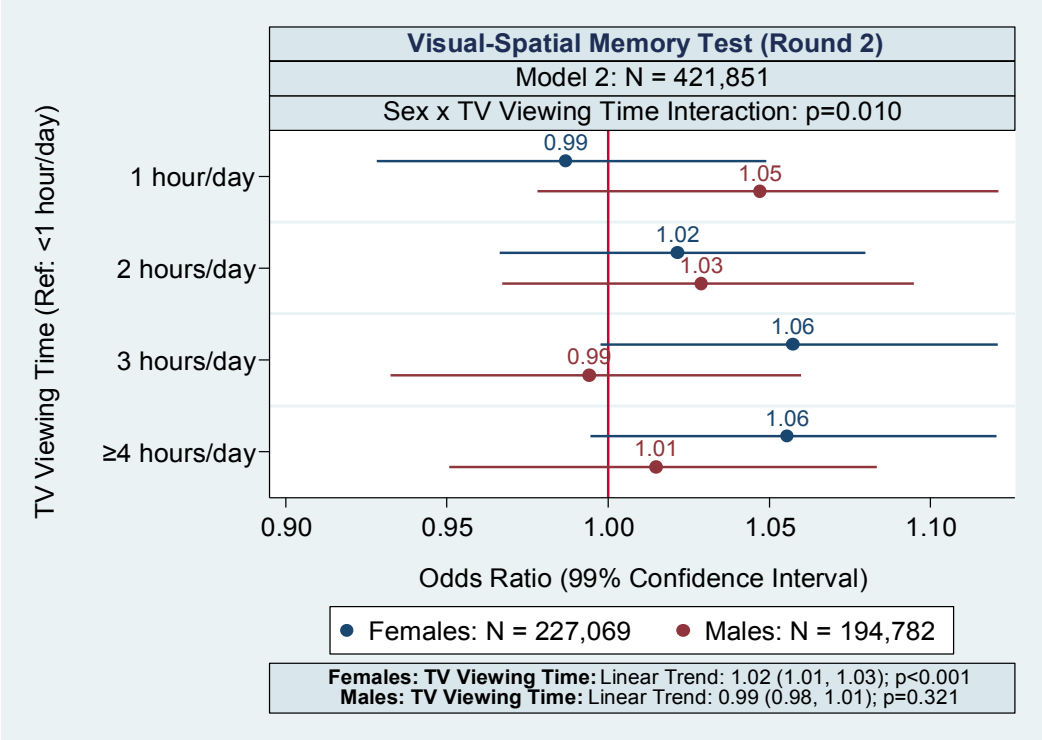
Figure 6 - Observational study (UK Biobank data): Interactions by sex: cross-sectional associations at baseline between sedentary behaviours and cognitive function

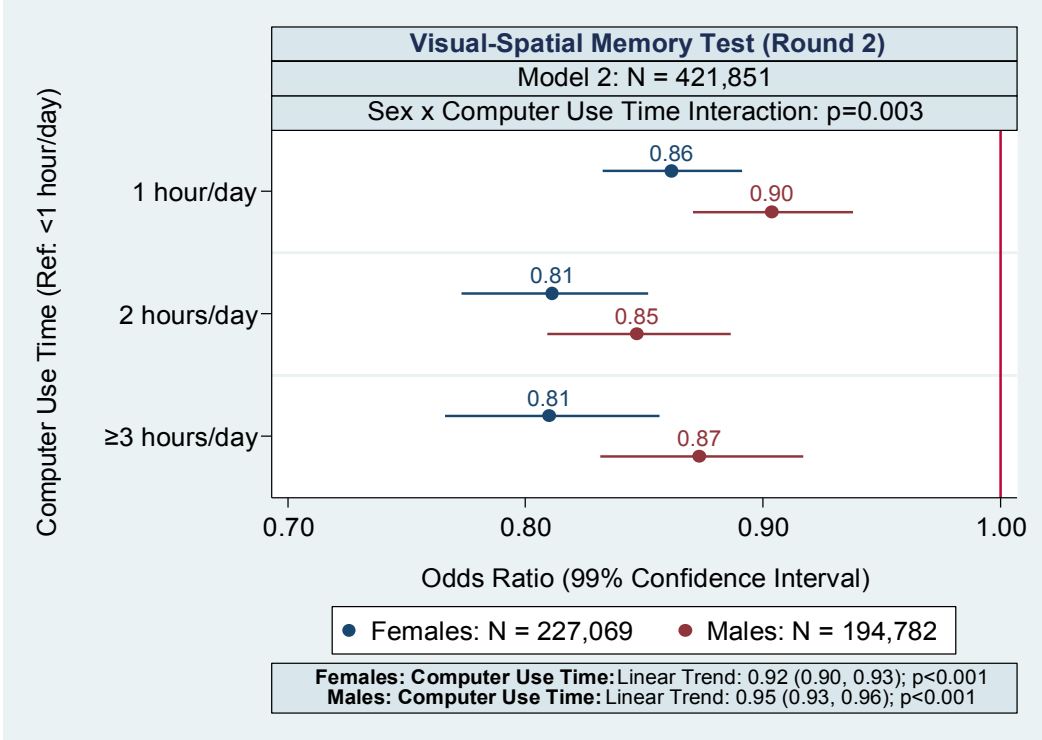


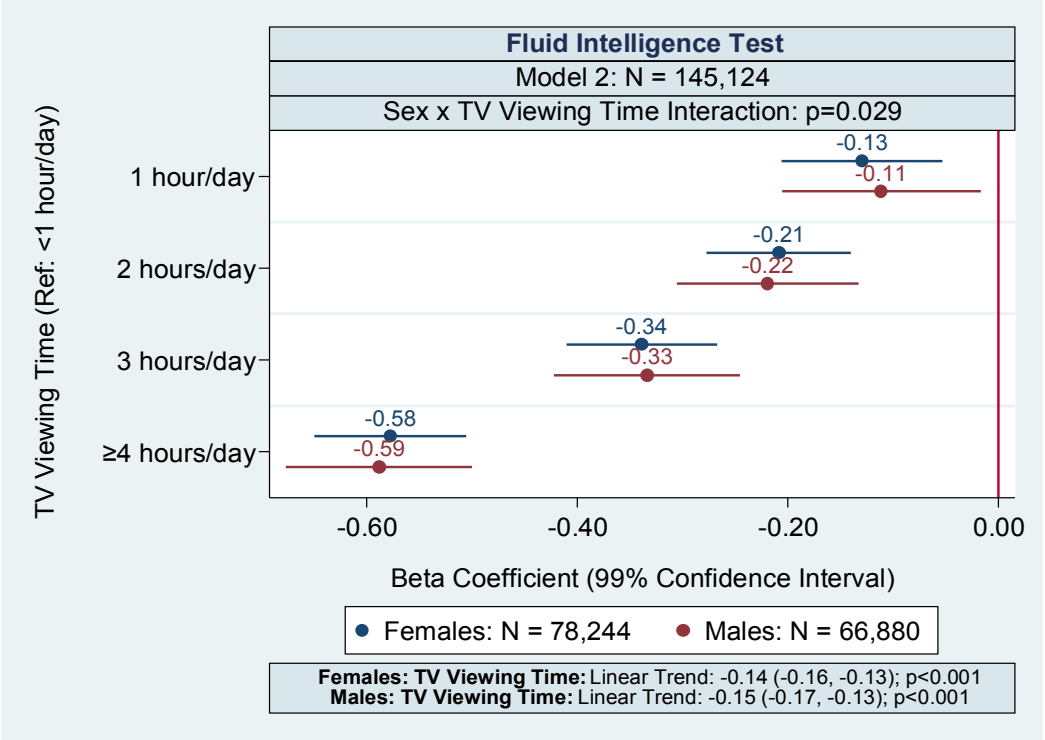


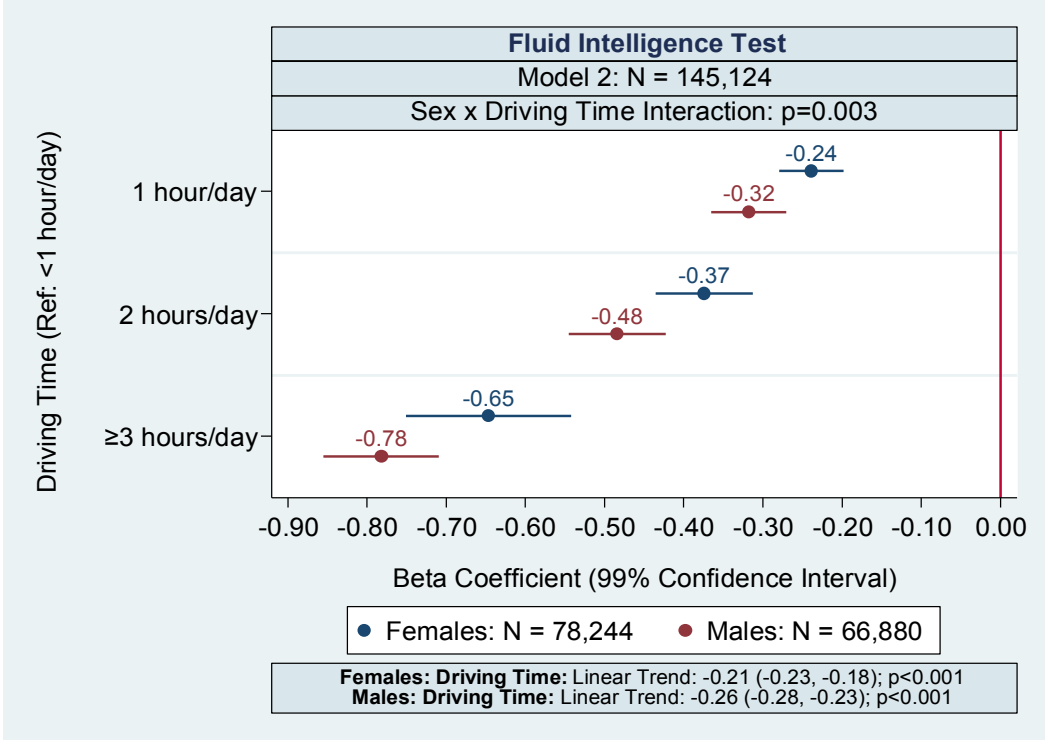

Prospective Memory Test
Model 2: N = 148,327
Sex x Computer Use Time Interaction: p<0.001
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.82
0.72
0.79
0.68
0.94
0.78
0.60
0.70
0.80
0.90
1.00
Odds Ratio (99% Confidence Interval)
Females: N = 79,860
Males: N = 68,467
Females: Computer Use Time: Linear Trend: 0.94 (0.92, 0.96); p<0.001
Males: Computer Use Time: Linear Trend: 0.90 (0.87, 0.92); p<0.001

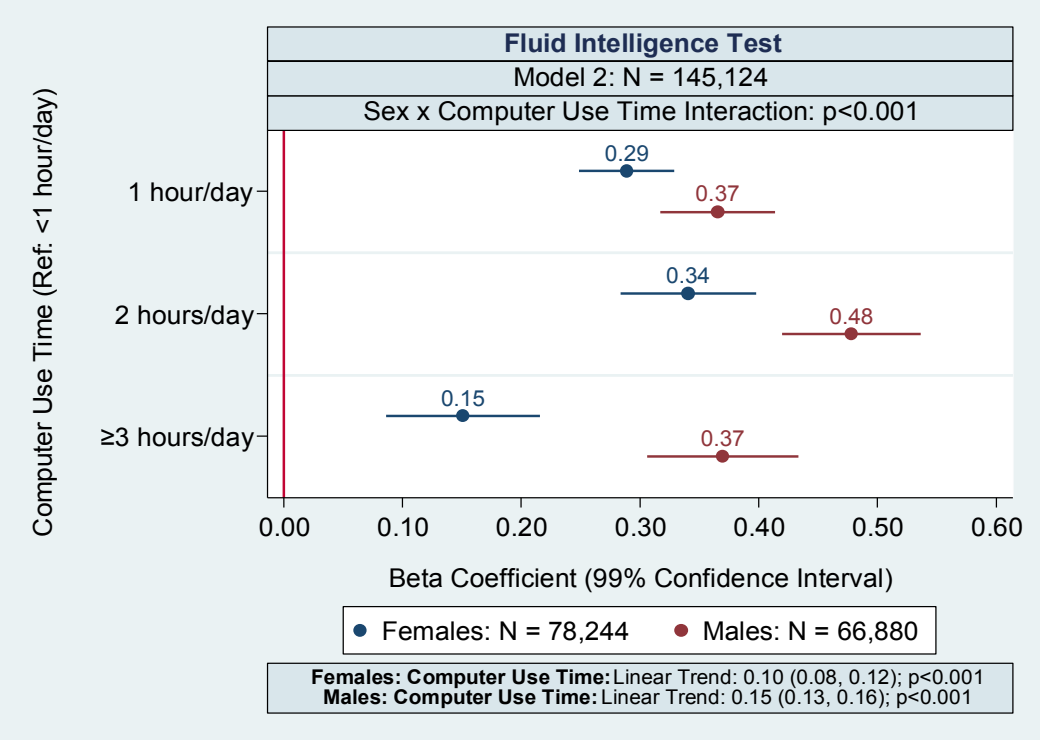

Visual-Spatial Memory Test (Round 1)
Model 2: N = 422,731
Sex x Computer Use Time Interaction: p=0.035
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.86
0.83
0.82
0.80
0.86
0.81
0.70
0.80
0.90
1.00
Odds Ratio (99% Confidence Interval)
Females: N = 227,471
Males: N = 195,260
Females: Computer Use Time: Linear Trend: 0.93 (0.91, 0.94); p<0.001
Males: Computer Use Time: Linear Trend: 0.92 (0.91, 0.93); p<0.001


Visual-Spatial Memory Test (Round 2)
Model 2: N = 421,851
Sex x TV Viewing Time Interaction: p=0.010
TV Viewing Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
0.99
1.05
1.02
1.03
1.06
0.99
1.06
1.01
0.90
0.95
1.00
1.05
1.10
Odds Ratio (99% Confidence Interval)
Females: N = 227,069
Males: N = 194,782
Females: TV Viewing Time: Linear Trend: 1.02 (1.01, 1.03); p<0.001
Males: TV Viewing Time: Linear Trend: 0.99 (0.98, 1.01); p=0.321


Visual-Spatial Memory Test (Round 2)
Model 2: N = 421,851
Sex x Computer Use Time Interaction: p=0.003
Computer Use Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
0.86
0.90
0.81
0.85
0.81
0.87
0.70
0.80
0.90
1.00
Odds Ratio (99% Confidence Interval)
Females: N = 227,069
Males: N = 194,782
Females: Computer Use Time: Linear Trend: 0.92 (0.90, 0.93); p<0.001
Males: Computer Use Time: Linear Trend: 0.95 (0.93, 0.96); p<0.001


Fluid Intelligence Test
Model 2: N = 145,124
Sex x TV Viewing Time Interaction: p=0.029
TV Viewing Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
-0.13
-0.11
-0.21
-0.22
-0.34
-0.33
-0.58
-0.59
-0.60
-0.40
-0.20
0.00
Beta Coefficient (99% Confidence Interval)
Females: N = 78,244
Males: N = 66,880
Females: TV Viewing Time: Linear Trend: -0.14 (-0.16, -0.13); p<0.001
Males: TV Viewing Time: Linear Trend: -0.15 (-0.17, -0.13); p<0.001


Fluid Intelligence Test
Model 2: N = 145,124
Sex x Driving Time Interaction: p=0.003
Driving Time (Ref: <1 hour/day)
1 hour/day
2 hours/day
≥3 hours/day
-0.24
-0.32
-0.37
-0.48
-0.65
-0.78
-0.90
-0.80
-0.70
-0.60
-0.50
-0.40
-0.30
-0.20
-0.10
0.00
Beta Coefficient (99% Confidence Interval)
Females: N = 78,244
Males: N = 66,880
Females: Driving Time: Linear Trend: -0.21 (-0.23, -0.18); p<0.001
Males: Driving Time: Linear Trend: -0.26 (-0.28, -0.23); p<0.001



Prospective memory result: categorical (binary): good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 1): categorical (binary): good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 2): categorical (binary): good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Interaction between sex and TV viewing time (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were adjusted for age, body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, driving time, and computer use time.

Interaction between sex and driving time (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were adjusted for age, body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, TV viewing time, and computer use time.

Interaction between sex and computer use time (statistical significance was established at p-value<0.05): stratified model (statistical significance was established at p-value<0.01) were adjusted for age, body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, TV viewing time, and driving time.

Prospective Findings

Table 12 also presents the cognitive function data of the participants with cognitive data at both baseline and follow-up. Cognitive decline over time was apparent since participants performed better in each cognitive test at baseline than at follow-up. For example, the mean (SD) fluid intelligence scores (N = 46,704) at baseline and follow-up were 6.7 (2.1) and 5.5 (2.0), respectively; with 15,384 (32.9%) individuals reporting a good outcome at follow-up (baseline fluid intelligence score ≤ follow-up fluid intelligence score) and 31,320 (67.1) individuals reporting a poor outcome at follow-up (baseline fluid intelligence score > follow-up fluid intelligence score). The other tests followed a similar pattern.

Those with follow-up data had similar characteristics to the full UK Biobank cohort, although they were better educated and more likely to be employed (see Table 14).

Table 14 - Observational study (UK Biobank data): Comparing the characteristics of the baseline sample and the follow-up sample

Participant characteristics	Baseline sample (N = 502,643)	Follow-up sample (N = 125,301) [a]
Anthropometric		
Body mass index (kg/m^2) [b]	27.4 (4.8); 12.1 - 74.7	26.8 (4.6); 12.1 - 67.3
Missing [c]	3,105 (0.6)	304 (0.2)
Demographic		
Age (years) [b]	56.5 (8.1); 37.0 - 73.0	56.1 (7.7); 38.0 - 72.0
Missing [c]	0 (0.0)	0 (0.0)
Ethnicity [d]		
White British	442,699 (88.1)	113,378 (90.5)
Other	57,166 (11.4)	11,463 (9.1)
Missing [c]	2,778 (0.5)	460 (0.4)
Sex [d]		
Female	273,467 (54.4)	70,229 (56.0)
Male	229,176 (45.6)	55,072 (44.0)
Missing [c]	0 (0.0)	0 (0.0)
Social deprivation index [b]	-1.3 (3.1); -6.3 - 11.0	-1.7 (2.8); -6.3 - 11.0
Missing [c]	627 (0.1)	134 (0.1)
Employment status [d]		
In paid employment or self-employed	287,234 (57.1)	77,661 (62.0)
Not in paid employment or self-employed	212,451 (42.3)	47,375 (37.8)
Missing [c]	2,958 (0.6)	265 (0.2)
Education level [d]		
College or university degree	161,210 (32.1)	56,683 (45.3)
No college or university degree	331,291 (65.9)	67,574 (53.9)
Missing [c]	10,142 (2.0)	1,044 (0.8)
Lifestyle		
Smoking status [d]		
Never	273,603 (54.4)	71,052 (56.7)
Previous	173,099 (34.4)	44,857 (35.8)
Current	52,989 (10.6)	9,091 (7.3)
Missing [c]	2,952 (0.6)	301 (0.2)
Alcohol drinking status [d]		
Never	22,547 (4.5)	3,534 (2.8)
Previous	18,114 (3.6)	3,549 (2.8)
Current	460,479 (91.6)	118,122 (94.3)

Missing [c]	1,503 (0.3)	96 (0.1)
Fruit and vegetable consumption (portions/day) [d]		
<5	300,352 (59.8)	74,356 (59.3)
≥5	189,979 (37.8)	49,693 (39.7)
Missing [c]	12,312 (2.4)	1,252 (1.0)
Sleep duration (hours/day) [b]	7.2 (1.1); 1.0 - 23.0	7.2 (1.0); 1.0 - 16.0
Missing [c]	4,218 (0.8)	357 (0.3)
Frequency of ≥10 minutes of walking (days/week) [d]		
0	12,455 (2.5)	2,576 (2.1)
1	13,459 (2.7)	3,924 (3.1)
2	29,991 (6.0)	8,433 (6.7)
3	39,339 (7.8)	10,819 (8.6)
4	40,036 (8.0)	10,984 (8.8)
5	80,039 (15.9)	20,052 (16.0)
6	50,082 (9.9)	13,263 (10.6)
7	228,697 (45.5)	54,423 (43.4)
Missing [c]	8,545 (1.7)	827 (0.7)
Frequency of ≥10 minutes of moderate-intensity physical activity (days/week) [d]		
0	61,178 (12.2)	15,129 (12.1)
1	38,290 (7.6)	11,501 (9.2)
2	69,799 (13.9)	19,694 (15.7)
3	71,507 (14.2)	19,381 (15.5)
4	47,201 (9.4)	12,621 (10.1)
5	71,441 (14.2)	16,766 (13.4)
6	26,436 (5.3)	6,284 (5.0)
7	89,506 (17.8)	20,481 (16.3)
Missing [c]	27,285 (5.4)	3,444 (2.7)
Frequency of ≥10 minutes of vigorous-intensity physical activity (days/week) [d]		
0	178,275 (35.5)	42,892 (34.2)
1	66,853 (13.3)	19,638 (15.7)
2	75,055 (14.9)	20,877 (16.6)
3	65,276 (13.0)	18,261 (14.6)
4	30,705 (6.1)	8,315 (6.6)
5	32,452 (6.5)	7,233 (5.8)
6	9,430 (1.9)	2,214 (1.8)
7	17,005 (3.4)	3,249 (2.6)
Missing [c]	27,592 (5.5)	2,622 (2.1)
Health		
Number of cancers [d]		
0	460,075 (91.5)	115,365 (92.1)

≥1	41,706 (8.3)	9,901 (7.9)
Missing [c]	862 (0.2)	35 (0.0)
Number of non-cancer illnesses [d]		
0	126,639 (25.2)	34,590 (27.6)
1	134,113 (26.7)	35,106 (28.0)
2	98,825 (19.6)	24,164 (19.3)
3	62,828 (12.5)	14,667 (11.7)
≥4	79,376 (15.8)	16,739 (13.4)
Missing [c]	862 (0.2)	35 (0.0)
Number of medications/treatments [d]		
0	137,704 (27.4)	38,534 (30.7)
1	94,776 (18.8)	25,046 (20.0)
2	77,673 (15.4)	19,731 (15.8)
3	57,819 (11.5)	14,051 (11.2)
4	42,211 (8.4)	9,774 (7.8)
5	29,937 (6.0)	6,643 (5.3)
≥6	61,661 (12.3)	11,487 (9.2)
Missing [c]	862 (0.2)	35 (0.0)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [d]		
No	402,897 (80.2)	103,926 (82.9)
Yes	99,746 (19.8)	21,375 (17.1)
Missing [c]	0 (0.0)	0 (0.0)
Sedentary behaviours		
TV viewing time (hours/day) [d]		
<1	39,456 (7.8)	13,429 (10.7)
1	62,503 (12.4)	19,263 (15.4)
2	132,780 (26.4)	36,706 (29.3)
3	116,940 (23.3)	28,217 (22.5)
≥4	145,546 (29.0)	27,254 (21.8)
Missing [c]	5,418 (1.1)	432 (0.3)
Driving time (hours/day) [d]		
<1	259,920 (51.7)	69,957 (55.8)
1	140,144 (27.9)	34,971 (27.9)
2	60,977 (12.1)	13,715 (11.0)
≥3	31,663 (6.3)	5,607 (4.5)
Missing [c]	9,939 (2.0)	1,051 (0.8)
Computer use time (hours/day) [d]		
<1	240,648 (47.9)	44,716 (35.7)
1	140,821 (28.0)	43,234 (34.5)
2	62,859 (12.5)	20,818 (16.6)
≥3	48,939 (9.7)	15,575 (12.4)

Missing [c]	9,376 (1.9)	958 (0.8)

[a] *Participants with follow-up data on at least one cognitive function test (visual-spatial memory (round 1), visual-spatial memory (round 2), fluid intelligence, short-term numeric memory)*
[b] *Continuous variable: mean (standard deviation); minimum - maximum*
[c] *Number (%)*
[d] *Categorical variable: number (%)*

Table 15 presents the associations between the sedentary behaviours at baseline and cognitive function at follow-up. In the fully adjusted models (Model 2), both TV viewing and driving time at baseline were positively associated with the odds of having cognitive decline at follow-up across most outcomes. For example, for each additional hour spent watching TV up to ≥4 hours/day at baseline, the odds of a lower fluid intelligence score at follow-up were 9% (6%, 11%) higher. Similarly, for each additional hour spent driving up to ≥3 hours/day at baseline, the odds of a lower fluid intelligence score at follow-up were 11% (7%, 15%) higher. In contrast, computer use time at baseline was inversely associated with the odds of having cognitive decline at follow-up across most outcomes. Model assumptions were satisfied.

Table 15 - Observational study (UK Biobank data): Prospective associations between sedentary behaviours at baseline and cognitive function at follow-up

Sedentary behaviours and cognitive function (Model 1 and Model 2) [a b]	Visual-spatial memory test (round 1) [c]	Visual-spatial memory test (round 2) [d]	Fluid intelligence test [e]	Short-term numeric memory test [f]
	Good outcome at follow-up or Poor outcome at follow-up	Good outcome at follow-up or Poor outcome at follow-up	Good outcome at follow-up or Poor outcome at follow-up	Good outcome at follow-up or Poor outcome at follow-up
Model 1 [a]	N = 113,129	N = 112,252	N = 46,158	N = 11,957
	OR (99% CI) [g]; p-value	OR (99% CI) [g]; p-value	OR (99% CI) [g]; p-value	OR (99% CI) [g]; p-value
TV viewing time (hours/day)				
<1 (Reference)	-	-	-	-
1	1.04 (0.97, 1.11); 0.154	1.02 (0.93, 1.11); 0.623	**1.15 (1.02, 1.28); 0.002**	1.05 (0.85, 1.31); 0.557
2	**1.09 (1.03, 1.15); <0.001**	1.00 (0.92, 1.08); 0.961	**1.24 (1.12, 1.37); <0.001**	1.13 (0.93, 1.37); 0.112
3	**1.13 (1.07, 1.20); <0.001**	1.03 (0.94, 1.12); 0.439	**1.37 (1.24, 1.52); <0.001**	**1.26 (1.03, 1.55); 0.003**
≥4	**1.17 (1.10, 1.25); <0.001**	1.01 (0.93, 1.10); 0.672	**1.66 (1.50, 1.84); <0.001**	**1.43 (1.17, 1.76); <0.001**
Linear trend	**1.04 (1.03, 1.06); <0.001**	1.00 (0.99, 1.02); 0.612	**1.13 (1.10, 1.15); <0.001**	**1.10 (1.05, 1.15); <0.001**
Driving time (hours/day)				
<1 (Reference)	-	-	-	-
1	**1.06 (1.02, 1.10); <0.001**	1.01 (0.96, 1.07); 0.480	**1.15 (1.08, 1.22); <0.001**	1.05 (0.93, 1.18); 0.319
2	**1.07 (1.01, 1.12); 0.002**	1.00 (0.93, 1.08); 0.903	**1.10 (1.00, 1.21); 0.008**	1.09 (0.92, 1.30); 0.193
≥3	**1.18 (1.09, 1.28); <0.001**	1.01 (0.90, 1.13); 0.831	**1.44 (1.25, 1.66); <0.001**	1.11 (0.85, 1.44); 0.318
Linear trend	**1.05 (1.03, 1.07); <0.001**	1.00 (0.98, 1.03); 0.709	**1.10 (1.06, 1.14); <0.001**	1.04 (0.98, 1.11); 0.108
Computer use time (hours/day)				
<1 (Reference)	-	-	-	-
1	0.96 (0.93, 1.00); 0.013	0.96 (0.91, 1.02); 0.068	**0.93 (0.87, 1.00); 0.006**	0.90 (0.79, 1.02); 0.034
2	**0.90 (0.86, 0.94); <0.001**	**0.87 (0.81, 0.93); <0.001**	0.94 (0.86, 1.02); 0.041	**0.77 (0.65, 0.90); <0.001**
≥3	**0.91 (0.86, 0.96); <0.001**	**0.89 (0.83, 0.96); <0.001**	0.96 (0.88, 1.05); 0.293	0.86 (0.72, 1.03); 0.035

Linear trend	**0.96 (0.95, 0.98); <0.001**	**0.95 (0.93, 0.97); <0.001**	0.98 (0.96, 1.01); 0.150	**0.93 (0.88, 0.98); 0.001**

Model 2 [b]	N = 106,665 OR (99% CI) [g]; p-value	N = 105,861 OR (99% CI) [g]; p-value	N = 43,350 OR (99% CI) [g]; p-value	N = 11,299 OR (99% CI) [g]; p-value
TV viewing time (hours/day)				
<1 (reference)	-	-	-	-
1	1.02 (0.96, 1.09); 0.348	1.03 (0.94, 1.12); 0.470	**1.16 (1.03, 1.30); 0.001**	1.02 (0.82, 1.28); 0.817
2	**1.07 (1.00, 1.13); 0.006**	1.01 (0.93, 1.09); 0.815	**1.21 (1.09, 1.35); <0.001**	1.08 (0.88, 1.33); 0.310
3	**1.08 (1.02, 1.15); 0.001**	1.03 (0.94, 1.12); 0.416	**1.29 (1.15, 1.44); <0.001**	1.16 (0.94, 1.44); 0.066
≥4	**1.09 (1.02, 1.17); 0.001**	1.00 (0.91, 1.10); 0.993	**1.45 (1.29, 1.62); <0.001**	**1.29 (1.04, 1.61); 0.003**
Linear trend	**1.02 (1.01, 1.04); <0.001**	1.00 (0.98, 1.02); 0.955	**1.09 (1.06, 1.11); <0.001**	**1.07 (1.02, 1.12); <0.001**
Driving time (hours/day)				
<1 (reference)	-	-	-	-
1	**1.07 (1.03, 1.12); <0.001**	1.02 (0.97, 1.08); 0.294	**1.19 (1.11, 1.27); <0.001**	1.05 (0.92, 1.19); 0.363
2	**1.08 (1.02, 1.14); 0.001**	1.01 (0.94, 1.10); 0.624	**1.15 (1.04, 1.27); <0.001**	1.05 (0.88, 1.27); 0.466
≥3	**1.16 (1.06, 1.26); <0.001**	1.01 (0.90, 1.13); 0.895	**1.43 (1.24, 1.66); <0.001**	1.05 (0.80, 1.39); 0.650
Linear trend	**1.05 (1.03, 1.07); <0.001**	1.01 (0.98, 1.04); 0.552	**1.11 (1.07, 1.15); <0.001**	1.02 (0.96, 1.10); 0.363
Computer use time (hours/day)				
<1 (reference)	-	-	-	-
1	0.97 (0.93, 1.01); 0.053	0.97 (0.92, 1.03); 0.250	0.94 (0.87, 1.01); 0.020	0.92 (0.80, 1.05); 0.090
2	**0.91 (0.86, 0.95); <0.001**	**0.88 (0.82, 0.94); <0.001**	0.94 (0.86, 1.03); 0.073	**0.76 (0.64, 0.90); <0.001**
≥3	**0.90 (0.85, 0.96); <0.001**	**0.90 (0.83, 0.98); 0.001**	0.97 (0.88, 1.06); 0.359	0.84 (0.69, 1.01); 0.016
Linear trend	**0.96 (0.95, 0.98); <0.001**	**0.96 (0.93, 0.98); <0.001**	0.99 (0.96, 1.02); 0.207	**0.92 (0.87, 0.98); <0.001**

[a] *Model 1 was mutually adjusted for the other sedentary behaviours and for age, sex and the baseline result/score of the cognitive test under consideration*

[b] *Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments*

[c] *Pairs matching result (round 1): categorical (binary): good outcome at follow-up [<1 incorrect matches at follow-up]; or poor outcome at follow-up [≥1 incorrect matches at follow-up]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up)*

[d] *Pairs matching result (round 2): categorical (binary): good outcome at follow-up [<2 incorrect matches at follow-up]; or poor outcome at follow-up [≥2 incorrect matches at follow-up]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up)*

[e] *Fluid intelligence score: categorical (binary): good outcome at follow-up [baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up)*

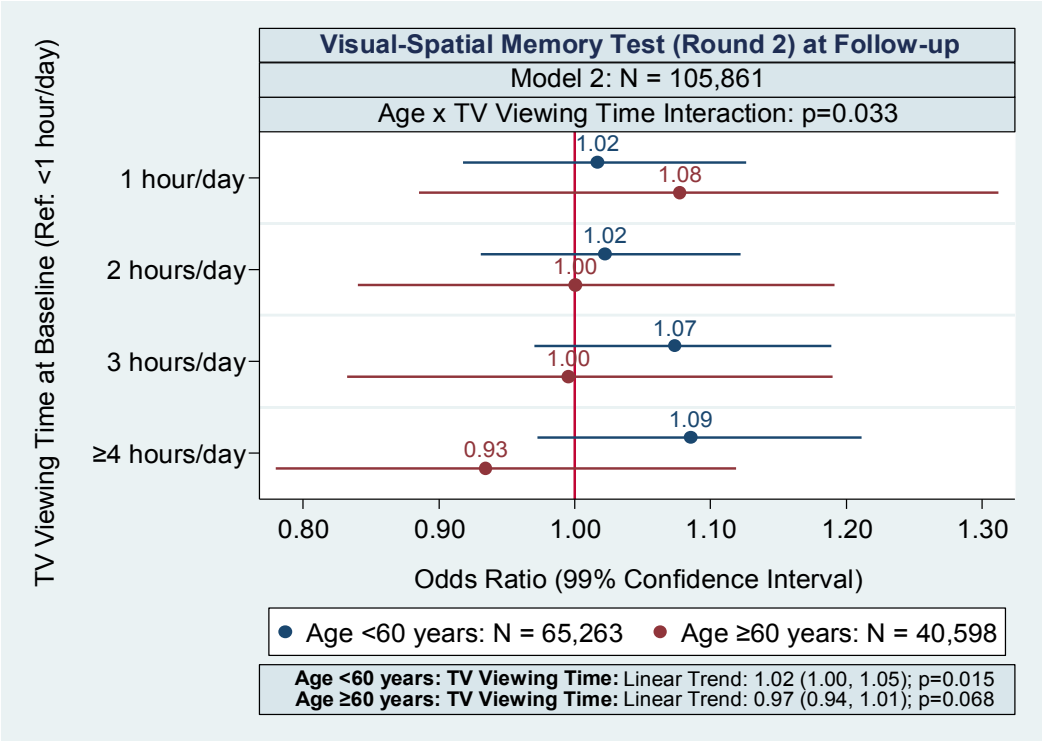
[f] *Numeric memory score: categorical (binary): good outcome at follow-up [baseline numeric memory score ≤ follow-up numeric memory score]; or poor outcome at follow-up [baseline numeric memory score > follow-up numeric memory score]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up)*

[g] *Odds ratio (99% confidence interval)*

Bold *indicates statistical significance (i.e. p-value<0.01).*

Interaction analyses showed that only the associations between TV viewing time and visual-spatial memory (round 2) were modified by age (p-value<0.05) (see Figure 7). Findings were not modified by sex. Model assumptions were satisfied.

Figure 7 - Observational study (UK Biobank data): Interactions by age: prospective associations between sedentary behaviours at baseline and cognitive function at follow-up



Pairs matching result (round 2): categorical (binary): good outcome at follow-up [<2 incorrect matches at follow-up]; or poor outcome at follow-up [≥2 incorrect matches at follow-up]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Interaction between age and TV viewing time (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were adjusted for baseline result/score of the cognitive test under consideration, body mass index, ethnicity, sex, social deprivation index, employment status, education level, smoking status, alcohol drinking status,

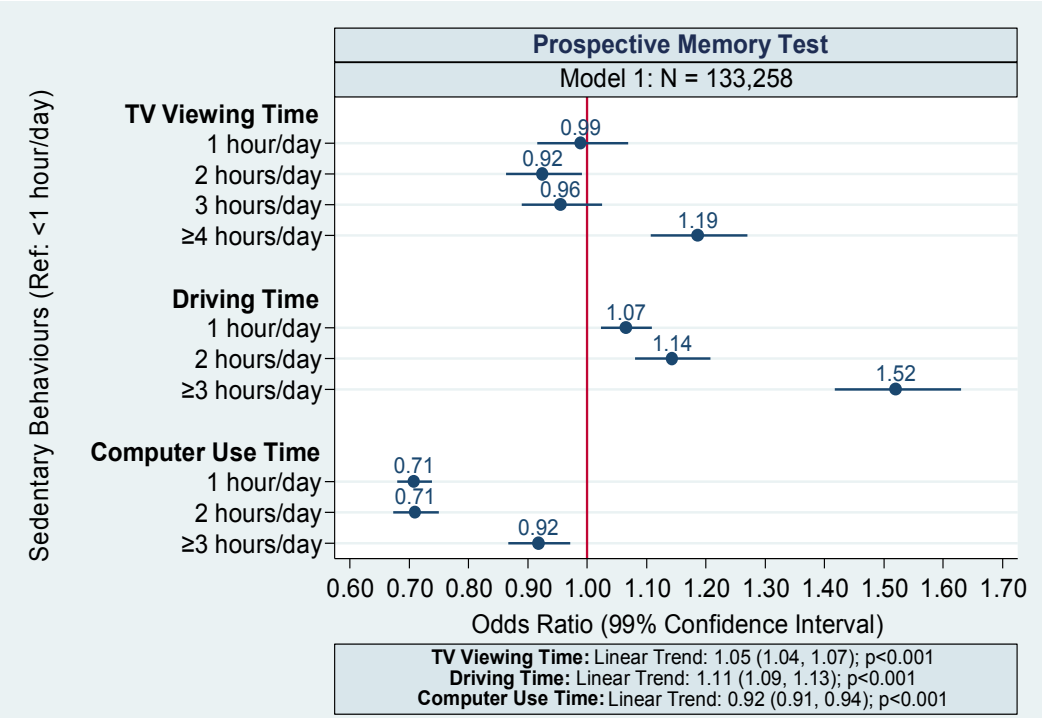
fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments, driving time, and computer use time.

Sensitivity Analysis

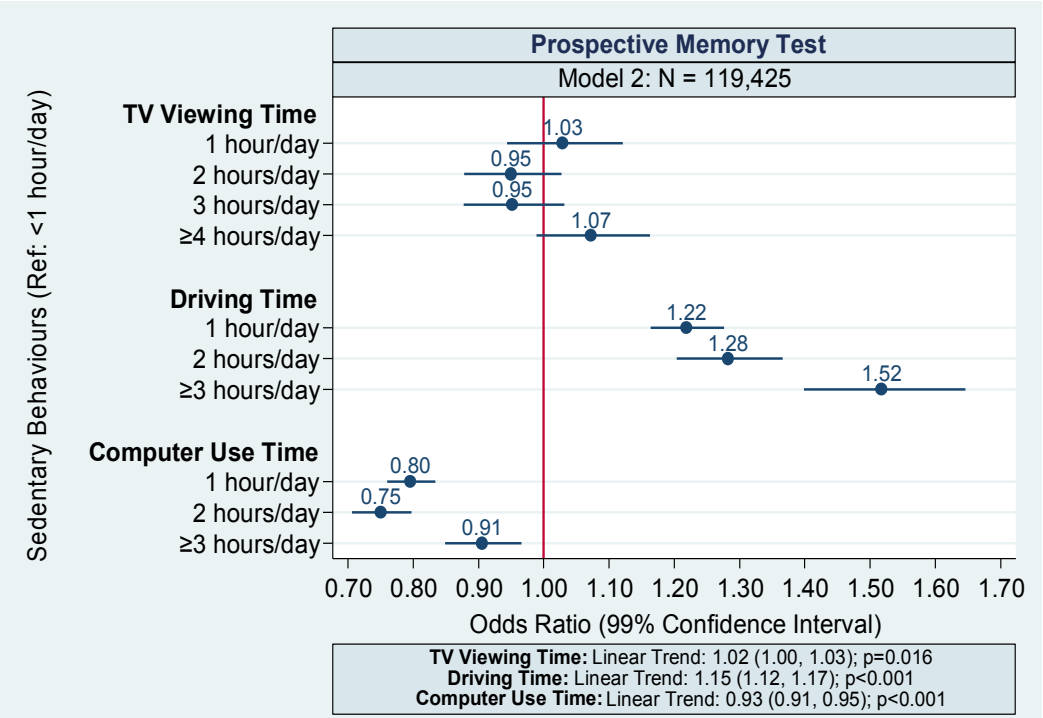
The cross-sectional and prospective findings were generalizable across the sample of participants without cancer, CVD, and/or cognitive/psychiatric illnesses (see Figures 8 (cross-sectional associations) and 9 (prospective associations)). Here, the associations between the different sedentary behaviours and cognitive function tests remained unchanged; suggesting that the inclusion of these individuals in the main analyses was having minimal confounding impact.

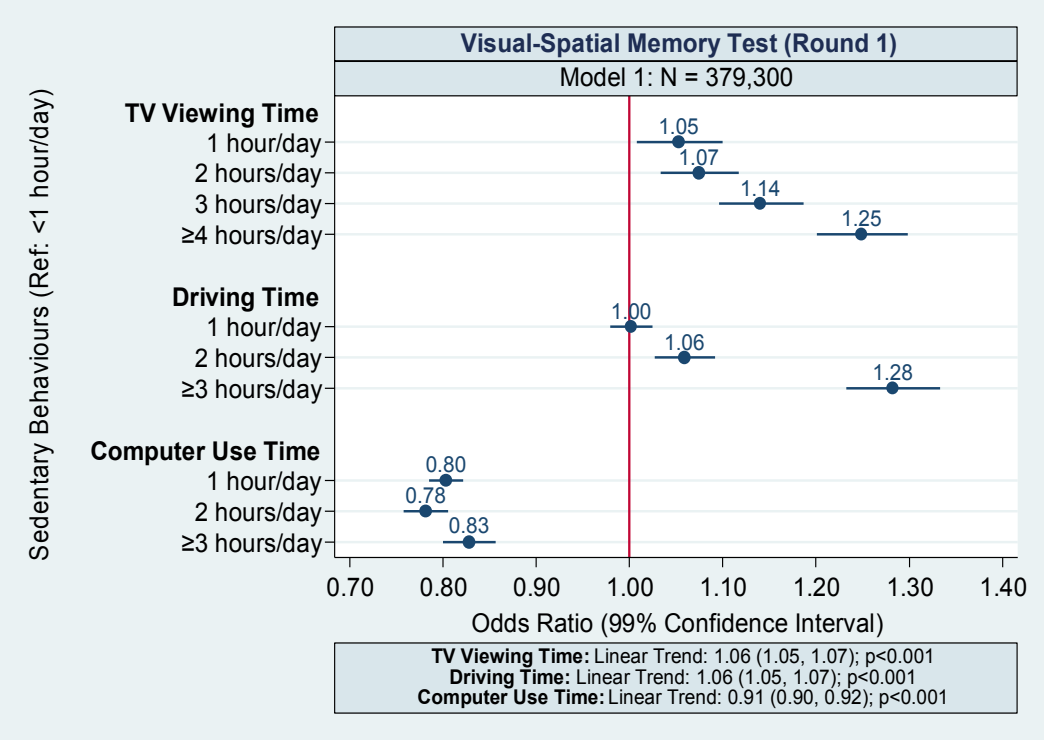
Figure 8 - Observational study (UK Biobank data): Sensitivity analysis: cross-sectional associations at baseline between sedentary behaviours and cognitive function (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses)

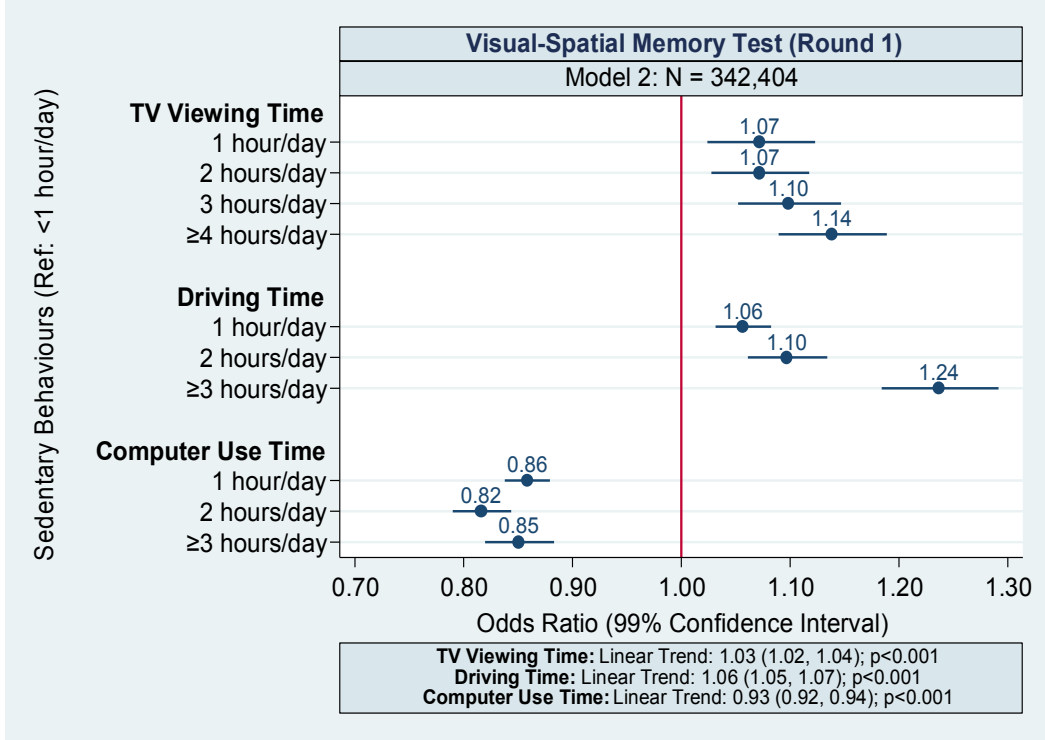
MODEL 1

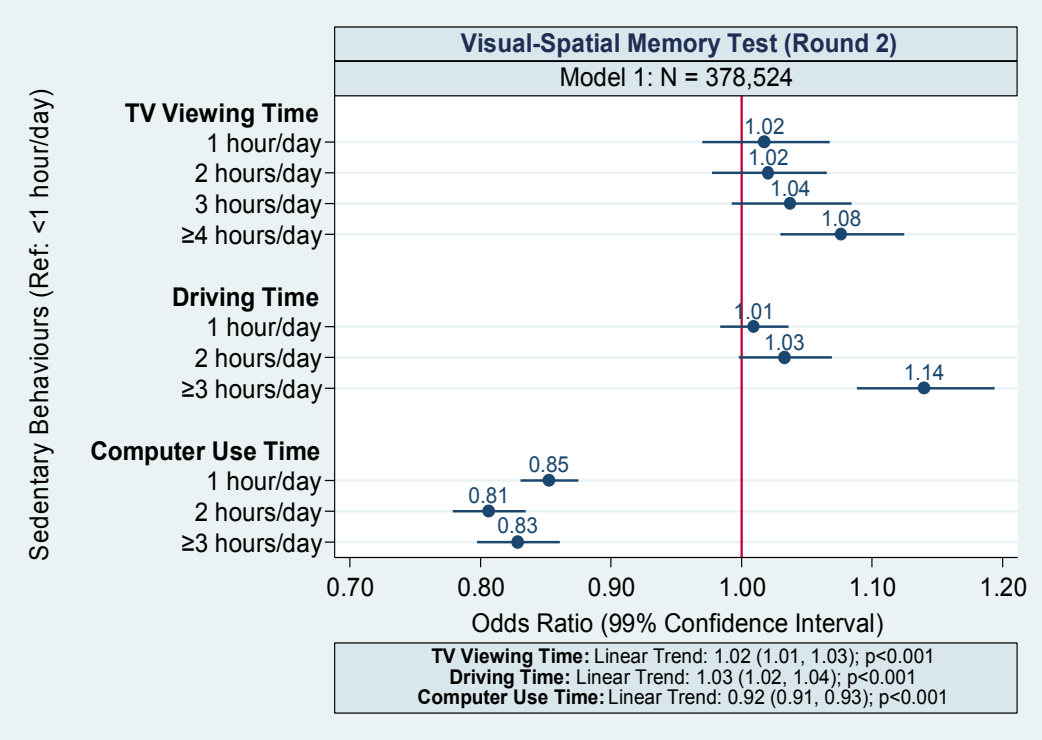


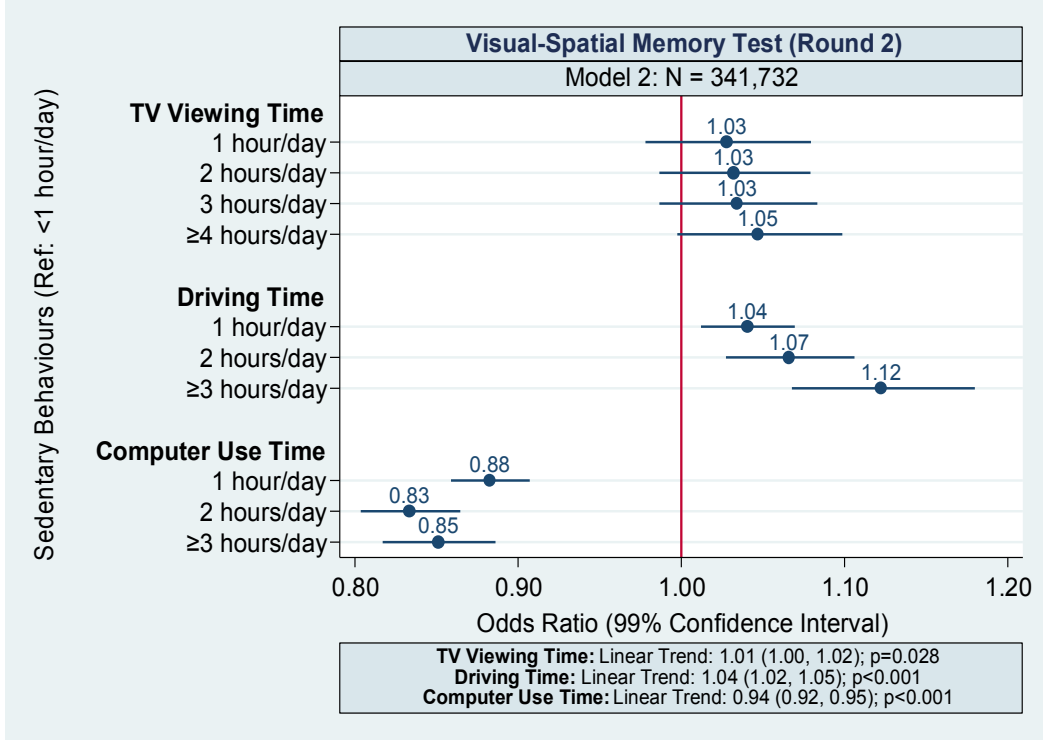
MODEL 2

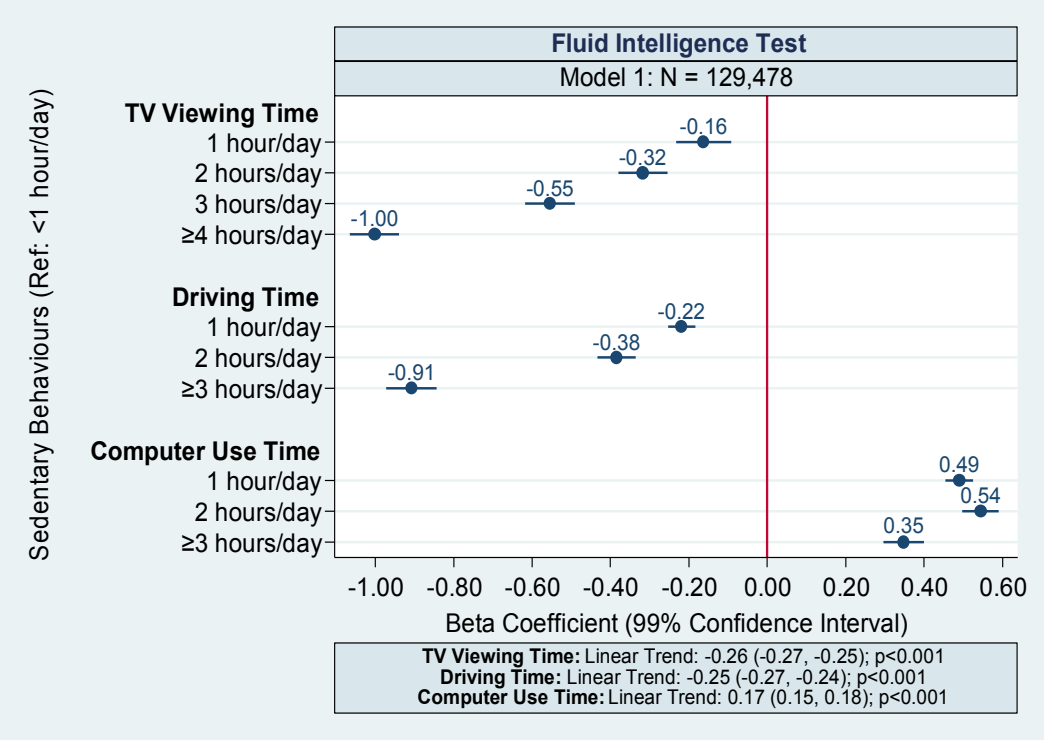


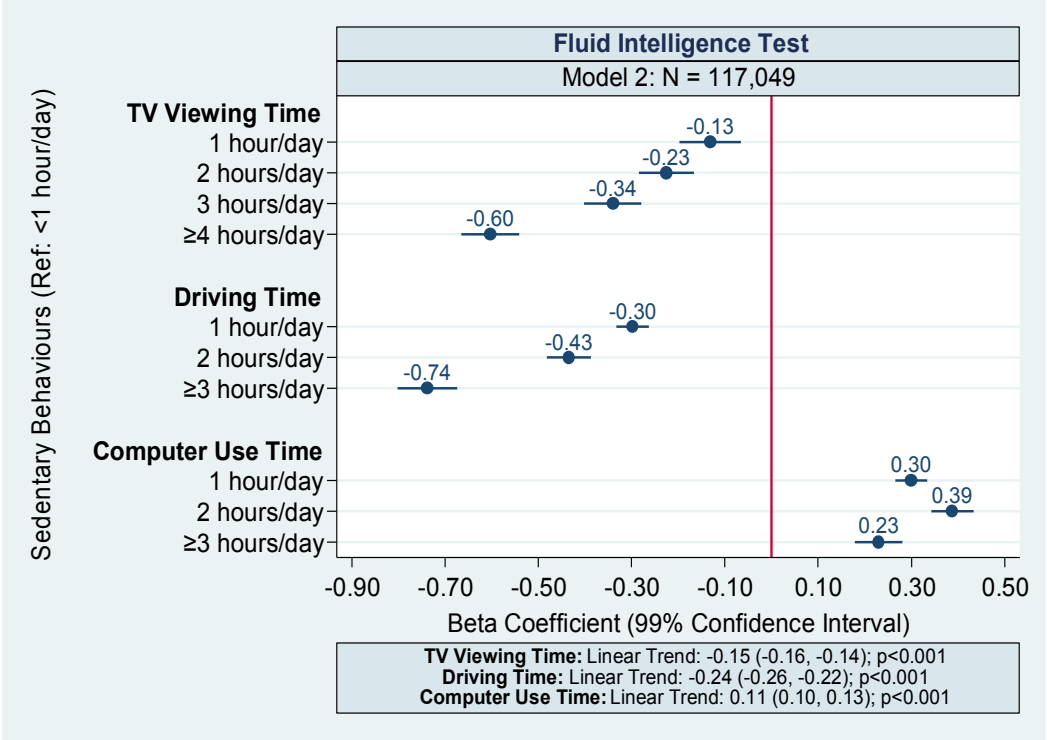

Visual-Spatial Memory Test (Round 1)
Model 1: N = 379,300
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.05
1.07
1.14
1.25
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.00
1.06
1.28
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.80
0.78
0.83
0.70 0.80 0.90 1.00 1.10 1.20 1.30 1.40
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.06 (1.05, 1.07); p<0.001
Driving Time: Linear Trend: 1.06 (1.05, 1.07); p<0.001
Computer Use Time: Linear Trend: 0.91 (0.90, 0.92); p<0.001

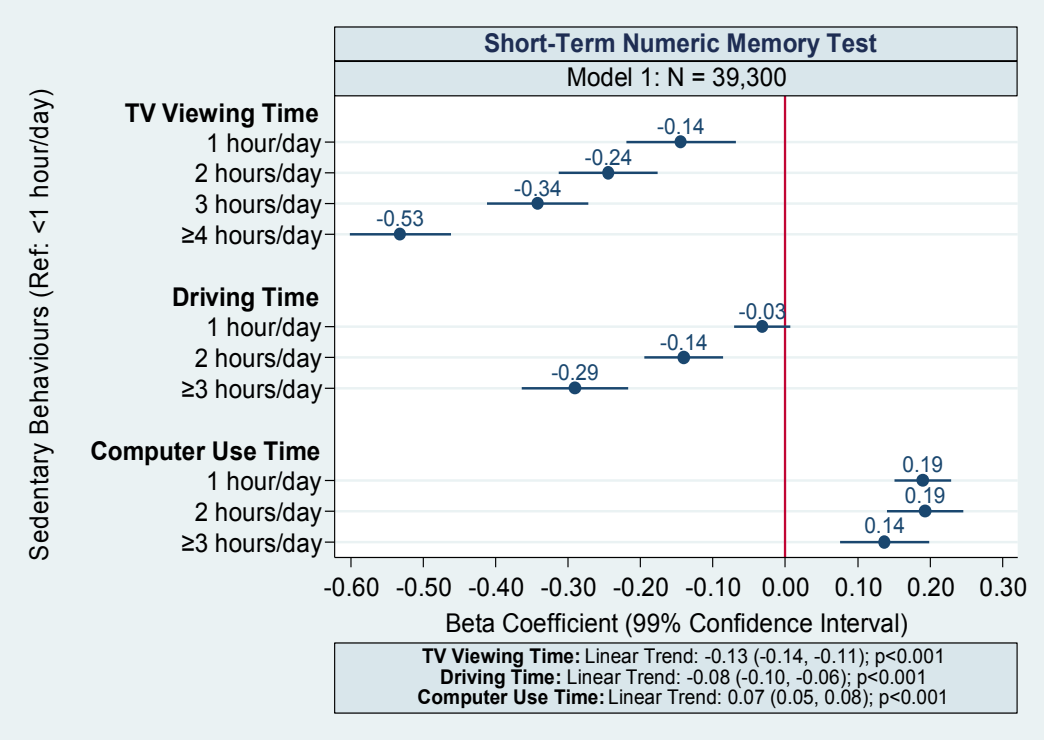

Visual-Spatial Memory Test (Round 1)
Model 2: N = 342,404
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.07
1.07
1.10
1.14
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.06
1.10
1.24
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.86
0.82
0.85
0.70 0.80 0.90 1.00 1.10 1.20 1.30
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.03 (1.02, 1.04); p<0.001
Driving Time: Linear Trend: 1.06 (1.05, 1.07); p<0.001
Computer Use Time: Linear Trend: 0.93 (0.92, 0.94); p<0.001

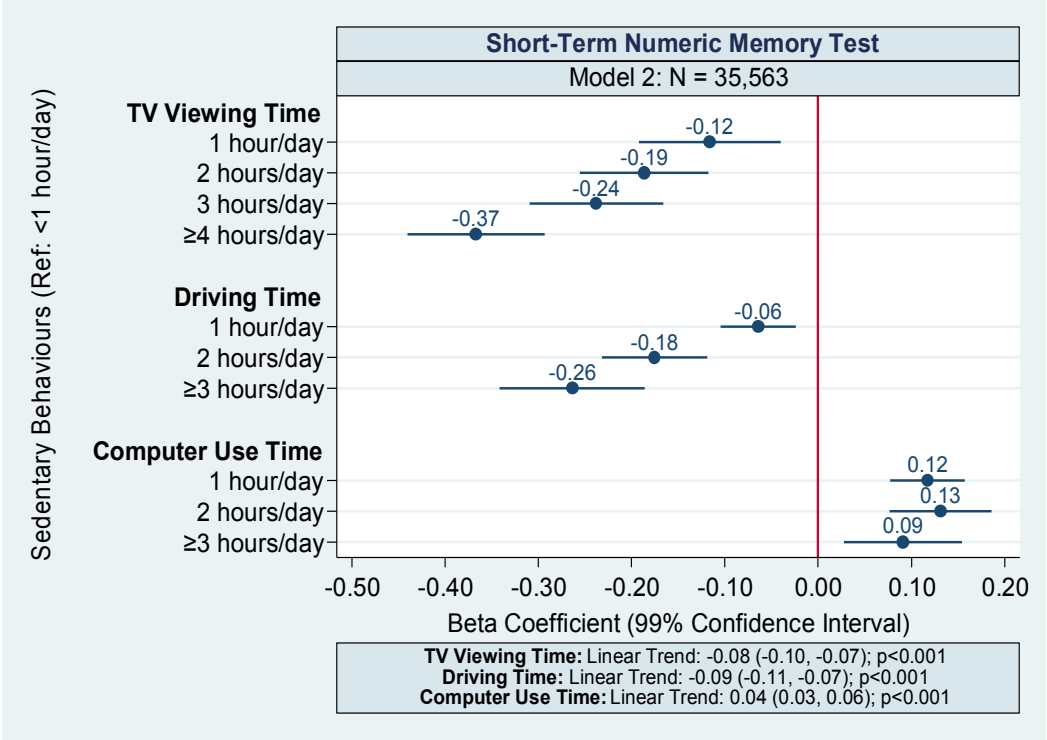

Visual-Spatial Memory Test (Round 2)
Model 1: N = 378,524
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.02
1.02
1.04
1.08
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.01
1.03
1.14
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.85
0.81
0.83
0.70
0.80
0.90
1.00
1.10
1.20
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.02 (1.01, 1.03); p<0.001
Driving Time: Linear Trend: 1.03 (1.02, 1.04); p<0.001
Computer Use Time: Linear Trend: 0.92 (0.91, 0.93); p<0.001


Visual-Spatial Memory Test (Round 2)
Model 2: N = 341,732
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.03
1.03
1.03
1.05
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.04
1.07
1.12
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.88
0.83
0.85
0.80
0.90
1.00
1.10
1.20
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.01 (1.00, 1.02); p=0.028
Driving Time: Linear Trend: 1.04 (1.02, 1.05); p<0.001
Computer Use Time: Linear Trend: 0.94 (0.92, 0.95); p<0.001


Fluid Intelligence Test
Model 1: N = 129,478
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
-0.16
-0.32
-0.55
-1.00
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
-0.22
-0.38
-0.91
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.49
0.54
0.35
-1.00 -0.80 -0.60 -0.40 -0.20 0.00 0.20 0.40 0.60
Beta Coefficient (99% Confidence Interval)
TV Viewing Time: Linear Trend: -0.26 (-0.27, -0.25); p<0.001
Driving Time: Linear Trend: -0.25 (-0.27, -0.24); p<0.001
Computer Use Time: Linear Trend: 0.17 (0.15, 0.18); p<0.001


Fluid Intelligence Test
Model 2: N = 117,049
Sedentary Behaviours (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
-0.13
-0.23
-0.34
-0.60
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
-0.30
-0.43
-0.74
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.30
0.39
0.23
-0.90 -0.70 -0.50 -0.30 -0.10 0.10 0.30 0.50
Beta Coefficient (99% Confidence Interval)
TV Viewing Time: Linear Trend: -0.15 (-0.16, -0.14); p<0.001
Driving Time: Linear Trend: -0.24 (-0.26, -0.22); p<0.001
Computer Use Time: Linear Trend: 0.11 (0.10, 0.13); p<0.001



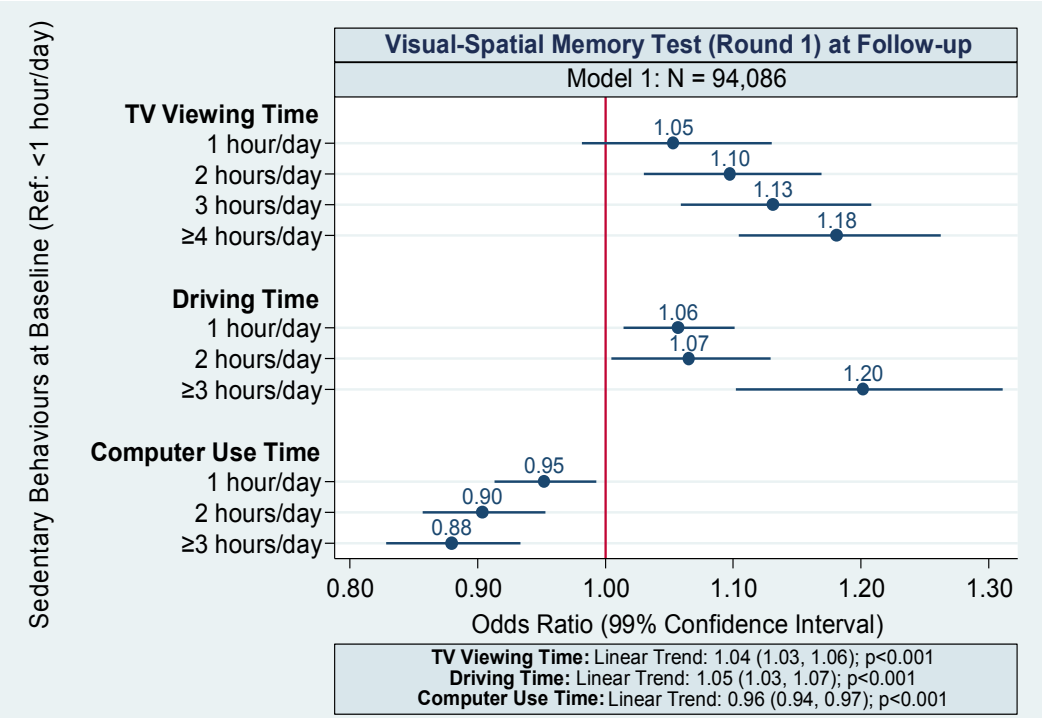


Prospective memory result: categorical (binary): good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 1): categorical (binary): good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result (round 2): categorical (binary): good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.
Numeric memory score: continuous: maximum digits remembered correctly. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

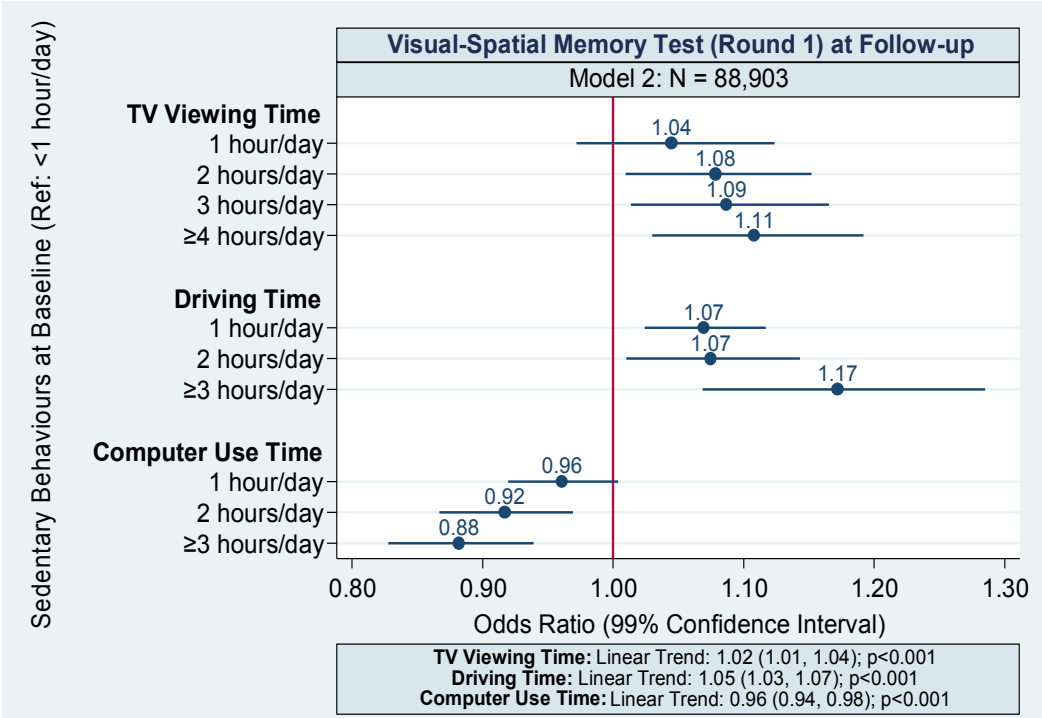
Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex. Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.01.

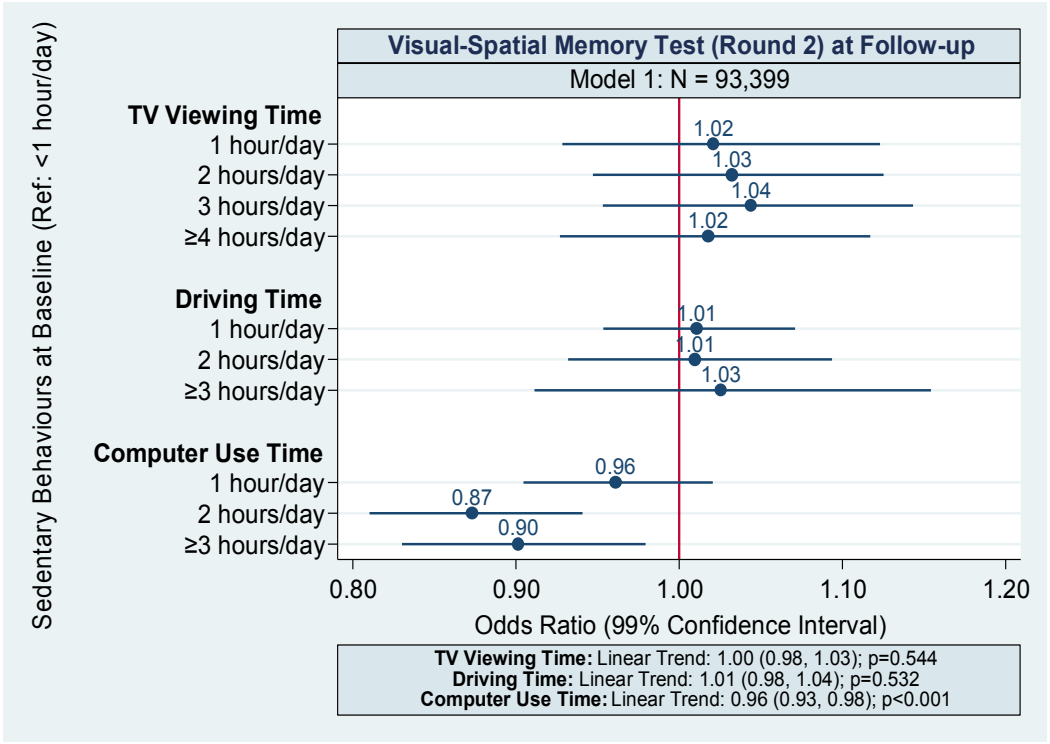
Figure 9 - Observational study (UK Biobank data): Sensitivity analysis: prospective associations between sedentary behaviours at baseline and cognitive function at follow-up (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses)

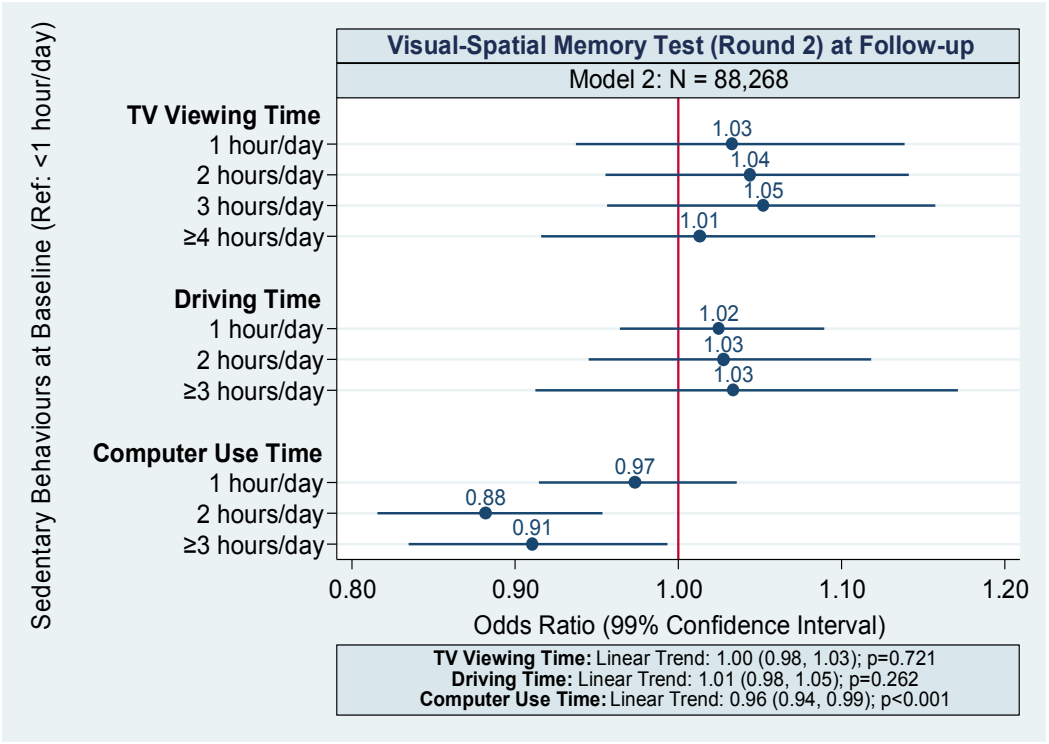
MODEL 1

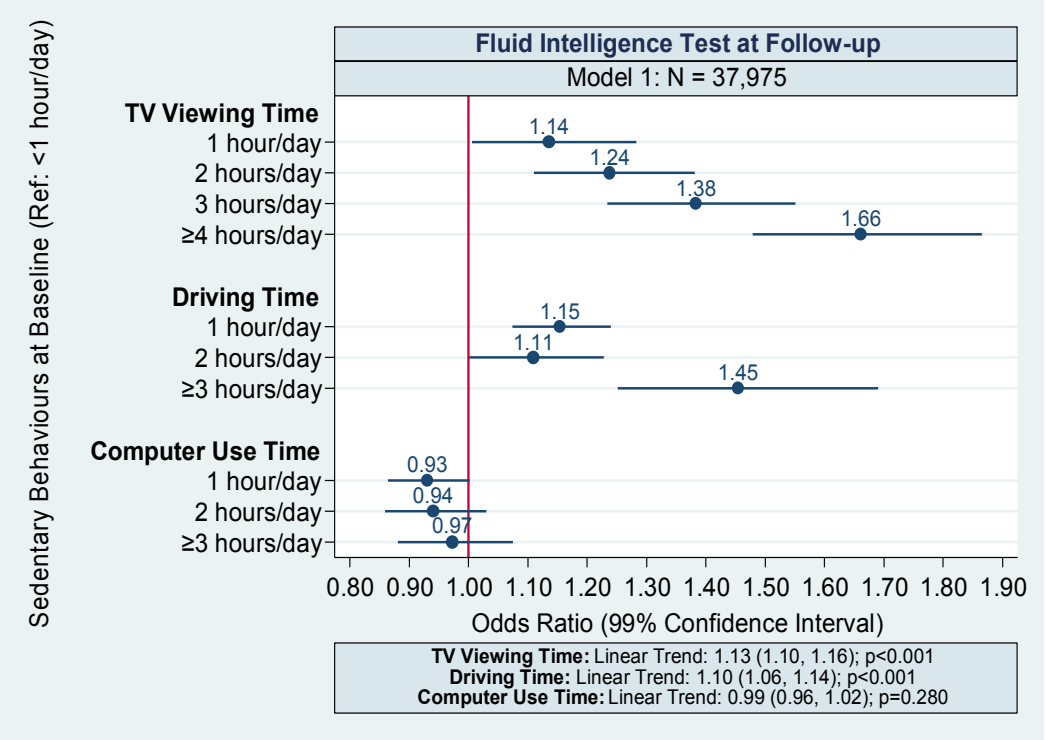


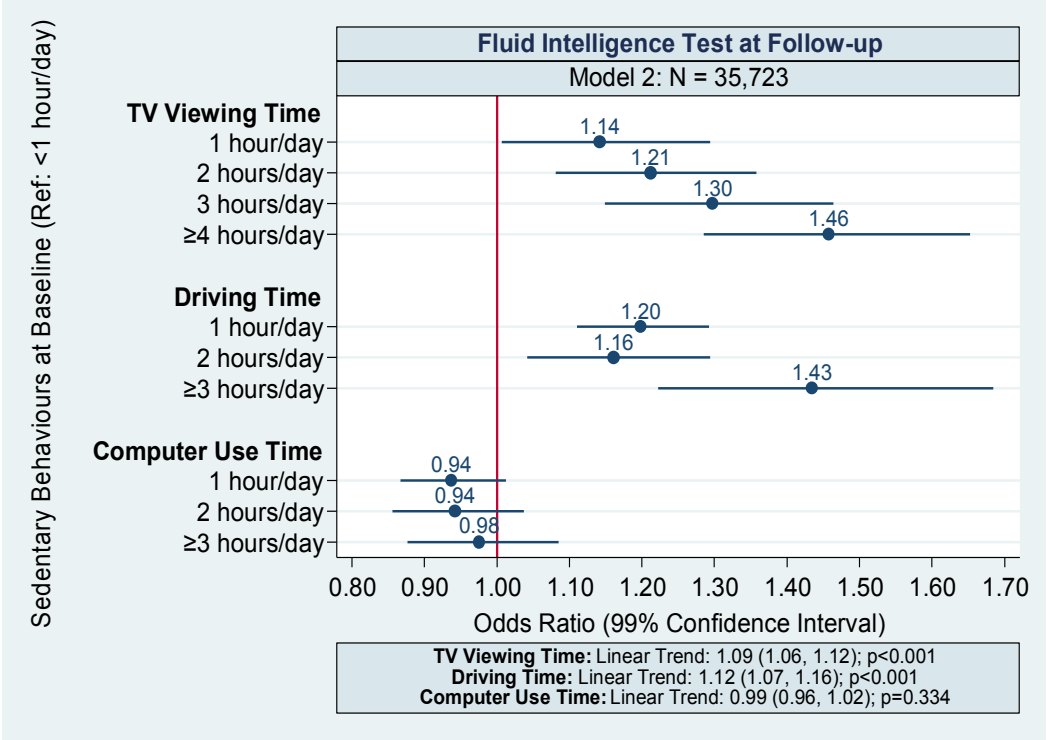
MODEL 2

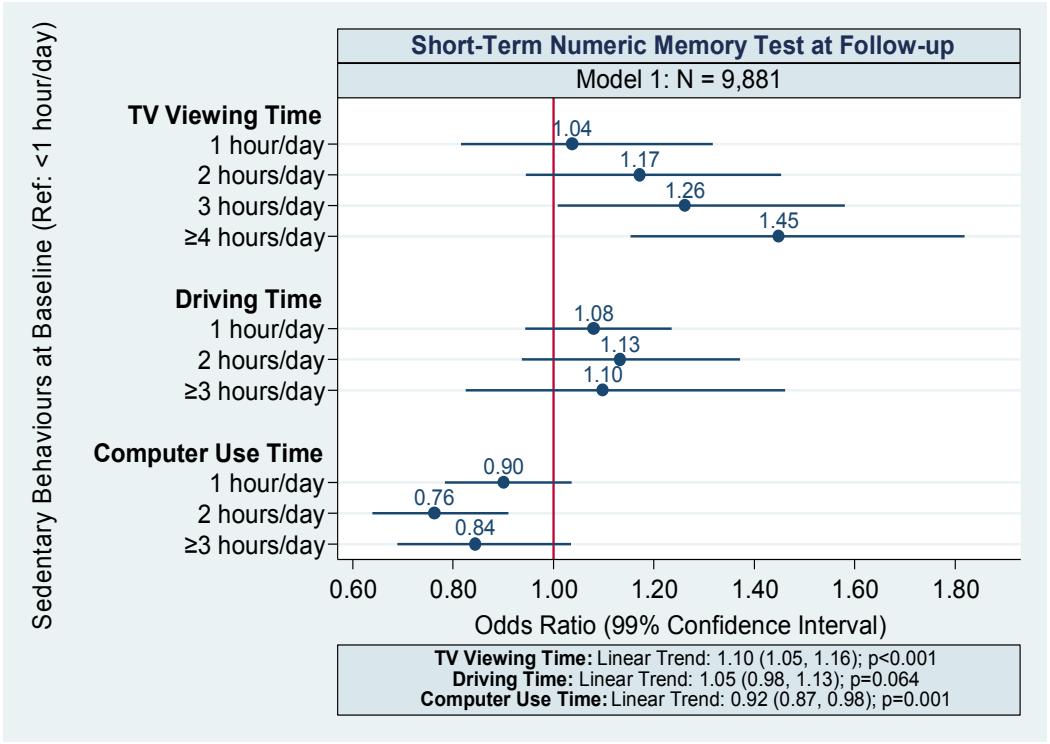


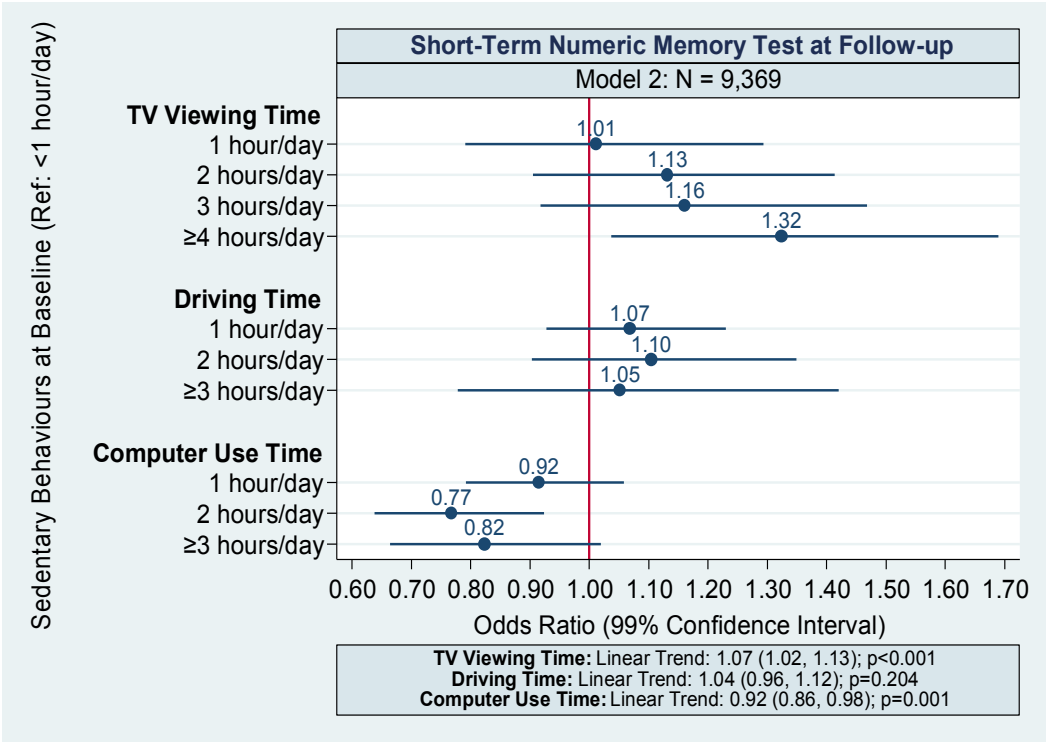

Visual-Spatial Memory Test (Round 2) at Follow-up
Model 1: N = 93,399
Sedentary Behaviours at Baseline (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.02
1.03
1.04
1.02
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.01
1.01
1.03
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.96
0.87
0.90
0.80
0.90
1.00
1.10
1.20
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.00 (0.98, 1.03); p=0.544
Driving Time: Linear Trend: 1.01 (0.98, 1.04); p=0.532
Computer Use Time: Linear Trend: 0.96 (0.93, 0.98); p<0.001


Visual-Spatial Memory Test (Round 2) at Follow-up
Model 2: N = 88,268
Sedentary Behaviours at Baseline (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.03
1.04
1.05
1.01
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.02
1.03
1.03
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.97
0.88
0.91
0.80
0.90
1.00
1.10
1.20
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.00 (0.98, 1.03); p=0.721
Driving Time: Linear Trend: 1.01 (0.98, 1.05); p=0.262
Computer Use Time: Linear Trend: 0.96 (0.94, 0.99); p<0.001


Fluid Intelligence Test at Follow-up
Model 1: N = 37,975
Sedentary Behaviours at Baseline (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.14
1.24
1.38
1.66
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.15
1.11
1.45
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.93
0.94
0.97
0.80 0.90 1.00 1.10 1.20 1.30 1.40 1.50 1.60 1.70 1.80 1.90
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.13 (1.10, 1.16); p<0.001
Driving Time: Linear Trend: 1.10 (1.06, 1.14); p<0.001
Computer Use Time: Linear Trend: 0.99 (0.96, 1.02); p=0.280


Fluid Intelligence Test at Follow-up
Model 2: N = 35,723
Sedentary Behaviours at Baseline (Ref: <1 hour/day)
TV Viewing Time
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
1.14
1.21
1.30
1.46
Driving Time
1 hour/day
2 hours/day
≥3 hours/day
1.20
1.16
1.43
Computer Use Time
1 hour/day
2 hours/day
≥3 hours/day
0.94
0.94
0.98
0.80 0.90 1.00 1.10 1.20 1.30 1.40 1.50 1.60 1.70
Odds Ratio (99% Confidence Interval)
TV Viewing Time: Linear Trend: 1.09 (1.06, 1.12); p<0.001
Driving Time: Linear Trend: 1.12 (1.07, 1.16); p<0.001
Computer Use Time: Linear Trend: 0.99 (0.96, 1.02); p=0.334





Pairs matching result (round 1): categorical (binary): good outcome at follow-up [<1 incorrect matches at follow-up]; or poor outcome at follow-up [≥1 incorrect matches at follow-up]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).
Pairs matching result (round 2): categorical (binary): good outcome at follow-up [<2 incorrect matches at follow-up]; or poor outcome at follow-up [≥2 incorrect matches at follow-up]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).
Fluid intelligence score: categorical (binary): good outcome at follow-up [baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Numeric memory score: categorical (binary): good outcome at follow-up [baseline numeric memory score ≤ follow-up numeric memory score]; or poor outcome at follow-up [baseline numeric memory score > follow-up numeric memory score]. An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Model 1 was mutually adjusted for the other sedentary behaviours and for age, sex and the baseline result/score of the cognitive test under consideration. Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.01.

The prospective findings from the mixed-effects logistic and linear regression models were consistent with the main results (see Table 16).

Table 16 - Observational study (UK Biobank data): Prospective associations between sedentary behaviours at baseline and cognitive function at follow-up using mixed-effects logistic and linear regression models

Sedentary behaviours and cognitive function (Model 1 and Model 2) [a b]	Visual-spatial memory test (round 1) [c]	Visual-spatial memory test (round 2) [d]	Fluid intelligence test [e]	Short-term numeric memory test [f]
	Good result or Poor result	Good result or Poor result	Total number of correct answers	Maximum digits remembered correctly
Model 1 [a]	N (observations) = 585,236 N (groups) = 472,107	N (observations) = 583,435 N (groups) = 471,183	N (observations) = 282,956 N (groups) = 236,798	N (observations) = 158,389 N (groups) = 146,432
	OR (99% CI) [g]; p-value	OR (99% CI) [g]; p-value	β (99% CI) [h]; p-value	β (99% CI) [h]; p-value
TV viewing time (hours/day)				
<1 (reference)	-	-	-	-
1	**1.05 (1.01, 1.09); <0.001**	1.01 (0.97, 1.05); 0.575	**-0.20 (-0.25, -0.16); <0.001**	**-0.13 (-0.17, -0.10); <0.001**
2	**1.08 (1.05, 1.12); <0.001**	1.01 (0.98, 1.05); 0.316	**-0.37 (-0.41, -0.33); <0.001**	**-0.24 (-0.28, -0.21); <0.001**
3	**1.15 (1.11, 1.19); <0.001**	1.03 (1.00, 1.08); 0.024	**-0.62 (-0.66, -0.57); <0.001**	**-0.37 (-0.41, -0.33); <0.001**
≥4	**1.27 (1.23, 1.31); <0.001**	**1.07 (1.03, 1.11); <0.001**	**-1.03 (-1.07, -0.99); <0.001**	**-0.55 (-0.58, -0.51); <0.001**
Linear trend	**1.06 (1.06, 1.07); <0.001**	**1.02 (1.01, 1.03); <0.001**	**-0.26 (-0.27, -0.25); <0.001**	**-0.14 (-0.14, -0.13); <0.001**
Driving time (hours/day)				
<1 (reference)	-	-	-	-
1	1.00 (0.98, 1.02); 0.783	1.01 (0.98, 1.03); 0.530	**-0.19 (-0.21, -0.16); <0.001**	**-0.06 (-0.08, -0.04); <0.001**
2	**1.05 (1.03, 1.08); <0.001**	1.02 (0.99, 1.06); 0.046	**-0.33 (-0.36, -0.29); <0.001**	**-0.12 (-0.15, -0.09); <0.001**
≥3	**1.27 (1.22, 1.31); <0.001**	**1.11 (1.07, 1.16); <0.001**	**-0.84 (-0.89, -0.79); <0.001**	**-0.29 (-0.34, -0.25); <0.001**
Linear trend	**1.05 (1.04, 1.06); <0.001**	**1.02 (1.01, 1.04); <0.001**	**-0.22 (-0.24, -0.21); <0.001**	**-0.08 (-0.09, -0.07); <0.001**
Computer use time (hours/day)				
<1 (reference)	-	-	-	-
1	**0.81 (0.80, 0.83); <0.001**	**0.86 (0.84, 0.88); <0.001**	**0.40 (0.38, 0.43); <0.001**	**0.15 (0.13, 0.17); <0.001**

2	**0.79 (0.77, 0.81); <0.001**	**0.80 (0.78, 0.83); <0.001**	**0.45 (0.42, 0.48); <0.001**	**0.16 (0.13, 0.19); <0.001**
≥3	**0.82 (0.80, 0.85); <0.001**	**0.82 (0.79, 0.85); <0.001**	**0.28 (0.25, 0.32); <0.001**	**0.12 (0.09, 0.15); <0.001**
Linear trend	**0.92 (0.91, 0.92); <0.001**	**0.92 (0.91, 0.93); <0.001**	**0.13 (0.12, 0.15); <0.001**	**0.05 (0.04, 0.06); <0.001**
Time (years)	**1.10 (1.10, 1.10); <0.001**	**1.07 (1.06, 1.07); <0.001**	**-0.15 (-0.15, -0.15); <0.001**	**0.02 (0.02, 0.03); <0.001**
Model 2 [b]	N (observations) = 529,936 N (groups) = 423,271	N (observations) = 528,358 N (groups) = 422,497	N (observations) = 259,555 N (groups) = 216,205	N (observations) = 147,342 N (groups) = 136,043
	OR (99% CI) [g]; p-value	OR (99% CI) [g]; p-value	β (99% CI) [h]; p-value	β (99% CI) [h]; p-value
TV viewing time (hours/day)				
<1 (reference)	-	-	-	-
1	**1.07 (1.03, 1.11); <0.001**	1.02 (0.98, 1.06); 0.277	**-0.18 (-0.22, -0.13); <0.001**	**-0.12 (-0.16, -0.08); <0.001**
2	**1.08 (1.04, 1.12); <0.001**	1.02 (0.98, 1.07); 0.124	**-0.26 (-0.30, -0.22); <0.001**	**-0.20 (-0.23, -0.16); <0.001**
3	**1.10 (1.06, 1.14); <0.001**	1.03 (0.99, 1.07); 0.085	**-0.38 (-0.43, -0.34); <0.001**	**-0.28 (-0.32, -0.25); <0.001**
≥4	**1.14 (1.10, 1.19); <0.001**	1.03 (0.99, 1.08); 0.066	**-0.61 (-0.66, -0.57); <0.001**	**-0.39 (-0.43, -0.35); <0.001**
Linear trend	**1.03 (1.02, 1.04); <0.001**	1.01 (1.00, 1.02); 0.084	**-0.15 (-0.16, -0.14); <0.001**	**-0.09 (-0.10, -0.09); <0.001**
Driving time (hours/day)				
<1 (reference)	-	-	-	-
1	**1.06 (1.04, 1.08); <0.001**	**1.04 (1.02, 1.07); <0.001**	**-0.26 (-0.29, -0.24); <0.001**	**-0.08 (-0.11, -0.06); <0.001**
2	**1.10 (1.07, 1.13); <0.001**	**1.06 (1.03, 1.10); <0.001**	**-0.39 (-0.43, -0.36); <0.001**	**-0.15 (-0.18, -0.12); <0.001**
≥3	**1.24 (1.19, 1.29); <0.001**	**1.11 (1.06, 1.16); <0.001**	**-0.70 (-0.75, -0.65); <0.001**	**-0.28 (-0.33, -0.23); <0.001**
Linear trend	**1.06 (1.05, 1.07); <0.001**	**1.03 (1.02, 1.05); <0.001**	**-0.22 (-0.24, -0.21); <0.001**	**-0.08 (-0.10, -0.07); <0.001**
Computer use time (hours/day)				
<1 (reference)	-	-	-	-
1	**0.87 (0.85, 0.89); <0.001**	**0.89 (0.87, 0.91); <0.001**	**0.25 (0.22, 0.27); <0.001**	**0.12 (0.10, 0.15); <0.001**
2	**0.82 (0.80, 0.84); <0.001**	**0.83 (0.80, 0.85); <0.001**	**0.32 (0.29, 0.35); <0.001**	**0.14 (0.12, 0.17); <0.001**

≥3	**0.84 (0.82, 0.87); <0.001**	**0.85 (0.82, 0.88); <0.001**	**0.18 (0.14, 0.21); <0.001**	**0.12 (0.08, 0.15); <0.001**
Linear trend	**0.93 (0.92, 0.94); <0.001**	**0.93 (0.92, 0.94); <0.001**	**0.09 (0.08, 0.10); <0.001**	**0.05 (0.04, 0.06); <0.001**
Time (years)	**1.12 (1.11, 1.12); <0.001**	**1.08 (1.07, 1.08); <0.001**	**-0.18 (-0.18, -0.17); <0.001**	**0.01 (0.01, 0.01); <0.001**

[a] *Model 1 was mutually adjusted for the other sedentary behaviours and for age, sex and time*
[b] *Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments*
[c] *Pairs matching result (round 1): categorical: good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*
[d] *Pairs matching result (round 2): categorical: good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*
[e] *Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*
[f] *Numeric memory score: continuous: maximum digits remembered correctly. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*
[g] *Odds ratio (99% confidence interval)*
[h] *Beta coefficient (99% confidence interval)*
***Bold** indicates statistical significance (i.e. p-value<0.01).*

The findings from the Poisson regression analysis were consistent and robust with the main results (see Table 17).

Table 17 - Observational study (UK Biobank data): Cross-sectional associations at baseline between sedentary behaviours and cognitive function using Poisson regression models

Sedentary behaviours and cognitive function (Model 1 and Model 2) [a b]	Fluid intelligence test [c]	Short-term numeric memory test [d]
	Total number of correct answers	Maximum digits remembered correctly
Model 1 [a]	N = 161,348	N = 49,035
	IRR (99% CI) [e]; p-value	IRR (99% CI) [e]; p-value
TV viewing time (hours/day)		
<1 (reference)	-	-
1	**0.98 (0.97, 0.99); <0.001**	**0.98 (0.97, 0.99); <0.001**
2	**0.95 (0.95, 0.96); <0.001**	**0.96 (0.96, 0.97); <0.001**
3	**0.92 (0.91, 0.93); <0.001**	**0.95 (0.94, 0.96); <0.001**
≥4	**0.85 (0.84, 0.86); <0.001**	**0.92 (0.91, 0.93); <0.001**
Linear trend	**0.96 (0.96, 0.96); <0.001**	**0.98 (0.98, 0.98); <0.001**
Driving time (hours/day)		
<1 (reference)	-	-
1	**0.97 (0.96, 0.97); <0.001**	1.00 (0.99, 1.00); 0.144
2	**0.94 (0.93, 0.95); <0.001**	**0.98 (0.97, 0.99); <0.001**
≥3	**0.86 (0.85, 0.87); <0.001**	**0.96 (0.95, 0.97); <0.001**
Linear trend	**0.96 (0.96, 0.96); <0.001**	**0.99 (0.99, 0.99); <0.001**
Computer use time (hours/day)		
<1 (reference)	-	-
1	**1.09 (1.09, 1.10); <0.001**	**1.03 (1.03, 1.04); <0.001**
2	**1.10 (1.09, 1.11); <0.001**	**1.03 (1.02, 1.04); <0.001**
≥3	**1.07 (1.06, 1.08); <0.001**	**1.02 (1.02, 1.03); <0.001**
Linear trend	**1.03 (1.03, 1.03); <0.001**	**1.01 (1.01, 1.01); <0.001**
Model 2 [b]	N = 145,124	N = 44,097
	IRR (99% CI) [e]; p-value	IRR (99% CI) [e]; p-value
TV viewing time (hours/day)		
<1 (reference)	-	-
1	**0.98 (0.97, 0.99); <0.001**	**0.98 (0.97, 0.99); <0.001**
2	**0.97 (0.96, 0.98); <0.001**	**0.97 (0.96, 0.98); <0.001**
3	**0.95 (0.94, 0.96); <0.001**	**0.96 (0.96, 0.97); <0.001**
≥4	**0.91 (0.90, 0.92); <0.001**	**0.95 (0.94, 0.96); <0.001**
Linear trend	**0.98 (0.97, 0.98); <0.001**	**0.99 (0.99, 0.99); <0.001**
Driving time (hours/day)		
<1 (reference)	-	-
1	**0.96 (0.95, 0.96); <0.001**	**0.99 (0.99, 1.00); <0.001**
2	**0.93 (0.92, 0.94); <0.001**	**0.97 (0.97, 0.98); <0.001**
≥3	**0.88 (0.87, 0.89); <0.001**	**0.96 (0.95, 0.97); <0.001**

Linear trend	**0.96 (0.96, 0.96); <0.001**	**0.99 (0.98, 0.99); <0.001**
Computer use time (hours/day)		
<1 (reference)	-	-
1	**1.05 (1.05, 1.06); <0.001**	**1.02 (1.02, 1.03); <0.001**
2	**1.07 (1.06, 1.08); <0.001**	**1.02 (1.02, 1.03); <0.001**
≥3	**1.05 (1.04, 1.05); <0.001**	**1.02 (1.01, 1.03); <0.001**
Linear trend	**1.02 (1.02, 1.02); <0.001**	**1.01 (1.01, 1.01); <0.001**

[a] *Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex*
[b] *Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments*
[c] *Fluid intelligence score: counts: total number of correct answers. An incidence rate ratio of greater than 1 indicates a higher rate of a high score; and an incidence rate ratio of less than 1 indicates a lower rate of a high score*
[d] *Numeric memory score: counts: maximum digits remembered correctly. An incidence rate ratio of greater than 1 indicates a higher rate of a high score; and an incidence rate ratio of less than 1 indicates a lower rate of a high score*
[e] *Incidence Rate Ratio (99% confidence interval)*
***Bold** indicates statistical significance (i.e. p-value<0.01).*

After conducting the initial planned statistical analyses and comprehending the findings, the associations between some sedentary behaviours, in particular computer use time, and cognitive function did not seem to be linear, but they appeared to be of quadratic nature. Therefore, to test this theory further, I used the cross-sectional data at baseline (i.e. the maximum available data) to investigate the quadratic associations (Model 1 and Model 2) between computer use time and the cognitive function tests (prospective memory, visual-spatial memory, fluid intelligence, short-term numeric memory). Here, the models included both a linear and quadratic term for computer use time, and these findings have been added to the categorical data presented previously (see Table 18). These trend analyses showed several statistically significant inverted 'U' shaped quadratic relationships between computer use time and cognitive function; indicating that most of the differences in cognition are apparent at low levels of computer use time (2 hours/day), and the favourable associations do not markedly change with increasing levels, i.e. there is no additional protective advantage on cognitive function with increasing levels of computer use time.

Table 18 - Observational study (UK Biobank data): Cross-sectional quadratic associations at baseline between computer use time and cognitive function

Sedentary behaviours and cognitive function (Model 1 and Model 2) [a b]	Prospective memory test [c]	Visual-spatial memory test (round 1) [d]	Visual-spatial memory test (round 2) [e]	Fluid intelligence test [f]	Short-term numeric memory test [g]
	Good result or Poor result	Good result or Poor result	Good result or Poor result	Total number of correct answers	Maximum digits remembered correctly
Model 1 [a]	N = 166,401	N = 471,474	N = 470,433	N = 161,348	N = 49,035
	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	β (99% CI) [i]; p-value	β (99% CI) [i]; p-value
Computer use time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**0.68 (0.66, 0.71); <0.001**	**0.79 (0.77, 0.80); <0.001**	**0.85 (0.83, 0.87); <0.001**	**0.52 (0.49, 0.55); <0.001**	**0.21 (0.17, 0.25); <0.001**
2	**0.69 (0.66, 0.72); <0.001**	**0.77 (0.75, 0.79); <0.001**	**0.80 (0.78, 0.83); <0.001**	**0.58 (0.53, 0.62); <0.001**	**0.21 (0.16, 0.26); <0.001**
≥3	**0.86 (0.82, 0.90); <0.001**	**0.81 (0.79, 0.84); <0.001**	**0.82 (0.79, 0.85); <0.001**	**0.40 (0.35, 0.44); <0.001**	**0.16 (0.11, 0.22); <0.001**
Linear trend	**0.91 (0.89, 0.92); <0.001**	**0.91 (0.90, 0.92); <0.001**	**0.92 (0.91, 0.93); <0.001**	**0.18 (0.17, 0.20); <0.001**	**0.07 (0.06, 0.09); <0.001**
Test for quadratic relationship					
Linear term	**0.60 (0.57, 0.63); <0.001**	**0.74 (0.72, 0.76); <0.001**	**0.81 (0.79, 0.84); <0.001**	**0.68 (0.64, 0.72); <0.001**	**0.26 (0.22, 0.31); <0.001**
Quadratic term	**1.17 (1.15, 1.19); <0.001**	**1.08 (1.07, 1.09); <0.001**	**1.05 (1.04, 1.06); <0.001**	**-0.18 (-0.20, -0.17); <0.001**	**-0.07 (-0.09, -0.06); <0.001**
Model 2 [b]	N = 148,327	N = 422,731	N = 421,851	N = 145,124	N = 44,097
	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	OR (99% CI) [h]; p-value	β (99% CI) [i]; p-value	β (99% CI) [i]; p-value
Computer use time (hours/day)					
<1 (reference)	-	-	-	-	-
1	**0.77 (0.74, 0.81); <0.001**	**0.85 (0.83, 0.87); <0.001**	**0.88 (0.86, 0.90); <0.001**	**0.32 (0.29, 0.35); <0.001**	**0.14 (0.10, 0.17); <0.001**
2	**0.74 (0.70, 0.78); <0.001**	**0.81 (0.79, 0.83); <0.001**	**0.83 (0.80, 0.86); <0.001**	**0.40 (0.36, 0.44); <0.001**	**0.15 (0.10, 0.20); <0.001**
≥3	**0.86 (0.81, 0.91); <0.001**	**0.84 (0.81, 0.86); <0.001**	**0.84 (0.81, 0.88); <0.001**	**0.26 (0.22, 0.31); <0.001**	**0.13 (0.07, 0.18); <0.001**
Linear trend	**0.92 (0.90, 0.94); <0.001**	**0.92 (0.91, 0.93); <0.001**	**0.93 (0.92, 0.94); <0.001**	**0.12 (0.11, 0.14); <0.001**	**0.06 (0.04, 0.07); <0.001**

Test for quadratic relationship					
Linear term	**0.70 (0.66, 0.74); <0.001**	**0.81 (0.79, 0.83); <0.001**	**0.85 (0.82, 0.87); <0.001**	**0.43 (0.39, 0.47); <0.001**	**0.17 (0.13, 0.22); <0.001**
Quadratic term	**1.11 (1.09, 1.13); <0.001**	**1.05 (1.04, 1.06); <0.001**	**1.04 (1.03, 1.05); <0.001**	**-0.12 (-0.13, -0.10); <0.001**	**-0.04 (-0.06, -0.03); <0.001**

[a] *Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex*

[b] *Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, smoking status, alcohol drinking status, fruit and vegetable consumption, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate-intensity physical activity, frequency of ≥10 minutes of vigorous-intensity physical activity, number of cancers, number of non-cancer illnesses, number of medications/treatments, TV viewing time, and driving time*

[c] *Prospective memory result: categorical (binary): good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[d] *Pairs matching result (round 1): categorical (binary): good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[e] *Pairs matching result (round 2): categorical (binary): good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]. An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result*

[f] *Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*

[g] *Numeric memory score: continuous: maximum digits remembered correctly. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score*

[h] *Odds ratio (99% confidence interval)*

[i] *Beta coefficient (99% confidence interval)*

***Bold** indicates statistical significance (i.e. p-value<0.01).*

Discussion

Key Findings

This is the first study to quantify the cross-sectional and prospective associations between domains of sedentary behaviour and cognitive function in a large cohort of UK adults. At baseline, both TV viewing and driving time were inversely associated with cognitive function. In contrast, computer use time was positively associated with cognitive function. Most findings were modified by age and sex, with stronger relationships generally observed in older adults and in males. These novel results suggest that the impact of sedentary behaviour on cognition is enhanced in older age and in men. Both TV viewing and driving time at baseline were positively associated with the odds of having cognitive decline at follow-up across most outcomes. In contrast, computer use time at baseline was inversely associated with the odds of having cognitive decline at follow-up across most outcomes. The cross-sectional and prospective findings were robust and generalizable across the sample of participants without cancer, CVD, and/or cognitive/psychiatric illnesses, and the findings were consistent when the data were analysed using mixed-effects regression and Poisson regression models. Lastly, inverted 'U' shaped relationships were observed between computer use time and cognitive function, suggesting that a greater amount of time spent using a computer was not associated with better cognition above that observed for low levels of computer use.

Interpretations

To my knowledge, only a few number of studies have attempted to examine the prospective associations between the different types of sedentary behaviours and cognitive function (56-59, 159-163). However, these studies have all been limited by a small sample size (N ranging between 469 and 8,462), populations that only involved children or older adults, analyses that only considered one domain or test of cognitive function, and/or cognitive data that were only collected at a single time point. Therefore, this novel study in a large sample of middle-aged adults provides the most comprehensive observational analysis to date.

These findings are consistent with the existing data in this research area. Observational studies have previously demonstrated an inverse association between TV viewing and cognition (56-59), and a positive association between computer/internet use and cognition (57-60). However, until this study, the interactions with age or the deleterious impact of driving on cognitive health were less clear. The inverse associations of TV viewing and driving time with cognitive function could be due to several factors. Cognition has previously been linked to cardiometabolic health (164, 165), and numerous studies have demonstrated inverse associations of TV viewing and driving time with cardiometabolic health (8, 10, 11, 13, 166-168). Therefore, it is possible that the observed associations act via pathways linked to the risk of vascular dysfunction and chronic diseases. As vascular dysfunction and chronic diseases are linked to ageing, this mechanism would also help explain the observed interactions with age. Other mediating factors could also explain the results for driving. It is known that driving is related to stress and fatigue (26), and with several studies previously showing the links between these factors and cognitive decline (169-171), it is plausible that the observed relationships are enhanced via this pathway. Furthermore, some types of sedentary behaviours, such as TV viewing and driving, could possibly segregate individuals from social networks and restrict external collaborations, factors which are known to affect cognition (172-174); this again could be particularly important in older adults. In contrast, the positive relationship shared between computer use and cognitive function coincides with previous work where improved cognition or a lower risk of dementia were reported in those engaging in cognitively vitalising sedentary behaviours or leisure activities (57-60). Therefore, as computer use is likely to involve some level of cognitive challenge, stimulate social interactions and reduce solitariness, it may compensate for the associated sedentary behaviour in relation to cognitive health. Some of the mechanisms mentioned above are also linked to and vary by gender (175, 176); and therefore, they could help explain the observed interactions with sex.

The differences observed in cognitive function across the categories of sedentary behaviour in these analyses are likely to be clinically important beyond the risk of cognitive decline. For example, higher fluid intelligence scores have previously been

shown to be strongly associated with a lower risk of all-cause mortality (177, 178). In a sample of 5,572 middle-aged British adults, Sabia and colleagues observed that a higher fluid intelligence score by 1 SD was associated with a 14% lower risk of all-cause mortality (177). Similarly, in a sample of 896 older Australian adults, Batterham and colleagues observed that a higher fluid intelligence score by 1 SD was associated with a 24% lower risk of all-cause mortality (178). In my analysis at baseline (Model 2), the SD of fluid intelligence score was 2.1. Regression analyses investigating the associations of sedentary behaviours with fluid intelligence demonstrated that TV viewing and driving time were linearly associated with lower fluid intelligence scores of 0.15 and 0.24 units, respectively. In contrast, computer use time was linearly associated with a higher fluid intelligence score of 0.12 units. Hence, using the data above, it can be estimated that lower fluid intelligence scores by 0.15 and 0.24 units would approximately equate to a 1.1%-3.2% higher risk of all-cause mortality. In contrast, a higher fluid intelligence score by 0.12 units would approximately equate to a 0.9%-1.6% lower risk of all-cause mortality. For more details on these calculations, see Calculation S1 in Appendix Three: Supplementary Material: Supplementary Calculations. This implies that high computer use time may lower the risk of all-cause mortality; and to test this, I directly examined the associations between the computer use time and all-cause mortality in the UK Biobank. Here, to a certain extent, I observed that computer use time was in fact associated with a lower risk of all-cause mortality. For example, after adjustment for age, sex, TV viewing time and driving time (Model 1 as reported), in comparison to those reporting less than 1 hour per day of computer use time, participants reporting 1 or 2 hours per day of computer use time were associated with hazard ratios for all-cause mortality of 0.82 (95% CI: 0.78, 0.85) or 0.90 (95% CI: 0.85, 0.95), respectively. Those reporting 3 or more hours per day of computer use time had no difference in risk. This indicated that whilst some computer use time may be beneficial against an early death, excessive use might not actually be protective from a premature mortality. The wider literature on the association between screen time and mortality has predominantly focused on TV viewing or combined screen use; studies specifically concentrating on computer use in comparison to other forms of screen use or sedentary behaviours are scarce. To my

knowledge, only one other study has compared the associations of TV viewing time, driving time, and computer use time with all-cause mortality (179). Here, using data on 13,284 adults (mean age = 37 years; median follow-up period of 8.2 years), for every 2 hours per day of computer use time, Basterra-Gortari and colleagues observed a non-significant lower risk of all-cause mortality (IRR: 0.96 (95% CI: 0.79, 1.18)) (179). TV viewing time was associated with a higher risk of all-cause mortality (IRR: 1.40 (95% CI: 1.06, 1.84)) (179). Driving time was also associated with a higher risk of all-cause mortality (179); however, the association here was not statistically significant (IRR: 1.14 (95% CI: 0.90, 1.44)) (179). More research studies are required in this area to fully understand the impact of computer use time on mortality, to assess any dose-response associations, and to determine the biological mechanisms and pathways explaining these relationships.

Strengths and Limitations

This study has several strengths and some limitations. Strengths include: exploitation of a large sample of adults, follow-up cognitive function data allowing for prospective associations to be investigated, evaluation of dose-response and linear relationships between mutually adjusted and time quantified sedentary behaviours with a wide range of comprehensive cognitive outcomes, detailed covariate data enabling several important and relevant factors to be controlled for, interactions by age and sex, and robust sensitivity analyses investigating the associations in the healthy population. Although the UK Biobank is representative of the general population with respect to age, sex, ethnicity, and deprivation within the age range recruited, it may not be representative in other regards (180). While this limits the ability to generalize prevalence rates, estimates of the magnitude of associations in this analysis are unlikely to have been substantially affected by this due to the large and multifaceted base population (180, 181). The cognitive data from the UK Biobank cohort have recently been shown to be an important, reliable and valid resource for investigating predictors and modifiers of cognitive abilities and associated health outcomes (182). These data have also shown consistency when repeated after an average of 4 years (e.g. fluid intelligence (Intraclass Correlation Coefficient (ICC) (95% CI): 0.65 (0.63 to

0.67))) (182). Recall that cognitive functioning is associated to health conditions such as dementia (45); and impaired memory, visual perception, reasoning and judgement are all core symptoms of dementia. In particular, a deterioration in these features is crucial as dementia is defined as "a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities" (183). Therefore, with respect to this, the prospective nature of these data is especially important. Furthermore, note that the cognitive data in the UK Biobank were collected with an intention to cover the different domains of cognition. In relation to this, I had also tested the correlations between the different UK Biobank cognitive tests at baseline to observe whether any of these domains were associated to one another. Here, the correlation coefficients ranged from a minimum of -0.313 to a maximum of 0.393 (see Table S1 in Appendix Three: Supplementary Material: Supplementary Data). These negligible/low correlations indicated that the associations between the different cognitive variables were weak (184), and suggested that the tests in the UK Biobank were in fact measuring different facets of cognitive function. In addition, these statistics were in full agreement with the UK Biobank cognitive data findings by Lyall and colleagues (182).

The sedentary behaviour data used in this study have both strengths and limitations. Only three sedentary domains included; thus, the findings are restricted and cannot be generalized to other types of sedentary behaviour. Self-reported assessments of sedentary behaviour are subjective and are influenced by recall and response issues (62, 63); hence, they tend to have low validity and increase the risk of regression dilution (185). Regression dilution is a form of statistical bias whereby random measurement error (i.e. when the recorded values of a variable fluctuate randomly around the true values) in the values of an exposure variable causes an attenuation of the slope of the line describing the association between the exposure and an outcome of interest (185). However, although data that are more robust can be obtained using objective measurement tools (e.g. accelerometers) (62, 63), they would not provide information on the specific type of sedentary behaviour performed. Furthermore, since the reasons for using the computer outside work were unknown (e.g. utilised for activities such as: reading, watching videos, internet browsing, playing games, etc.), it

is not possible to accurately classify or infer the type of computer use undertaken, and it may have involved crossover into cognitively inert tasks. Note, in the UK Biobank, data on the sedentary behaviours were collected in order to generate a composite measure of physical inactivity (94). However, although these data have yet to be validated specifically within the UK Biobank, comparable self-reported measures of TV viewing, driving and non-occupational computer use time have been investigated in the literature for their reliability and validity, and these have been shown to be reasonably acceptable markers of sedentary behaviour (186-191). Reliability has largely been assessed via the test-retest method. For example, Cauwenberg and colleagues reported good levels of reliability when questions on these three measures of sedentary behaviour were repeated [TV viewing time: ICC (95% CI): 0.92 (0.83, 0.96); driving time: ICC (95% CI): 0.79 (0.59, 0.90); computer use time: ICC (95% CI): 0.76 (0.54, 0.88)] (191). Similarly, other studies have also demonstrated relatively high reliability; although a majority of these predominantly focused on TV viewing and/or computer use (186-190). Research has pushed towards refining measurement instruments that assess multiple and specific sedentary behaviours (187, 190). This is important since different sedentary behaviours may share different relationships with different health outcomes; as this analysis demonstrated with cognitive function. However, regarding the validity of these specific sedentary behaviour questionnaires, more evidence is required. Clark and colleagues conducted a review of 60 research articles that examined the validity and reliability of measures of specific sedentary behaviours, and a majority of the studies included a measure of TV viewing, driving and/or non-occupational computer use (190). In general, the reliability coefficients, derived from retesting, were moderate to high (range: 0.32 - 0.93, with most greater >0.70). However, depending on referent measure used (behavioural log, activity diary, heart rate monitoring, accelerometer), there were large variations in the validity coefficients (range: -0.19 - 0.80) (190). A key barrier to signifying validity is the lack of a recognised ‘gold standard’ measure of specific sedentary behaviours (186). Furthermore, using one type of self-report to validate another type of self-report is unsuitable due to the correlated error. Future validation studies could be strengthened via using objective tools that evaluate changes in posture (e.g. the activPAL device).

Therefore, in context of this analysis, until more evidence emerges, specifically from the sedentary behaviour data in the UK Biobank, findings from analyses using these variables should be interpreted with caution.

Moving on, although the categorisations in the prospective memory and visual-spatial memory tests were justified based on the distributions of the data (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data), it is possible that significant information may have been lost when truncating these data into binary variables. In addition, specifically for the visual-spatial memory test, the data on the 'number of incorrect matches' could have also been categorised using several different thresholds than the ones used in this analysis. These points extend to the sedentary behaviour variables (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data); however, here, the linear associations across the categories were also examined, and as mentioned earlier, these categorisations were based on those commonly-used in this research area. Nonetheless, putting these factors together, these findings should be interpreted cautiously. Furthermore, only those who provided an email address at baseline (~300,000) were contacted to participate in the online follow-up of cognitive function. Therefore, these participants all had computer access and presumably, some computer use experience. This may also have resulted in the small differences in characteristics (including level of education and employment status) in the follow-up sample (see Table 14). Consequently, the prospective analysis may be biased and lack generalizability. Moreover, at baseline, the cognitive function tests were implemented using questionnaires that were administered via a touchscreen interface. At follow-up, the measurements were obtained remotely via online questionnaires that were administered on a computer via a mouse interface. Therefore, this difference in the mode of administration could possibly account for some of the variability in cognitive performance and change over time. Nevertheless, the prospective analysis broadly supports and is consistent with the cross-sectional associations reported for the full cohort at baseline. Although a wide range of covariates were adjusted for, some unmeasured factors (e.g. type of employment/occupation) may have further confounded the reported associations. The results may be subject to residual confounding or reverse causality. For example, it is

possible that the positive association observed between computer use and cognitive function was simply reflecting greater familiarity for interacting with a computer rather than better cognitive function as such. Correspondingly, individuals with better cognitive function are more likely to engage in healthy behaviours and abstain from unhealthy ones, a concept known as neuroselection (192, 193). Whilst the interactions by age and sex were investigated in this study, it must be highlighted that similar differences observed in cognitive function across different groups (i.e. in younger adults vs. older adults, and females vs. males) may have different clinical meanings and should be interpreted with caution. For example, a unit difference in a cognitive function test score in a younger adult may not have the same effect on cognitive health as a unit difference in an older adult. Lastly, due to large variations between the numbers of individuals who completed each cognitive assessment at both baseline and follow-up, analyses were based on different sample sizes.

A broader discussion on the strengths and limitations of the UK Biobank database is provided in Chapter Two.

Conclusion

This analysis, conducted in a large sample of adults, demonstrates that some sedentary domains, but not all, are associated with poor cognition. Watching TV and driving are inversely associated with cognitive function, whereas computer use is positively associated with cognitive function. Of note, the associations were consistently stronger in older adults. Intervention studies are required to confirm these findings. Nevertheless, these results provide robust observational data supporting public health policies aimed at reducing TV viewing and driving time in adults.

The Associations between Sedentary Behaviours and Cognitive Function are not Modified by Cardiorespiratory Fitness: A Cross-Sectional Analysis of 51,892 Adults from the UK Biobank

Abstract

Following on from the previous analysis, the aim of this study was to examine whether the associations between different sedentary behaviours and fluid intelligence were modified by levels of CRF. Baseline data from the UK Biobank [years: 2006-2010; location: England, Scotland, and Wales] were used. Sedentary behaviours included TV viewing, driving, and non-occupational computer use time (hours/day). CRF (ml/kg/min) was estimated using data collected from a six-minute submaximal cycle ergometer test. Fluid intelligence involved solving 13 numeric and verbal problems over a period of two-minutes. 51,892 participants with complete fluid intelligence, sedentary behaviour, CRF, and covariate data were included. After adjustment for each other and important confounders, regression analyses showed that TV viewing and driving were inversely associated with fluid intelligence, whereas computer use and CRF were positively associated with fluid intelligence [e.g. lowest quartile of CRF (reference) vs. highest quartile of CRF (β (99% CI): 0.29 (0.21, 0.36))]. Interaction analyses showed that the associations between the sedentary behaviours and fluid intelligence were not modified by CRF [p-value=0.623 (interaction with TV viewing); p-value=0.837 (interaction with driving); p-value=0.547 (interaction with computer use)]. In both low and high levels of CRF, the observed associations between the sedentary behaviours and fluid intelligence maintained similar direction, magnitude, and significance. Sensitivity analyses indicated robustness. These data show that CRF does not modify the associations between different sedentary behaviours and fluid intelligence. Higher levels of CRF may not provide protection from the potentially deleterious impact of TV viewing and driving on cognitive function. This study supports public health policies designed to reduce these two activities in adults.

Introduction

Time spent in sedentary behaviours has been associated with a wide range of adverse health outcomes, including a greater risk of morbidity and mortality (8-14, 38). This has led interventions and guidance designed to reduce sitting time within the general and high risk populations. However, recent advances in the literature have suggested that the adverse effects of engaging in high levels of sedentary behaviour are largely attenuated in the presence of other factors. In particular, high levels of moderate-to-vigorous physical activity and CRF may provide protection against the increased risk of poor cardiometabolic health and mortality observed in those with high levels of sedentary time (8, 37, 38, 194, 195). This suggests that interventions to reduce sedentary time should be tailored towards inactive or unfit individuals. Nevertheless, the evidence supporting this hypothesis is relatively underdeveloped and has been limited to measures of physical health.

Time spent in sedentary behaviour has consistently been associated with cognitive function and health (56-60, 196); however, the direction of the association is dependent on the type of sedentary behaviour. For example, whilst TV viewing and driving can be deleterious for cognitive well-being, engaging in activities such as computer use can be beneficial for cognitive health (56-60, 196). CRF has also been associated with cognitive function (197-204), with interventional and mechanistic studies supporting a causal relationship indicating direct and positive effects on the structure and function of the brain (50-53, 205-208). Therefore, it is possible that CRF may be an important confounder or modifier in the associations between sedentary behaviour and cognitive function.

The aim of this study is to use the UK Biobank dataset to investigate whether the associations between different sedentary behaviours (TV viewing, driving and computer time) and fluid intelligence are modified by levels of CRF. Previous research has shown fluid intelligence to be strongly associated with sedentary behaviour (57, 60, 161, 196, 209-211); and in the UK Biobank, this assessment was recorded as a continuous measure and assessed using a broad range of numeric and verbal problems that required logic and reasoning ability, discrete of any acquired knowledge; resulting in a wide response distribution; and therefore, a comprehensive and sensitive measure

of cognitive ability within this cohort. Here, it is hypothesised that CRF may provide a protective effect on cognitive function and attenuate some of the deleterious impact of TV viewing and driving, and the beneficial impact of computer use.

Methods

Design and Population

Approximately 500,000 adults (aged 37-73 years) were recruited between 2006-2010 via mailing out invitations to those registered with the NHS and living within 25 miles of one of the 22 study assessment centres across England, Scotland, and Wales. Participants provided baseline data on a broad range of biological, cognition, demographic, health, lifestyle, mental, social, and well-being outcomes. All participants provided written informed consent and the study was approved by the NHS National Research Ethics Service (Ref: 11/NW/0382). Further details are available elsewhere (92-94).

Sedentary Behaviours

Similar to the first analysis of the UK Biobank project presented within this thesis, data on three types of sedentary behaviours variables were included: TV viewing time (<1, 1, 2, 3, ≥4 hours/day), driving time (<1, 1, 2, ≥3 hours/day), and non-occupational computer use time (<1, 1, 2, ≥3 hours/day). For each sedentary behaviour, the '<1 hour/day' group was selected as the reference category.

CRF

CRF was examined using a six-minute incremental submaximal ramp cycle ergometer test (212, 213). UK Biobank introduced this measure towards the end of recruitment at each assessment centre; and therefore, CRF data are only available in a subsample of participants. Before performing the exercise test on a stationary bike (eBike, firmware version 1.7), participants were first stratified into five risk categories (minimal risk, small risk, medium risk, high risk, or electrocardiography (ECG) to be avoided) based

on the following risk factors: heart condition (small risk), chest pain during physical activity (medium risk), chest pain at rest (high risk), unable to walk/cycle (high risk), pregnant (high risk), height unknown (medium risk), weight unknown (high risk), heart rate unknown (medium risk), BP unknown (high risk), BP very high (high risk), BP high (small risk), weight high (high risk), pacemaker unknown (high risk), and pacemaker (ECG to be avoided) (212). The risk categorisation determined allocation to a personalised exercise protocol. The absolute maximum workload was estimated according to age, height, weight, resting heart rate and sex using the formula below (212):

Absolute Maximum Workload (watts) = 105.2749 + (-0.0935 x Age) + (-0.0280973 x Age x Age) + (2.809493 x Sex) + (119.0087 x Height) + (0.309456 x Weight) + (-2.698067 x Resting Heart Rate) + (0.0090985 x Resting Heart Rate x Resting Heart Rate) + (-0.3783405 x Age x Sex) + (60.72548 x Height x Sex) + (-0.15016 x Weight x Sex) + (-0.3730664 x Resting Heart Rate x Sex) + (0.0180811 x Resting Heart Rate x Age). Here, Age is in years, Sex is 0 for females and 1 for males, Height is in metres, Weight is in kg, and Resting Heart Rate is in beats per minute (bpm).

For each participant, the level of effort during the graded test was determined according to their risk category: minimal risk (cycle at 50% level of estimated maximum workload), small risk (cycle at 35% level of estimated maximum workload), medium risk (cycle at constant level), high risk (take measurement at rest-only), or ECG to be avoided (either unsafe or pointless) (212). Participants classified as ‘minimal risk’ or ‘small risk’ carried out the standard bike protocols; which consisted of an initial 15 second seated rest period, followed by a 2 minute period of cycling at constant power (30 watts for females and 40 watts for males), then a 4 minute period of cycling with linear increases in power from constant power to their individually allocated peak power (e.g. to 50 and 35% of estimated maximum workload for ‘minimal risk’ and ‘small risk’, respectively), and finally a 1 minute recovery period (212). Participants classified as ‘medium risk’ cycled at the constant power for 6 minutes (212). During the cycling phases, participants were instructed to cycle at 60 revolutions per minute (212). The ECG measurements were taken throughout the entire period (7 minutes and 15 seconds) (212). The examination was terminated early if 75% of the age-predicted

maximum heart rate was reached, if the participant reported any serious issues during the assessment (e.g. chest pains, dizziness, etc.), or if the participant reported any non-serious issues during the assessment (e.g. muscle fatigue or mild joint pain) and specifically requested to stop the test (212). Participants classified as 'high risk' only engaged in a 2 minute seated rest assessment (212).

ECG data were recorded at 500 Hz with a 4-lead electrocardiograph device (CAM-USB 6.5; Cardiosoft v6.51). The 4-lead ECG electrodes were placed on the left antecubital fossa (i.e. elbow pit / region of the arm in front of the elbow), right antecubital fossa, left wrist, and right wrist (212). In order to derive heart rate from raw 4-lead ECG data in the UK Biobank, the electrocardiograph signal was processed using the PhysioNet Toolkit (213-216). This executed the SQRS algorithm (216-218); which applied a digital filter to the signal and classified the typical downward slopes of QRS complexes. Using "ihr" (instantaneous heart rate) of the PhysioNet Toolkit (limiting beat-to-beat heart rate changes to ≤10 bpm) (216, 219), the resulting inter-beat-intervals were transformed to bpm values.

In this analysis, CRF was only estimated in participants who undertook the bike test (i.e. those classified as minimal risk, small risk, or medium risk) and fully completed it. The following data cleaning procedures were also carried out: participants with heart rate values of <40 bpm or >220 bpm at any stage of the fitness test were excluded; participants with a maximum workload value equal to 0 watts during the fitness test were excluded; participants with a maximum heart rate value during the fitness test < resting heart rate were excluded; and participants with a maximum workload value during the fitness test < resting workload were excluded. CRF was estimated via largely following previously reported methods (220). Maximal CRF was estimated by: (1) fitting a linear regression line between heart rate and workload at the start and during the fitness test (heart rate values used: resting heart rate and maximum heart rate during the fitness test; workload values used: resting workload (i.e. 0 watts) and maximum workload during the fitness test), (2) extrapolating the regression line to the age-predicted maximal heart rate using the equation: 208 - (0.7 x age) in order to estimate the workload at maximal heart rate, and (3) using the regression equation for the relationship between workload and oxygen uptake (oxygen uptake (ml/kg/min) = 7

+ (10.8 x workload (in Watts))/body mass (in kg)) to estimate the maximal oxygen uptake. For the main analysis, CRF (ml/kg/min) was categorised into quartiles (quartile 1 was selected as the reference category). For sensitivity analyses, CRF was also categorised into age- and sex-specific quartiles, as well as used as a continuous variable. For more details, see the Sensitivity Analysis section.

Cognitive Function Tests

This analysis is focussed on the fluid intelligence test. Here, the fluid intelligence score, quantified as the 'total number of correct answers', was used as a continuous outcome variable. Further details are available elsewhere (110, 221).

As sensitivity analyses, other cognitive tests administered in the UK Biobank (prospective memory and visual-spatial memory) were also used to ensure that the findings for fluid intelligence were consistent and generalizable across other measures of cognitive function. These data were used in the same fashion as they were in the previous UK Biobank analysis. However, here, for the visual-spatial memory test, I solely focused on round 2 of this assessment.

Confounders

Covariate data included: anthropometric (BMI), demographic (age, sex, ethnicity, social deprivation index, employment status, education level), health (number of cancers, number of non-cancer illnesses, number of medications/treatments), and lifestyle (smoking status, alcohol drinking status, sleep duration, fruit and vegetable consumption, physical activity) variables. These data were used in the same fashion as they were in the previous UK Biobank analysis.

Data Inclusion

For the present study, only those that undertook the CRF test were included (n = 68,679). Of these, 51,892 individuals provided complete and valid fluid intelligence, sedentary behaviour, CRF, and covariate data (see Figure 10).

Figure 10 - Observational study (UK Biobank data): Flow chart of participants

Statistical Analysis

Statistical analyses were executed using Stata/MP V14.0 (Stata Corporation, College Station, Texas, USA). Data were analysed in May 2017. Participant characteristics, stratified by quartiles of CRF, were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and SDs; and presented with their minimum and maximum values. The characteristics of the included and excluded participants were also compared.

Multiple linear regression models investigated the associations of sedentary behaviours and CRF with fluid intelligence (Stata command: 'regress') (121). Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex. Model 2 was further adjusted for BMI, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Linear trends (linear terms) across the categories of each sedentary behaviour and CRF were reported.

Interaction analyses were implemented to observe whether the associations between sedentary behaviours and fluid intelligence were modified by CRF. The following three interaction terms were separately added to the fully adjusted model (Model 2): 'TV viewing time x CRF', 'driving time x CRF', and 'computer use time x CRF'. For descriptive purposes, the results were stratified at the median CRF level: $<50^{th}$ percentile (i.e. quartiles 1 or 2) = Low CRF; and $\geq 50^{th}$ percentile (i.e. quartiles 3 or 4) = High CRF. The assumptions of linear regression were assessed (121).

Sensitivity Analysis

To assess the robustness and generalizability of the findings, a wide range of sensitivity analyses were executed. All interaction analyses were repeated: (1) across the sample of participants without a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses, (2) across other cognitive tests (prospective memory and visual-spatial memory) administered in the UK Biobank, (3) using age- and sex-specific quartiles for CRF (with age categorised at 60 years), and (4) using a continuous CRF variable (i.e.

included as an independent variable in the models and used for the derivation of the interaction terms). The reasons for selecting these particular sensitivity analyses are as follows. Similar to the first UK Biobank analysis presented earlier in this chapter, (1) was implemented to assess the confounding impact of participants with a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses on the associations. After taking out these 'unhealthy' participants, the remaining sample of 'healthier' individuals would potentially provide more dependable and unbiased findings. Moreover, (2) was carried out to ensure that the findings for fluid intelligence were consistent across the other cognitive domains. Furthermore, CRF is strongly associated with age and sex (222); and a CRF value of 35 ml/kg/min means something different for a 40 year old male that it does for a 70 year old female. Here, for example, it is likely that the 40 year old male would be categorised in Q1, whereas the 70 year old female would be in Q4. Therefore, (3) was implemented to try and take this into account. Lastly, information is potentially lost when a continuous variable is split into groups and treated as a categorical variable. Hence, in (4), as opposed to a categorical variable, CRF was used as a continuous variable to see if this had any impact on the findings.

The statistical models described in this section (linear (continuous outcome data) and logistic (binary outcome data) regression analyses) were chosen after studying the distributions of all of the key outcomes and exposures used in this analysis. For more details, see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data.

Statistical Reporting

For each variable of interest, β (linear regression model) or OR (logistic regression model (e.g. sensitivity analysis: prospective memory test)) with 99% CIs and p-values are reported. All analyses employed robust SEs and all reported p-values are two-sided. To account for multiple comparisons, p-value<0.01 was considered to be

statistically significant for the main effects. For the interaction effects, p-value<0.05 was considered to be statistically significant.

Results

Cross-Sectional Findings

Table 19 presents the characteristics of the 51,892 participants with complete fluid intelligence, sedentary behaviour, CRF, and covariate data. The mean (SD) age of these individuals was 56.2 (8.1) years and 26,847 (51.7%) were female. The mean (SD) fluid intelligence score was 6.2 (2.1) out of 13; implying that the average participant answered a total of 6.2 questions correctly out of a maximum of 13.

Table 19 - Observational study (UK Biobank data): Participant characteristics

Participant characteristics	Included sample	Cardiorespiratory fitness (ml/kg/min)			
		Quartile 1	Quartile 2	Quartile 3	Quartile 4
	N = 51,892	N = 12,973	N = 12,973	N = 12,973	N = 12,973
Anthropometrics					
Body mass index (kg/m2) [a]	27.1 (4.4); 14.5 - 59.2	29.0 (5.1); 16.5 - 59.2	27.1 (4.2); 15.2 - 52.0	26.4 (3.9); 15.7 - 51.9	25.7 (3.6); 14.5 - 43.4
Demographics					
Age (years) [a]	56.2 (8.1); 39.0 - 70.0	59.4 (7.1); 40.0 - 70.0	56.7 (7.8); 40.0 - 70.0	55.0 (8.1); 40.0 - 70.0	53.7 (8.2); 39.0 - 70.0
Sex ‡					
Female	26,847 (51.7)	10,395 (80.1)	7,831 (60.4)	5,408 (41.7)	3,213 (24.8)
Male	25,045 (48.3)	2,578 (19.9)	5,142 (39.6)	7,565 (58.3)	9,760 (75.2)
Ethnicity [b]					
White British	44,409 (85.6)	10,995 (84.7)	11,060 (85.2)	11,090 (85.5)	11,264 (86.8)
Other	7,483 (14.4)	1,978 (15.3)	1,913 (14.8)	1,883 (14.5)	1,709 (13.2)
Social deprivation index [a]	-1.3 (2.9); -6.3 - 9.3	-1.2 (2.9); -6.3 - 8.9	-1.3 (2.8); -6.3 - 8.7	-1.3 (2.8); -6.3 - 8.7	-1.4 (2.8); -6.3 - 9.3
Employment status [b]					
In paid employment or self-employed	31,909 (61.5)	6,133 (47.3)	7,763 (59.8)	8,718 (67.2)	9,295 (71.6)
Not in paid employment or self-employed	19,983 (38.5)	6,840 (52.7)	5,210 (40.2)	4,255 (32.8)	3,678 (28.4)
Education level [b]					
College or university degree	20,476 (39.5)	3,902 (30.1)	4,814 (37.1)	5,547 (42.8)	6,213 (47.9)
No college or university degree	31,416 (60.5)	9,071 (69.9)	8,159 (62.9)	7,426 (57.2)	6,760 (52.1)
Lifestyle					

Fruit and vegetable consumption (portions/day) [b]					
<5	31,859 (61.4)	7,587 (58.5)	8,004 (61.7)	8,243 (63.5)	8,025 (61.9)
≥5	20,033 (38.6)	5,386 (41.5)	4,969 (38.3)	4,730 (36.5)	4,948 (38.1)
Smoking status [b]					
Never	28,888 (55.7)	7,620 (58.7)	7,173 (55.3)	6,976 (53.8)	7,119 (54.9)
Previous	18,484 (35.6)	4,568 (35.2)	4,715 (36.3)	4,728 (36.4)	4,473 (34.5)
Current	4,520 (8.7)	785 (6.1)	1,085 (8.4)	1,269 (9.8)	1,381 (10.6)
Alcohol drinking status [b]					
Never	1,692 (3.3)	702 (5.4)	428 (3.3)	322 (2.5)	240 (1.8)
Previous	1,496 (2.9)	427 (3.3)	377 (2.9)	371 (2.9)	321 (2.5)
Current	48,704 (93.9)	11,844 (91.3)	12,168 (93.8)	12,280 (94.6)	12,412 (95.7)
Sleep duration (hours/day) [a]	7.1 (1.0); 1.0 - 16.0	7.2 (1.1); 1.0 - 16.0	7.2 (1.0); 2.0 - 13.0	7.2 (1.0); 2.0 - 14.0	7.1 (0.9); 1.0 - 13.0
Frequency of ≥10 minutes of walking (days/week) [b]					
0	890 (1.7)	240 (1.9)	233 (1.8)	224 (1.7)	193 (1.5)
1	1,269 (2.4)	305 (2.3)	321 (2.5)	304 (2.4)	339 (2.6)
2	2,884 (5.6)	711 (5.5)	691 (5.3)	753 (5.8)	729 (5.6)
3	3,973 (7.7)	1,067 (8.2)	1,015 (7.8)	952 (7.3)	939 (7.2)
4	4,177 (8.0)	1,120 (8.6)	1,075 (8.3)	976 (7.5)	1,006 (7.8)
5	8,545 (16.5)	2,190 (16.9)	2,230 (17.2)	2,115 (16.3)	2,010 (15.5)
6	5,565 (10.7)	1,453 (11.2)	1,410 (10.9)	1,399 (10.8)	1,303 (10.0)
7	24,589 (47.4)	5,887 (45.4)	5,998 (46.2)	6,250 (48.2)	6,454 (49.8)
Frequency of ≥10 minutes of moderate physical activity (days/week) [b]					
0	5,643 (10.9)	1,707 (13.2)	1,477 (11.4)	1,373 (10.6)	1,086 (8.4)
1	4,200 (8.1)	1,090 (8.4)	1,090 (8.4)	1,050 (8.1)	970 (7.5)
2	7,827 (15.1)	2,014 (15.5)	2,058 (15.9)	1,959 (15.1)	1,796 (13.8)
3	8,117 (15.6)	2,000 (15.4)	2,077 (16.0)	2,085 (16.1)	1,955 (15.1)
4	5,488 (10.6)	1,288 (9.9)	1,342 (10.3)	1,400 (10.8)	1,458 (11.2)

5	7,968 (15.3)	1,862 (14.4)	1,905 (14.7)	2,052 (15.8)	2,149 (16.6)
6	2,865 (5.5)	608 (4.7)	636 (4.9)	747 (5.8)	874 (6.7)
7	9,784 (18.9)	2,404 (18.5)	2,388 (18.4)	2,307 (17.8)	2,685 (20.7)
Frequency of ≥10 minutes of vigorous physical activity (days/week) [b]					
0	16,666 (32.1)	5,579 (43.0)	4,695 (36.2)	3,815 (29.4)	2,577 (19.9)
1	8,111 (15.6)	2,066 (15.9)	2,159 (16.7)	2,078 (16.0)	1,808 (13.9)
2	8,781 (16.9)	2,025 (15.6)	2,234 (17.2)	2,268 (17.5)	2,254 (17.4)
3	7,929 (15.3)	1,520 (11.7)	1,780 (13.7)	2,154 (16.6)	2,475 (19.1)
4	3,767 (7.3)	625 (4.8)	767 (5.9)	983 (7.6)	1,392 (10.7)
5	3,752 (7.2)	621 (4.8)	756 (5.8)	992 (7.6)	1,383 (10.6)
6	1,081 (2.1)	154 (1.2)	193 (1.5)	271 (2.1)	463 (3.6)
7	1,805 (3.5)	383 (3.0)	389 (3.0)	412 (3.2)	621 (4.8)
Health					
Number of cancers [b]					
0	47,477 (91.5)	11,556 (89.1)	11,737 (90.5)	12,006 (92.5)	12,178 (93.9)
≥1	4,415 (8.5)	1,417 (10.9)	1,236 (9.5)	967 (7.5)	795 (6.1)
Number of non-cancer illnesses [b]					
0	13,685 (26.4)	2,495 (19.2)	3,365 (26.0)	3,699 (28.5)	4,126 (31.8)
1	13,984 (27.0)	3,203 (24.7)	3,469 (26.7)	3,616 (27.9)	3,696 (28.5)
2	10,110 (19.5)	2,724 (21.0)	2,541 (19.6)	2,474 (19.1)	2,371 (18.3)
3	6,458 (12.4)	1,923 (14.8)	1,661 (12.8)	1,503 (11.6)	1,371 (10.6)
≥4	7,655 (14.7)	2,628 (20.3)	1,937 (14.9)	1,681 (12.9)	1,409 (10.8)
Number of medications/treatments [b]					
0	17,189 (33.1)	3,126 (24.1)	4,041 (31.1)	4,655 (35.9)	5,367 (41.4)
1	10,757 (20.7)	2,455 (18.9)	2,798 (21.6)	2,741 (21.1)	2,763 (21.3)
2	8,080 (15.6)	2,157 (16.6)	2,067 (15.9)	2,034 (15.7)	1,822 (14.0)
3	5,635 (10.9)	1,667 (12.9)	1,463 (11.3)	1,320 (10.2)	1,185 (9.1)
4	3,802 (7.3)	1,224 (9.4)	994 (7.7)	855 (6.6)	729 (5.6)

5	2,471 (4.8)	822 (6.4)	664 (5.1)	538 (4.1)	447 (3.5)
≥6	3,958 (7.6)	1,522 (11.7)	946 (7.3)	830 (6.4)	660 (5.1)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [b]					
No	42,823 (82.5)	10,292 (79.3)	10,578 (81.5)	10,825 (83.4)	11,128 (85.8)
Yes	9,069 (17.5)	2,681 (20.7)	2,395 (18.5)	2,148 (16.6)	1,845 (14.2)
Sedentary behaviours					
TV viewing time (hours/day) [b]					
<1	4,703 (9.1)	760 (5.9)	1,084 (8.4)	1,289 (9.9)	1,570 (12.1)
1	7,451 (14.4)	1,249 (9.6)	1,735 (13.4)	2,025 (15.6)	2,442 (18.8)
2	14,859 (28.6)	3,245 (25.0)	3,752 (28.9)	3,892 (30.0)	3,970 (30.6)
3	12,009 (23.1)	3,234 (24.9)	3,052 (23.5)	2,990 (23.1)	2,733 (21.1)
≥4	12,870 (24.8)	4,485 (34.6)	3,350 (25.8)	2,777 (21.4)	2,258 (17.4)
Driving time (hours/day) [b]					
<1	27,973 (53.9)	7,650 (59.0)	6,976 (53.8)	6,675 (51.5)	6,672 (51.4)
1	14,515 (28.0)	3,527 (27.2)	3,593 (27.7)	3,715 (28.6)	3,680 (28.4)
2	6,316 (12.2)	1,270 (9.8)	1,621 (12.5)	1,685 (13.0)	1,740 (13.4)
≥3	3,088 (5.9)	526 (4.0)	783 (6.0)	898 (6.9)	881 (6.8)
Computer use time (hours/day) [b]					
<1	20,174 (38.9)	5,751 (44.3)	5,173 (39.8)	4,742 (36.6)	4,508 (34.7)
1	17,193 (33.1)	3,858 (29.8)	4,262 (32.9)	4,403 (33.9)	4,670 (36.0)
2	8,057 (15.5)	1,922 (14.8)	1,921 (14.8)	2,158 (16.6)	2,056 (15.9)
≥3	6,468 (12.5)	1,442 (11.1)	1,617 (12.5)	1,670 (12.9)	1,739 (13.4)
Cardiorespiratory fitness					
Cardiorespiratory fitness (ml/kg/min) [a]	36.2 (10.2); 10.7 - 80.0	24.6 (3.2); 10.7 - 28.9	31.9 (1.7); 28.9 - 34.9	38.3 (2.1); 34.9 - 42.2	50.1 (7.2); 42.2 - 80.0
Age- and sex-specific quartiles [a c]	36.2 (10.2); 10.7 - 80.0	26.1 (4.8); 10.7 - 35.6	32.6 (4.7); 24.1 - 41.3	37.9 (5.4); 27.9 - 48.1	48.3 (9.0); 32.7 - 80.0

Cognitive function					
Fluid intelligence score [a]					
Total number of correct answers	6.2 (2.1); 0.0 - 13.0	5.9 (2.0); 0.0 - 13.0	6.2 (2.1); 0.0 - 13.0	6.3 (2.1); 0.0 - 13.0	6.5 (2.2); 0.0 - 13.0
Prospective memory result [b]					
Correct recall on first attempt	42,241 (81.4)	10,069 (77.6)	10,501 (80.9)	10,732 (82.7)	10,939 (84.3)
Incorrect recall on first attempt	9,651 (18.6)	2,904 (22.4)	2,472 (19.1)	2,241 (17.3)	2,034 (15.7)
Visual-spatial memory (pairs matching) result [b]					
<2 incorrect matches	9,924 (19.1)	2,181 (16.8)	2,442 (18.8)	2,567 (19.8)	2,734 (21.1)
≥2 incorrect matches	41,738 (80.4)	10,727 (82.7)	10,464 (80.7)	10,353 (79.8)	10,194 (78.6)
Missing [d]	230 (0.5)	65 (0.5)	67 (0.5)	53 (0.4)	45 (0.3)

[a] *Continuous variable: mean (standard deviation); minimum - maximum*

[b] *Categorical variable: number (%)*

[c] *Sensitivity analysis 3: using age- and sex-specific quartiles for cardiorespiratory fitness (with age categorised at 60 years). Quartile 1: n = 12,974, quartile 2: n = 12,973, quartile 3: n = 12,973, quartile 4: n = 12,972*

[d] *Number (%)*

The characteristics of the included and excluded participants were similar (see Table 20); however, included participants tended to be slightly healthier given that they were eligible for the CRF test.

Table 20 - Observational study (UK Biobank data): Comparing the characteristics of the included sample and the excluded sample

	Included sample	Excluded sample
Anthropometrics	N = 51,892	N = 450,751
Body mass index (kg/m^2) [a]	27.1 (4.4); 14.5 - 59.2	27.5 (4.8); 12.1 - 74.7
Missing [b]	0 (0.0)	3,105 (0.7)
Demographics		
Age (years) [a]	56.2 (8.1); 39.0 - 70.0	56.6 (8.1); 37.0 - 73.0
Missing [b]	0 (0.0)	0 (0.0)
Sex [c]		
Female	26,847 (51.7)	246,620 (54.7)
Male	25,045 (48.3)	204,131 (45.3)
Missing [b]	0 (0.0)	0 (0.0)
Ethnicity [c]		
White British	44,409 (85.6)	398,290 (88.4)
Other	7,483 (14.4)	49,683 (11.0)
Missing [b]	0 (0.0)	2,778 (0.6)
Social deprivation index [a]	-1.3 (2.9); -6.3 - 9.3	-1.3 (3.1); -6.3 - 11.0
Missing [b]	0 (0.0)	627 (0.1)
Employment status [c]		
In paid employment or self-employed	31,909 (61.5)	255,325 (56.6)
Not in paid employment or self-employed	19,983 (38.5)	192,468 (42.7)
Missing [b]	0 (0.0)	2,958 (0.7)
Education level [c]		
College or university degree	20,476 (39.5)	140,734 (31.2)
No college or university degree	31,416 (60.5)	299,875 (66.5)
Missing [b]	0 (0.0)	10,142 (2.3)
Lifestyle		
Fruit and vegetable consumption (portions/day) [c]		
<5	31,859 (61.4)	268,493 (59.6)
≥5	20,033 (38.6)	169,946 (37.7)
Missing [b]	0 (0.0)	12,312 (2.7)
Smoking status [c]		
Never	28,888 (55.7)	244,715 (54.3)
Previous	18,484 (35.6)	154,615 (34.3)
Current	4,520 (8.7)	48,469 (10.8)
Missing [b]	0 (0.0)	2,952 (0.6)

Alcohol drinking status [c]		
Never	1,692 (3.3)	20,855 (4.6)
Previous	1,496 (2.9)	16,618 (3.7)
Current	48,704 (93.9)	411,775 (91.4)
Missing [b]	0 (0.0)	1,503 (0.3)
Sleep duration (hours/day) [a]	7.1 (1.0); 1.0 - 16.0	7.2 (1.1); 1.0 - 23.0
Missing [b]	0 (0.0)	4,218 (0.9)
Frequency of ≥10 minutes of walking (days/week) [c]		
0	890 (1.7)	11,565 (2.6)
1	1,269 (2.4)	12,190 (2.7)
2	2,884 (5.6)	27,107 (6.0)
3	3,973 (7.7)	35,366 (7.8)
4	4,177 (8.0)	35,859 (7.9)
5	8,545 (16.5)	71,494 (15.9)
6	5,565 (10.7)	44,517 (9.9)
7	24,589 (47.4)	204,108 (45.3)
Missing [b]	0 (0.0)	8,545 (1.9)
Frequency of ≥10 minutes of moderate physical activity (days/week) [c]		
0	5,643 (10.9)	55,535 (12.3)
1	4,200 (8.1)	34,090 (7.6)
2	7,827 (15.1)	61,972 (13.7)
3	8,117 (15.6)	63,390 (14.1)
4	5,488 (10.6)	41,713 (9.3)
5	7,968 (15.3)	63,473 (14.1)
6	2,865 (5.5)	23,571 (5.2)
7	9,784 (18.9)	79,722 (17.7)
Missing [b]	0 (0.0)	27,285 (6.0)
Frequency of ≥10 minutes of vigorous physical activity (days/week) [c]		
0	16,666 (32.1)	161,609 (35.8)
1	8,111 (15.6)	58,742 (13.0)
2	8,781 (16.9)	66,274 (14.7)
3	7,929 (15.3)	57,347 (12.7)
4	3,767 (7.3)	26,938 (6.0)
5	3,752 (7.2)	28,700 (6.4)
6	1,081 (2.1)	8,349 (1.9)
7	1,805 (3.5)	15,200 (3.4)
Missing [b]	0 (0.0)	27,592 (6.1)
Health		
Number of cancers [c]		
0	47,477 (91.5)	412,598 (91.5)
≥1	4,415 (8.5)	37,291 (8.3)
Missing [b]	0 (0.0)	862 (0.2)

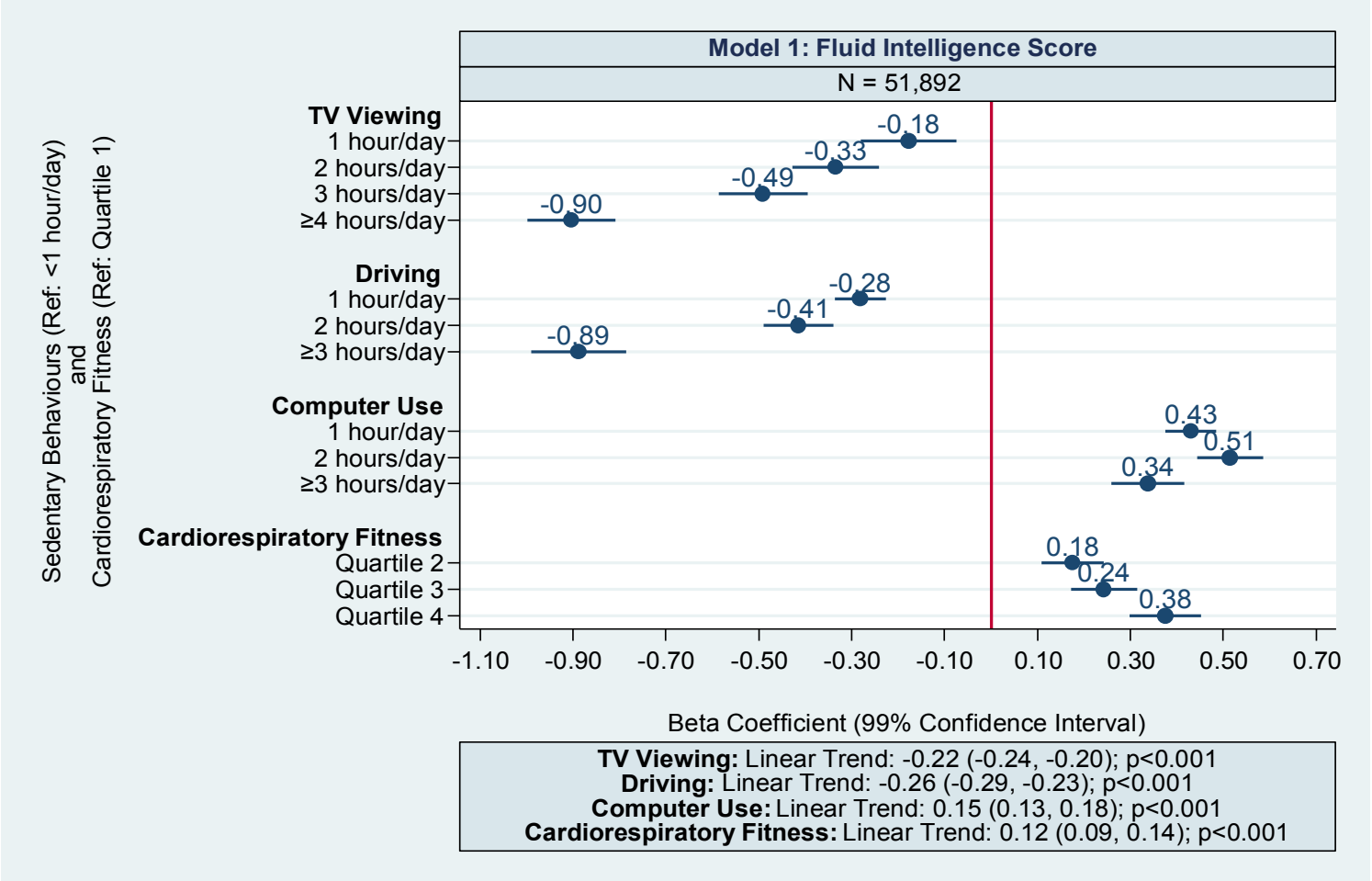
Number of non-cancer illnesses [c]		
0	13,685 (26.4)	112,954 (25.1)
1	13,984 (27.0)	120,129 (26.6)
2	10,110 (19.5)	88,715 (19.7)
3	6,458 (12.4)	56,370 (12.5)
≥4	7,655 (14.7)	71,721 (15.9)
Missing [b]	0 (0.0)	862 (0.2)
Number of medications/treatments [c]		
0	17,189 (33.1)	120,515 (26.7)
1	10,757 (20.7)	84,019 (18.6)
2	8,080 (15.6)	69,593 (15.5)
3	5,635 (10.9)	52,184 (11.6)
4	3,802 (7.3)	38,409 (8.5)
5	2,471 (4.8)	27,466 (6.1)
≥6	3,958 (7.6)	57,703 (12.8)
Missing [b]	0 (0.0)	862 (0.2)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [c]		
No	42,823 (82.5)	360,074 (79.9)
Yes	9,069 (17.5)	90,677 (20.1)
Missing [b]	0 (0.0)	0 (0.0)
Sedentary behaviours		
TV viewing time (hours/day) [c]		
<1	4,703 (9.1)	34,753 (7.7)
1	7,451 (14.4)	55,052 (12.2)
2	14,859 (28.6)	117,921 (26.2)
3	12,009 (23.1)	104,931 (23.3)
≥4	12,870 (24.8)	132,676 (29.4)
Missing [b]	0 (0.0)	5,418 (1.2)
Driving time (hours/day) [c]		
<1	27,973 (53.9)	231,947 (51.5)
1	14,515 (28.0)	125,629 (27.9)
2	6,316 (12.2)	54,661 (12.1)
≥3	3,088 (5.9)	28,575 (6.3)
Missing [b]	0 (0.0)	9,939 (2.2)
Computer use time (hours/day) [c]		
<1	20,174 (38.9)	220,474 (48.9)
1	17,193 (33.1)	123,628 (27.4)
2	8,057 (15.5)	54,802 (12.2)
≥3	6,468 (12.5)	42,471 (9.4)
Missing [b]	0 (0.0)	9,376 (2.1)
Cardiorespiratory fitness		

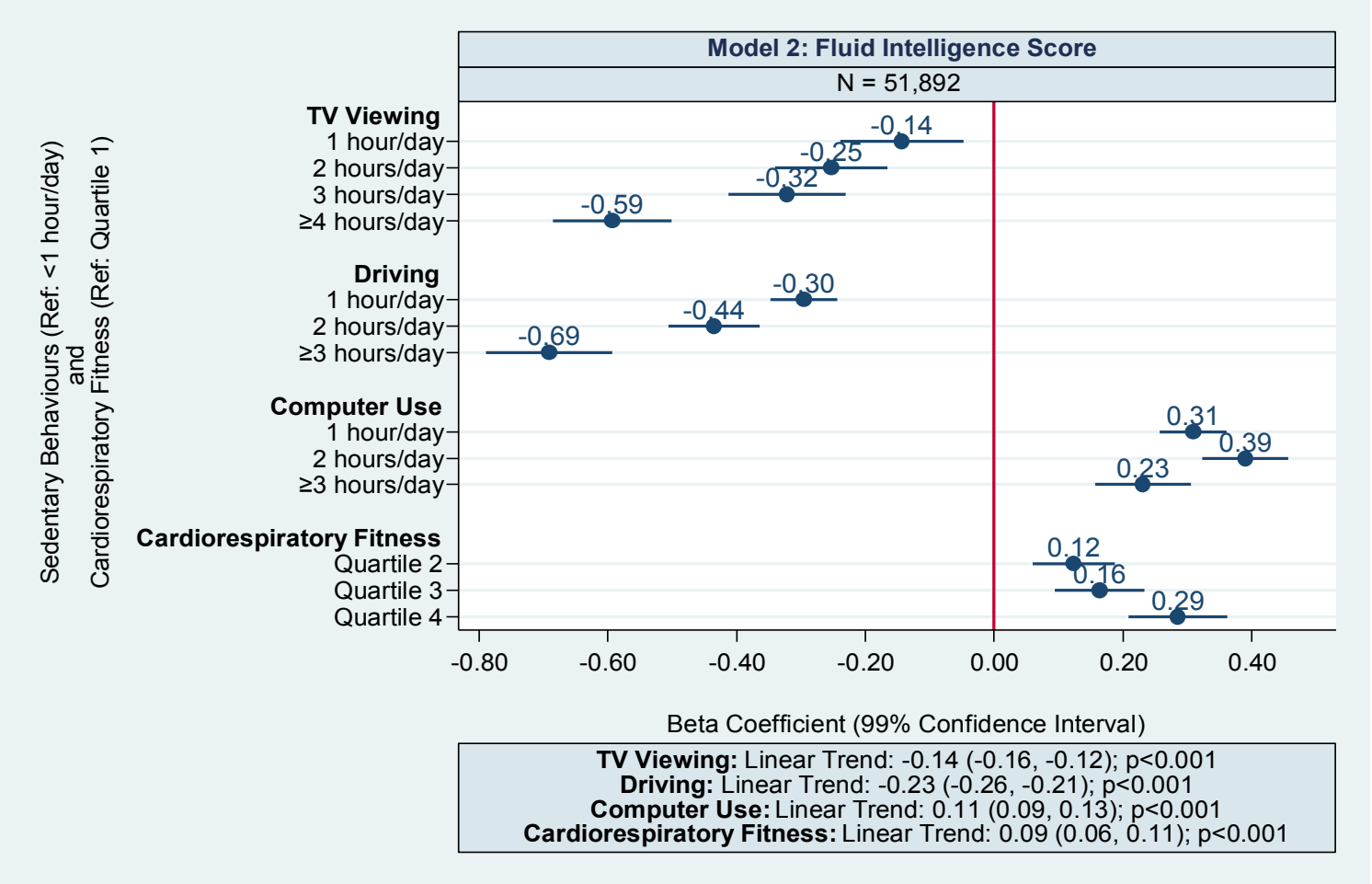
Cardiorespiratory fitness (ml/kg/min) [a]	36.2 (10.2); 10.7 - 80.0	33.0 (9.6); 10.0 - 79.7
Missing [b]	0 (0.0)	443,575 (98.4)

[a] *Continuous variable: mean (standard deviation); minimum - maximum*
[b] *Number (%)*
[c] *Categorical variable: number (%)*

Figure 11 presents the associations of sedentary behaviours and CRF with fluid intelligence. After adjustment for each other and confounders, TV viewing and driving time were inversely associated with fluid intelligence, whereas computer use time and CRF were positively associated with fluid intelligence. For example, in comparison to adults watching <1 hour of TV per day, the fluid intelligence score (i.e. the total number of correct answers) was 0.59 (99% CI: 0.50, 0.69) units lower in those watching ≥4 hours of TV per day. In contrast, in comparison to adults categorised in the lowest quartile of CRF, the fluid intelligence score was 0.29 (99% CI: 0.21, 0.36) units higher in those categorised in the highest quartile of CRF. Model assumptions were satisfied.

Figure 11 - Observational study (UK Biobank data): Associations of sedentary behaviours and cardiorespiratory fitness with fluid intelligence



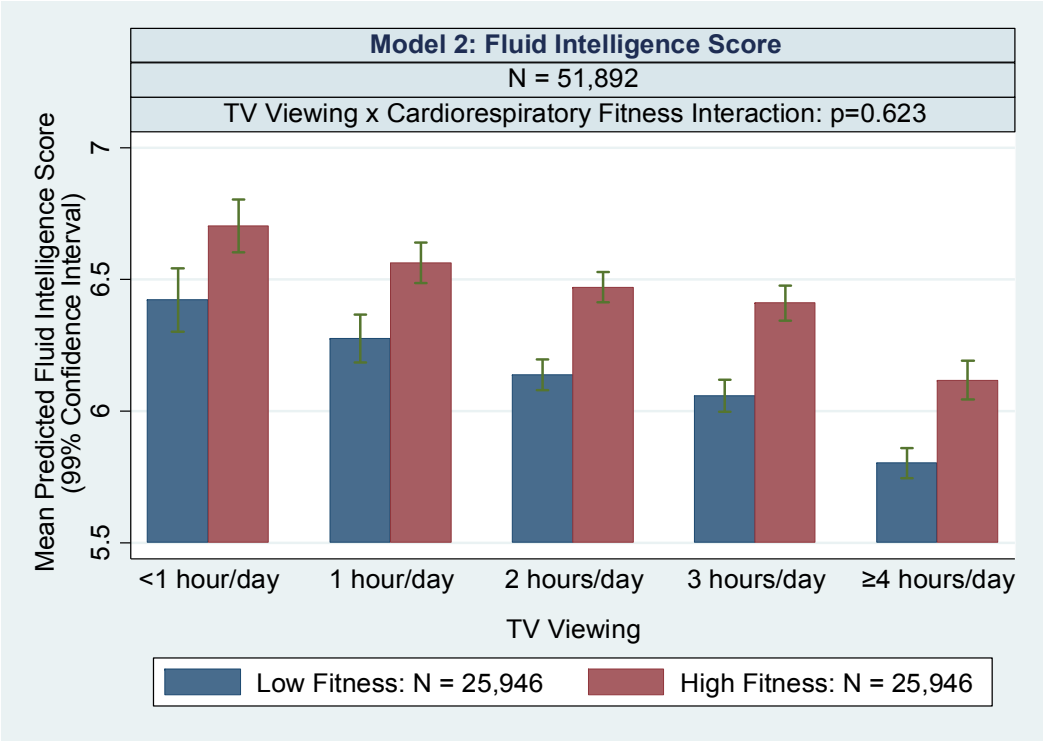


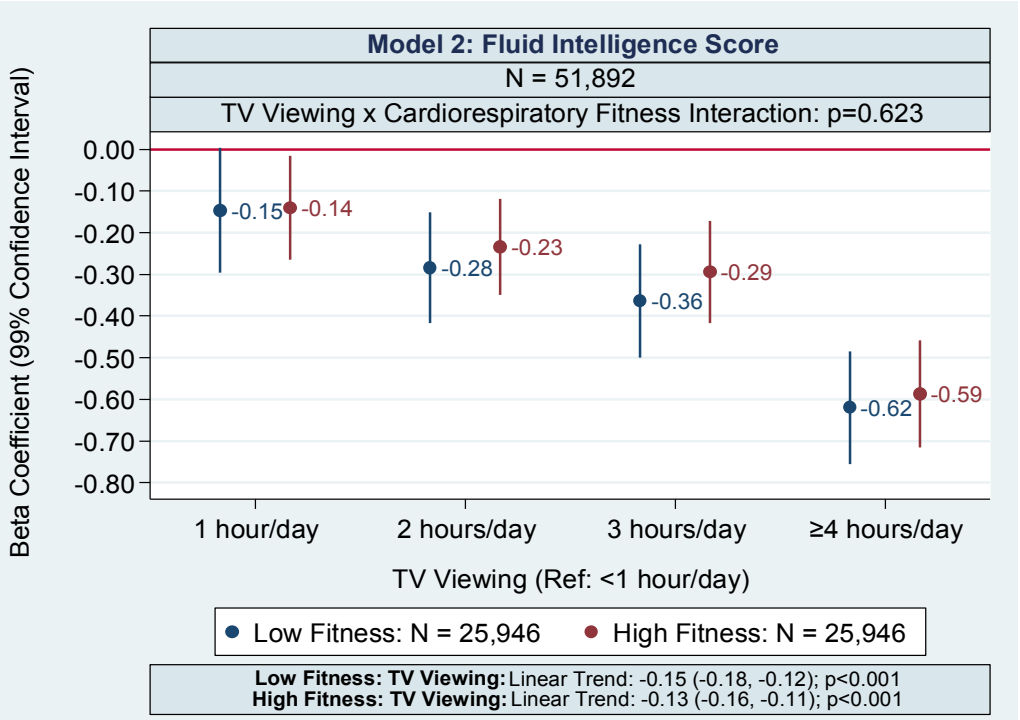
Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

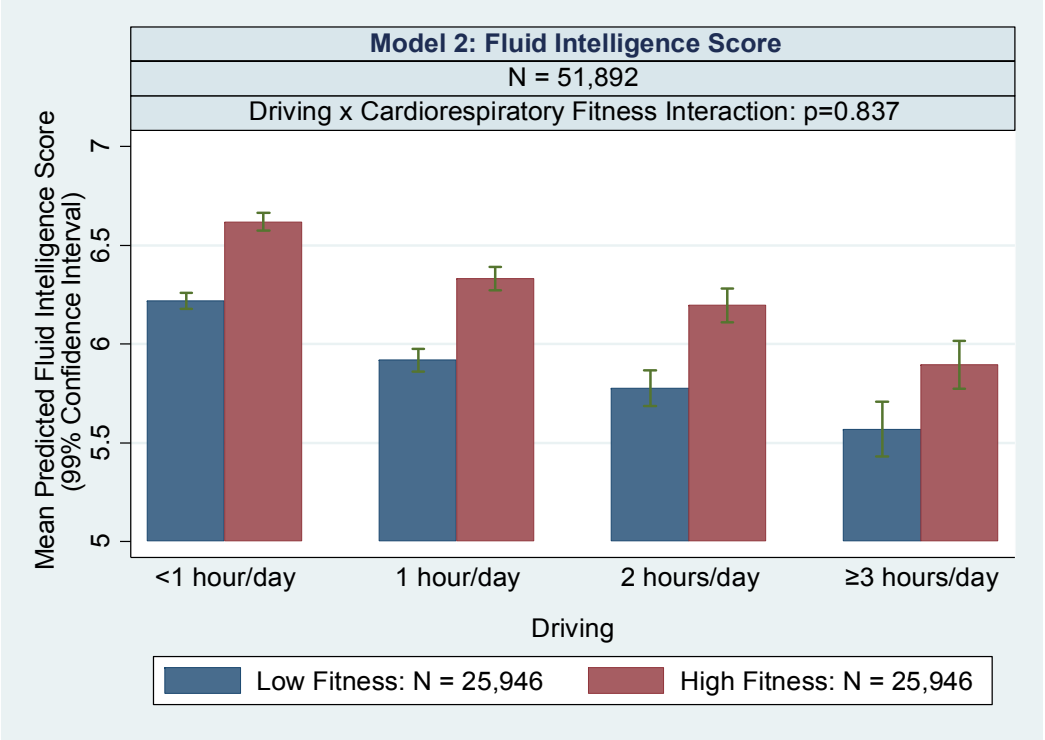
Model 1 was mutually adjusted for the other sedentary behaviours and for age and sex. Model 2 was further adjusted for body mass index, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.01.

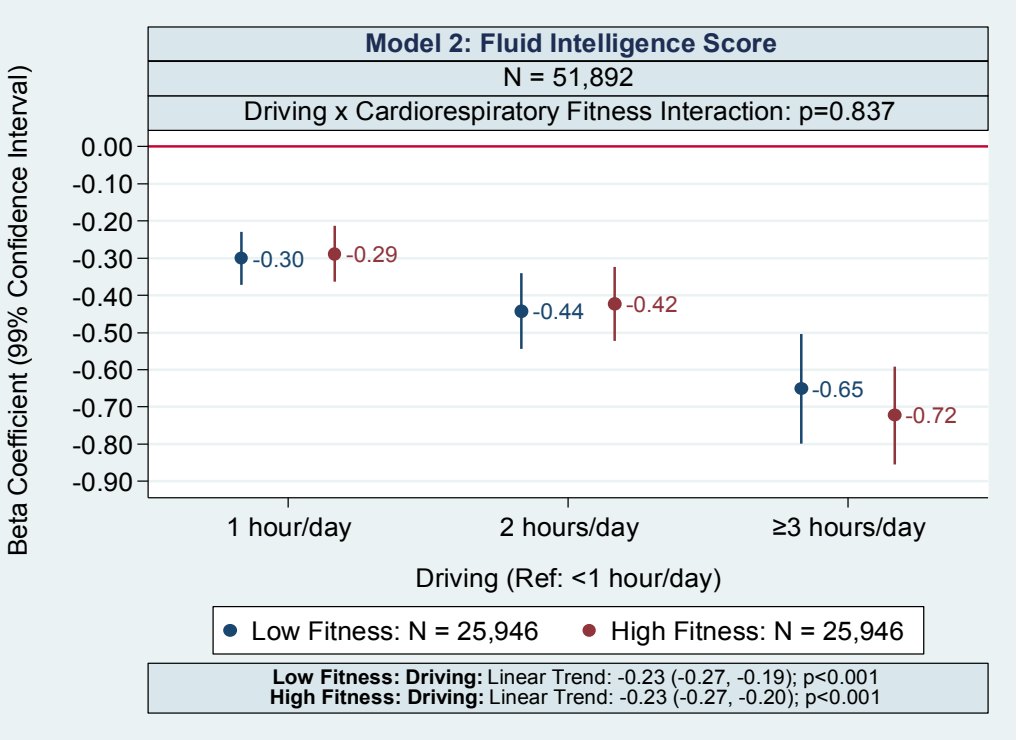
Figure 12 presents the results from the interaction analyses. These analyses indicated that the associations between sedentary behaviours and fluid intelligence were not modified by CRF (p-value=0.623 for interaction with TV viewing time, p-value=0.837 for interaction with driving time, and p-value=0.547 for interaction with computer use time). In both low and high levels of CRF, the observed associations between the three sedentary behaviours and fluid intelligence maintained similar direction, magnitude, and significance (see Figure 12). Model assumptions were satisfied.

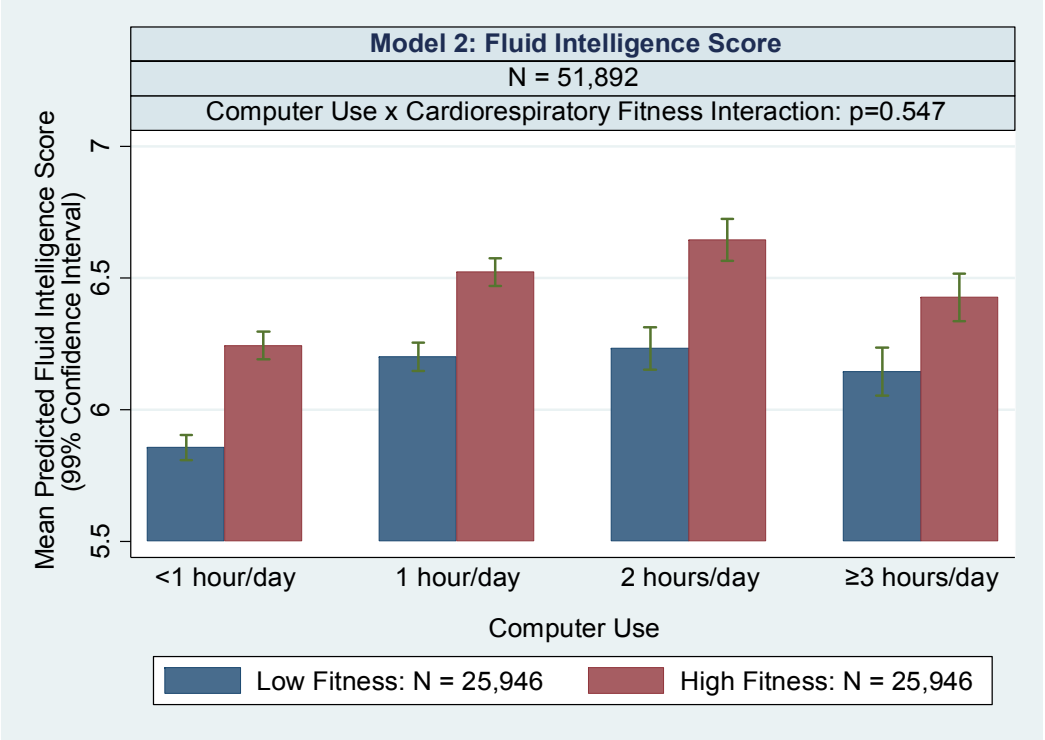
Figure 12 - Observational study (UK Biobank data): Interactions with cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence

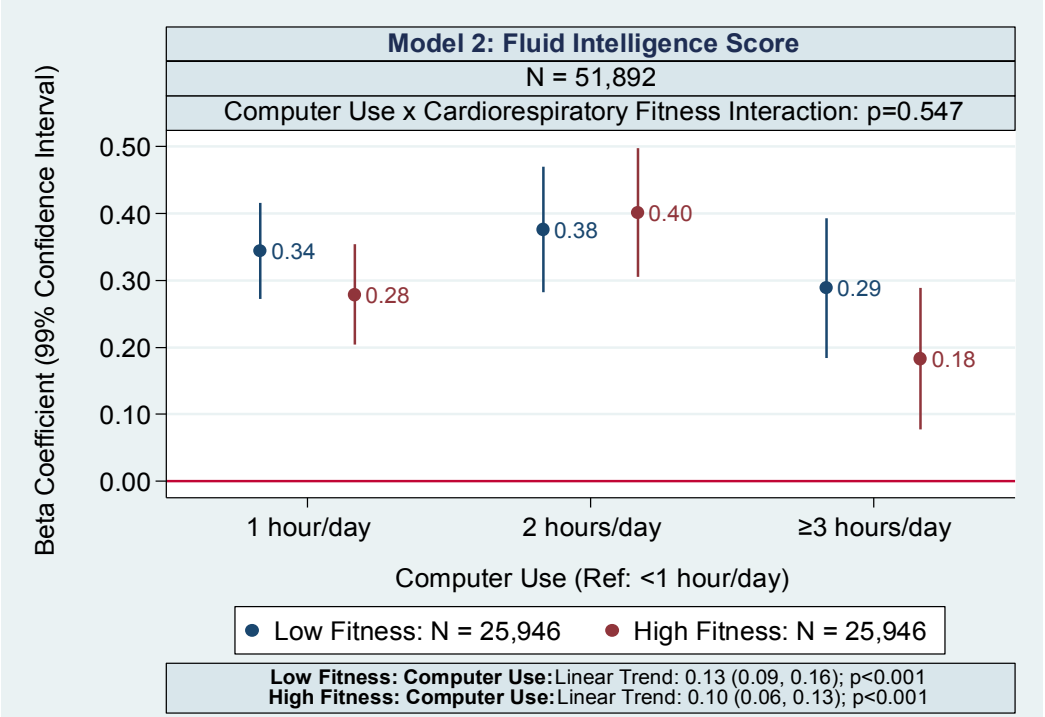





Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.837
Mean Predicted Fluid Intelligence Score (99% Confidence Interval)
5
5.5
6
6.5
7
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 25,946
High Fitness: N = 25,946


Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.837
Beta Coefficient (99% Confidence Interval)
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
-0.30
-0.29
-0.44
-0.42
-0.65
-0.72
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 25,946
High Fitness: N = 25,946
Low Fitness: Driving: Linear Trend: -0.23 (-0.27, -0.19); p<0.001
High Fitness: Driving: Linear Trend: -0.23 (-0.27, -0.20); p<0.001





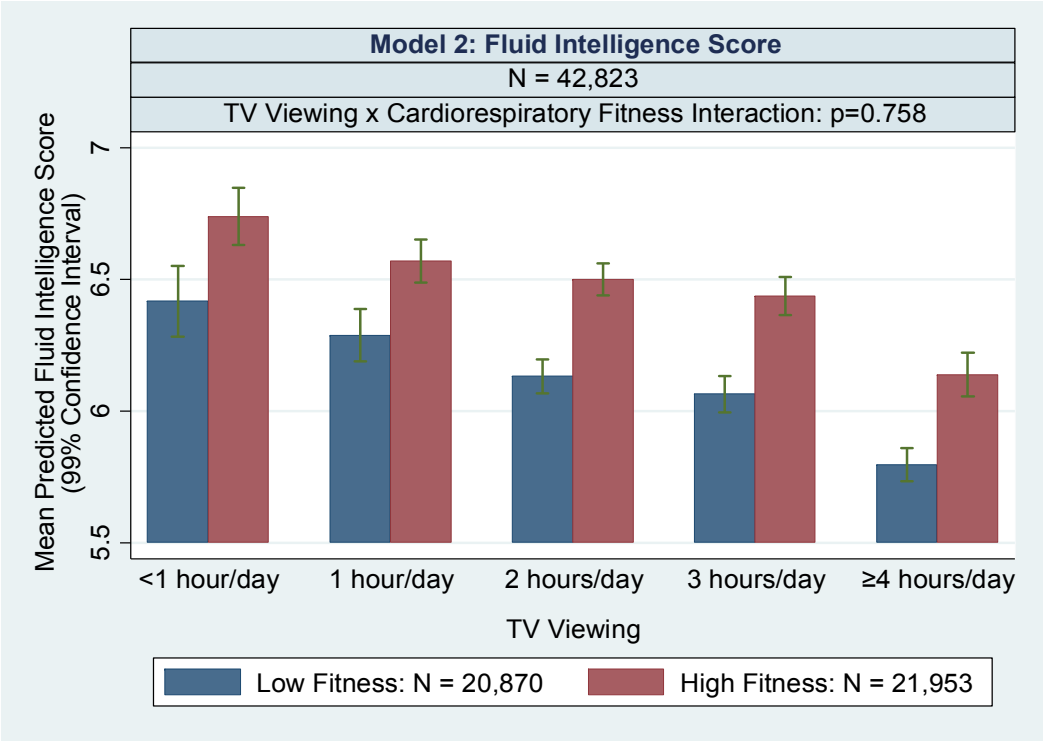
Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

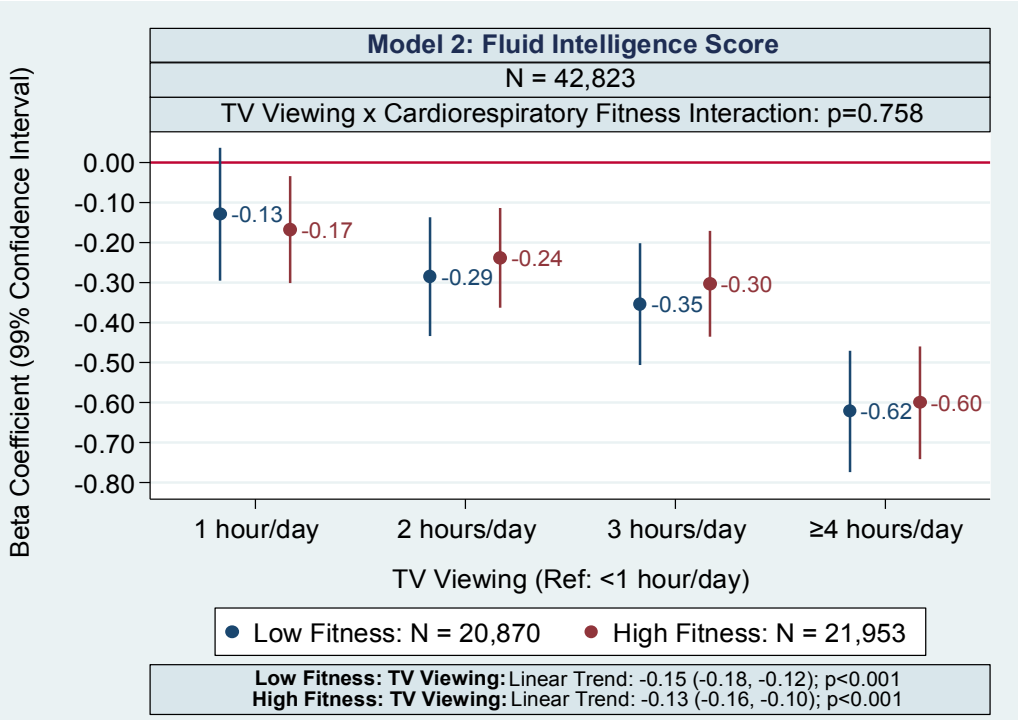
Interaction between sedentary behaviours and cardiorespiratory fitness (statistical significance was established at p-value< 0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments.

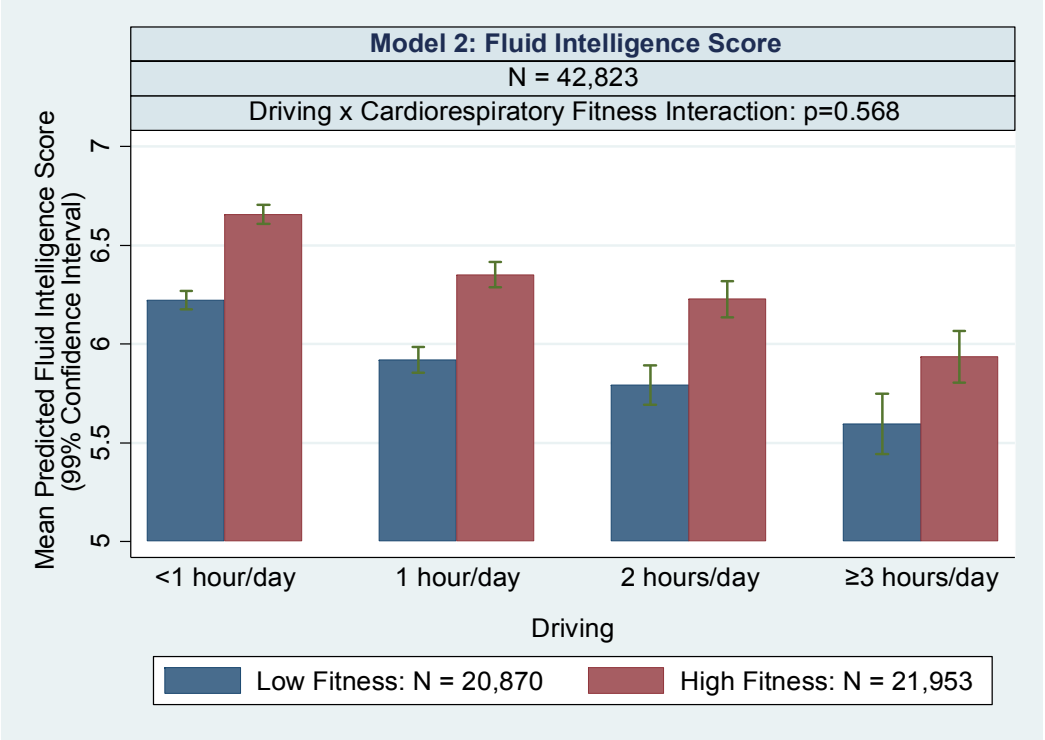
Sensitivity Analysis

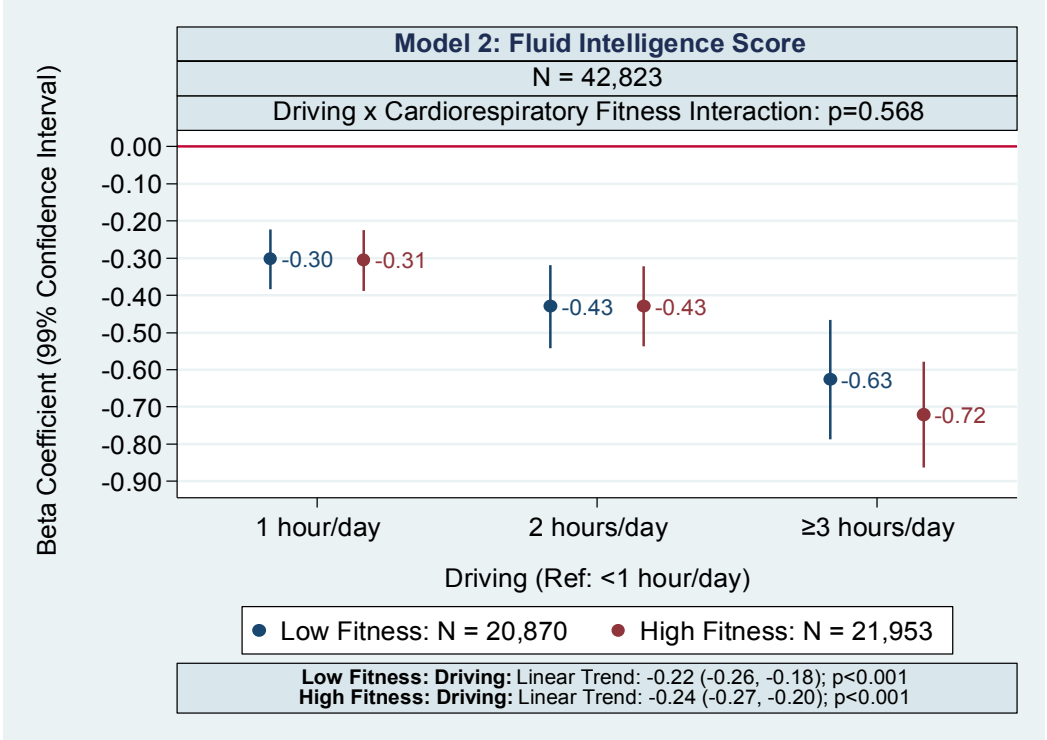
Findings from the interaction models were robust and generalizable: (1) across the sample of participants without cancer, CVD, and/or cognitive/psychiatric illnesses (Figure 13), (2) across other cognitive tests (Figure 14), (3) when using age- and sex-specific quartiles for CRF (Figure 15), and (4) when using a continuous CRF variable (Figure 16). These data suggested that: (1) the inclusion of these individuals in the main analyses was having minimal confounding impact, (2) the findings for fluid intelligence were consistent across the other cognitive domains, (3) the associations were similar regardless of the type of CRF quartiles used (i.e. age- and sex-specific quartiles or simple quartiles computed across the sample), and (4) the associations were similar regardless of the nature of the CRF variable used (i.e. continuous or categorical). For more details, see Figures 13 - 16.

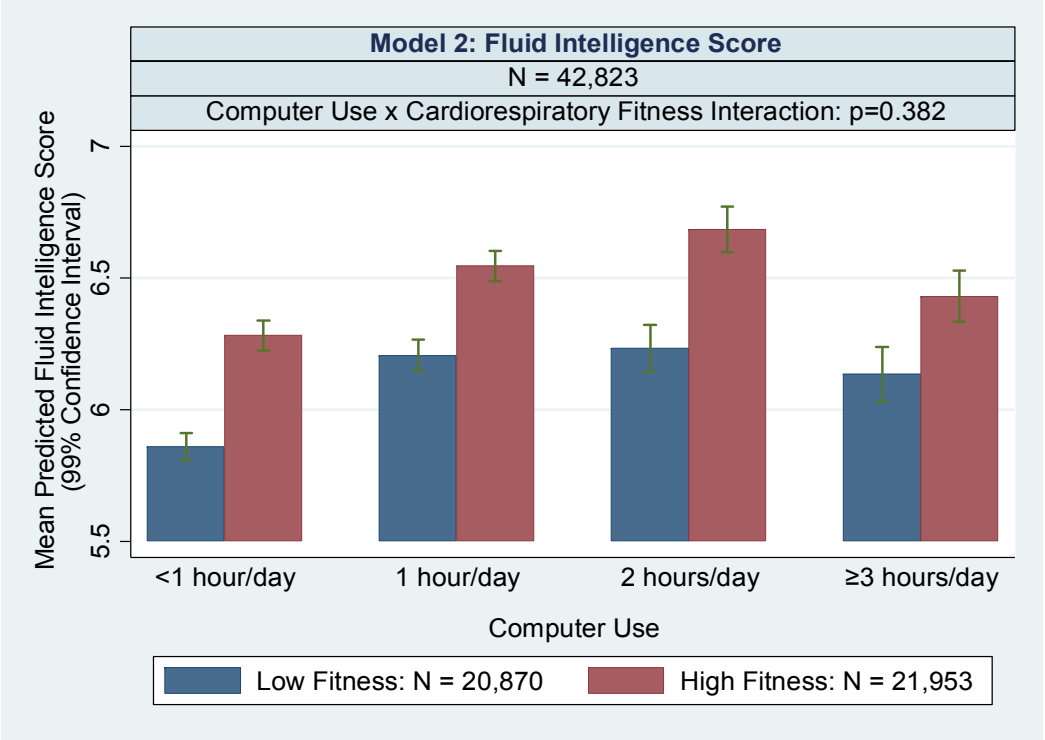
Figure 13 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses)

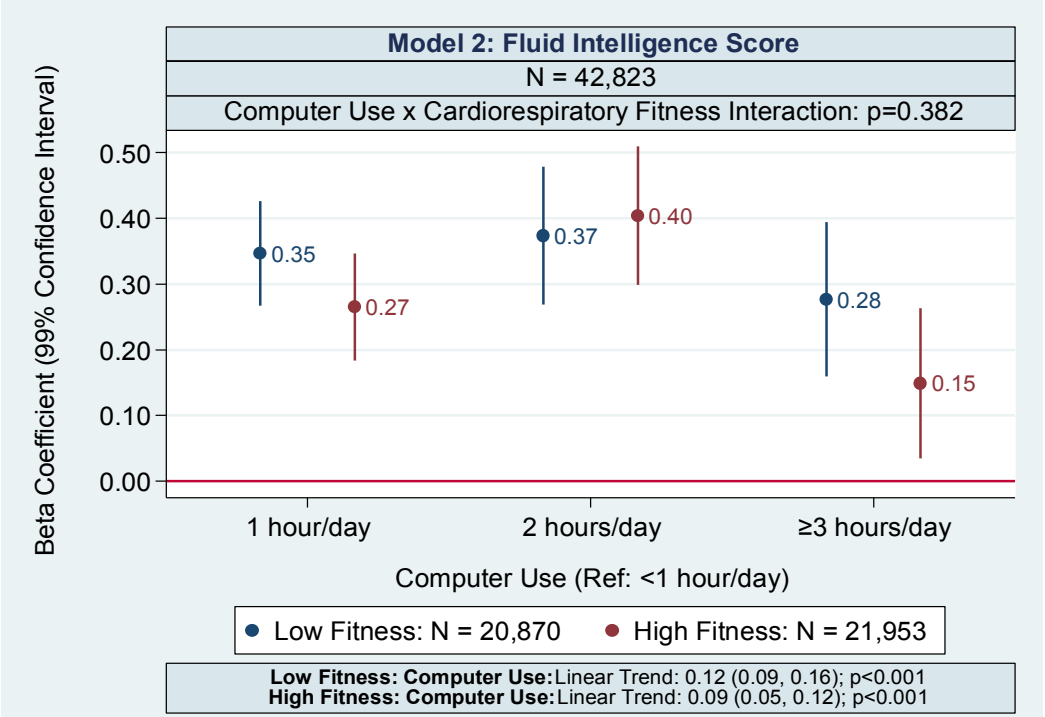





Model 2: Fluid Intelligence Score
N = 42,823
Driving x Cardiorespiratory Fitness Interaction: p=0.568
Mean Predicted Fluid Intelligence Score (99% Confidence Interval)
5
5.5
6
6.5
7
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 20,870
High Fitness: N = 21,953


Model 2: Fluid Intelligence Score
N = 42,823
Driving x Cardiorespiratory Fitness Interaction: p=0.568
Beta Coefficient (99% Confidence Interval)
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
-0.30
-0.31
-0.43
-0.43
-0.63
-0.72
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 20,870
High Fitness: N = 21,953
Low Fitness: Driving: Linear Trend: -0.22 (-0.26, -0.18); p<0.001
High Fitness: Driving: Linear Trend: -0.24 (-0.27, -0.20); p<0.001

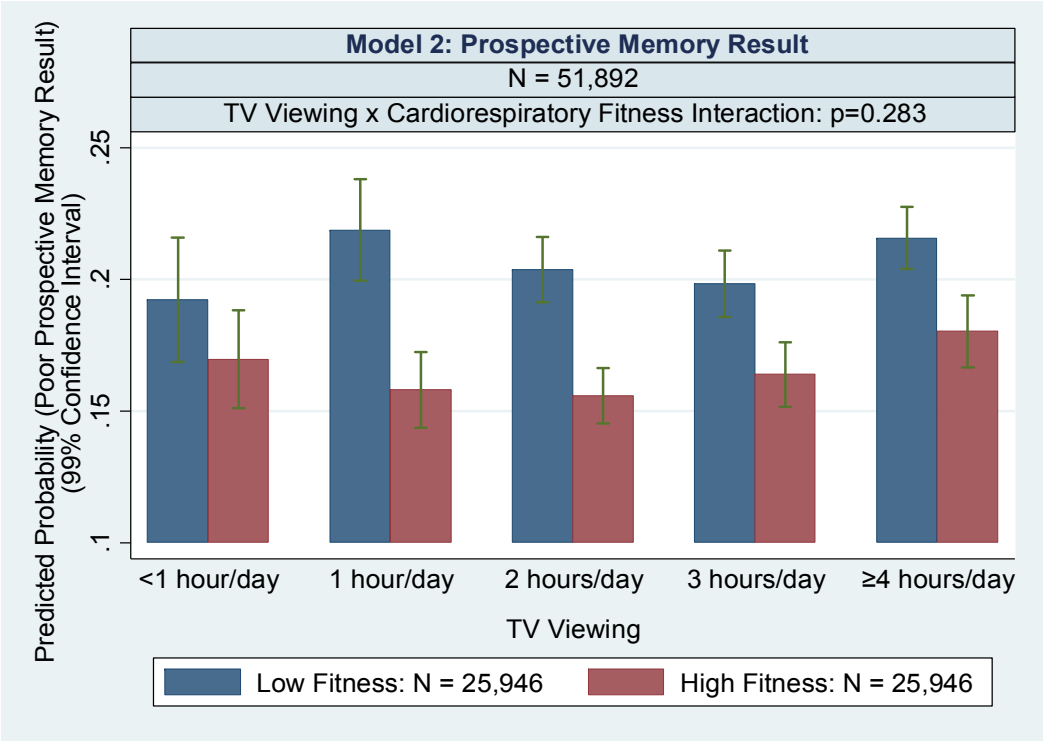


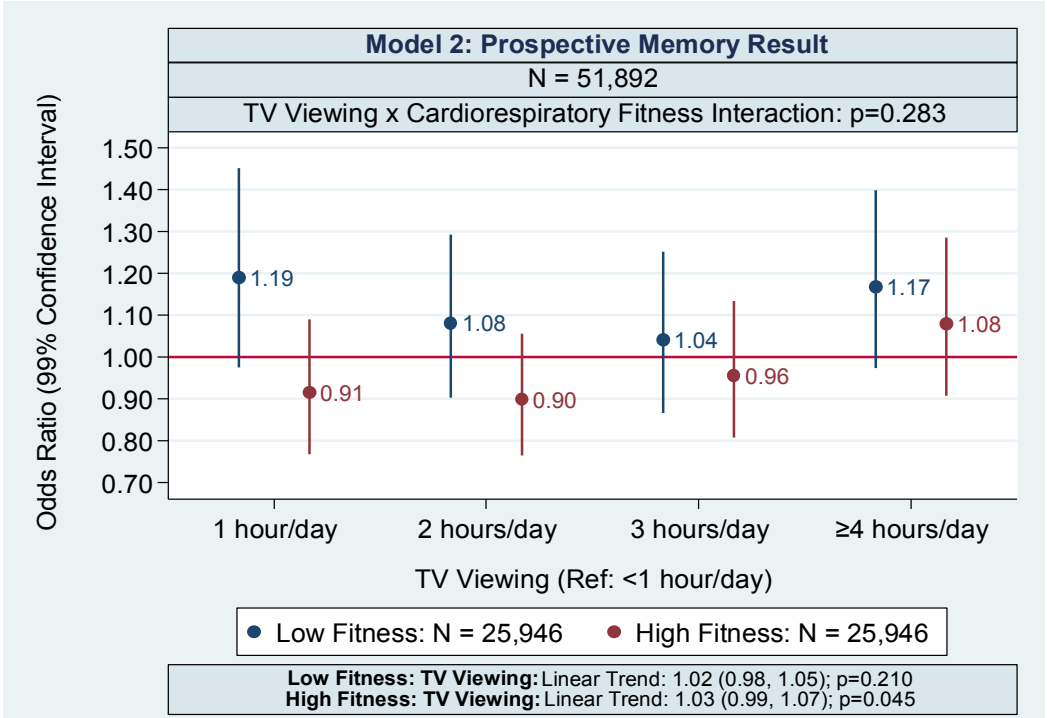


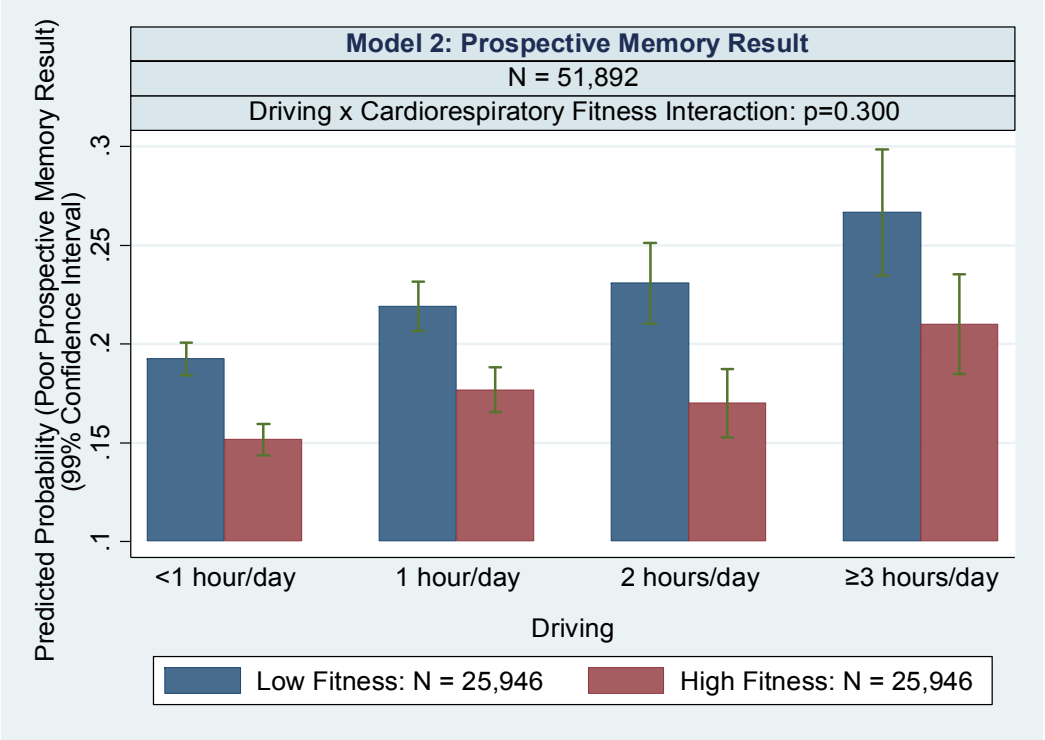
Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

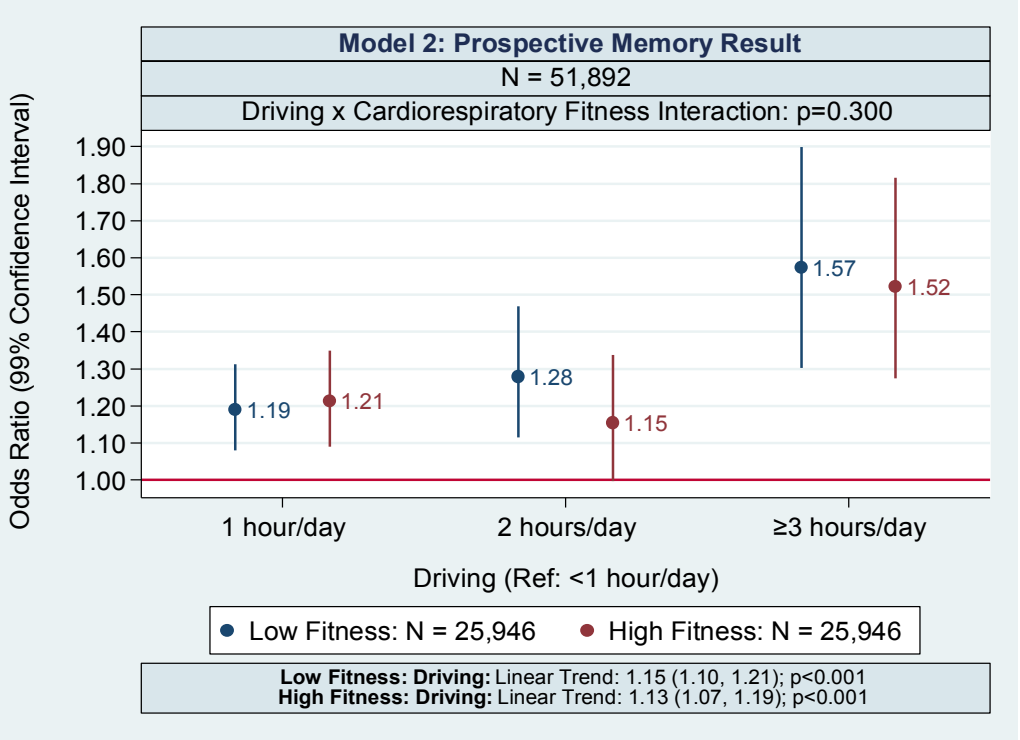
Interaction between sedentary behaviours and cardiorespiratory fitness (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of non-cancer illnesses, and number of medications/treatments.

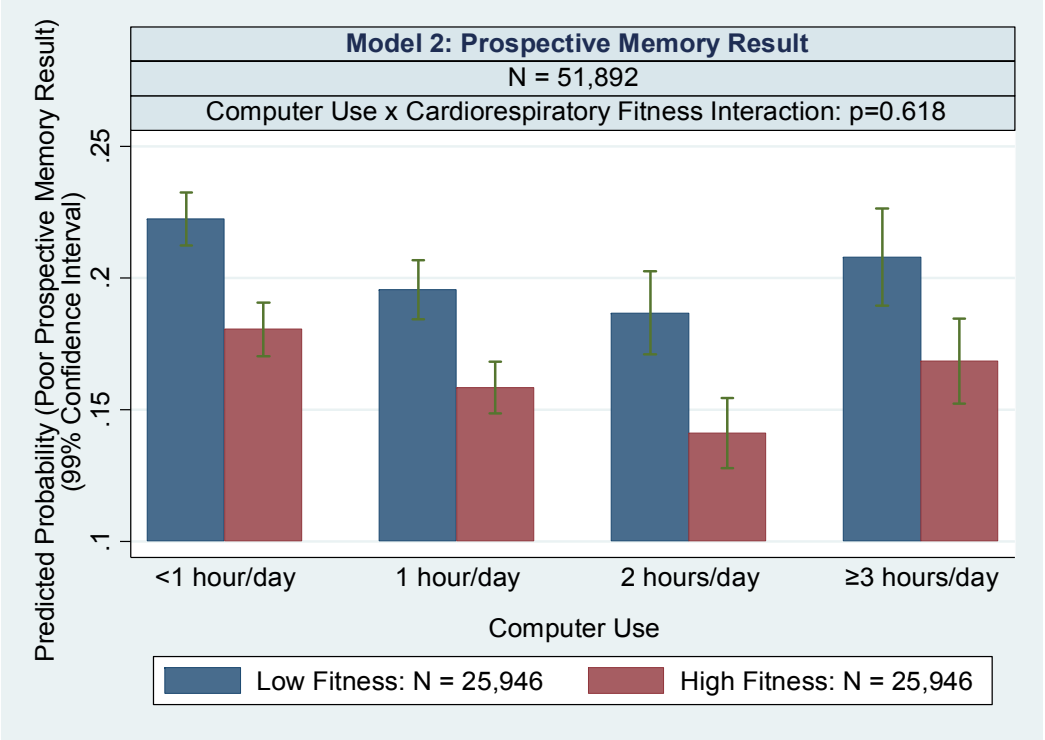
Figure 14 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and other cognitive tests (prospective memory and visual-spatial memory)

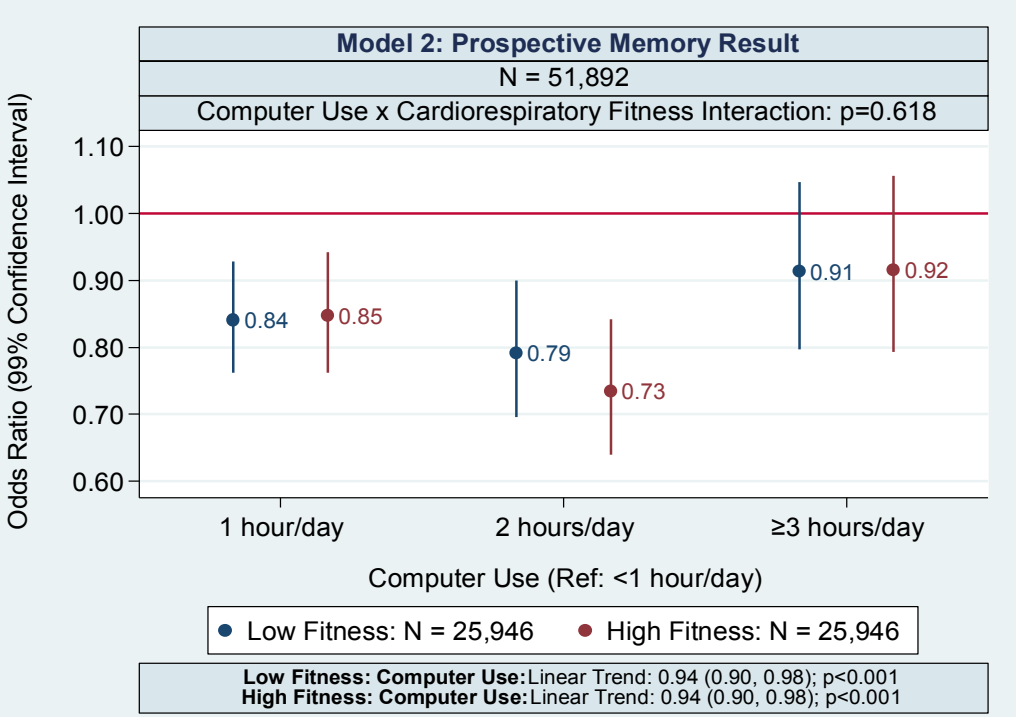


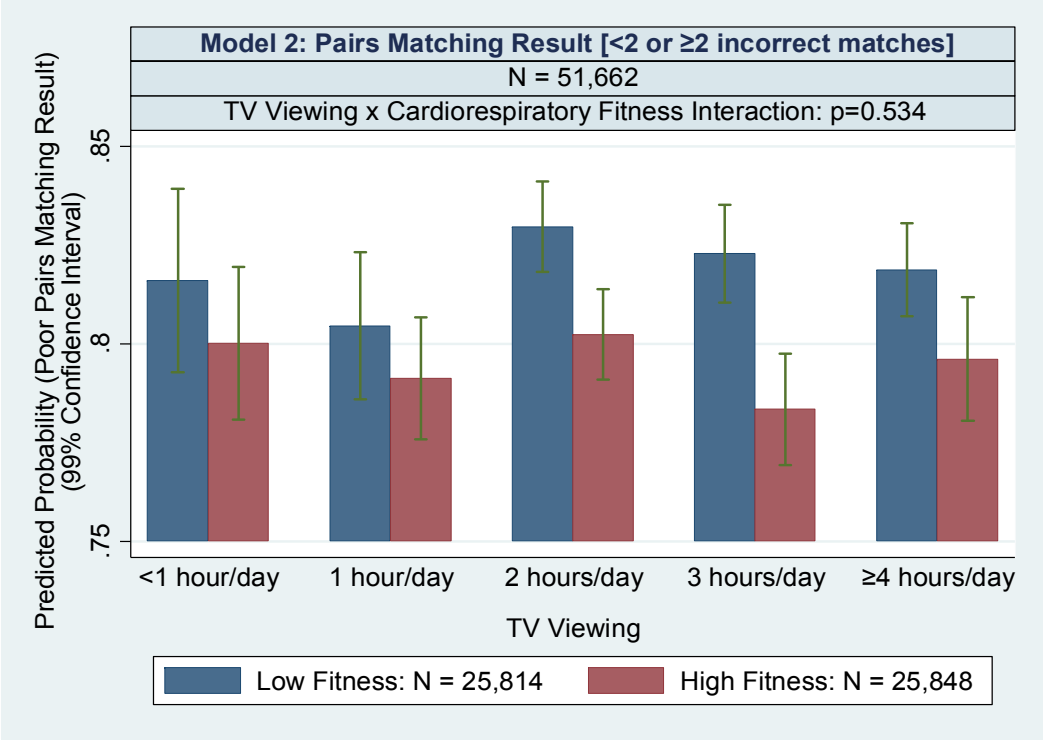


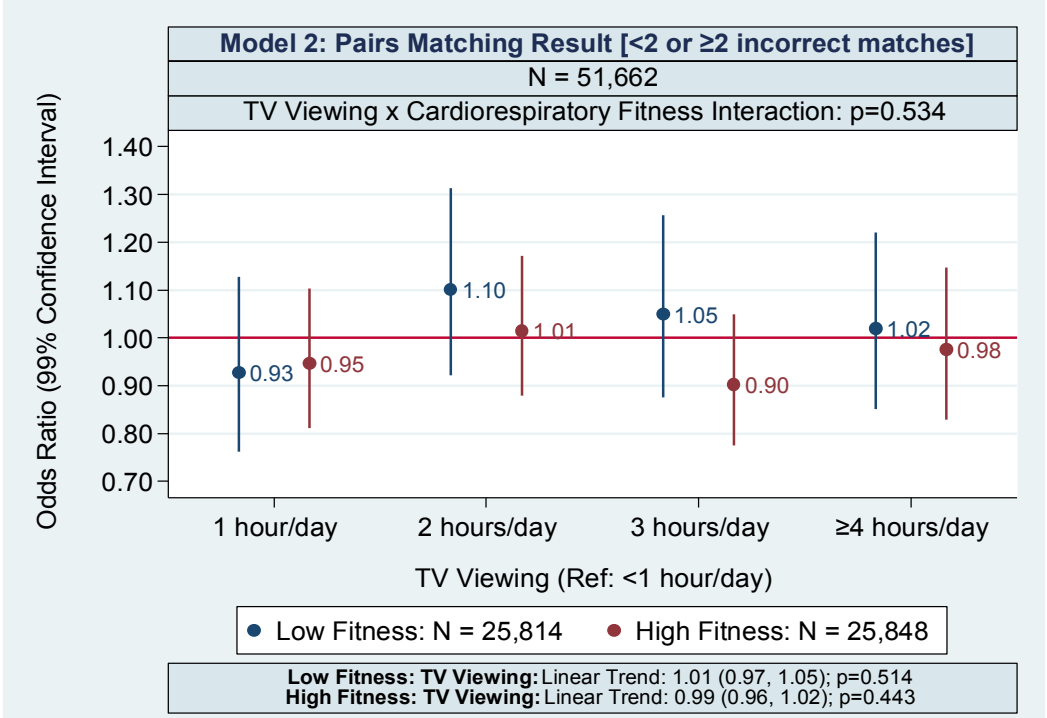

Model 2: Prospective Memory Result
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.300
Predicted Probability (Poor Prospective Memory Result) (99% Confidence Interval)
.1
.15
.2
.25
.3
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 25,946
High Fitness: N = 25,946

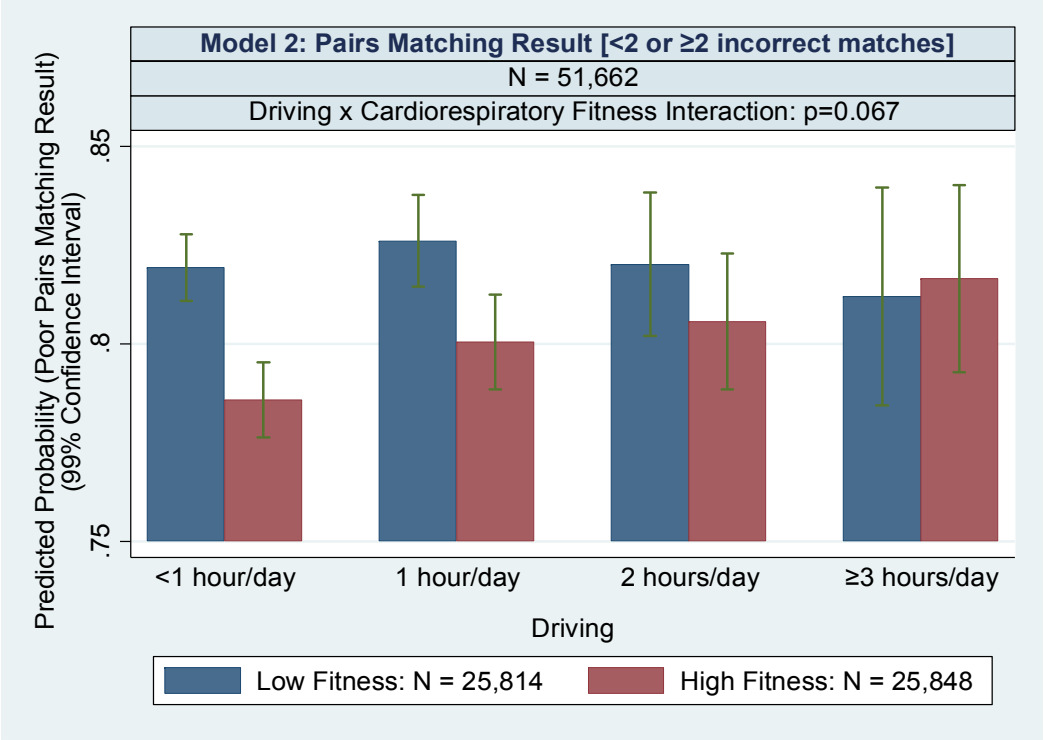

Model 2: Prospective Memory Result
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.300
Odds Ratio (99% Confidence Interval)
1.00
1.10
1.20
1.30
1.40
1.50
1.60
1.70
1.80
1.90
1.19
1.21
1.28
1.15
1.57
1.52
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 25,946
High Fitness: N = 25,946
Low Fitness: Driving: Linear Trend: 1.15 (1.10, 1.21); p<0.001
High Fitness: Driving: Linear Trend: 1.13 (1.07, 1.19); p<0.001

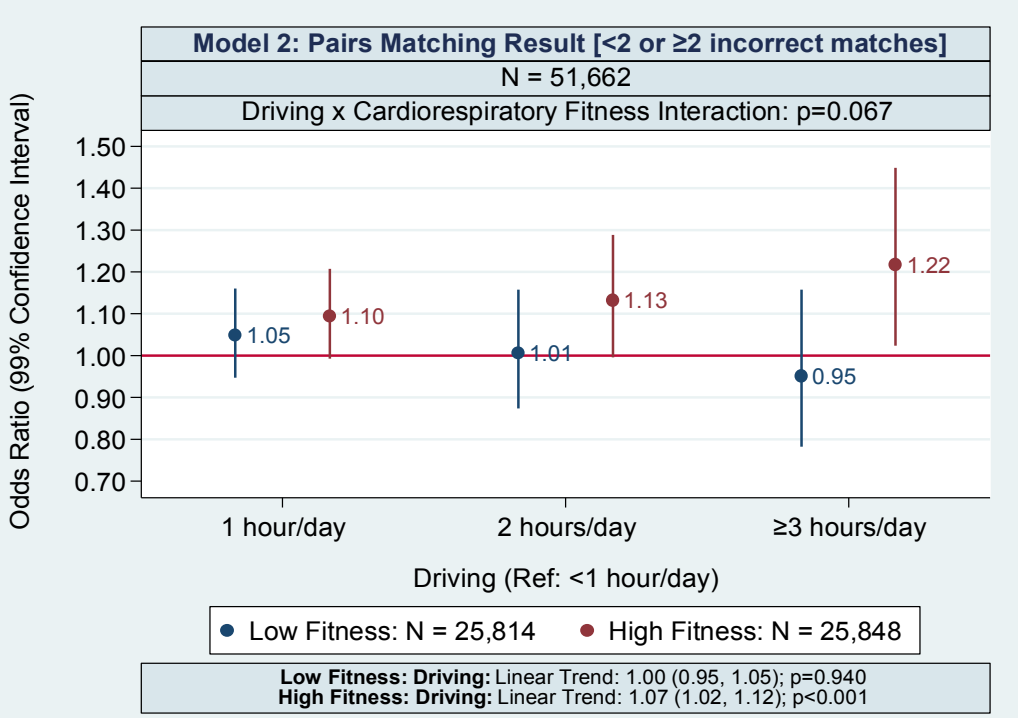

Model 2: Prospective Memory Result
N = 51,892
Computer Use x Cardiorespiratory Fitness Interaction: p=0.618
Predicted Probability (Poor Prospective Memory Result) (99% Confidence Interval)
.1
.15
.2
.25
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Computer Use
Low Fitness: N = 25,946
High Fitness: N = 25,946

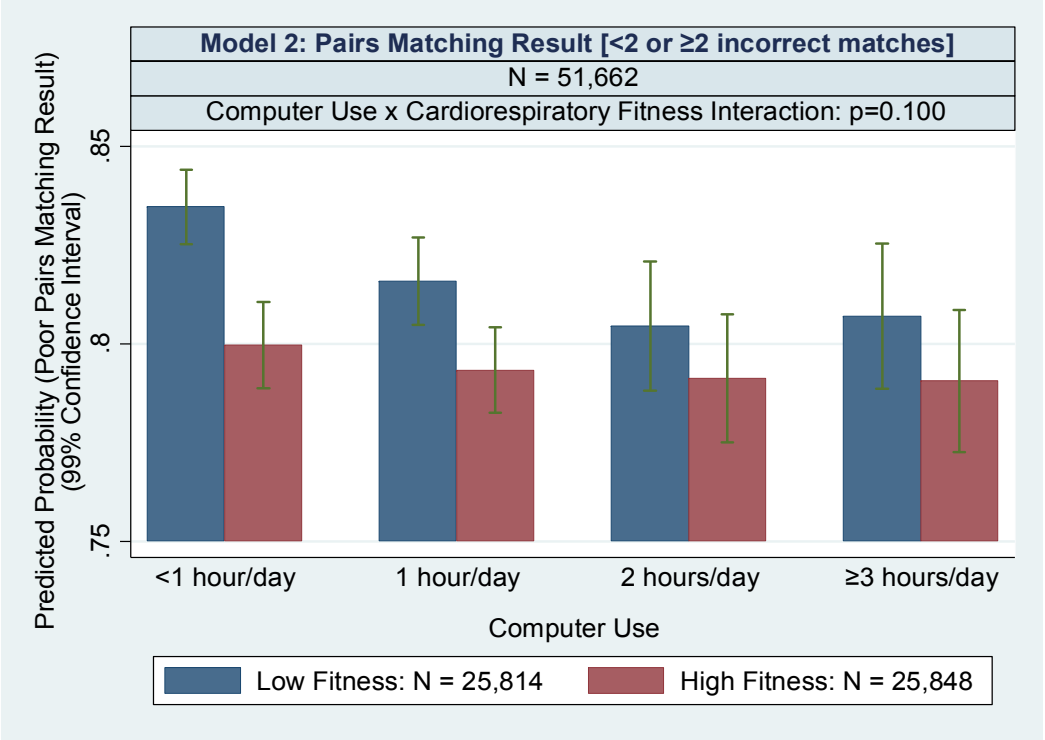

Model 2: Prospective Memory Result
N = 51,892
Computer Use x Cardiorespiratory Fitness Interaction: p=0.618
Odds Ratio (99% Confidence Interval)
1.10
1.00
0.90
0.80
0.70
0.60
0.84
0.85
0.79
0.73
0.91
0.92
1 hour/day
2 hours/day
≥3 hours/day
Computer Use (Ref: <1 hour/day)
Low Fitness: N = 25,946
High Fitness: N = 25,946
Low Fitness: Computer Use: Linear Trend: 0.94 (0.90, 0.98); p<0.001
High Fitness: Computer Use: Linear Trend: 0.94 (0.90, 0.98); p<0.001

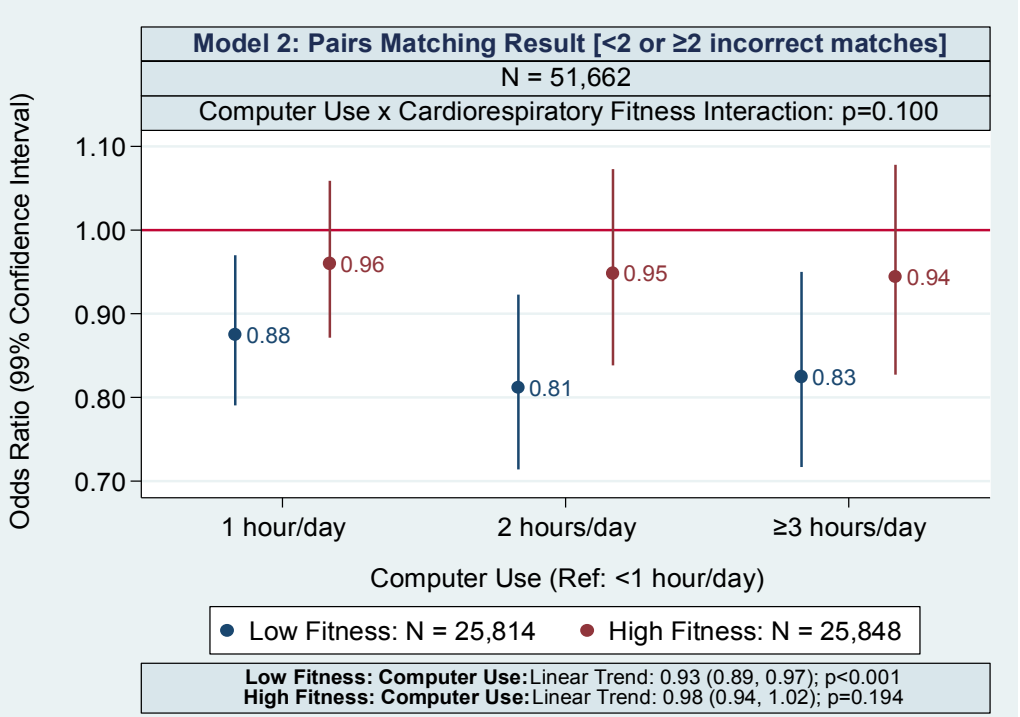

Model 2: Pairs Matching Result [<2 or ≥2 incorrect matches]
N = 51,662
TV Viewing x Cardiorespiratory Fitness Interaction: p=0.534
Predicted Probability (Poor Pairs Matching Result) (99% Confidence Interval)
.75
.8
.85
<1 hour/day
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
TV Viewing
Low Fitness: N = 25,814
High Fitness: N = 25,848


Model 2: Pairs Matching Result [<2 or ≥2 incorrect matches]
N = 51,662
TV Viewing x Cardiorespiratory Fitness Interaction: p=0.534
Odds Ratio (99% Confidence Interval)
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
0.93
0.95
1.10
1.01
1.05
0.90
1.02
0.98
1 hour/day
2 hours/day
3 hours/day
≥4 hours/day
TV Viewing (Ref: <1 hour/day)
Low Fitness: N = 25,814
High Fitness: N = 25,848
Low Fitness: TV Viewing: Linear Trend: 1.01 (0.97, 1.05); p=0.514
High Fitness: TV Viewing: Linear Trend: 0.99 (0.96, 1.02); p=0.443


Model 2: Pairs Matching Result [<2 or ≥2 incorrect matches]
N = 51,662
Driving x Cardiorespiratory Fitness Interaction: p=0.067
Predicted Probability (Poor Pairs Matching Result) (99% Confidence Interval)
.75
.8
.85
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 25,814
High Fitness: N = 25,848


Model 2: Pairs Matching Result [<2 or ≥2 incorrect matches]
N = 51,662
Driving x Cardiorespiratory Fitness Interaction: p=0.067
Odds Ratio (99% Confidence Interval)
1.50
1.40
1.30
1.20
1.10
1.00
0.90
0.80
0.70
1.05
1.10
1.01
1.13
0.95
1.22
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 25,814
High Fitness: N = 25,848
Low Fitness: Driving: Linear Trend: 1.00 (0.95, 1.05); p=0.940
High Fitness: Driving: Linear Trend: 1.07 (1.02, 1.12); p<0.001

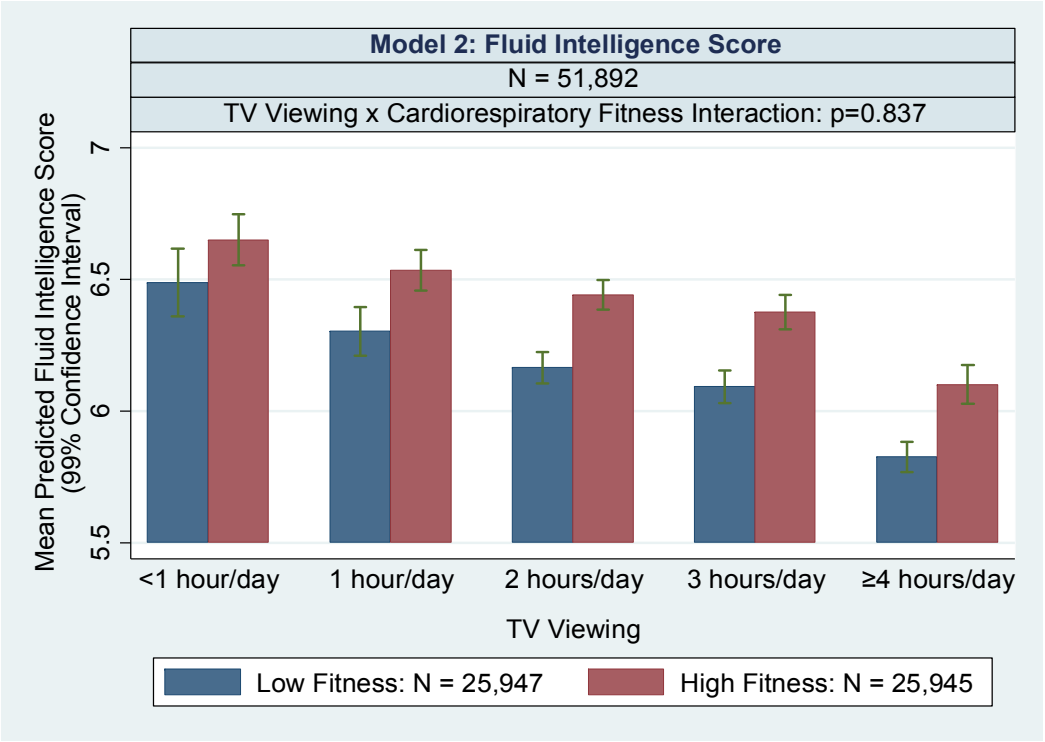


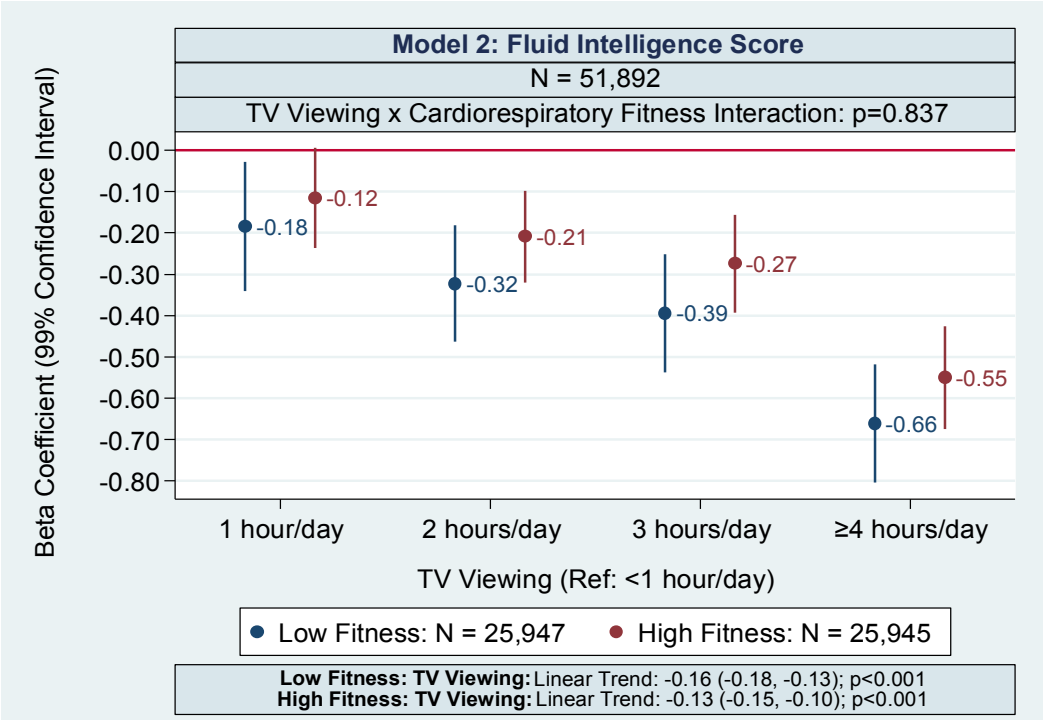


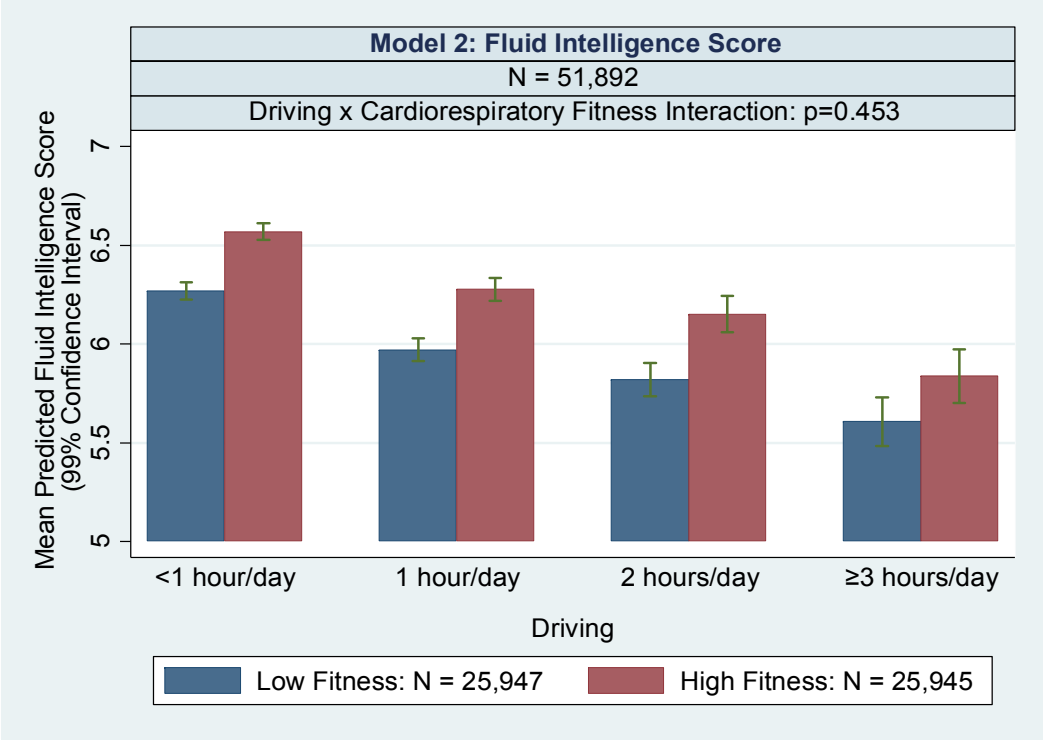
Prospective memory result: categorical binary (good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]). An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.
Pairs matching result: categorical binary (good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]). An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.

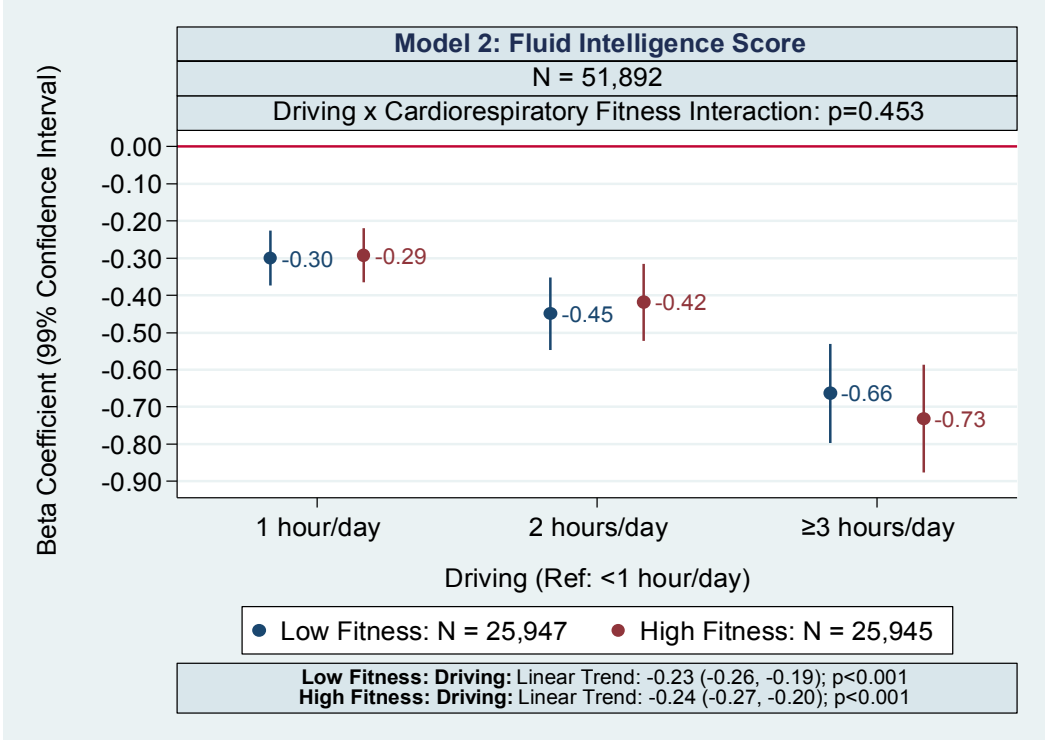
Interaction between sedentary behaviours and cardiorespiratory fitness (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments.

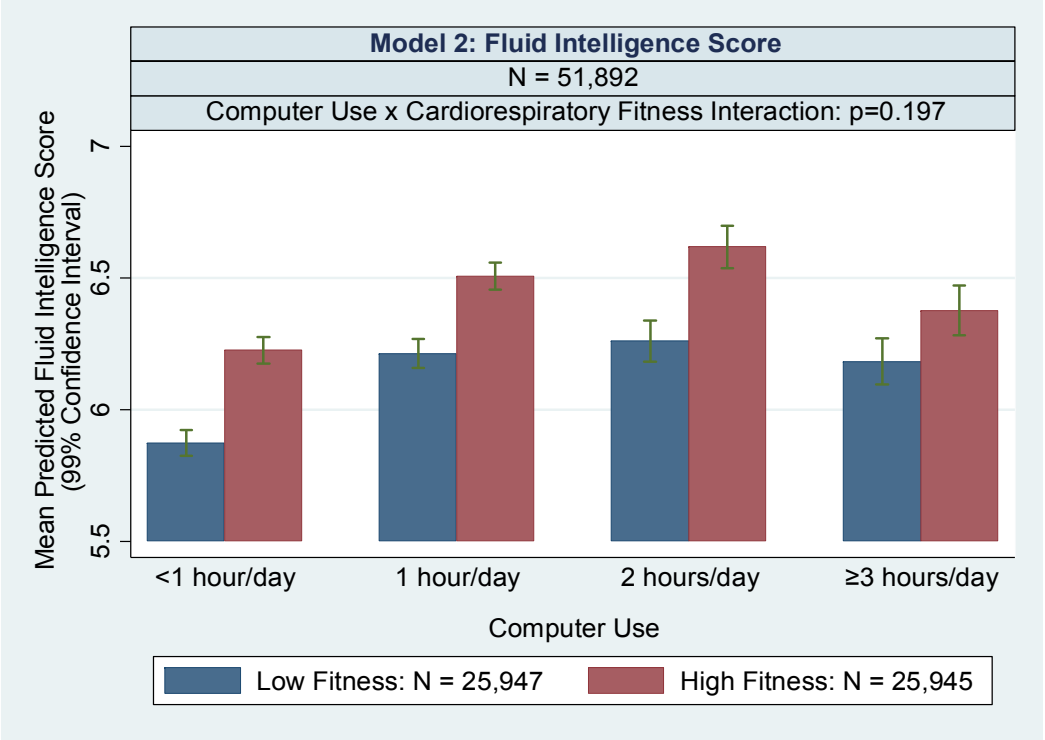
Figure 15 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (analysis executed using age- and sex-specific tertiles for cardiorespiratory fitness)

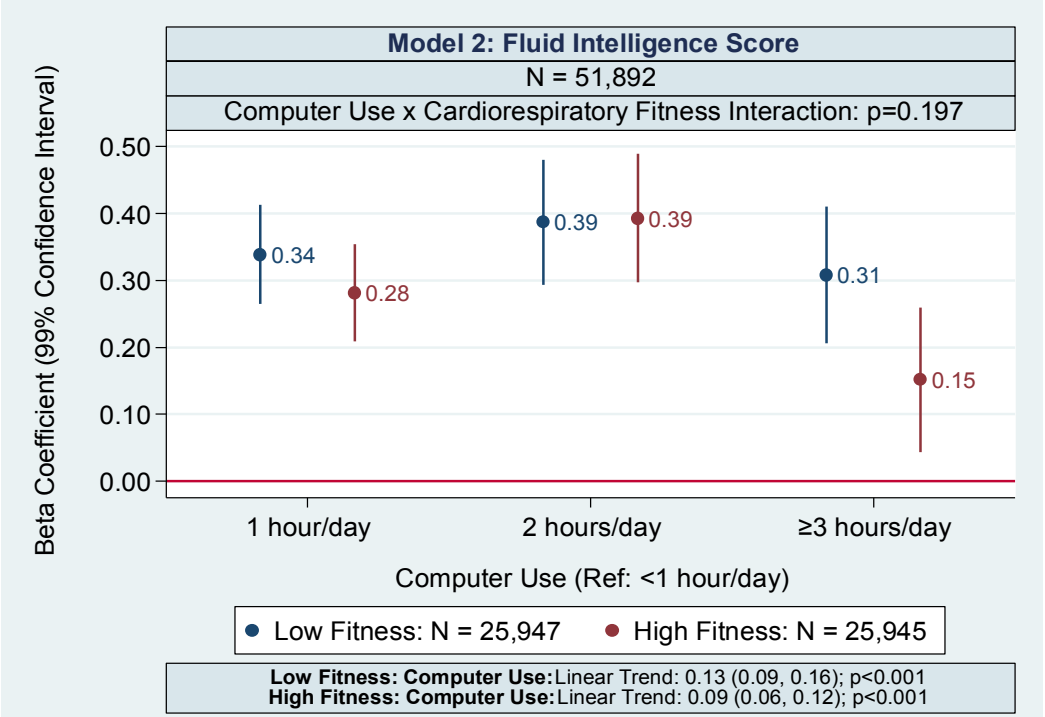





Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.453
Mean Predicted Fluid Intelligence Score (99% Confidence Interval)
5
5.5
6
6.5
7
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 25,947
High Fitness: N = 25,945


Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.453
Beta Coefficient (99% Confidence Interval)
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
-0.30
-0.29
-0.45
-0.42
-0.66
-0.73
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 25,947
High Fitness: N = 25,945
Low Fitness: Driving: Linear Trend: -0.23 (-0.26, -0.19); p<0.001
High Fitness: Driving: Linear Trend: -0.24 (-0.27, -0.20); p<0.001

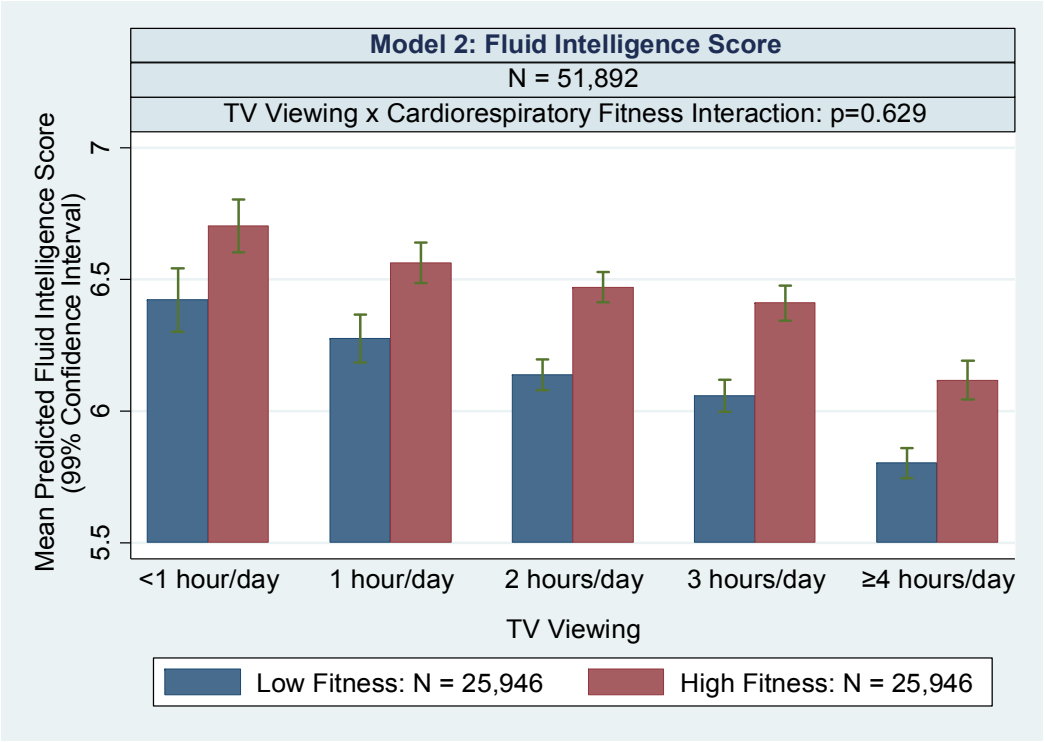


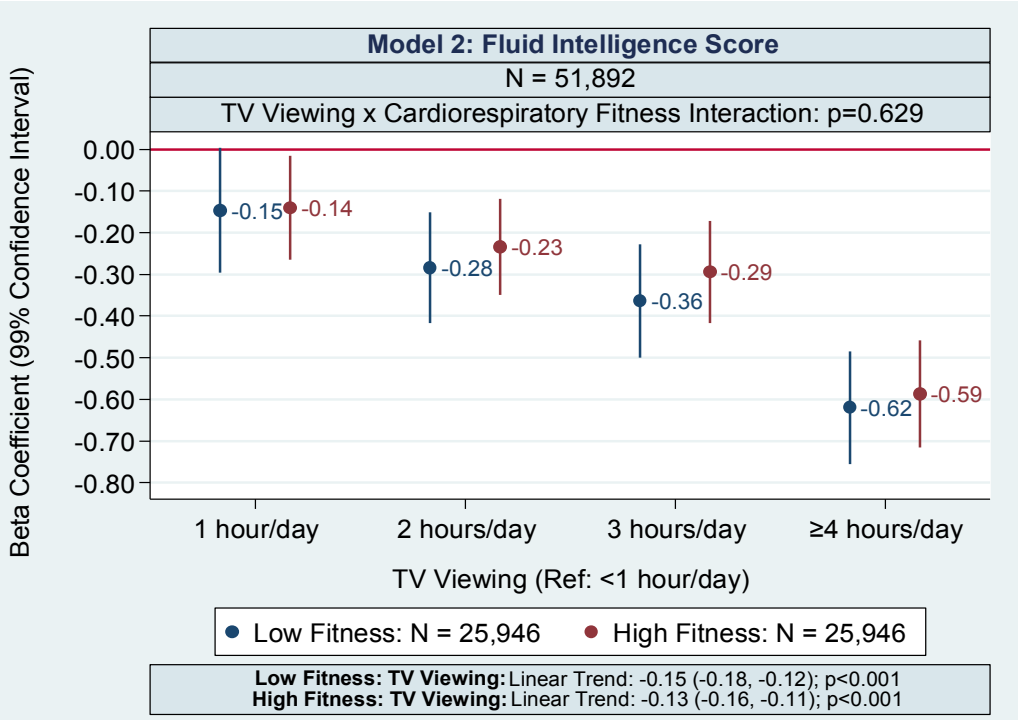


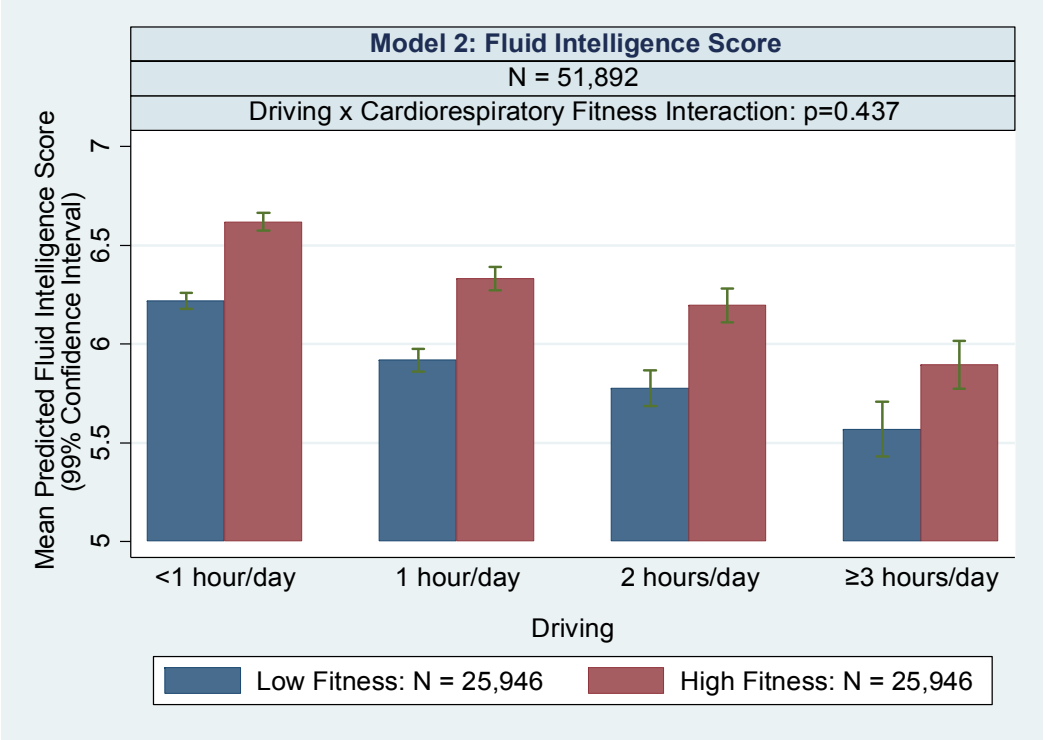
Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

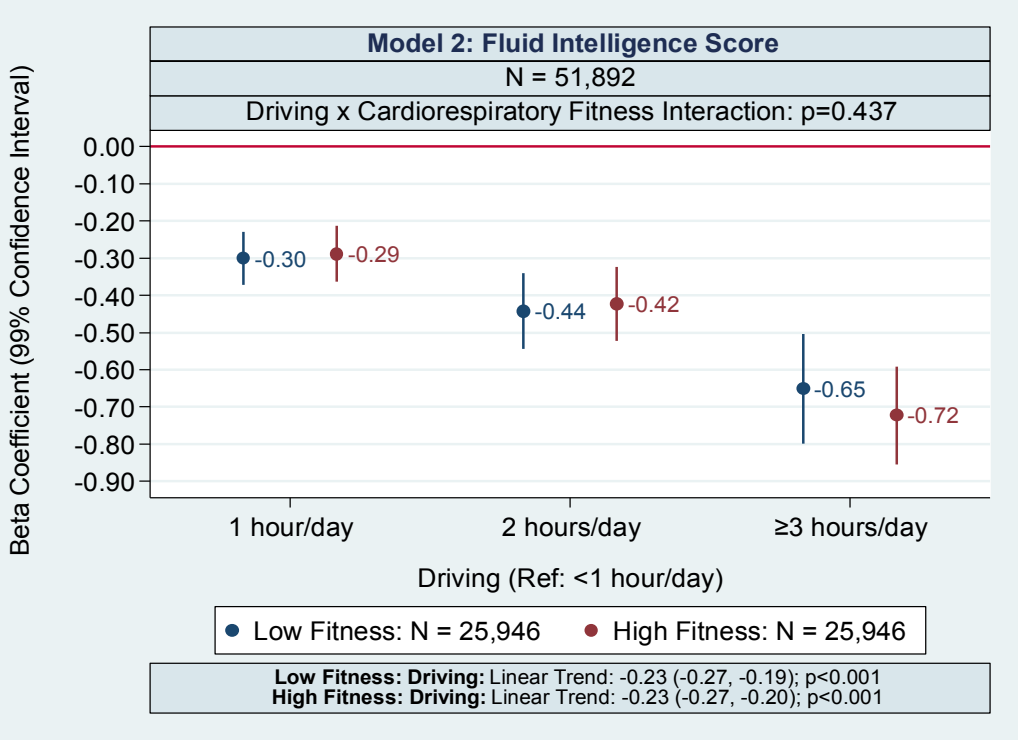
Interaction between sedentary behaviours and cardiorespiratory fitness (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments.

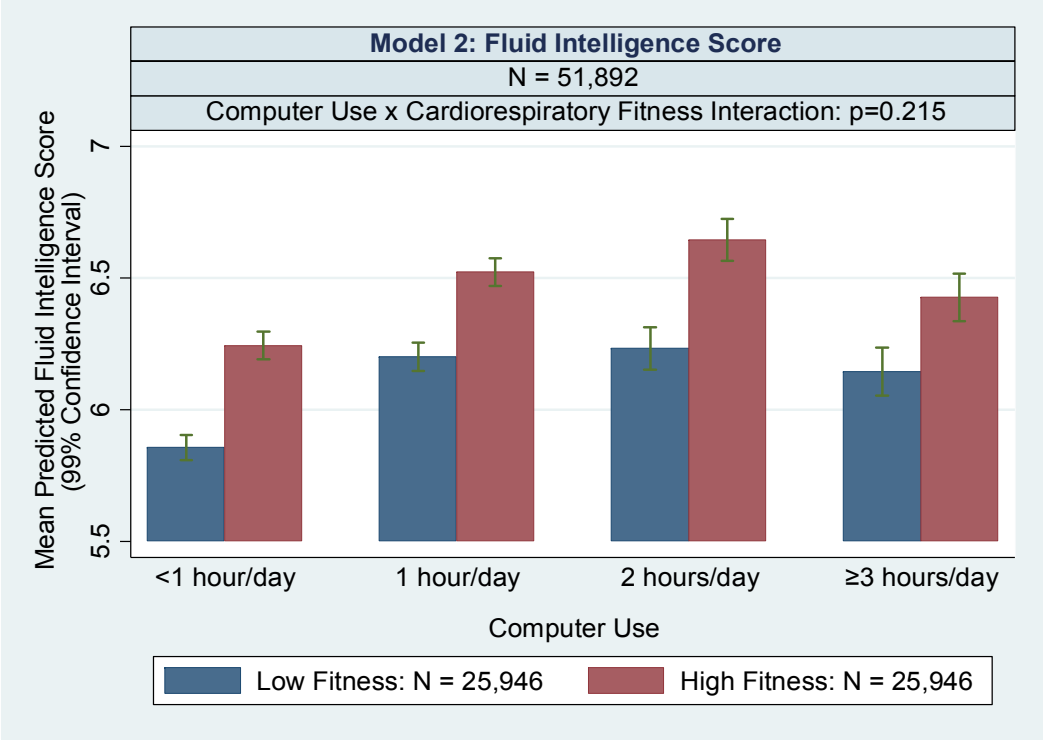
Figure 16 - Observational study (UK Biobank data): Interactions by cardiorespiratory fitness: associations between sedentary behaviours and fluid intelligence (analysis executed using a continuous cardiorespiratory fitness variable)

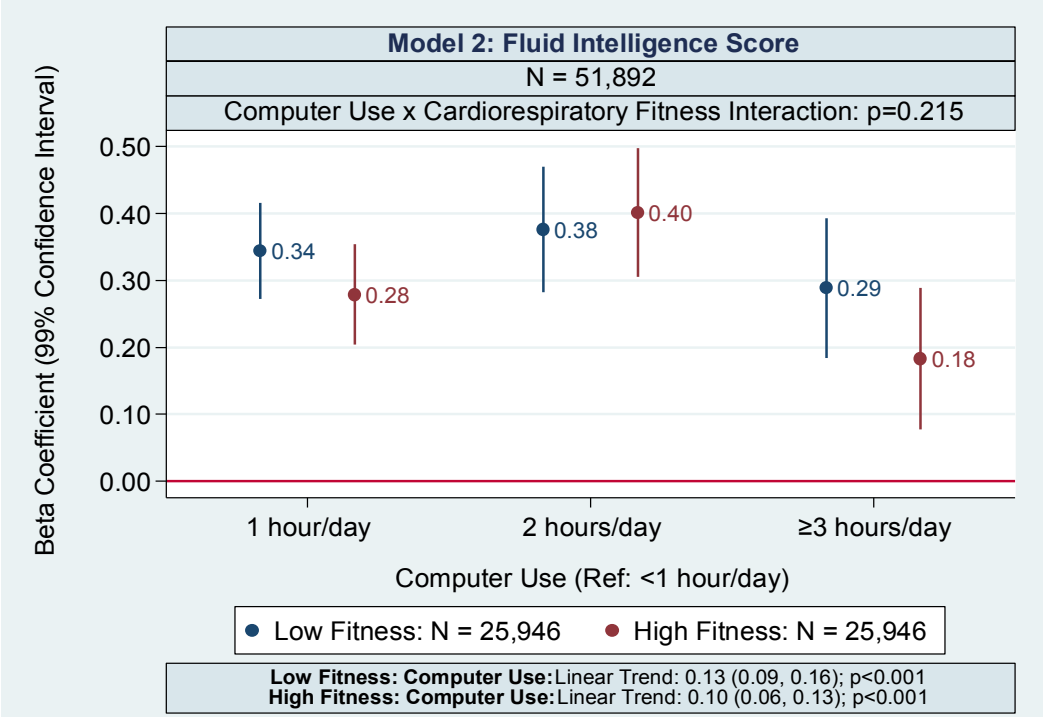





Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.437
Mean Predicted Fluid Intelligence Score (99% Confidence Interval)
5
5.5
6
6.5
7
<1 hour/day
1 hour/day
2 hours/day
≥3 hours/day
Driving
Low Fitness: N = 25,946
High Fitness: N = 25,946


Model 2: Fluid Intelligence Score
N = 51,892
Driving x Cardiorespiratory Fitness Interaction: p=0.437
Beta Coefficient (99% Confidence Interval)
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
-0.30
-0.29
-0.44
-0.42
-0.65
-0.72
1 hour/day
2 hours/day
≥3 hours/day
Driving (Ref: <1 hour/day)
Low Fitness: N = 25,946
High Fitness: N = 25,946
Low Fitness: Driving: Linear Trend: -0.23 (-0.27, -0.19); p<0.001
High Fitness: Driving: Linear Trend: -0.23 (-0.27, -0.20); p<0.001





Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Interaction between sedentary behaviours and cardiorespiratory fitness (statistical significance was established at p-value<0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments.

Discussion

Key Findings

This is the first study to investigate whether the associations between sedentary behaviours and fluid intelligence are modified by levels of CRF. Analysis on this subsample of participants with CRF data displayed the same associations between sedentary behaviours and fluid intelligence as those presented in the first part of this chapter. After adjustment for each other and several important confounders, it was observed that TV viewing and driving time were inversely associated with fluid intelligence, whereas computer use time and CRF were positively associated with fluid intelligence. However, interaction analyses showed that the associations between each sedentary behaviour and fluid intelligence were not modified by CRF. Therefore, the hypothesis that CRF may attenuate some of the deleterious impact of TV viewing and driving, and the beneficial impact of computer use was demonstrated to be false. Although those with low levels of CRF had lower fluid intelligence scores compared to those with high CRF, both groups demonstrated similar inverse associations of TV viewing and driving time with fluid intelligence, and positive associations of computer use time with fluid intelligence. Findings were generalizable across the wide range of sensitivity analyses implemented.

Interpretations

The associations observed between CRF and fluid intelligence are supported by interventional and mechanistic studies which have shown direct effects on the structure and function of the brain (50-53, 205-208); with higher levels of CRF associated with higher in vivo brain tissue density (207), gray matter volume (205), brain perfusion and responsiveness of blood vessels (208). This provides a plausible biological mechanism that explains the positive effects of CRF on cognitive health. In addition, there are many other possible overlapping mechanisms linking sedentary behaviours to cognitive health. Some of these pathways include: cardiometabolic health (8, 13, 164, 165), stress and fatigue (26, 169-171), and social networking and isolation (172, 174). This study suggests that sedentary behaviours and CRF are

independently associated with cognitive function, and that these associations are not modified by each other. This is an important finding in the context that CRF has been shown to modify the association between sedentary behaviour and physical health, with relationships weaker in those with high levels of physical CRF or undertaking high amounts of physical activity (8, 37, 38, 194, 195). This study shows that sedentary behaviour remains an important determinant of cognitive function even when combined with high CRF, suggesting that high levels of CRF may not protect against the inverse associations of engaging in prolonged TV viewing or driving.

To my knowledge, only one study has investigated the combined associations of CRF and sedentary time on cognitive function (197), whilst none have examined the interaction between these two factors or investigated whether the relationships shared between sedentary behaviours and cognitive function are modified by levels of CRF. In a national sample of 2,451 older US adults (mean age = 70 years), Edwards and Loprinzi found that low sedentary time and high CRF were independently and jointly associated with high cognitive function (197). However, in their study, CRF was not objectively assessed via a submaximal test, rather it was estimated using equations that combined data on anthropometrics, demographics, health, and lifestyle factors. Furthermore, variables assessing the time spent in different sedentary behaviours were combined into a single variable. As demonstrated in this analysis and previous studies, different sedentary behaviours may share different relationships with cognitive function (56-60, 196); thus, they should only be combined with caution.

Strengths and Limitations

This study has several strengths and some limitations. Strengths include: the large sample size, mutually adjusted and time quantified measures of sedentary behaviour, objectively measured CRF data, a robust statistical analysis plan with examinations of dose-response relationships, detailed covariate data, and a wide range of sensitivity analyses. In the UK Biobank, CRF was assessed using a six-minute incremental submaximal ramp cycle ergometer test in a subsample of adults (212, 213). The UK Biobank have yet to summarise these data into a form suitable for researchers to use;

and consequently, these data have yet to be validated within the UK Biobank. Hence, for my analyses, I manually estimated CRF using the available ECG data. Based on the approaches used (see the CRF estimation methods described on pages 195-198 of the thesis), the CRF data derived in this analysis can be considered to be relatively crude in nature. For example, when fitting the linear regression line to derive the relationship between heart rate and workload, only two sets of data points were used (i.e. resting heart rate and resting workload (i.e. 0 watts); and maximum heart rate during the fitness test and maximum workload during the fitness test). In addition, it is possible that the maximum heart rate during the fitness test may not have always corresponded with the maximum workload during the fitness test. Using all the paired heart rate and workload data points throughout the fitness test would have allowed for the establishment of a more accurate relationship between heart rate and workload, and consequently a more robust estimate of CRF. Another limitation includes the unconventional placements of the 4-lead ECG electrodes; in general, these are usually placed on the extremities i.e. left wrist, right wrist, left ankle, and right ankle (223). Furthermore, note that in order to determine the type of test to employ, the UK Biobank stratified participants into five risk categories (1. minimal risk: cycle at 50% level, 2. small risk: cycle at 35% level, 3. medium risk: cycle at constant level, 4. high risk: take measurement at rest-only, 5. ECG to be avoided, either unsafe or pointless) based on the following risk factors: heart condition, chest pain during physical activity, chest pain at rest, unable to walk/cycle, pregnant, height unknown, weight unknown, heart rate unknown, BP unknown, BP very high, BP high, weight high, pacemaker unknown, and pacemaker (212). Additionally, the UK Biobank also stratified the absolute maximum workload of the fitness test according to age, height, weight, resting heart rate, and sex (212). Hence, there is a considerable risk of bias involved here and it is possible that these estimated CRF data have low validity. Along with systematic bias, there is also a real risk of random measurement error, which could result in regression dilution (185); and therefore, these implications should be kept in mind when interpreting any findings from these data. In order to derive a more robust estimate of fitness, further work utilising the full wealth of the data available from this test would be required. Other recognised markers of physical function can

also be used to validate the observed associations between the three different sedentary behaviours and fluid intelligence presented within the thesis. To demonstrate this, I tested whether walking pace, a strong and established marker of physical function and mortality (224), which was assessed in the UK Biobank via questionnaire (225), modified the associations between the different sedentary behaviours and fluid intelligence. Similar to the findings from the interaction analyses presented earlier using CRF, these models (Model 2 as reported) also indicated that the associations between the three sedentary behaviours and fluid intelligence were not modified by walking pace (p-value=0.143 for interaction with TV viewing time, p-value=0.718 for interaction with driving time, and p-value=0.406 for interaction with computer use time) (see Figure S4 in Appendix Three: Supplementary Material: Supplementary Data). In all three walking pace groups (slow, steady average, brisk), the observed associations between the three sedentary behaviours and fluid intelligence maintained similar direction, magnitude, and significance.

Other important limitations remain. The cross-sectional design prohibits the possibility of establishing causality, whilst reverse-causality remains possible. Furthermore, the sample of adults analysed in this study may not be completely generalizable and representative of the full cohort. Besides the BMI and CRF data, all other covariates and exposure variables in this study were self-reported; methods which tend to have low validity and increase the risk of regression dilution (185). However, in reference to the self-reported sedentary behaviour measures, although data that are more robust can be obtained using objective tools (e.g. accelerometers) (62, 63), they would not provide information on the specific type of sedentary behaviour performed. Conversely, only three domains of sedentary behaviour were measured in this study; therefore, the findings are restricted and cannot be generalized to other types of sedentary behaviour. Lastly, even though a wide range of variables were adjusted for, some unmeasured features may have confounded the reported associations. For example, although social deprivation index was controlled for, the observed relationship between computer use and fluid intelligence may simply be a proxy for owning a computer; and therefore, a proxy for affluence.

Conclusion

In this cross-sectional analysis of a large cohort of adults, the associations between different sedentary behaviours and fluid intelligence were not modified by CRF. Higher levels of CRF may not provide protection from the potentially deleterious impact of TV viewing and driving on cognitive function, and this study supports public health policies designed to reduce these two activities in adults. However, interventional and longitudinal studies are required to establish causality and confirm these findings.

Associations between Lifestyle Factors and Cognitive Function: Cross-Sectional and Prospective Findings from the UK Biobank

Abstract

Here, I investigate the cross-sectional and prospective associations of modifiable lifestyle factors and their additive impact on fluid intelligence in a large sample of UK adults. Data from the UK Biobank were used. 165,492 participants provided fluid intelligence data (fluid intelligence score: total number of correct answers to 13 numeric and verbal problems solved within two-minutes) at baseline; and 46,704 participants provided fluid intelligence data at both baseline and follow-up (over a mean period of 4.9 years). Modifiable lifestyle factors, measured at baseline, included: BMI, diet, physical activity, smoking status, sleep duration, handgrip strength, walking pace, TV viewing time, driving time, and computer use time. Regression analysis investigated the cross-sectional associations at baseline, and the prospective associations from baseline to follow-up. At baseline, each lifestyle factor (except for BMI) was independently and positively associated with fluid intelligence. The number of healthy lifestyle factors at baseline was positively associated with fluid intelligence at both baseline (fluid intelligence score was 0.18 (95% CI: 0.17, 0.19) higher for each additional lifestyle factor, with the associations stronger in older adults (age ≥60 years) and in males) and over follow-up (odds of having a lower fluid intelligence score at follow-up were 7% (6%, 9%) lower for each additional lifestyle factor). Findings were generalizable across the other cognitive tests. In conclusion, an increasing number of healthy lifestyle factors at baseline was associated with better fluid intelligence at both baseline and over follow-up. This study supports public health policies designed to increase healthy behaviours in adults for cognitive well-being.

Introduction

Cognitive decline throughout adulthood is a recognised consequence of biological ageing, with accelerated cognitive decline resulting in dementia (45). Cognitive decline is influenced by many distinct lifestyle factors independently of chronological age (56, 59, 196, 204, 210, 226-232). Limited research has suggested that a clustering of healthy lifestyle behaviours may be associated with better cognitive function and could provide a mechanism to reduce the risk of cognitive decline (56, 233-239). However, the evidence has been restricted by cross-sectional designs, small sample sizes, and limited selections of lifestyle behaviours (56, 233-239).

The aim of this study is to quantify the cross-sectional and prospective associations of modifiable lifestyle factors and their additive impact on fluid intelligence; and to assess any potential interactions by age or sex within the large UK Biobank cohort. Previous research has shown fluid intelligence to be strongly associated with several lifestyle factors (210, 226-232); and in the UK Biobank, this assessment was recorded as a continuous measure and assessed using a broad range of numeric and verbal problems that required logic and reasoning ability, discrete of any acquired knowledge; resulting in a wide response distribution; and therefore, a comprehensive and sensitive measure of cognitive ability within this cohort.

Methods

Design and Population

The UK Biobank recruited approximately 500,000 adults (aged 37-73 years) between 2006-2010 via mailing out invitations to those registered with the NHS and living within 25 miles of one of the 22 assessment centres across England, Scotland and Wales. Participants provided baseline data on biological, cognition, demographic, health, lifestyle, mental, social, and well-being outcomes. For the present study, baseline fluid intelligence data were available on 165,492 individuals (see Figure 17). Approximately 300,000 participants provided an email address for the remote follow-up of cognitive function in the future. From 2014-2015, around 125,000 participants provided online follow-up cognitive function data; and a subset (n=46,704) provided

both baseline and follow-up fluid intelligence data, after a mean period of 4.9 years (see Figure 18). Further details are available elsewhere (92-94).

Figure 17 - Observational study (UK Biobank data): Flow chart of participants (cross-sectional data)

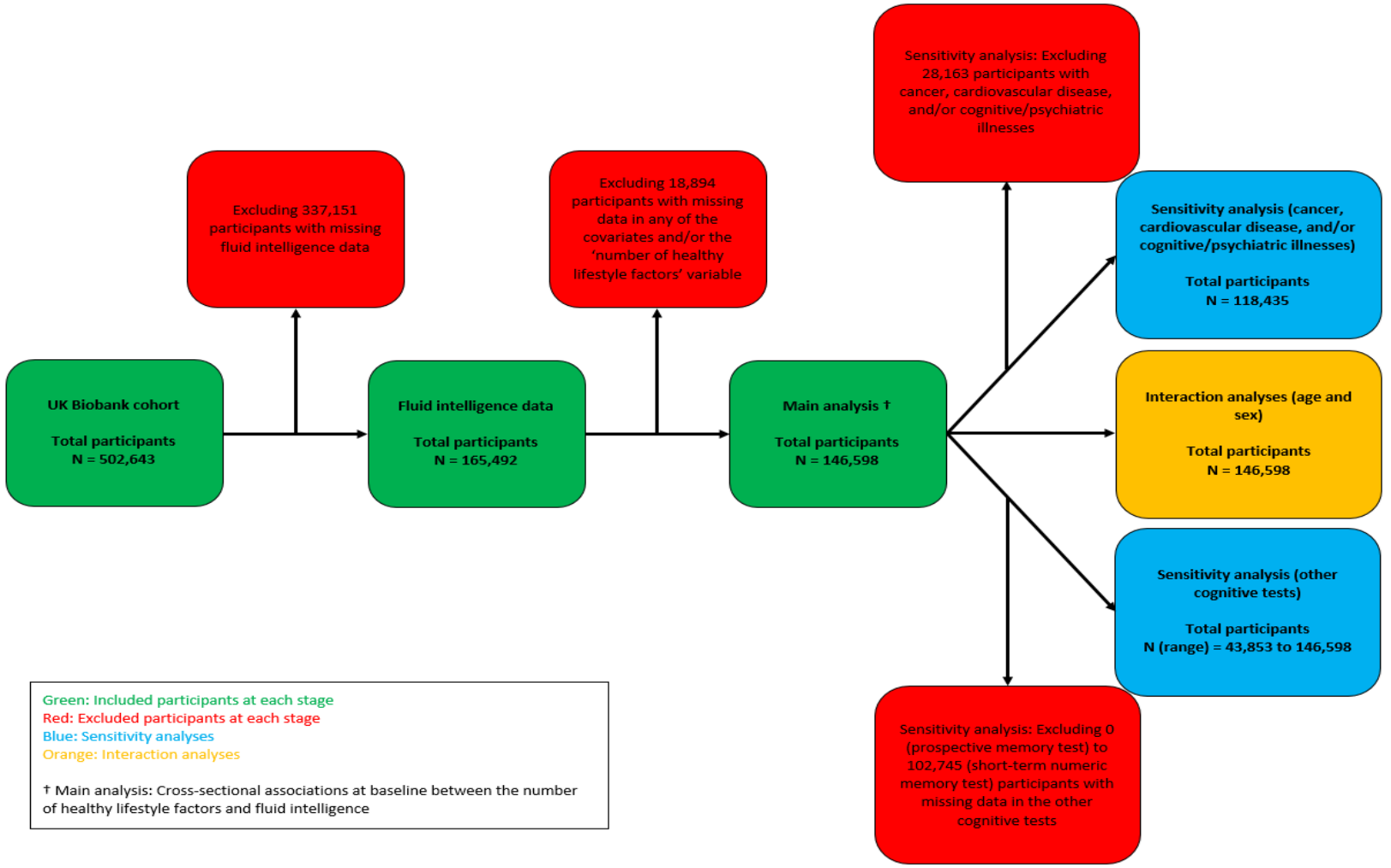
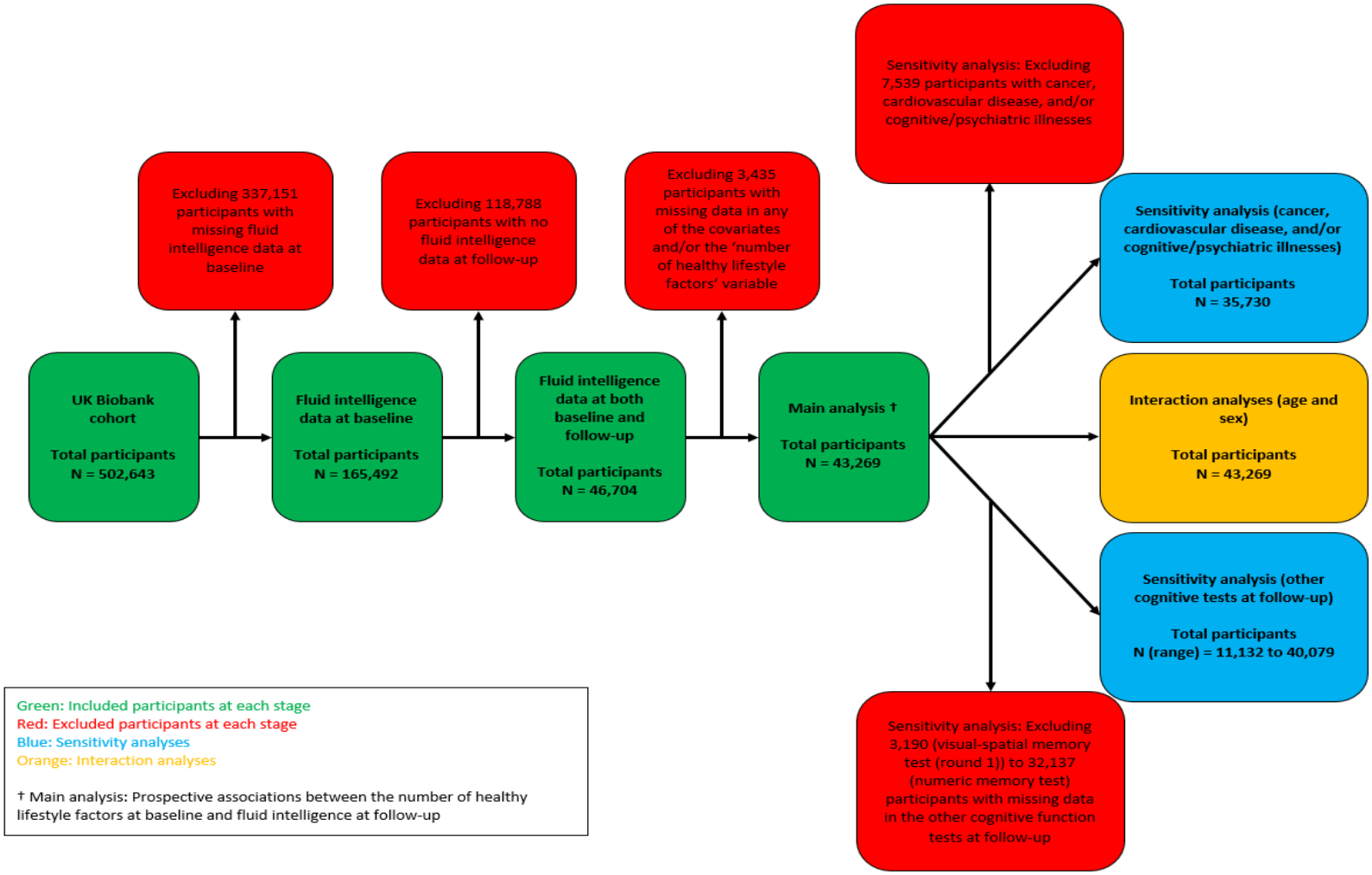


Figure 18 - Observational study (UK Biobank data): Flow chart of participants (prospective data)



Cognitive Function Tests

This analysis is focused on the fluid intelligence test (available at baseline and follow-up). For the cross-sectional analyses, the fluid intelligence score at baseline, quantified as the 'total number of correct answers', was used as a continuous variable. For the prospective analyses, the fluid intelligence score at follow-up was used to derive a binary variable: good outcome at follow-up [(reference) baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score]. Further details are available elsewhere (101, 110, 221).

For sensitivity analyses, other cognitive tests administered in the UK Biobank [prospective memory (available at baseline only), visual-spatial memory (available at baseline and follow-up), reaction time (available at baseline only), and short-term numeric memory (available at baseline and follow-up)] were also used to ensure that the pattern of associations was generalizable across the other cognitive assessments. The reaction time assessment measured the cognitive processing speed via recording the response time to perception of visual stimuli. The test was implemented at the baseline assessment centre as follows: participants were asked to play 12 rounds of 'Snap'; which involved pressing a physical push button as soon as 2 identical cards on the touchscreen were observed. For the cross-sectional analyses, the 'mean time taken to correctly identify matches' (i.e. the mean time to first press the button over the rounds in which both cards matched; measured in milliseconds) indicated a normal distribution (see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data) and was therefore used as a continuous outcome variable. Note, the first 4 rounds were declared as practice rounds and were not utilised (i.e. the mean reaction time was only calculated from the last 8 rounds). In addition, reaction times under 50 milliseconds (anticipation as opposed to reaction) and over 2000 milliseconds (cards no longer visible at that point) were considered invalid; and thus, they were omitted. The other cognitive data were used in the same fashion as they were in the previous UK Biobank analyses.

Lifestyle Factors

Data on BMI, diet, leisure time physical activity, smoking status, sleep duration, functional measures relating to lifestyle (handgrip strength and walking pace), and sedentary behaviours (TV viewing, driving, and non-occupational computer use time) were included. A wide spectrum of lifestyle data was collected at the baseline assessment centre. Height was measured using the Seca 202 medical measuring rod (Seca, Hamburg, Germany) and weight was measured to the nearest 0.1 kilograms using the Tanita BC-418MA body composition analyser (Tanita, Tokyo, Japan). BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres). Dietary data were collected using a food frequency questionnaire. For this analysis, information on fruit and vegetables (fresh fruit, dried fruit, cooked vegetable, salad/raw vegetable), salt, fish, bread, cereal, red meats (beef, lamb/mutton, and pork), and processed meats were combined to create a 'diet score' variable (0 points for each unhealthy dietary factor, and 1 point for each healthy dietary factor) (see Table 21). The categorisations here were largely based on health guidelines and messages (240, 241).

Table 21 - Observational study (UK Biobank data): Dietary data

Dietary factor	Question(s) asked in UK Biobank	Unhealthy (0 points)	Healthy (1 point)
Fruit and Vegetables	About how many pieces of fresh fruit would you eat per day? + About how many pieces of dried fruit would you eat per day? + On average how many heaped tablespoons of cooked vegetables would you eat per day? + On average how many heaped tablespoons of salad or raw vegetables would you eat per day?	<5/day	≥5/day
Salt	Do you add salt to your food?	Sometimes, usually, or always	Never/rarely
Fish	How often do you eat oily fish (e.g. sardines, salmon, mackerel, herring)? + How often do you eat other types of fish (e.g. cod, tinned tuna, haddock)?	<2 times/week	≥2 times/week
Bread	What type of bread do you mainly eat?	Other (white, brown, other type of bread, or do not know)	Wholemeal, wholegrain or do not eat bread
Cereal	What type of cereal do you mainly eat?	Other (other (e.g. Cornflakes, Frosties), or do not know)	Bran cereal (e.g. All Bran, Branflakes), biscuit cereal (e.g. Weetabix), oat cereal (e.g. Ready Brek, Porridge), muesli, or do not eat cereal
Processed and red meat	How often do you eat beef? + How often do you eat lamb/mutton? + How often do you eat pork? + How often do you eat processed meats?	≥2 times/week	<2 times/week

The raw dietary points were summated to form the diet score (ranging from 0 (unhealthy) to 6 (healthy)); which was then split into tertiles. Data on the duration [less than 15 minutes, between 15 and 30 minutes, between 30 minutes and 1 hour, between 1 and 1.5 hours, between 1.5 and 2 hours, between 2 and 3 hours, over 3 hours], frequency [once in the last 4 weeks, 2-3 times in the last 4 weeks, once a week, 2-3 times a week, 4-5 times a week, everyday], and MET scores of five leisure time physical activities (4, 242) [light DIY (1.5 METs), walking for pleasure (3.5 METs), other exercises (4 METs), heavy DIY (5.5 METs), strenuous sports (8 METs)] were combined to create the 'physical activity' variable (MET-minutes/week); which was then split into tertiles. To be specific, this was executed via first calculating the midpoints of the duration data on each activity (i.e. less than 15 minutes = 7.5 minutes (note, here 0 was used as the minimum), between 15 and 30 minutes = 22.5 minutes, between 30 minutes and 1 hour = 45 minutes, between 1 and 1.5 hours = 75 minutes, between 1.5 and 2 hours = 105 minutes, between 2 and 3 hours = 150 minutes, over 3 hours = 180 minutes (note, here 180 was capped as the maximum)). Similarly, where required, midpoints were also used to transform the frequency data on each activity into 'per week' data (i.e. once in the last 4 weeks = 0.25/week, 2-3 times in the last 4 weeks = 0.625/week, once a week = 1/week, 2-3 times a week = 2.5/week, 4-5 times a week = 4.5/week, everyday = 7/week). In individuals who provided information on both the duration and frequency of all five activities, the data on each activity were combined together via multiplication to form 'mins/week' variables. These data were then multiplied by their relevant MET scores (4). The total across all five activities were then summed up as the 'physical activity' variable, before being categorised into tertiles. UK Biobank includes several different methods of measuring overall and leisure time physical activity. The method in this study was chosen based on running face validity checks assessing which variables achieved the expected correlations with age (i.e. an inverse linear relationship between age and physical activity). Smoking status was defined as never, previous, or current. Sleep duration data were collected via asking the participants to quantify the number of hours they typically sleep in every 24-hour period. Handgrip strength was examined using the Jamar J00105 hydraulic hand dynamometer (Lafayette Instrument Company, Indiana, USA). Participants were asked

to sit upright in a chair with their forearms placed on armrests and elbows placed against their sides at a 90° angle. Participants were then instructed to squeeze the handle of the dynamometer as strongly as they could for 3 seconds while keeping their wrist straight. Handgrip strength was measured in both hands and the mean of the right hand and left hand values, expressed in kilograms, was calculated and quantified as tertiles. Walking pace data were collected via asking the participants to describe their usual walking pace: slow pace, steady average pace, or brisk pace. Sedentary behaviour data (TV viewing time, driving time, and non-occupational computer use time) were collected via asking the participants to quantify the number of hours/day they typically spend in each behaviour.

To allow for the cumulative addition of lifestyle factors within this analysis, each lifestyle factor was categorised as a binary variable (unhealthy; or healthy). For continuous variables without clinical thresholds, categorisations were either data-driven or based on the previous literature (196). BMI: obese (BMI ≥30 kg/m^2); or non-obese (BMI <30 kg/m^2). Diet (based on a dietary score): unhealthy diet (tertile 1); or healthy diet (tertiles 2 or 3). Physical activity (based on the duration, frequency and MET scores of five leisure time physical activities (light DIY, walking for pleasure, other exercises, heavy DIY, strenuous sports; MET-minutes/week)): physically inactive (tertile 1); or physically active (tertiles 2 or 3). Smoking status: smoker (current); or non-smoker (never or previous). Sleep duration: unhealthy duration (<7 or >8 hours/day); or healthy duration (7 or 8 hours/day). Handgrip strength (expressed in kilograms): low (tertile 1); or high (tertiles 2 or 3). Walking pace: slow pace; or steady average or brisk pace. TV viewing time: high (≥3 hours/day); or low (<3 hours/day). Driving time: high (≥1 hour/day); or low (<1 hour/day). Computer use time: low (<1 hour/day); or high (≥1 hour/day). For each lifestyle factor, the 'unhealthy' group was selected as the reference category.

Confounders

Covariate data included: demographics (age, sex, ethnicity, social deprivation index, employment status, and education level) and health (number of cancers, number of

non-cancer illnesses, and number of medications/treatments) variables. These data were used in the same fashion as they were in the previous UK Biobank analyses.

Statistical Analysis

Statistical analyses were conducted using Stata/MP V14.0 (Stata Corporation, College Station, Texas, USA). With the intention of maximising the use of the data, pairwise deletion was used to handle missing data (see Figure 17 and Figure 18). Participant characteristics were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations (SD); and presented with their minimum and maximum values.

Cross-Sectional Analysis

Linear regression analysis was used to examine the cross-sectional associations between each lifestyle factor and fluid intelligence at baseline (Stata command: 'regress') (121). Model 1 adjusted for: age and sex. Model 2 further adjusted for: ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Lifestyle factors that were not associated with fluid intelligence at this stage were excluded from all subsequent analyses. Model 3 further mutually adjusted for the other lifestyle factors.

Lifestyle factors associated with fluid intelligence (i.e. those in Model 3) were used to derive a 'number of healthy lifestyle factors' variable (ranging from having no healthy factors to having all healthy factors). Due to the low number of individuals with 0-3 healthy lifestyle factors, these participants were combined and the '≤3' group was selected as the reference category. A further model, adjusting for all of the covariates mentioned previously (confounders in Model 1 and Model 2), investigated the associations between the number of healthy lifestyle factors and fluid intelligence. Interaction terms were fitted to test whether these associations were modified by age

(with significant findings stratified at 60 years) or sex. The assumptions of linear regression were assessed (121).

Prospective Analysis

A multiple logistic regression model, adjusting for baseline fluid intelligence and all of the covariates mentioned previously, investigated the associations between the number of healthy lifestyle factors at baseline and a poor outcome at follow-up (i.e. the model estimated the odds of having cognitive decline in fluid intelligence from baseline to follow-up) (Stata command: 'logit') (121). Interaction terms were fitted to test whether these associations were modified by age or sex. The assumptions of logistic regression were assessed (121).

Sensitivity Analysis

To assess the generalizability of the findings, the main cross-sectional and prospective analyses investigating the associations between the number of healthy lifestyle factors and fluid intelligence were repeated across the sample of participants without a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses as sensitivity analyses. Similar to the previous UK Biobank analyses, this was largely executed to assess the confounding effect of participants with a medical history of cancer, CVD, and/or cognitive/psychiatric illnesses on the associations. After eliminating these 'unhealthy' individuals, the remaining sample of 'healthier' participants would potentially provide more robust and unbiased results. The main cross-sectional and prospective analyses investigating the associations between the number of healthy lifestyle factors and fluid intelligence were also repeated across the other cognitive tests (prospective memory, visual-spatial memory, reaction time, and short-term numeric memory) administered in the UK Biobank as sensitivity analyses to establish that the findings for fluid intelligence were consistent across the other cognitive domains. For each of these four tests, the cross-sectional analyses were undertaken within the cohort that also had a measure of fluid intelligence at baseline; whereas the prospective analyses were undertaken within the cohort that had a measure of fluid

intelligence and the cognitive test under consideration at both baseline and follow-up. The models were adjusted for all of the covariates in Model 1 and Model 2. The prospective models were also adjusted for the baseline score/result of the cognitive test under consideration. This was carried out to confirm that the results for fluid intelligence were consistent across the other cognitive domains.

Similar to the previous two analyses, linear (continuous outcome data) and logistic (binary outcome data) regression models were selected after examining all of the key outcomes and exposures used in this study. For more details, see Figure S3 in Appendix Three: Supplementary Material: Supplementary Data.

Statistical Reporting

For each variable of interest, β (linear regression) or OR (logistic regression) with 95% CIs and p-values are reported. All cross-sectional and prospective regression analyses employed robust SEs and all reported p-values are two-sided. For the main effects, p-value<0.05 was considered to be statistically significant. For the interaction effects, p-value<0.10 was considered to be statistically significant.

Results

Cross-Sectional Findings

Table 22 presents the characteristics of the 165,492 participants with baseline fluid intelligence data. The mean (SD) age was 56.7 (8.1) years and 90,190 (54.5%) were female. The mean (SD) fluid intelligence score was 6.0 (2.2).

Table 22 - Observational study (UK Biobank data): Participant characteristics

Demographics and health at baseline	N = 165,492
Age (years) [a]	56.7 (8.1); 39.0 - 70.0
Missing [b]	0 (0.0)
Sex [c]	
Female	90,190 (54.5)
Male	75,302 (45.5)
Missing [b]	0 (0.0)
Ethnicity [c]	
White British	141,511 (85.5)
Other	23,332 (14.1)
Missing [b]	649 (0.4)
Social deprivation index [a]	-1.2 (2.9); -6.3 - 9.9
Missing [b]	272 (0.2)
Employment status [c]	
In paid employment or self-employed	93,023 (56.2)
Not in paid employment or self-employed	71,828 (43.4)
Missing [b]	641 (0.4)
Education level [c]	
College or university degree	56,619 (34.2)
No college or university degree	107,396 (64.9)
Missing [b]	1,477 (0.9)
Number of cancers [c]	
0	150,498 (90.9)
≥1	14,885 (9.0)
Missing [b]	109 (0.1)
Number of non-cancer illnesses [c]	
0	38,258 (23.1)
1	41,915 (25.3)
2	32,441 (19.6)
3	21,951 (13.3)
≥4	30,818 (18.6)
Missing [b]	109 (0.1)
Number of medications/treatments [c]	
0	49,118 (29.7)
1	32,276 (19.5)
2	25,513 (15.4)
3	18,368 (11.1)
4	13,267 (8.0)

5	9,070 (5.5)
≥6	17,771 (10.7)
Missing [b]	109 (0.1)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [c]	
No	132,635 (80.1)
Yes	32,857 (19.9)
Missing [b]	0 (0.0)
Lifestyle factors at baseline	
Body mass index [c]	
Obese	40,187 (24.3)
Non-obese	124,244 (75.1)
Missing [b]	1,061 (0.6)
Diet [c]	
Unhealthy diet	55,138 (33.3)
Healthy diet	106,905 (64.6)
Missing [b]	3,449 (2.1)
Physical activity [c]	
Physically inactive	52,440 (31.7)
Physically active	104,612 (63.2)
Missing [b]	8,440 (5.1)
Smoking status [c]	
Smoker	16,469 (10.0)
Non-smoker	148,470 (89.7)
Missing [b]	553 (0.3)
Sleep duration [c]	
Unhealthy duration	53,769 (32.5)
Healthy duration	110,879 (67.0)
Missing [b]	844 (0.5)
Handgrip strength [c]	
Low	58,579 (35.4)
High	105,385 (63.7)
Missing [b]	1,528 (0.9)
Walking pace [c]	
Slow pace	12,594 (7.6)
Steady average or brisk pace	151,937 (91.8)
Missing [b]	961 (0.6)

TV viewing time [c]	
High	85,939 (51.9)
Low	78,363 (47.4)
Missing [b]	1,190 (0.7)
Driving time [c]	
High	74,293 (44.9)
Low	88,605 (53.5)
Missing [b]	2,594 (1.6)
Computer use time [c]	
Low	70,829 (42.8)
High	93,456 (56.5)
Missing [b]	1,207 (0.7)
Number of healthy lifestyle factors [c]	
≤3	6,956 (4.2)
4	14,054 (8.5)
5	27,017 (16.3)
6	37,640 (22.7)
7	35,986 (21.8)
8	21,124 (12.8)
9	5,813 (3.5)
Missing [b]	16,902 (10.2)
Cognitive function at baseline	
Fluid intelligence [a]	
Fluid intelligence score	
Total number of correct answers	6.0 (2.2); 0.0 - 13.0
Missing [b]	0 (0.0)
Prospective memory [c]	
Prospective memory result	
Good result (correct recall on first attempt)	127,474 (77.0)
Poor result (incorrect recall on first attempt)	38,018 (23.0)
Missing [b]	0 (0.0)
Visual-spatial memory (round 1) [c]	
Pairs matching result	
Good result (<1 incorrect matches)	120,574 (72.9)
Poor result (≥1 incorrect matches)	44,051 (26.6)
Missing [b]	867 (0.5)
Visual-spatial memory (round 2) [c]	
Pairs matching result	
Good result (<2 incorrect matches)	29,622 (17.9)
Poor result (≥2 incorrect matches)	134,914 (81.5)

Missing [b]	956 (0.6)	
Reaction time [a]		
Reaction time Mean time taken to correctly identify matches (milliseconds)	567.4 (122.1); 78.0 - 1921.0	
Missing [b]	807 (0.5)	
Short-term numeric memory [a]		
Numeric memory score Maximum digits remembered	6.7 (1.3); 2.0 - 12.0	
Missing [b]	116,604 (70.5)	
Cognitive function at follow-up [d]	N = 46,704 [d]	
	Baseline	Follow-up
Fluid intelligence (n = 46,704) [a]		
Fluid intelligence score Total number of correct answers	6.7 (2.1); 0.0 - 13.0	5.5 (2.0); 0.0 - 13.0
Missing [b]	0 (0.0)	0 (0.0)
Good outcome at follow-up		15,384 (32.9)
Poor outcome at follow-up		31,320 (67.1)
Visual-spatial memory (round 1) (n = 43,201) [c]		
Pairs matching result		
Good result (<1 incorrect matches)	33,996 (72.8)	26,753 (57.3)
Poor result (≥1 incorrect matches)	9,205 (19.7)	16,448 (35.2)
Missing [b]	3,503 (7.5)	3,503 (7.5)
Good outcome at follow-up		26,753 (57.3)
Poor outcome at follow-up		16,448 (35.2)
Visual-spatial memory (round 2) (n = 42,920) [c]		
Pairs matching result		
Good result (<2 incorrect matches)	9,153 (19.6)	5,740 (12.3)
Poor result (≥2 incorrect matches)	33,767 (72.3)	37,180 (79.6)
Missing [b]	3,784 (8.1)	3,784 (8.1)
Good outcome at follow-up		5,740 (12.3)
Poor outcome at follow-up		37,180 (79.6)
Short-term numeric memory (n = 11,895) [a]		
Numeric memory score Maximum digits remembered	7.0 (1.2); 2.0 - 12.0	6.9 (1.5); 2.0 - 11.0
Missing [b]	34,809 (74.5)	34,809 (74.5)
Good outcome at follow-up		7,665 (16.4)

Poor outcome at follow-up	4,230 (9.1)

[a] *Continuous variable: mean (standard deviation); minimum - maximum*
[b] *Number (%)*
[c] *Categorical variable: number (%)*
[d] *Participants with fluid intelligence data at both baseline and follow-up*

Table 23 presents the associations between each lifestyle factor and fluid intelligence. In Model 1 (adjusted for age and sex), each lifestyle factor was individually and positively associated with fluid intelligence. In Model 2 (further adjusted for other demographics and health variables), the associations between each lifestyle factor (except for BMI) and fluid intelligence maintained direction and significance. Model assumptions were satisfied.

Table 23 - Observational study (UK Biobank data): Cross-sectional associations at baseline between each lifestyle factor and fluid intelligence

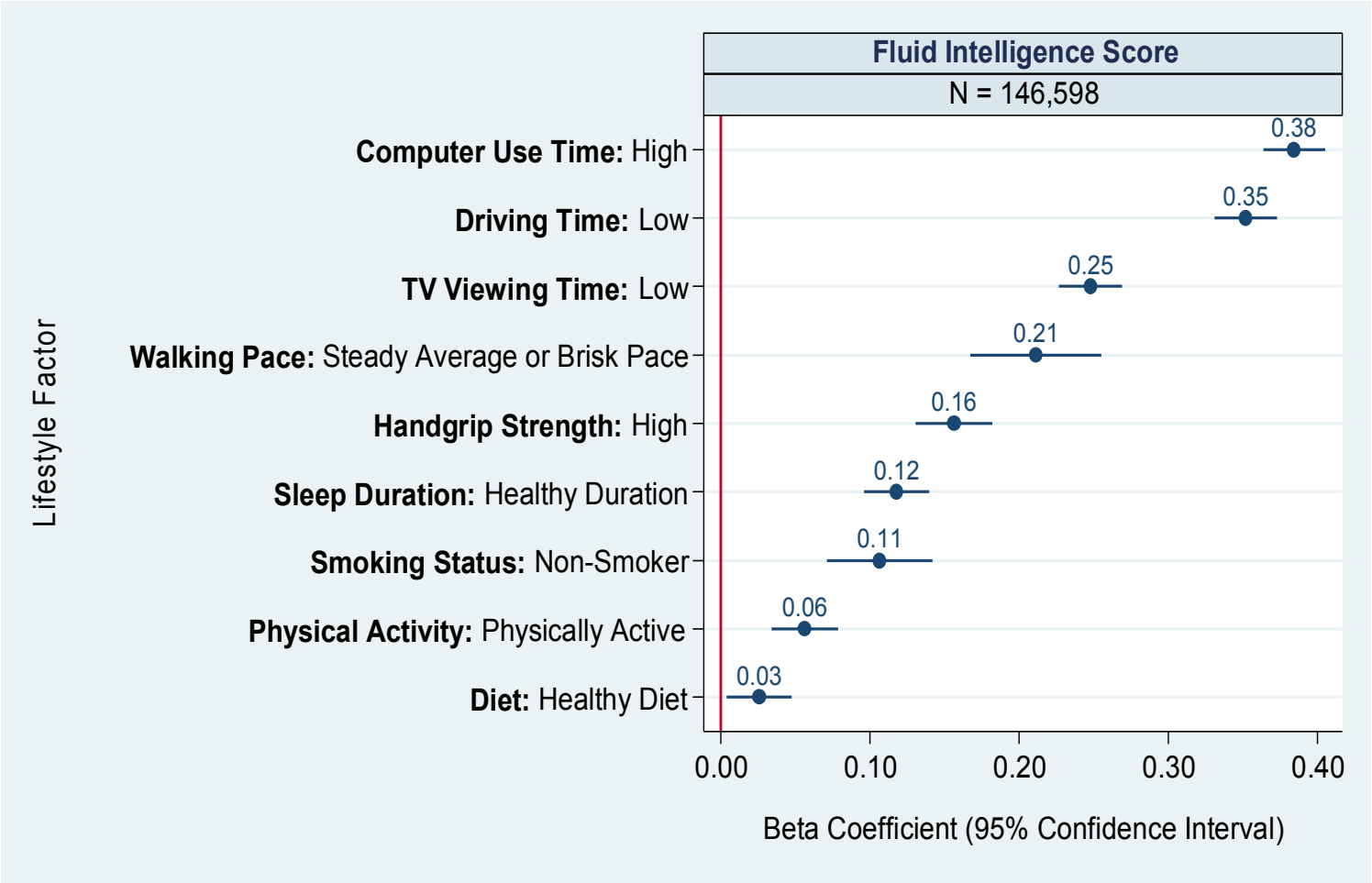
Lifestyle factor	Healthy behaviour	Model [a]	Fluid intelligence score (total number of correct answers) [b]	
			Number of observations	β (95% CI); p-value
Body mass index	Non-obese	1	164,431	**0.23 (0.21, 0.26); p-value<0.001**
		2	161,691	-0.00 (-0.03, 0.02); p-value = 0.702
Diet	Healthy diet	1	162,043	**0.27 (0.25, 0.29); p-value<0.001**
		2	159,398	**0.09 (0.07, 0.11); p-value<0.001**
Physical activity	Physically active	1	157,052	**0.40 (0.38, 0.43); p-value<0.001**
		2	154,470	**0.13 (0.11, 0.15); p-value<0.001**
Smoking status	Non-smoker	1	164,939	**0.50 (0.46, 0.53); p-value<0.001**
		2	162,118	**0.18 (0.15, 0.21); p-value<0.001**
Sleep duration	Healthy duration	1	164,648	**0.36 (0.34, 0.38); p-value<0.001**
		2	161,846	**0.16 (0.14, 0.18); p-value<0.001**
Handgrip strength	High	1	163,964	**0.42 (0.39, 0.45); p-value<0.001**
		2	161,226	**0.21 (0.18, 0.23); p-value<0.001**
Walking pace	Steady average or brisk pace	1	164,531	**0.80 (0.76, 0.84); p-value<0.001**
		2	161,711	**0.35 (0.31, 0.39); p-value<0.001**
TV viewing time	Low	1	164,302	**0.62 (0.60, 0.64); p-value<0.001**
		2	161,550	**0.29 (0.27, 0.31); p-value<0.001**

Driving time	Low	1	162,898	**0.28 (0.26, 0.30); p-value<0.001**
		2	160,256	**0.32 (0.30, 0.34); p-value<0.001**
Computer use time	High	1	164,285	**0.53 (0.51, 0.55); p-value<0.001**
		2	161,525	**0.38 (0.36, 0.40); p-value<0.001**

[a] Model 1 adjusted for: age and sex. Model 2 further adjusted for: ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments.
[b] Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Figure 19 presents the associations between the lifestyle factors and fluid intelligence after mutual adjustment (Model 3). The associations maintained direction and significance. Model assumptions were satisfied.

Figure 19 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the lifestyle factors and fluid intelligence

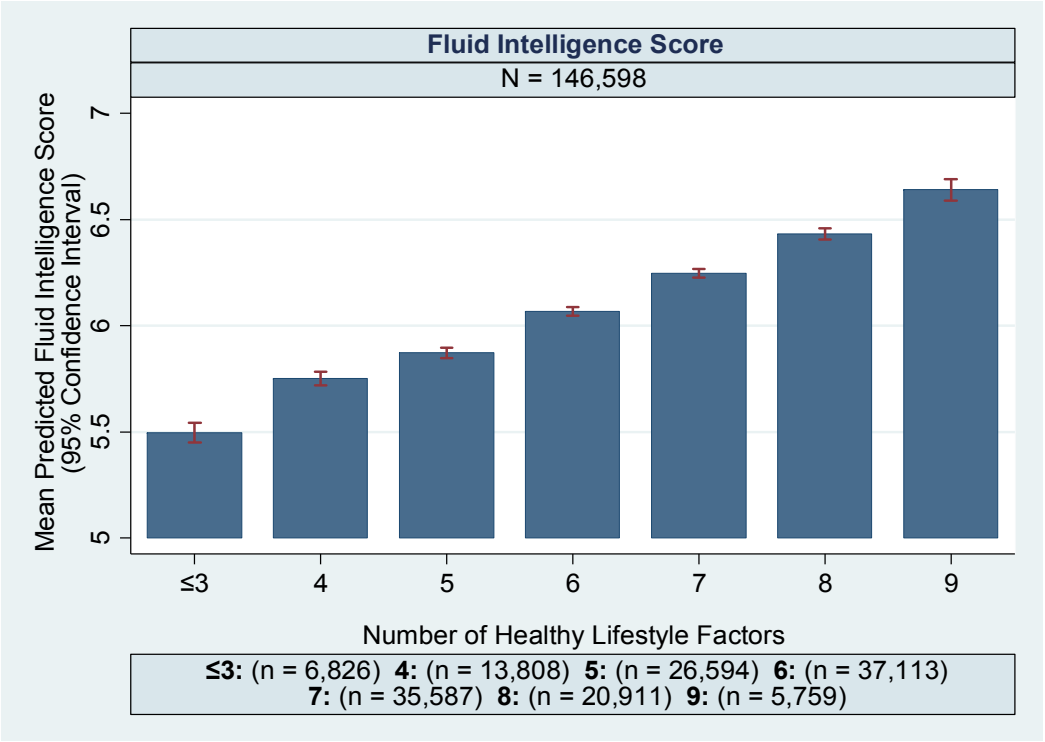


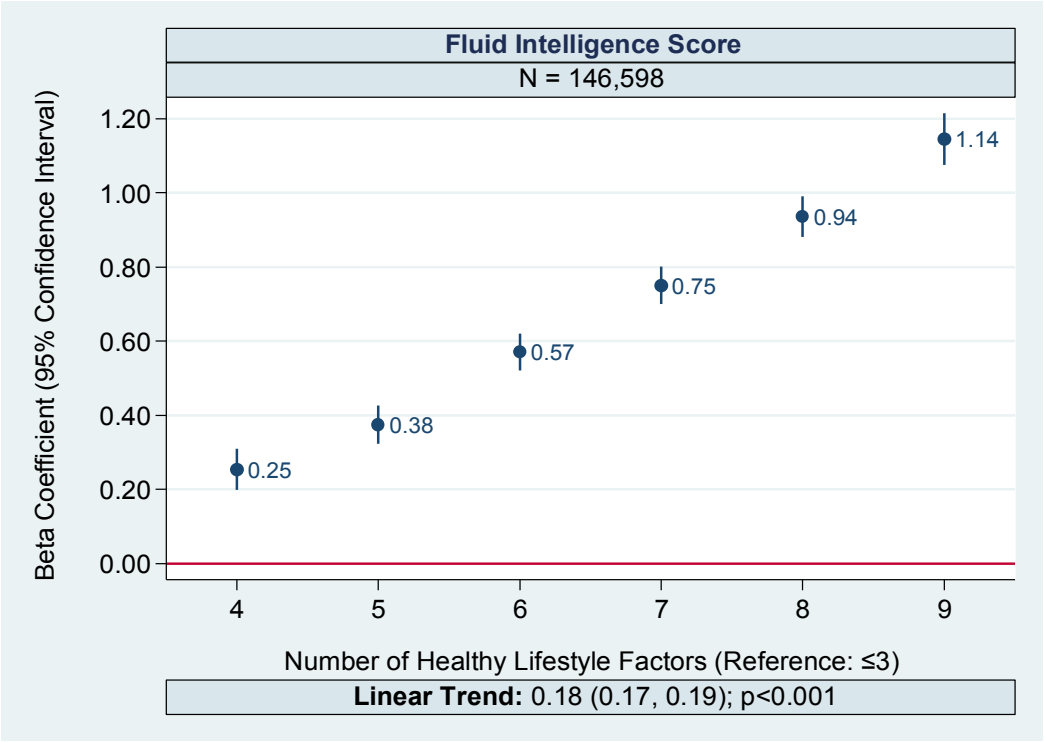
Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Model 3 mutually adjusted for the other lifestyle factors (excluding body mass index) and the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 20 presents the associations between the number of healthy lifestyle factors and fluid intelligence. The number of healthy lifestyle factors was positively associated with fluid intelligence [β: 0.18 (0.17, 0.19); p-value<0.001]; such that for each additional lifestyle factor >3, the total number of correct answers was 0.18 higher. Model assumptions were satisfied.

Figure 20 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence



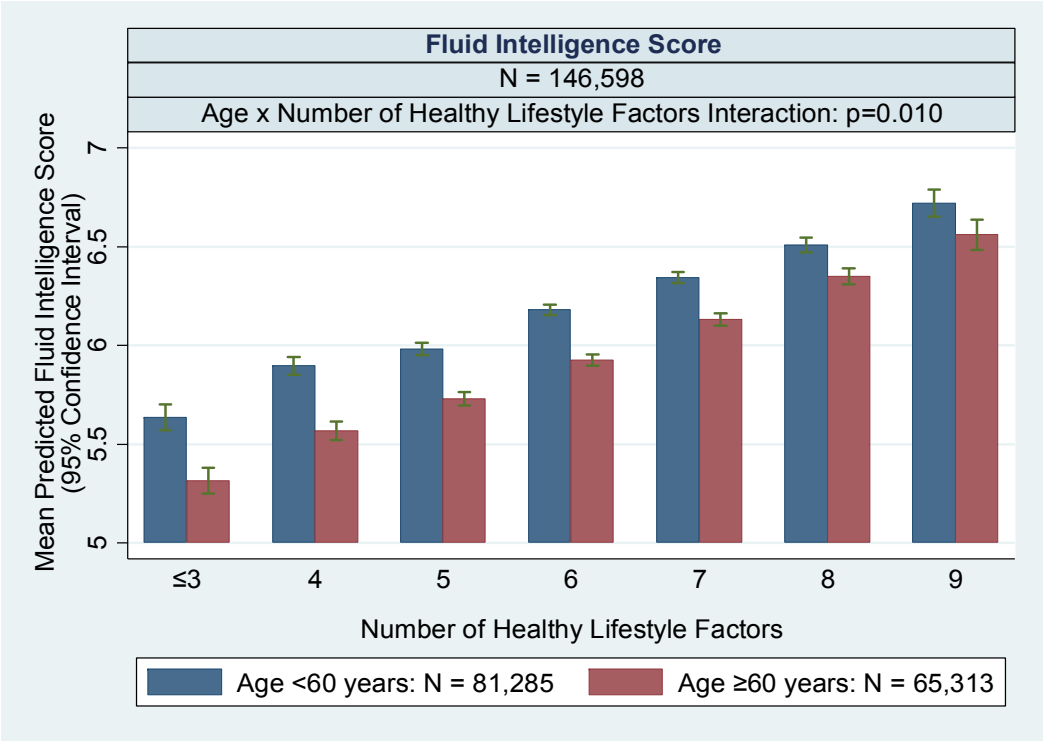


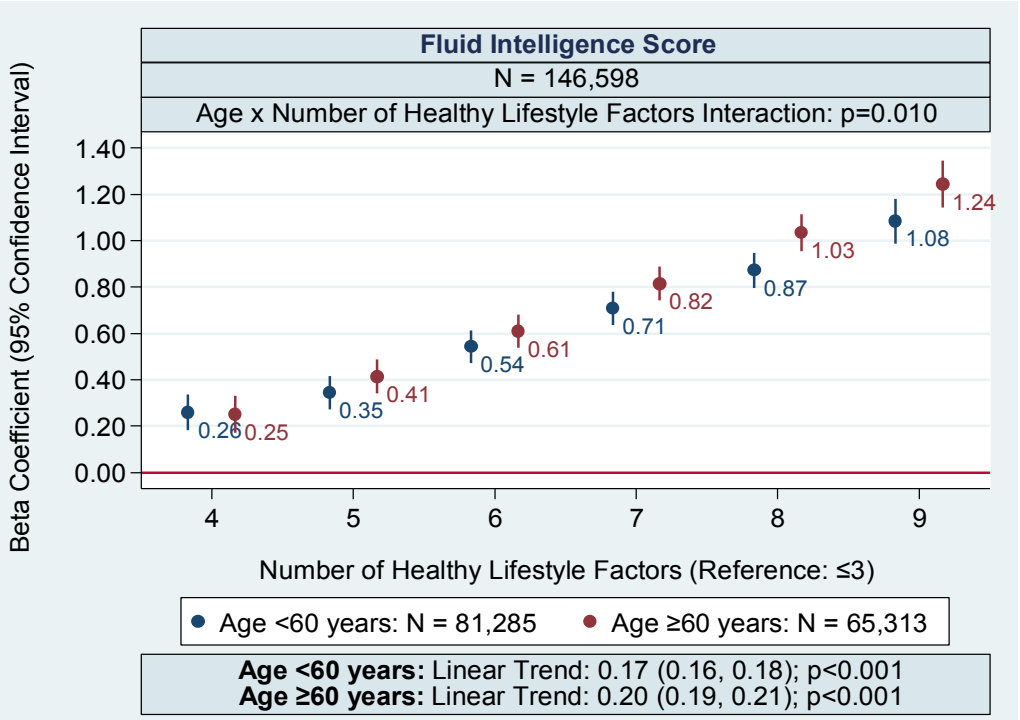
Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

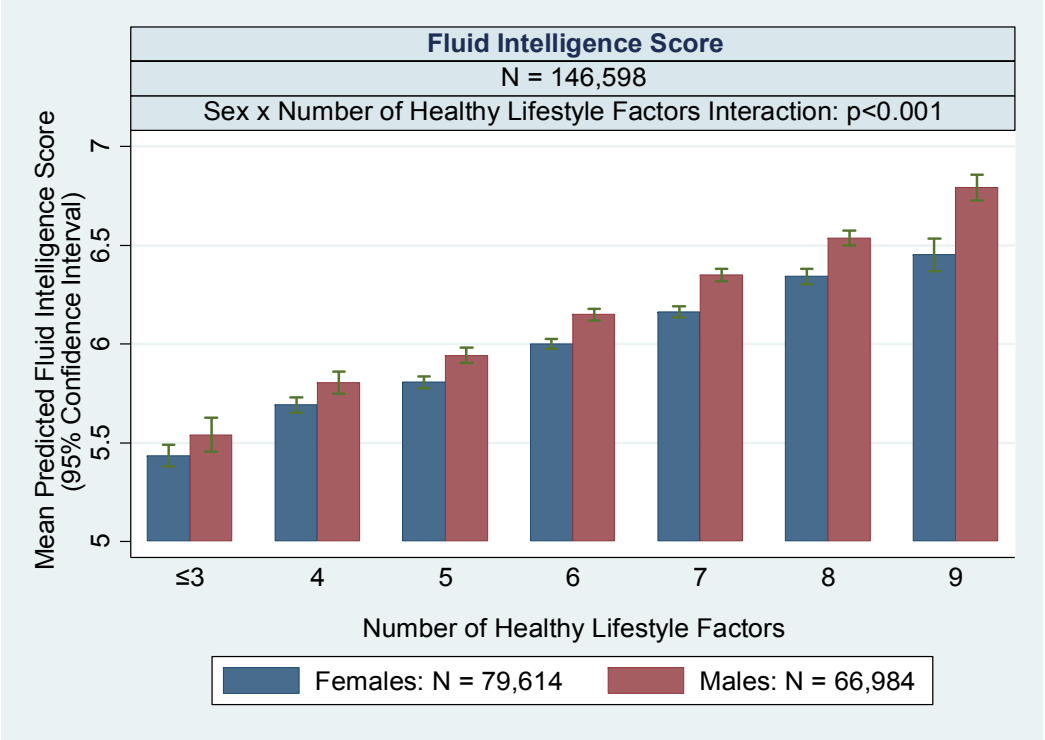
Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

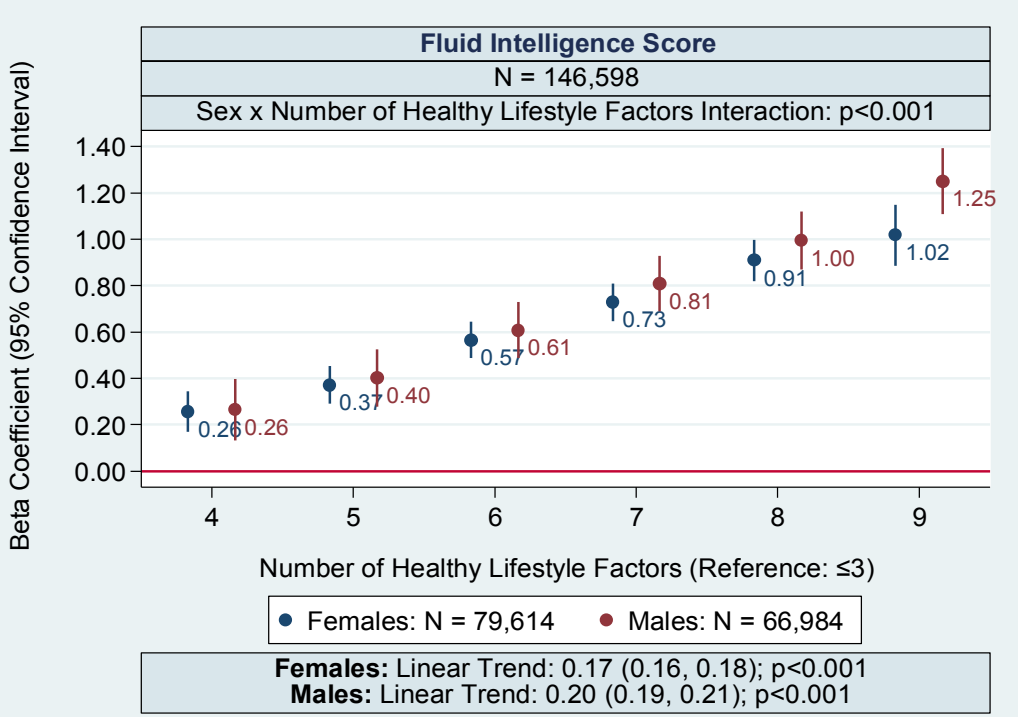
The associations between the number of healthy lifestyle factors and fluid intelligence were modified by age (p-value=0.010) and sex (p-value<0.001), with stronger relationships observed in older adults and in males (see Figure 21). Model assumptions were satisfied.

Figure 21 - Observational study (UK Biobank data): Interactions by age and sex: cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence









Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Age stratified models adjusted for the following variables: sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Sex stratified models adjusted for the following variables: age, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.10 for the interaction terms. Statistical significance was established at p-value<0.05 in the stratified models.

Prospective Findings

Table 22 also presents the follow-up cognitive function data of the 46,704 participants with both baseline and follow-up fluid intelligence data. Cognitive decline was apparent since the fluid intelligence score decreased from baseline to follow-up. The mean (SD) fluid intelligence scores at baseline and follow-up were 6.7 (2.1) and 5.5 (2.0), respectively; with 15,384 (32.9%) individuals recording a good outcome (baseline fluid intelligence score ≤ follow-up fluid intelligence score) at follow-up and 31,320 (67.1) individuals recording a poor outcome (baseline fluid intelligence score > follow-up fluid intelligence score) at follow-up.

The characteristics between those who only provided fluid intelligence data at baseline and those who provided fluid intelligence data at both baseline and follow-up were relatively comparable (see Table 24); however, participants with follow-up data were less socially deprived, better educated, more likely to be employed, and generally healthier.

Table 24 - Observational study (UK Biobank data): Comparing the characteristics of the participants with fluid intelligence data at baseline only against those with fluid intelligence data at both baseline and follow-up

Demographics and health	Sample	Fluid intelligence at baseline only	Fluid intelligence at both baseline and follow-up
	N = 165,492	N = 118,788	N = 46,704
Age (years) [a]	56.7 (8.1); 39.0 - 70.0	56.7 (8.3); 39.0 - 70.0	56.6 (7.8); 40.0 - 70.0
Missing [b]	0 (0.0)	0 (0.0)	0 (0.0)
Sex [c]			
Female	90,190 (54.5)	63,937 (53.8)	26,253 (56.2)
Male	75,302 (45.5)	54,851 (46.2)	20,451 (43.8)
Missing [b]	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity [c]			
White British	141,511 (85.5)	100,230 (84.4)	41,281 (88.4)
Other	23,332 (14.1)	18,078 (15.2)	5,254 (11.2)
Missing [b]	649 (0.4)	480 (0.4)	169 (0.4)
Social deprivation index [a]	-1.2 (2.9); -6.3 - 9.9	-1.1 (3.0); -6.3 - 9.9	-1.5 (2.7); -6.3 - 9.9
Missing [b]	272 (0.2)	205 (0.2)	67 (0.1)
Employment status [c]			
In paid employment or self-employed	93,023 (56.2)	65,501 (55.1)	27,522 (58.9)
Not in paid employment or self-employed	71,828 (43.4)	52,737 (44.4)	19,091 (40.9)
Missing [b]	641 (0.4)	550 (0.5)	91 (0.2)
Education level [c]			
College or university degree	56,619 (34.2)	35,311 (29.7)	21,308 (45.6)
No college or university degree	107,396 (64.9)	82,152 (69.2)	25,244 (54.1)
Missing [b]	1,477 (0.9)	1,325 (1.1)	152 (0.3)
Number of cancers [c]			
0	150,498 (90.9)	107,840 (90.8)	42,658 (91.3)
≥1	14,885 (9.0)	10,845 (9.1)	4,040 (8.7)
Missing [b]	109 (0.1)	103 (0.1)	6 (0.0)
Number of non-cancer illnesses [c]			
0	38,258 (23.1)	26,767 (22.5)	11,491 (24.6)
1	41,915 (25.3)	29,580 (24.9)	12,335 (26.4)
2	32,441 (19.6)	23,367 (19.7)	9,074 (19.4)
3	21,951 (13.3)	16,033 (13.5)	5,918 (12.7)
≥4	30,818 (18.6)	22,938 (19.3)	7,880 (16.9)
Missing [b]	109 (0.1)	103 (0.1)	6 (0.0)

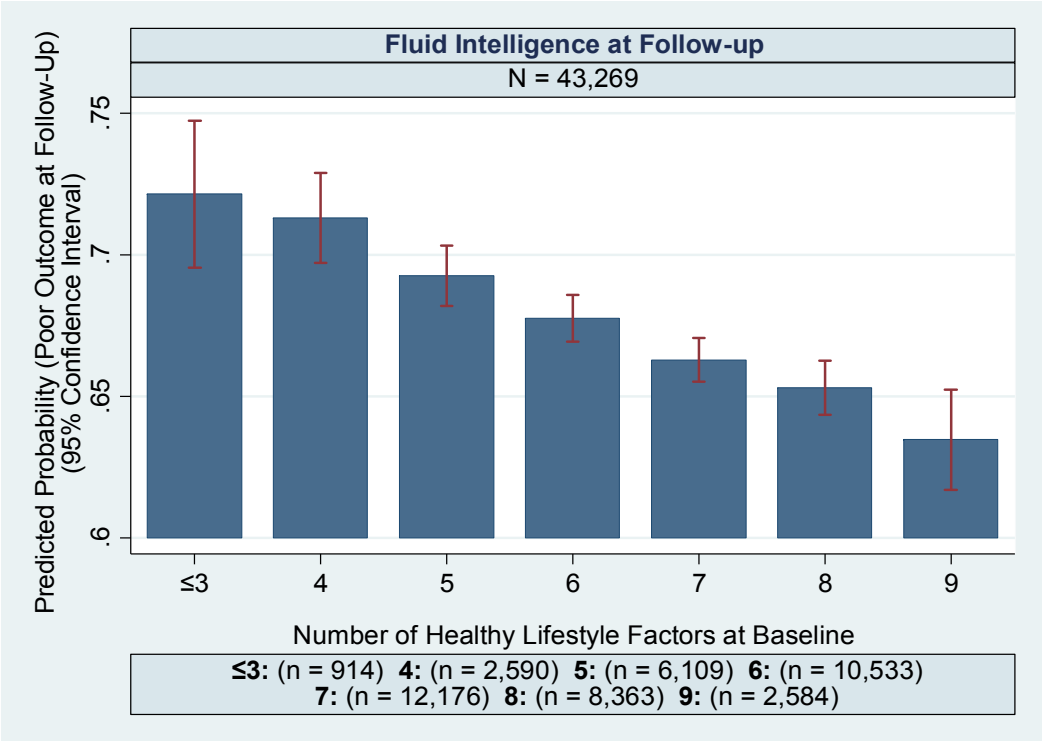
Number of medications/treatments [c]			
0	49,118 (29.7)	34,053 (28.7)	15,065 (32.3)
1	32,276 (19.5)	22,781 (19.2)	9,495 (20.3)
2	25,513 (15.4)	18,130 (15.3)	7,383 (15.8)
3	18,368 (11.1)	13,303 (11.2)	5,065 (10.8)
4	13,267 (8.0)	9,814 (8.3)	3,453 (7.4)
5	9,070 (5.5)	6,729 (5.7)	2,341 (5.0)
≥6	17,771 (10.7)	13,875 (11.7)	3,896 (8.3)
Missing [b]	109 (0.1)	103 (0.1)	6 (0.0)
Medical history of cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses [c]			
No	132,635 (80.1)	94,238 (79.3)	38,397 (82.2)
Yes	32,857 (19.9)	24,550 (20.7)	8,307 (17.8)
Missing [b]	0 (0.0)	0 (0.0)	0 (0.0)
Lifestyle factors			
Body mass index [c]			
Obese	40,187 (24.3)	30,647 (25.8)	9,540 (20.4)
Non-obese	124,244 (75.1)	87,231 (73.4)	37,013 (79.3)
Missing [b]	1,061 (0.6)	910 (0.8)	151 (0.3)
Diet [c]			
Unhealthy diet	55,138 (33.3)	41,395 (34.8)	13,743 (29.4)
Healthy diet	106,905 (64.6)	74,459 (62.7)	32,446 (69.5)
Missing [b]	3,449 (2.1)	2,934 (2.5)	515 (1.1)
Physical activity [c]			
Physically inactive	52,440 (31.7)	39,520 (33.3)	12,920 (27.7)
Physically active	104,612 (63.2)	72,507 (61.0)	32,105 (68.7)
Missing [b]	8,440 (5.1)	6,761 (5.7)	1,679 (3.6)
Smoking status [c]			
Smoker	16,469 (10.0)	13,140 (11.1)	3,329 (7.1)
Non-smoker	148,470 (89.7)	105,187 (88.5)	43,283 (92.7)
Missing [b]	553 (0.3)	461 (0.4)	92 (0.2)
Sleep duration [c]			
Unhealthy duration	53,769 (32.5)	40,291 (33.9)	13,478 (28.9)
Healthy duration	110,879 (67.0)	77,757 (65.5)	33,122 (70.9)
Missing [b]	844 (0.5)	740 (0.6)	104 (0.2)
Handgrip strength [c]			
Low	58,579 (35.4)	43,013 (36.2)	15,566 (33.3)
High	105,385 (63.7)	74,527 (62.7)	30,858 (66.1)

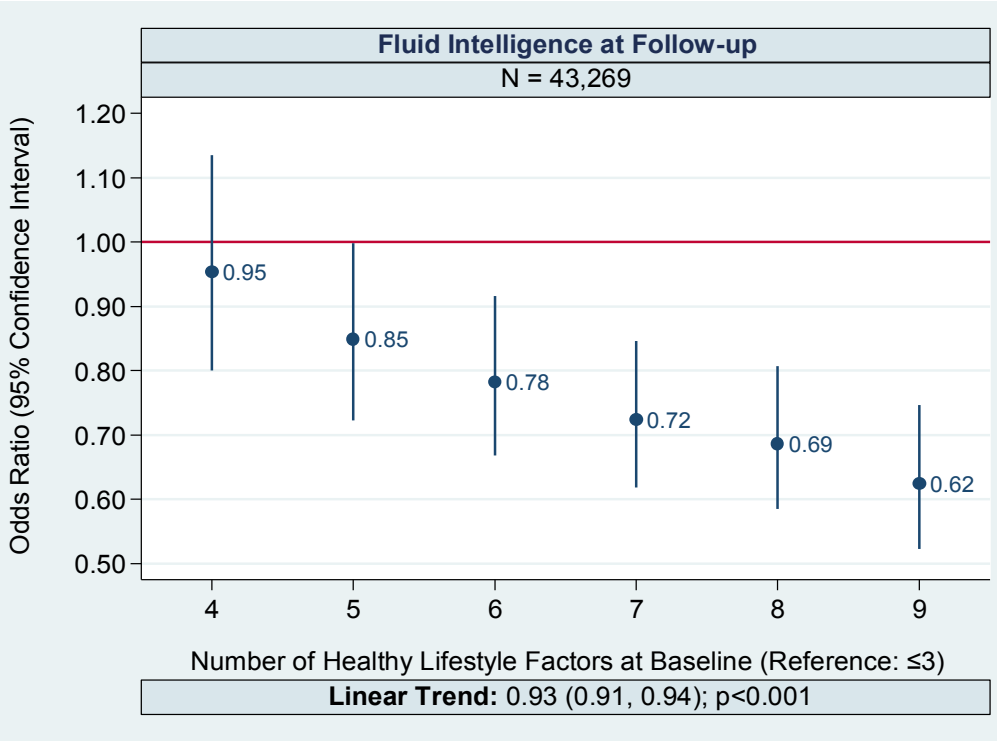
Missing [b]	1,528 (0.9)	1,248 (1.1)	280 (0.6)
Walking pace [c]			
Slow pace	12,594 (7.6)	10,308 (8.7)	2,286 (4.9)
Steady average or brisk pace	151,937 (91.8)	107,648 (90.6)	44,289 (94.8)
Missing [b]	961 (0.6)	832 (0.7)	129 (0.3)
TV viewing time [c]			
High	85,939 (51.9)	64,840 (54.6)	21,099 (45.2)
Low	78,363 (47.4)	52,905 (44.5)	25,458 (54.5)
Missing [b]	1,190 (0.7)	1,043 (0.9)	147 (0.3)
Driving time [c]			
High	74,293 (44.9)	55,132 (46.4)	19,161 (41.0)
Low	88,605 (53.5)	61,427 (51.7)	27,178 (58.2)
Missing	2,594 (1.6)	2,229 (1.9)	365 (0.8)
Computer use time [c]			
Low	70,829 (42.8)	55,983 (47.1)	14,846 (31.8)
High	93,456 (56.5)	61,710 (52.0)	31,746 (68.0)
Missing [b]	1,207 (0.7)	1,095 (0.9)	112 (0.2)
Number of healthy lifestyle factors [c]			
≤3	6,956 (4.2)	6,031 (5.1)	925 (2.0)
4	14,054 (8.5)	11,437 (9.6)	2,617 (5.6)
5	27,017 (16.3)	20,839 (17.5)	6,178 (13.2)
6	37,640 (22.7)	27,011 (22.7)	10,629 (22.8)
7	35,986 (21.8)	23,713 (20.0)	12,273 (26.3)
8	21,124 (12.8)	12,696 (10.7)	8,428 (18.0)
9	5,813 (3.5)	3,205 (2.7)	2,608 (5.6)
Missing [b]	16,902 (10.2)	13,856 (11.7)	3,046 (6.5)

[a] *Continuous variable: mean (standard deviation); minimum - maximum*
[b] *Number (%)*
[c] *Categorical variable: number (%)*

Figure 22 presents the associations between the number of healthy lifestyle factors at baseline and fluid intelligence at follow-up. The number of healthy lifestyle factors at baseline was inversely associated with the odds of having a poor outcome at follow-up [OR: 0.93 (0.91, 0.94); p-value<0.001]; such that for each additional lifestyle factor >3 at baseline, the odds of a poor outcome at follow-up were 7% lower. The associations between the number of healthy lifestyle factors and fluid intelligence were not modified by age (p-value=0.360) or sex (p-value=0.893). Model assumptions were satisfied.

Figure 22 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and fluid intelligence at follow-up





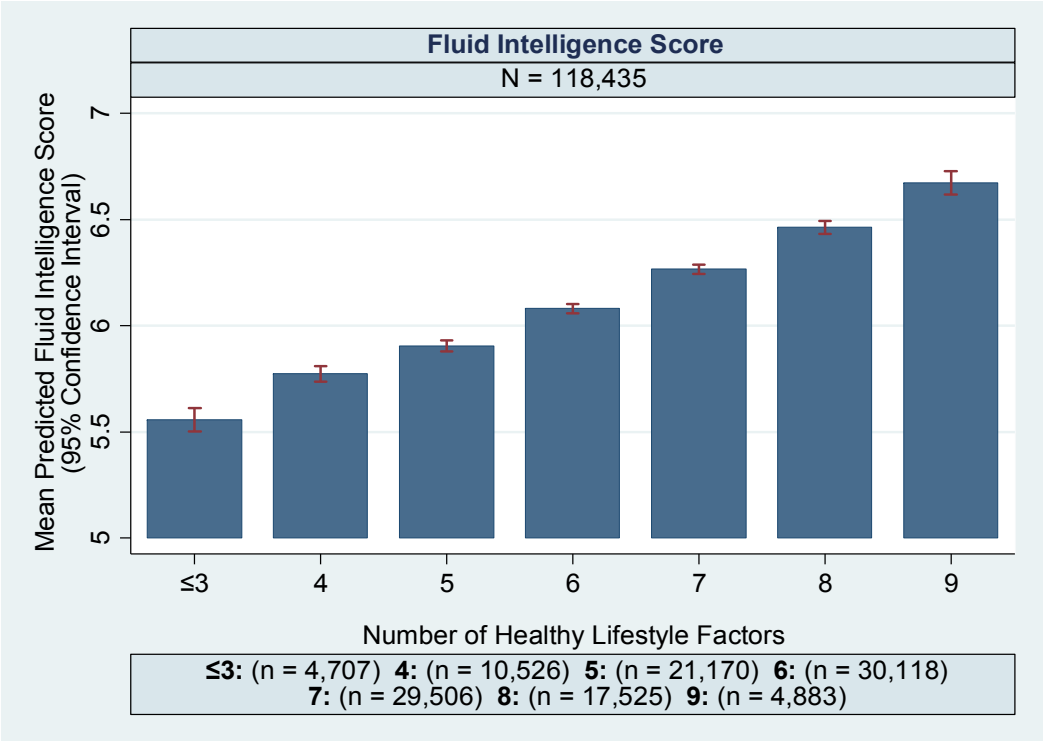
Fluid intelligence: categorical binary (good outcome at follow-up [(reference) baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score]). An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

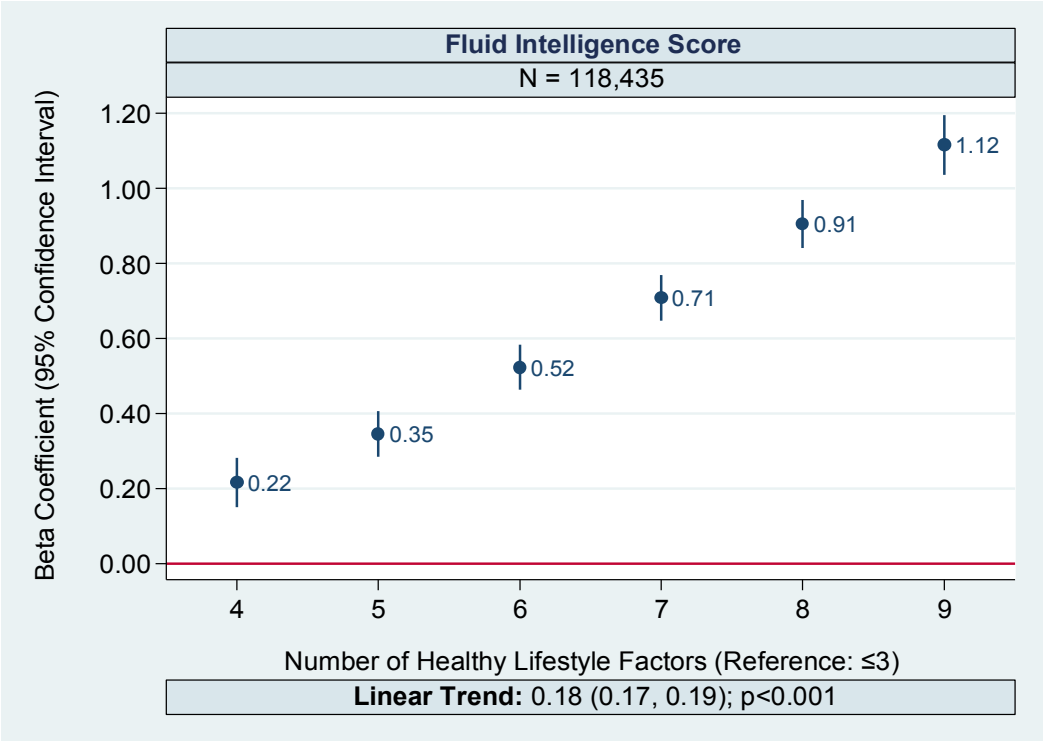
Model adjusted for the following variables: baseline fluid intelligence score, age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Sensitivity Analysis

The main cross-sectional and prospective findings were generalizable across the sample of participants without cancer, CVD, and/or cognitive/psychiatric illnesses (suggesting that the inclusion of these individuals in the main analyses was having minimal confounding impact), and across the other cognitive tests (suggesting that the findings for fluid intelligence were consistent across the other cognitive domains). For more details on the cross-sectional findings, see Figures 23 - 28. For more details on the prospective findings, see Figures 29 - 32.

Figure 23 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses)

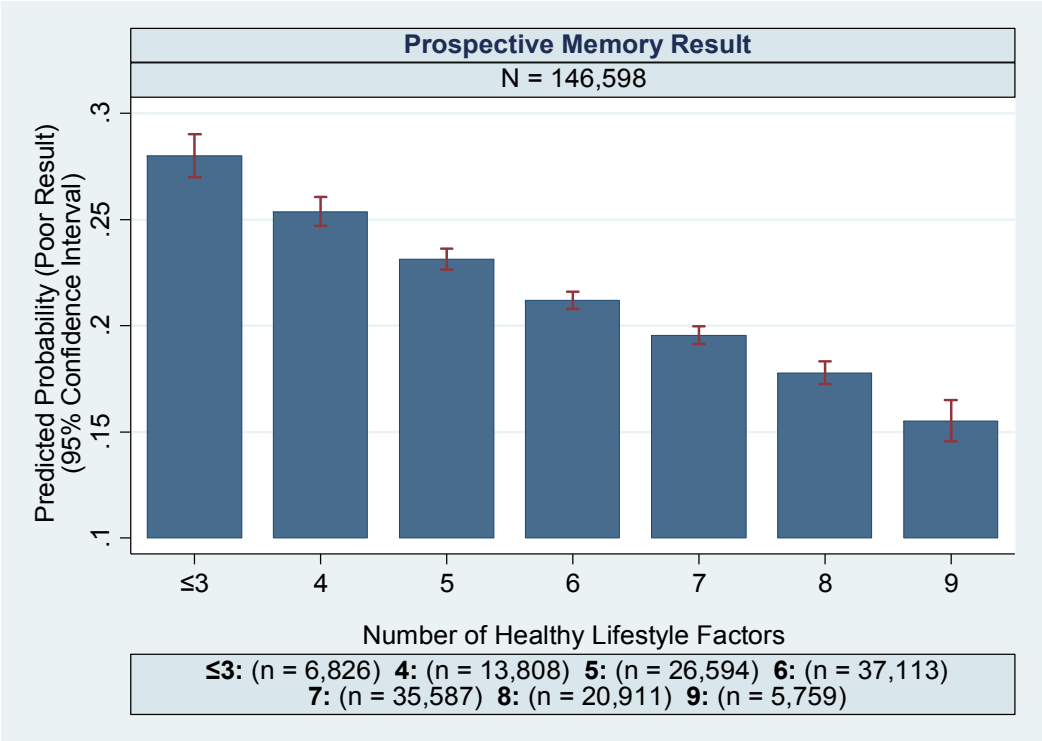


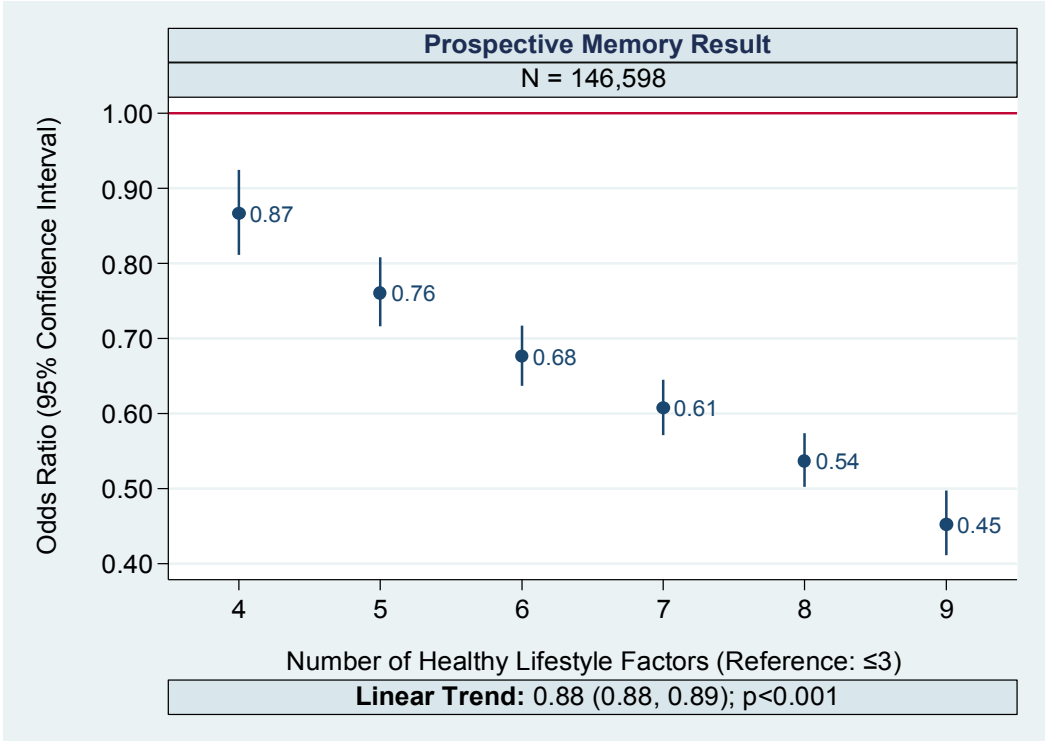


Fluid intelligence score: continuous (total number of correct answers). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 24 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and prospective memory

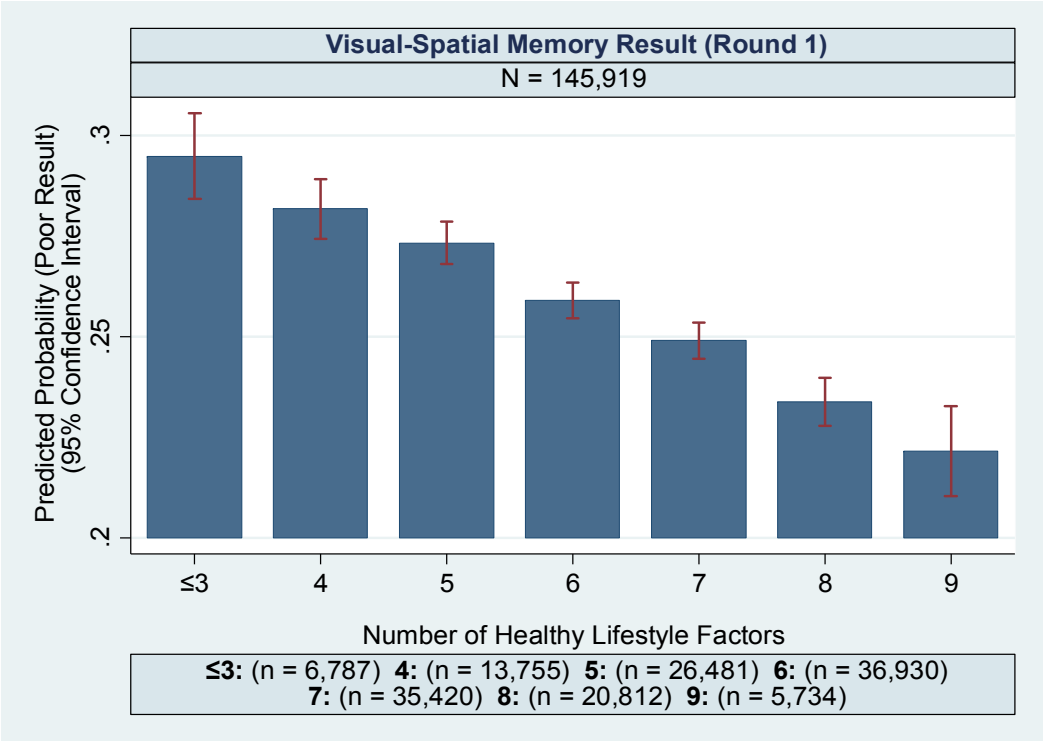


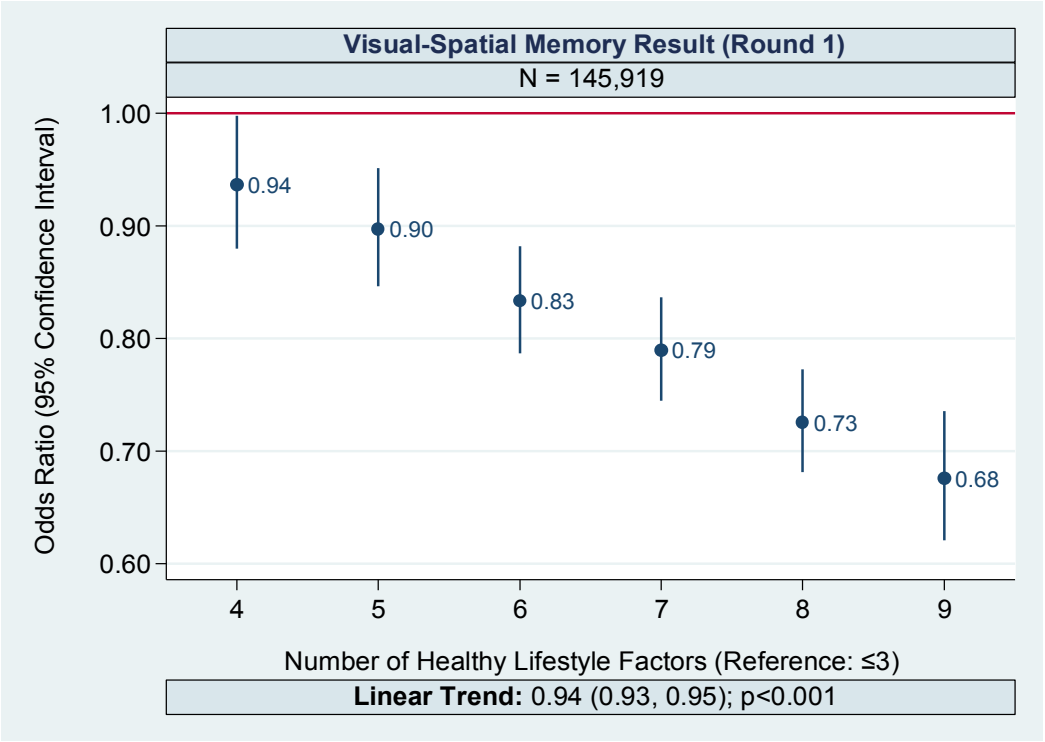


Prospective memory result: categorical binary (good result [(reference) correct recall on first attempt]; or poor result [incorrect recall on first attempt (i.e. correct recall on second attempt, instruction not recalled, skipped or incorrect)]). An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 25 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and visual-spatial memory (pairs matching - round 1)

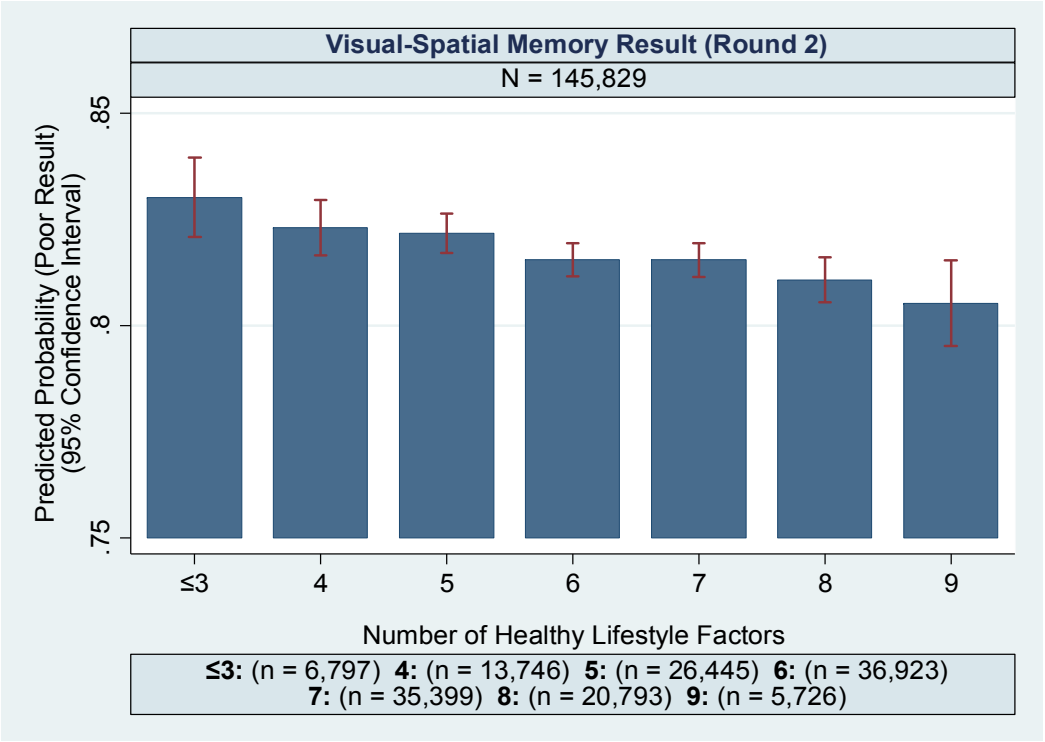


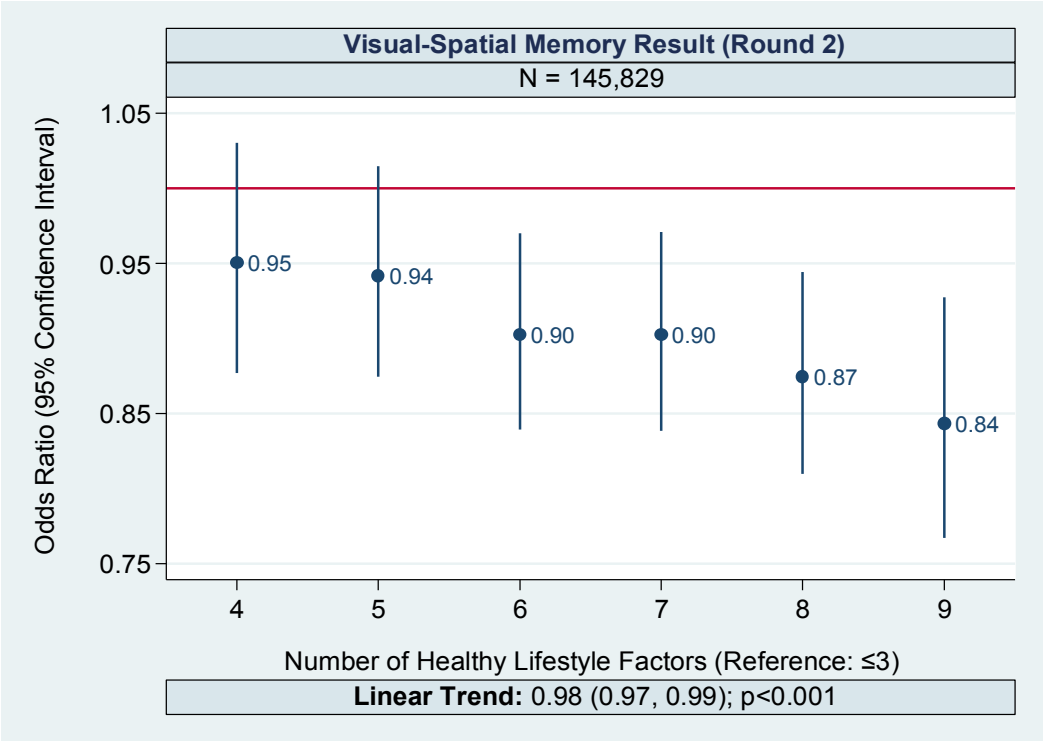


Pairs matching result: categorical binary (good result [(reference) <1 incorrect matches]; or poor result [≥1 incorrect matches]). An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 26 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and visual-spatial memory (pairs matching - round 2)

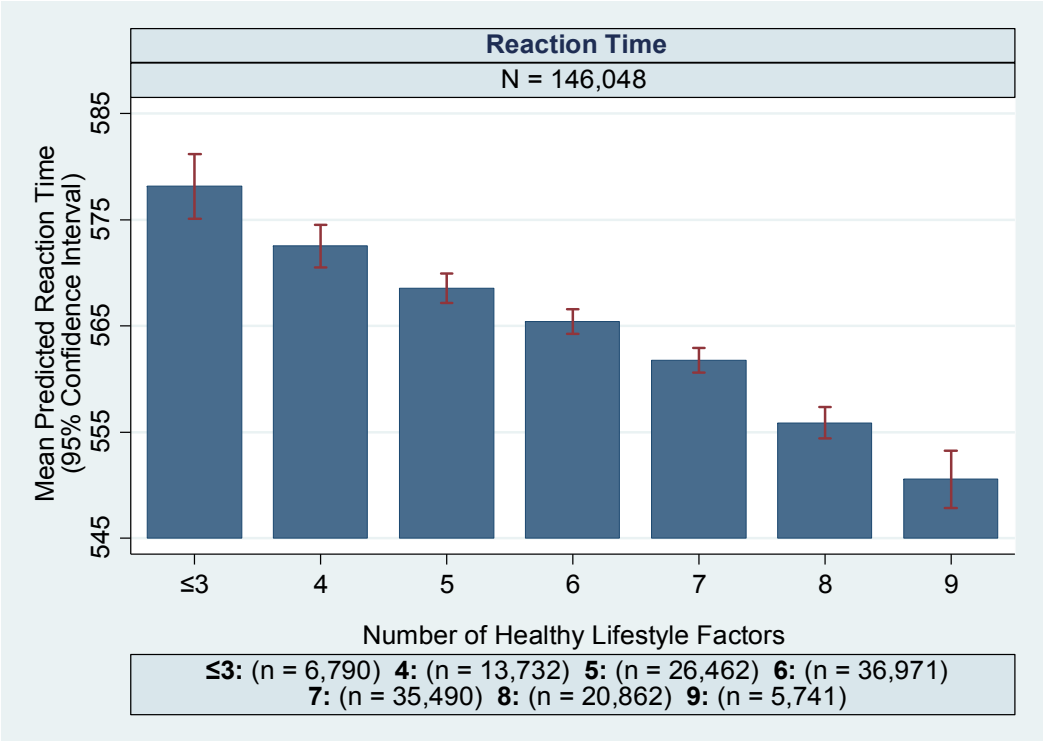


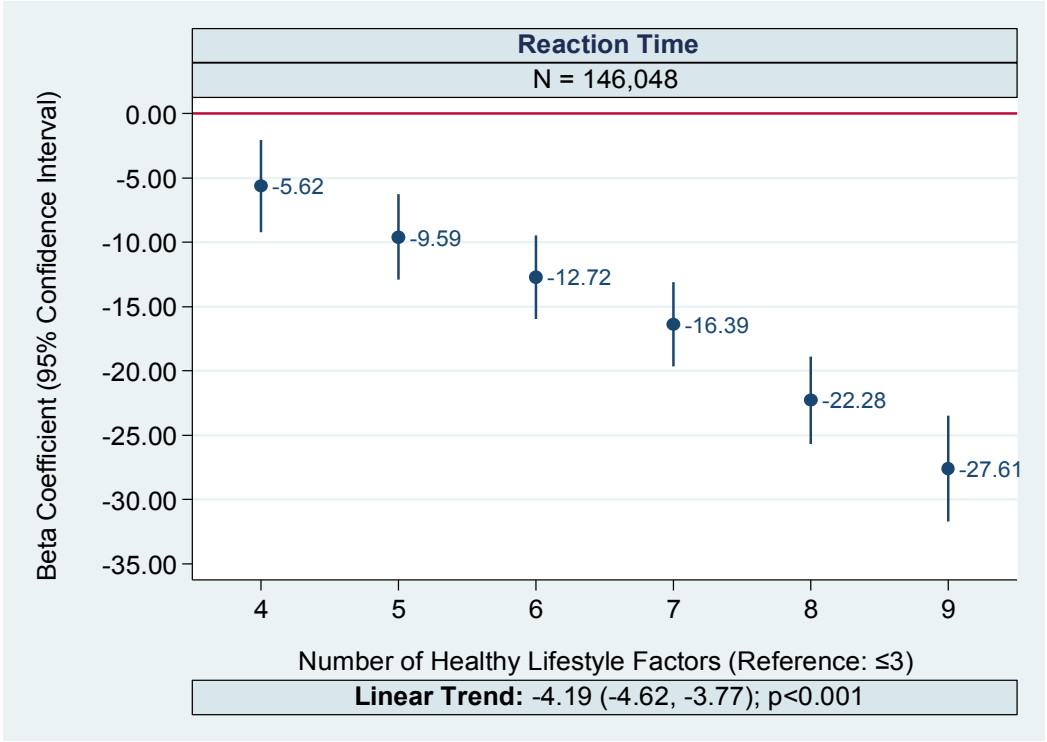


Pairs matching result: categorical binary (good result [(reference) <2 incorrect matches]; or poor result [≥2 incorrect matches]). An odds ratio of less than 1 indicates lower odds of a poor result; and an odds ratio of greater than 1 indicates higher odds of a poor result.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 27 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and reaction time

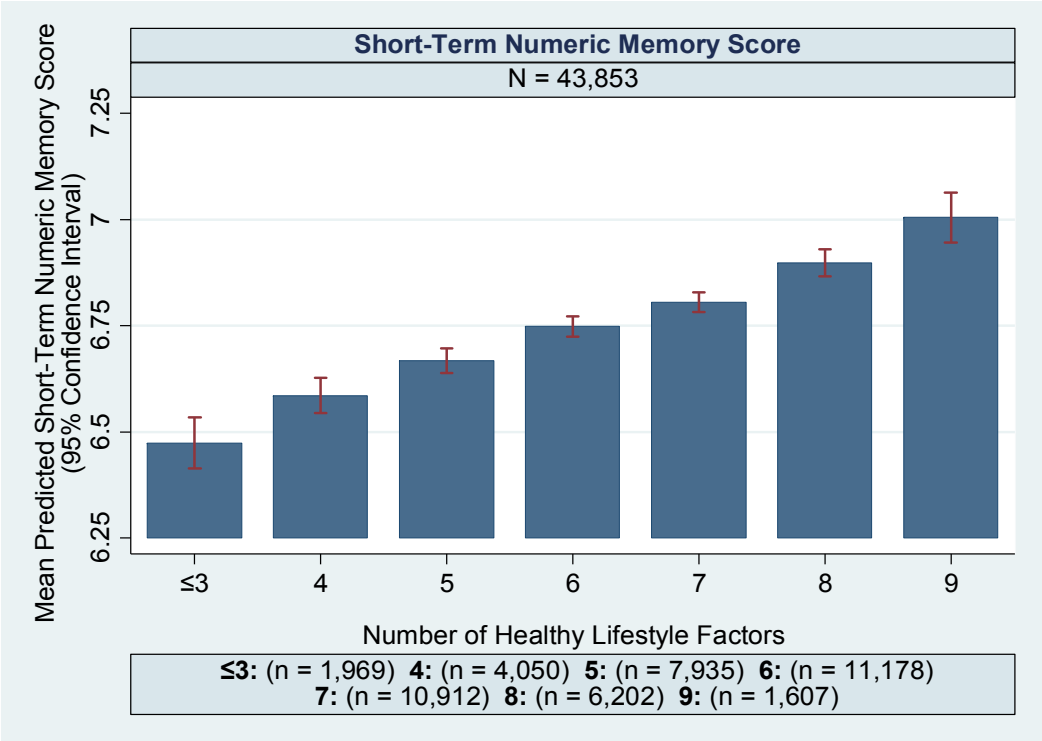


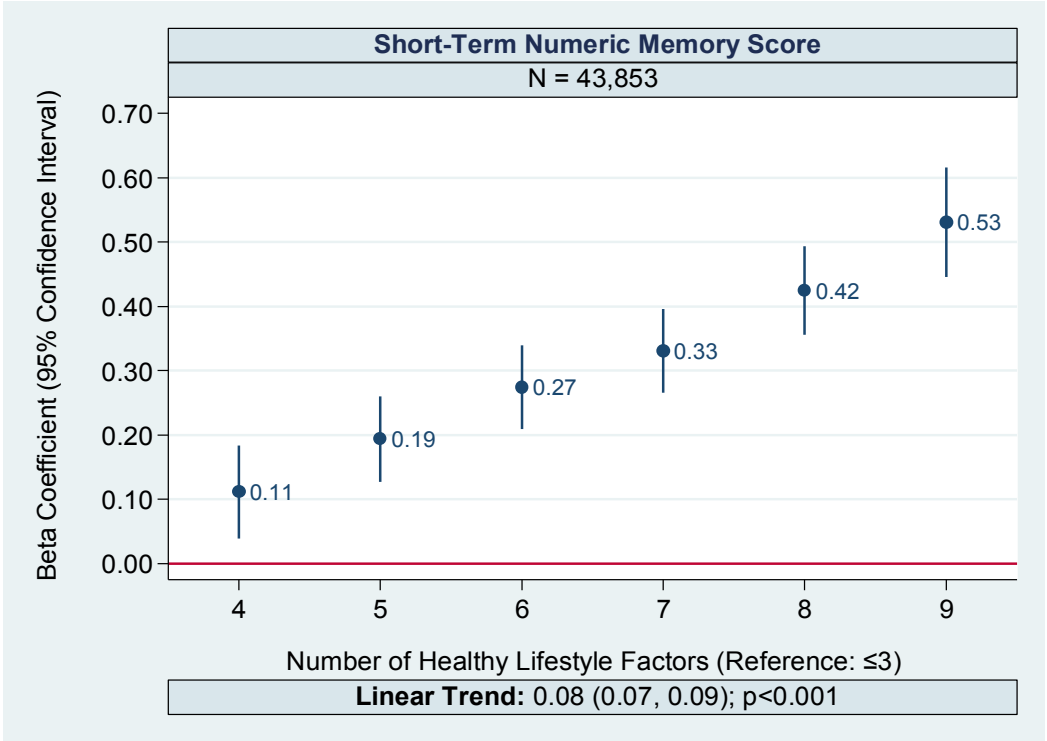


Reaction time: continuous (mean time taken to correctly identify matches). A beta coefficient of greater than 0 indicates a slower reaction time; and a beta coefficient of less than 0 indicates a faster reaction time.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 28 - Observational study (UK Biobank data): Cross-sectional associations at baseline between the number of healthy lifestyle factors and short-term numeric memory

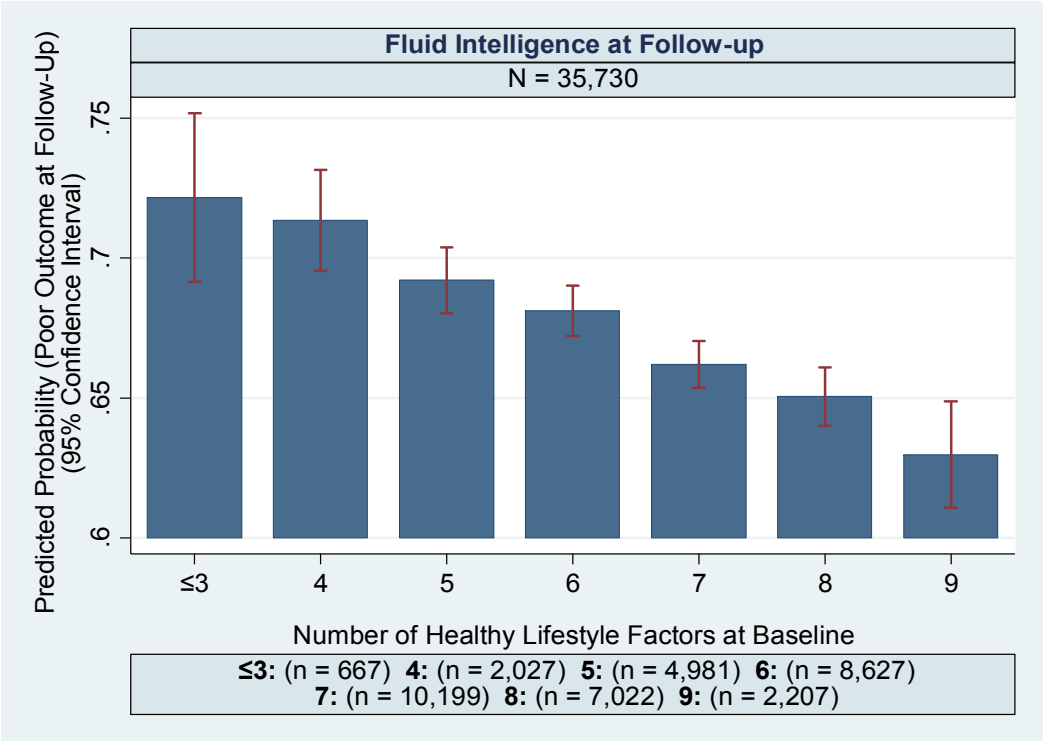


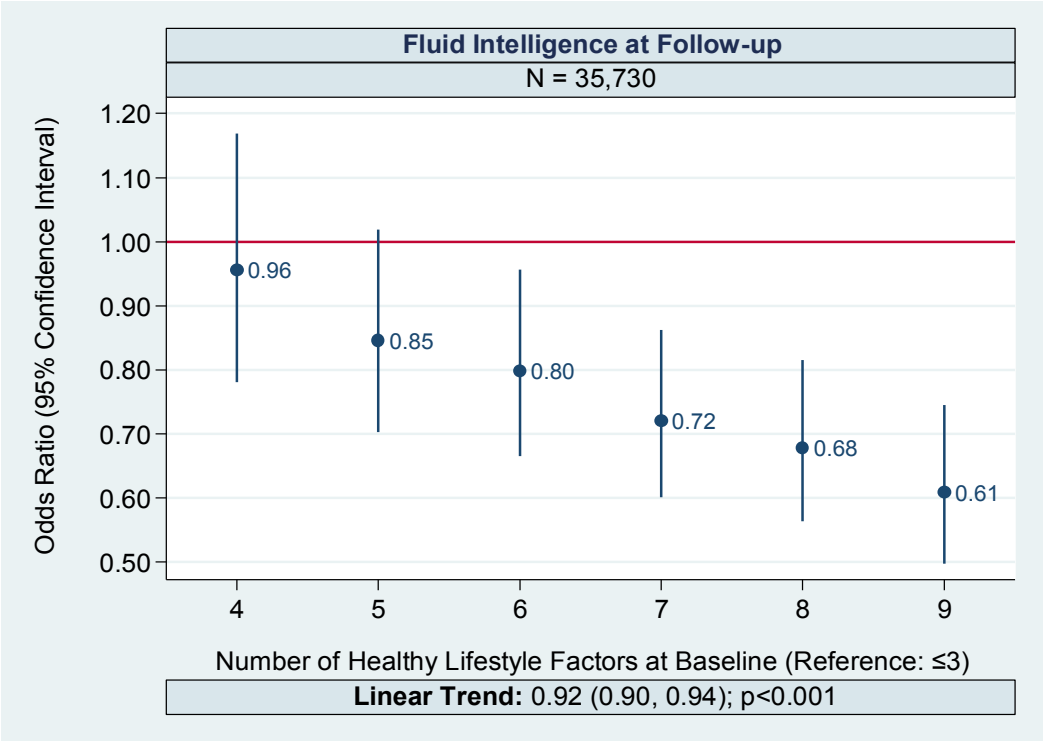


Numeric memory score: continuous (maximum digits remembered). A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Model adjusted for the following variables: age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 29 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and fluid intelligence at follow-up (excluding participants with cancer, cardiovascular disease, and/or cognitive/psychiatric illnesses)

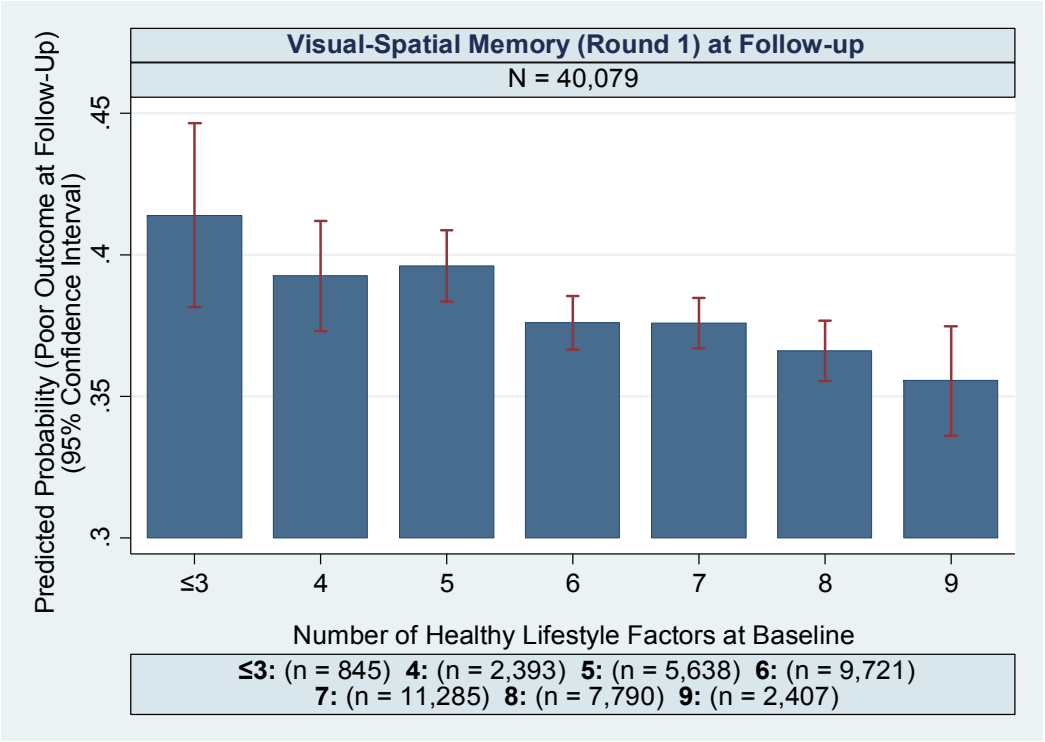


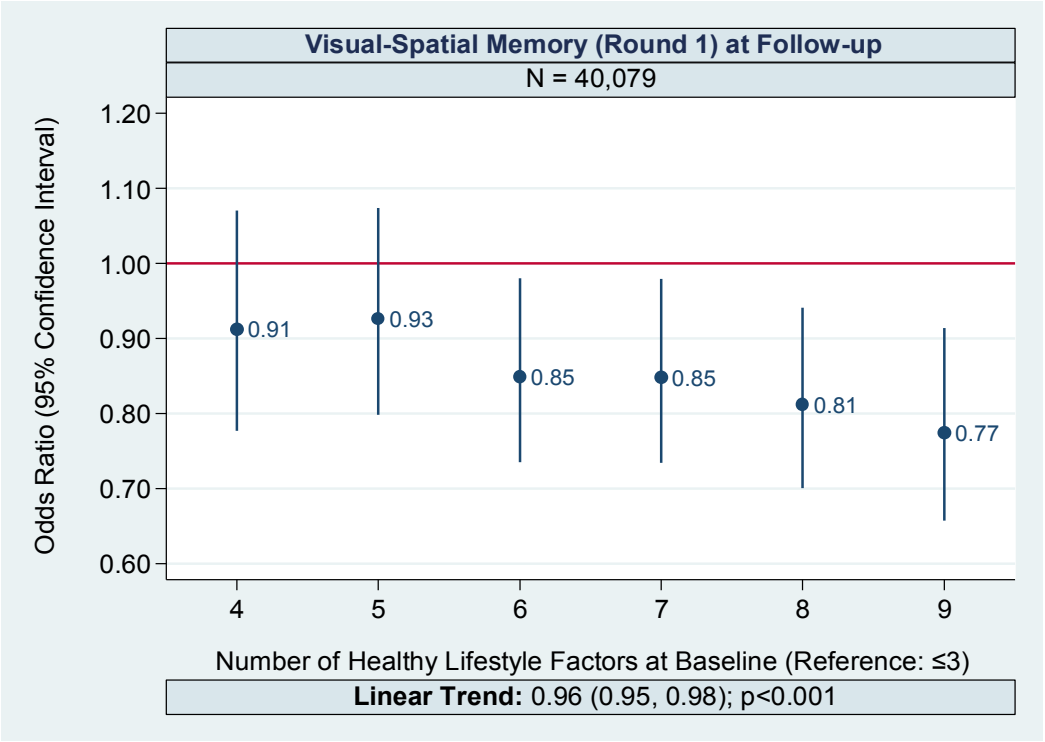


Fluid intelligence: categorical binary (good outcome at follow-up [(reference) baseline fluid intelligence score ≤ follow-up fluid intelligence score]; or poor outcome at follow-up [baseline fluid intelligence score > follow-up fluid intelligence score]). An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Model adjusted for the following variables: baseline fluid intelligence score, age, sex, ethnicity, social deprivation index, employment status, education level, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 30 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and visual-spatial memory (pairs matching - round 1) at follow-up

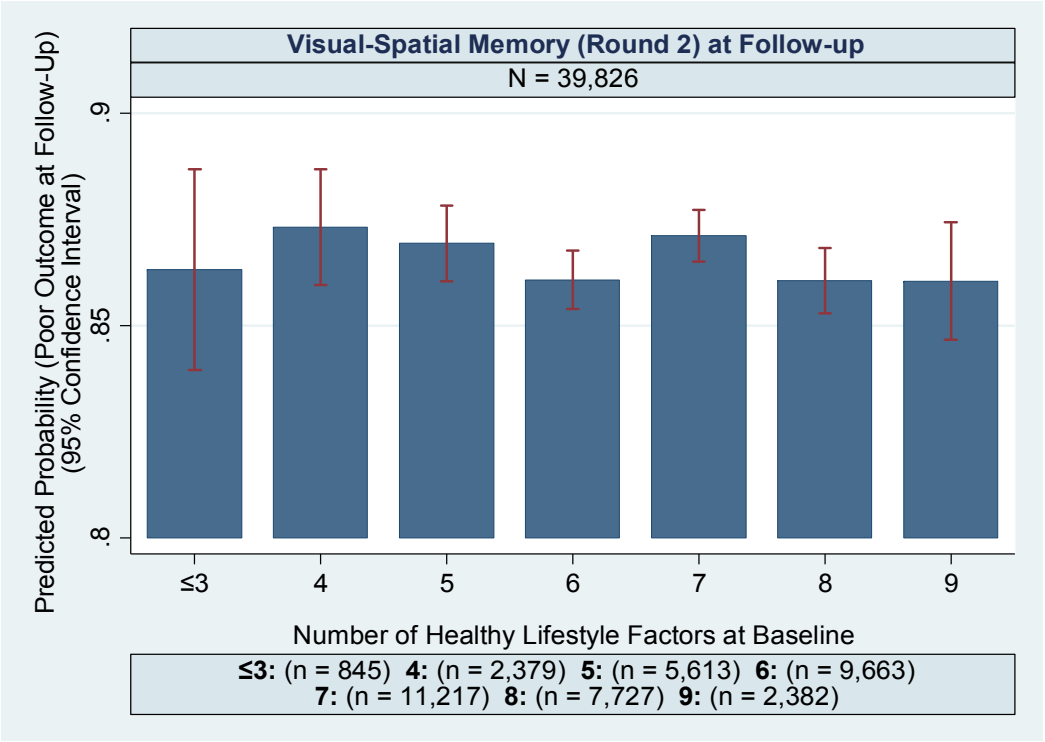


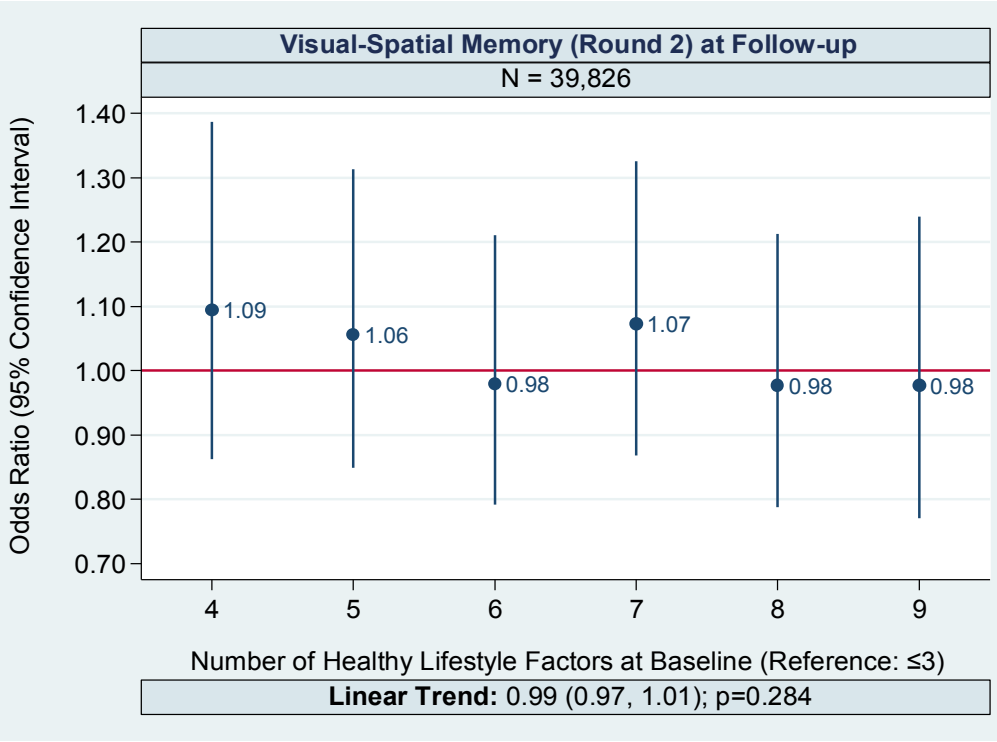


Pairs matching: categorical binary (good outcome at follow-up [(reference) <1 incorrect matches at follow-up]; or poor outcome at follow-up [≥1 incorrect matches at follow-up]). An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Model adjusted for the following variables: baseline pairs matching result (round 1), age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 31 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and visual-spatial memory (pairs matching - round 2) at follow-up

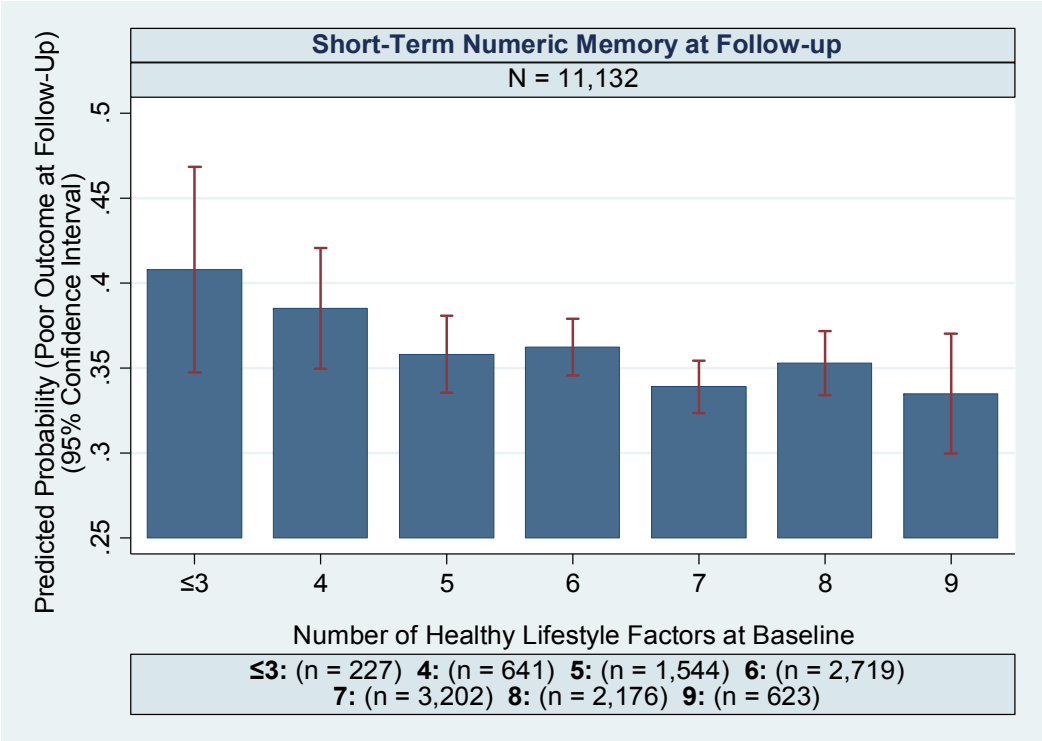


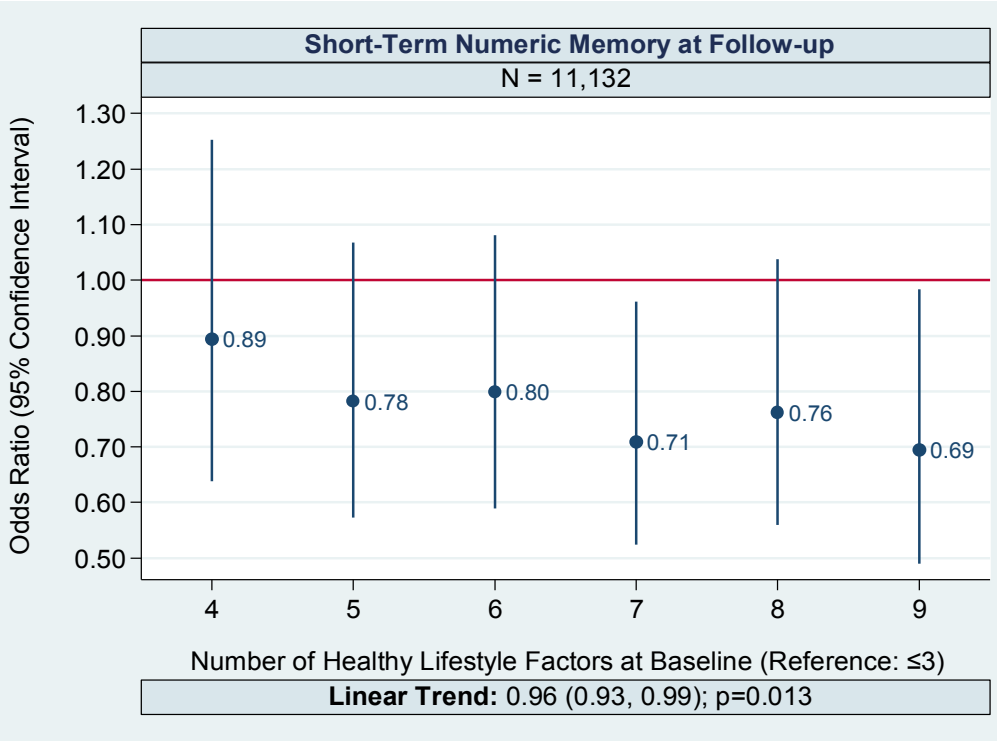


Pairs matching: categorical binary (good outcome at follow-up [(reference) <2 incorrect matches at follow-up]; or poor outcome at follow-up [≥2 incorrect matches at follow-up]). An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Model adjusted for the following variables: baseline pairs matching result (round 2), age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Figure 32 - Observational study (UK Biobank data): Prospective associations between the number of healthy lifestyle factors at baseline and short-term numeric memory at follow-up





Numeric memory: categorical binary (good outcome at follow-up [(reference) baseline numeric memory score ≤ follow-up numeric memory score]; or poor outcome at follow-up [baseline numeric memory score > follow-up numeric memory score]). An odds ratio of less than 1 indicates lower odds of having cognitive decline at follow-up (i.e. a good outcome at follow-up); and an odds ratio of greater than 1 indicates higher odds of having cognitive decline at follow-up (i.e. a poor outcome at follow-up).

Model adjusted for the following variables: baseline numeric memory score, age, sex, ethnicity, social deprivation index, employment status, education level, number of cancers, number of non-cancer illnesses, and number of medications/treatments. Statistical significance was established at p-value<0.05.

Discussion

Key Findings

This study reports the cross-sectional and prospective associations of modifiable lifestyle factors on fluid intelligence in a large cohort of UK adults. At baseline, diet, physical activity, smoking status, sleep duration, handgrip strength, walking pace, TV viewing time, driving time, and computer use time were all independently associated with fluid intelligence. A higher number of healthy lifestyle factors was positively associated with fluid intelligence; such that for each additional lifestyle factor >3, the total number of correct answers was 0.18 higher. These associations were modified by age and sex, with stronger relationships observed in older adults and in males. The number of healthy lifestyle factors at baseline was also inversely associated with the odds of having a lower fluid intelligence score at follow-up; such that for each additional lifestyle factor >3 at baseline, the odds of a poor outcome at follow-up were 7% lower. The main findings were robust and generalizable across the sample of participants without cancer, CVD, and/or cognitive/psychiatric illnesses, and across the other cognitive tests.

Interpretations

These findings extend the existing data investigating the associations of individual factors with cognitive function. The positive associations of eating well, physical activity, non-smoking, healthy duration of sleep, high handgrip strength, good walking speed, low TV viewing time, low driving time, and high computer use time on cognitive function have been consistently documented (56, 59, 196, 204, 210, 226-232). Some of these associations, such as those observed with physical activity, are supported by interventional and mechanistic studies which have shown direct effects on the structure and function of the brain (50-53). In addition, there are many other plausible overlapping mechanisms linking healthy lifestyle factors to optimal cognitive function. Some of these include: healthy functioning of the central nervous system (243), good cardiometabolic health (8, 13, 164, 165), delayed neurodegeneration (244, 245), low levels of stress and fatigue (26, 169, 171), and minimal social isolation and solitariness

(172, 174). These results suggest that whilst the independent associations between lifestyle factors and cognitive function may share several overlaying pathways and mechanisms, the associations are additive; such that an increasing number of healthy lifestyle factors linearly reflects better cognitive health.

The cross-sectional findings suggested that the associations may be stronger in older adults and in males. Some of the mechanisms mentioned above (i.e. cardiometabolic health, etc.) are closely linked to ageing and vary by gender (175, 176); and therefore, they could possibly explain the observed interactions with age and sex.

The differences observed in fluid intelligence across the number of healthy lifestyle factors in these analyses are likely to be clinically meaningful beyond the risk of cognitive decline. For example, higher fluid intelligence scores have previously been shown to be strongly associated with a lower risk of all-cause mortality (177, 178). In a sample of 5,572 middle-aged British adults, Sabia and colleagues observed that a higher fluid intelligence score by 1 SD was associated with a 14% lower risk of all-cause mortality (177). Similarly, in a sample of 896 older Australian adults, Batterham and colleagues observed that a higher fluid intelligence score by 1 SD was associated with a 24% lower risk of all-cause mortality (178). In my baseline analysis, the SD of fluid intelligence score in the sample of participants included in the multiple linear regression analysis was 2.1; and the model estimated that each additional healthy lifestyle factor >3 was associated with a higher fluid intelligence score by 0.18. Hence, using the data above, it can be estimated that a higher fluid intelligence score by 0.18 would approximately equate to a 1.3%-2.3% lower risk of all-cause mortality. For more details on these calculations, see Calculation S2 in Appendix Three: Supplementary Material: Supplementary Calculations.

Strengths and Limitations

This study has several strengths and some limitations. Strengths include: utilisation of a large cohort of UK adults, follow-up cognitive function data allowing for prospective associations to be investigated, analysis of an extensive range of lifestyle factors, evaluation of dose-response and additive relationships between the number of healthy

lifestyle factors and cognition, detailed covariate data, interactions by age and sex, and robust sensitivity analyses examining a wide range of cognitive outcomes. A limitation of this analysis was the derivation of the 'number of healthy lifestyle factors' variable, which by nature assumed that each lifestyle factor had the same effect on fluid intelligence. Although an attempt to overcome this was made by only including factors that were associated with fluid intelligence when formulating this variable, it was evident that some factors (e.g. computer use time) had a stronger association than others (e.g. diet). This implies that vital information was possibly being lost when truncating the data on the lifestyle factors into binary variables. In relation to this, a majority of the lifestyle factors used in this analysis could have also been categorised using several different yet rational methods. Putting these elements together, this could have significant implications on the observed associations; and thus, these results should be interpreted with some caution. Nevertheless, it has previously been reported that no particular combination of lifestyle factors drives the associations with cognitive outcomes; and therefore, a simple summary score of lifestyle factors may be sufficient to examine these relationships (237). Besides BMI and hand grip strength, all of the other lifestyle factors in this study were self-reported, measures which tend to have lower validity than objective measures and increase the risk of regression dilution (185). Although a wide range of demographic and health variables were adjusted for, it is possible that some unmeasured features may have confounded the reported relationships. Reverse causality also remains possible. Furthermore, only those who provided an email address at baseline (~300,000) were contacted for online follow-up of cognitive function. Therefore, these adults all had computer access and seemingly, some computer use experience. This may have also resulted in the small differences in characteristics between those who only provided fluid intelligence data at baseline and those who provided fluid intelligence data at both baseline and follow-up (see Table 24). Hence, the prospective analysis may lack generalizability and be biased. Lastly, at baseline, the cognitive function tests were implemented using questionnaires that were administered via a touchscreen interface. At follow-up, the measurements were obtained remotely via online questionnaires that were administered on a computer via a mouse interface. Thus, this difference in the mode of administration could possibly

account for some of the variability in cognitive performance and change over time. Nevertheless, the prospective findings largely support the cross-sectional associations reported at baseline.

Conclusion

A higher number of healthy lifestyle factors at baseline was associated with better cognitive function at both baseline (with stronger relationships observed in older adults and in males) and over follow-up. This suggests an important role for lifestyle factors in preserving cognitive function in adults within the general population. However, intervention studies are required to confirm these results.

CHAPTER SIX: ANALYSIS OF PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOUR DATA: RAW ACCELERATION DATA

Chapter Overview

This chapter is based on the analysis of raw acceleration data. In brief, this project exploited and examined accelerometry files to formulate intensity-based cut-off values on raw acceleration data (collected from different devices worn on the hip and wrist) for discriminating between sedentary behaviours and LIPA. The Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) are derivable raw acceleration metrics which have recently been shown to perform well in classifying the intensity of moderate and vigorous levels of physical activity. In this project, I developed and internally-validated ENMO and MAD thresholds for separating sedentary behaviours from common LIPA using raw acceleration data collected from both hip- and wrist-worn ActiGraph GT3X+ and GENEActiv tri-axial accelerometers. I also compared the performances between the ENMO and MAD metrics. Selections of these findings were presented as an oral talk at the Annual Health Sciences Conference (November 2014, University of Leicester, Leicester, UK) and as a poster at the International Society for the Measurement of Physical Behaviour: 4th International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM 2015) (June 2015, University of Limerick, Limerick, Ireland). The full findings of this original piece of work were published as a Research Article in PLOS ONE. It must be noted that I had no role in the design, the laboratory experiment, or the primary data collection aspects of the study. After the study was fully complete, I was given access to experimental laboratory data for my PhD.

Intensity Thresholds on Raw Acceleration Data: ENMO and MAD Approaches

Abstract

Objectives: (1) To develop and internally-validate ENMO and MAD thresholds for separating sedentary behaviours from common LIPA using raw acceleration data collected from both hip- and wrist-worn tri-axial accelerometers; and (2) to compare and evaluate the performances between the ENMO and MAD metrics.

Methods: Thirty-three adults [mean age (standard deviation (SD)) = 27.4 (5.9) years; mean BMI (SD) = 23.9 (3.7) kg/m^2; 20 females (60.6%)] wore four accelerometers; an ActiGraph GT3X+ and a GENEActiv on the right hip; and an ActiGraph GT3X+ and a GENEActiv on the non-dominant wrist. Under laboratory-conditions, participants performed 16 different activities (11 sedentary behaviours and 5 LIPA) for 5 minutes each. ENMO and MAD were computed from the raw acceleration data, and logistic regression and ROC analyses were implemented to derive thresholds for activity discrimination. Area under ROC curves (AUROCs) were calculated to summarise performances and thresholds were assessed via executing leave-one-out-cross-validations (LOOCVs).

Results: For both hip and wrist monitor placements, in comparison to the ActiGraph GT3X+ monitors, the ENMO and MAD values derived from the GENEActiv devices were observed to be slightly higher, particularly for the lower-intensity activities. Monitor-specific hip and wrist ENMO and MAD thresholds showed excellent ability for separating sedentary behaviours from motion-based LIPA (in general, AUROC >0.95), with validation indicating robustness. However, poor classification was experienced when attempting to isolate standing still from sedentary behaviours (in general, AUROC <0.65). The ENMO and MAD metrics tended to perform similarly across activities and accelerometer brands.

Conclusions: Researchers can utilise these robust monitor-specific hip and wrist ENMO and MAD thresholds to accurately separate sedentary behaviours from common motion-based LIPA. However, caution should be taken if isolating sedentary behaviours from standing is of particular interest.

Introduction

There is cumulative evidence that sedentary behaviour is detrimentally associated with a number of health outcomes including CVD, T2DM and all-cause mortality (8-13). Correspondingly, engaging in LIPA (e.g. standing and light walking) has been shown to have beneficial effects on health (19, 28, 61). Therefore, accurately identifying and distinguishing between sedentary behaviour and LIPA is extremely important. Tri-axial accelerometers, which quantify the acceleration and deceleration in orthogonal directions of three-dimensional space, have gained a reputation as the preferred method of collecting objective measurements of physical activity and sedentary behaviour data in health research (64, 65). These devices have the ability to accumulate large amounts of acceleration data (usually over an adjustable sampling frequency range) that can be translated into physical activity and sedentary behaviour parameters (i.e. duration, frequency and intensity) (66).

Accelerometers have historically provided data in the form of 'counts' - an aggregate measure of the intensity and magnitude of accelerations over a given time epoch (67-69). Count-based systems are straightforward to operate and do not expend substantial amounts of computational memory. However, counts are produced via proprietary algorithms which are developed and patented by the manufacturers of these monitors (entailing different amplifiers, filters, frequencies, etc.) (67-72). Therefore, even if the same reference acceleration signal is being measured, different devices can produce diverse count values (68, 69). This makes it difficult to equate data between different accelerometer brands; and thus, problematic to compare results from studies that have employed different devices. However, due to the significant improvements in technologies over the last few years, raw acceleration data can now be measured and stored at high frequencies, with no need to summarise into proprietary count-based epochs (68-77). Consequently, there is a necessity for the analysis of raw acceleration data using approaches that can be understood and used by all.

The challenge of analysing raw signals revolves around several factors: the management of vast amount of data which are generated, the requirement to remove the gravitational and noise components incorporated within the signals (246), and the

requirement of feasible mathematical and/or statistical tools to accurately analyse and make valid interpretations from the data. Procedures for processing the raw acceleration data and attempting to separate the movement and gravitational components of the signal include the: Signal Magnitude Area (SMA) (247-249), ENMO (246, 250, 251) and MAD methods (252-254). The SMA can be calculated after applying computationally expensive mathematical filters (e.g. Butterworth high pass filters, etc.) to remove the gravitational component (247-249). In contrast, the recently proposed ENMO and MAD metrics do not require the data to be filtered to correct for gravity - since they systematically take this element into account within their algorithms (246, 250-254), making these analytical techniques more attractive. For example, MAD represents the mean value of the dynamic acceleration component. It is computed from the resultant vector value of the measured orthogonal acceleration, which involves a dynamic component due to deviations in velocity, and a static element due to gravity. The static element is removed from the analysed epoch and the remaining dynamic component is revised. Thus, the MAD value can be regarded as the mean of the revised acceleration signal autonomous of the static element within the epoch. The ENMO metric, which is also computed from the resultant vector of the measured orthogonal acceleration, adjusts for gravity via subtracting a fixed offset of one gravitational unit from the Euclidean Norm of the three raw acceleration signals. Therefore, ENMO, which can also be regarded as the revised acceleration signal autonomous of the static gravitational element, equally signifies the dynamic acceleration component.

To my knowledge, only three studies have methodically investigated the use of the MAD metric with raw acceleration data relating to physical activity (252-254). Vähä-Ypyä and colleagues recently derived MAD-based universal thresholds for differentiating sedentary and standing activities from walking and different speeds of bipedal movement (254). Although these are useful, they are not beneficial for researchers focusing on the time spent in sedentary behaviours (e.g. lying/sitting) and common LIPA (e.g. washing pots, dusting, etc.). Besides the ActiGraph GT3X device [30 Hertz (Hz); ActiGraph Corporation, Pensacola, Florida, USA], the thresholds were defined for unconventional devices (Hookie AM13 [100 Hz; Hookie Technologies Ltd,

Espoo, Finland] and Gulfcoast X6-1A [20 Hz; Gulf Coast Data Concepts LLC, Waveland, Mississippi, USA]) that are not in widespread use. Vähä-Ypyä and colleagues proceeded to develop universal thresholds applicable to raw acceleration data collected from these monitors worn at the hip; however, as significantly large differences in MAD values were evident between accelerometer brands, these should be used with caution.

Accelerometers were traditionally worn on the hip; however, in recent years wrist-worn accelerometry has emerged and is now also being used in large national health surveys (e.g. UK Biobank (23) and NHANES (78)). Therefore, it is essential to also develop analytical methods which are appropriate for use with data from wrist-worn monitors and can be applied to existing methods for processing raw acceleration data (e.g. ENMO and MAD). Furthermore, to date, the MAD metric has not been compared to ENMO (252-254), which is emerging as the model metric for efficiently analysing raw acceleration data and classifying intensity (246, 250, 251). Although ENMO thresholds to classify moderate and vigorous physical activities using raw acceleration data have previously been developed (250), ENMO thresholds to separate sedentary behaviours from LIPA have yet to be proposed.

Therefore, by using raw acceleration data collected from both hip- and wrist-worn widely-used tri-axial accelerometers, the aims of this chapter are to: (1) extend the premise of the ENMO and MAD metrics via developing internally-validated monitor-specific intensity-based thresholds for discriminating between sedentary behaviours and common LIPA; and (2) compare and evaluate the performances between the ENMO and MAD metrics. The generation of ENMO and MAD thresholds developed will be sample and protocol specific. Hence, the classifications of sedentary behaviours and LIPA should be broadly comparable between studies - irrespective of the metric, accelerometer brand and wear-site used.

Methods

Design and Population

Investigations were carried out using data from a laboratory-based study which was conducted by the National Institute for Health Research (NIHR) Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit. The study was implemented within a bespoke laboratory, located at Loughborough University (Loughborough, Leicestershire, UK), which was furnished to enable the sedentary and non-sedentary tasks to be undertaken efficiently. Participants (aged ≥ 18 years) were recruited via email and word of mouth. All participants provided written informed consent, and the study was approved by the Ethics Committee of Loughborough University.

Accelerometer Devices

Two distinct and commercially available tri-axial accelerometers were utilised: the ActiGraph GT3X+ monitor (dynamic range: ± 6*g*, sampling frequency range: 30 - 100 Hz [ActiGraph Corporation, Pensacola, Florida, USA]) and the GENEActiv Original monitor (dynamic range: ± 8*g*, sampling frequency range: 10 - 100 Hz [Activinsights, Huntingdon, Cambridgeshire, UK]); where *g* is equal to the Earth's gravitational pull. The ActiGraph GT3X+ was initialised with a sampling frequency of 100 Hz using ActiLife software V6.10.2. The GENEActiv monitor was initialised with a sampling frequency of 100 Hz using the GENEActiv Personal Computer (PC) software V2.2. Both devices were initialised using the same computer.

As stated earlier in Chapter Four of this thesis, the GT3X model has been demonstrated to have acceptable intra- and inter-instrument reliability when verified on a vibration table at frequencies similar to the typical ranges of human movement (156). Furthermore, using mechanical shakers, Esliger and colleagues carried out a study to determine the reliability and validity of the GENEActiv (73). They observed that the GENEActiv was reliable for measuring accelerations (mean coefficient of variation (intra): 1.8% (low within variability); and mean coefficient of variation (inter): 2.4% (low between variability)) (73). The GENEActiv was also determined to be valid for

measuring accelerations (the correlation between the GENEActiv accelerations and multi-axis shaking table accelerations was excellent (r = 0.97)) (73). Similarly, John and colleagues carried out mechanical shaker testing on the ActiGraph GT3X+ and GENEActiv monitors to establish inter-unit reliability for each monitor type. For both monitors, they observed an intra-monitor coefficient of variation of <1.6% (75).

Procedures

Following arrival at the laboratory, study procedures were explained to the participants and written informed consent was obtained. The ActiGraph GT3X+ and GENEActiv accelerometers were then attached to both the hip (right side) and wrist (non-dominant). Consequently, a total of 4 devices were worn by each participant (1 ActiGraph GT3X+ on the hip and wrist; and 1 GENEActiv on the hip and wrist) whilst they performed 16 different activities (4 lying positions, 7 sitting postures and 5 upright activities) in a sequential order for 5 minutes each under laboratory-conditions. The start and end time of each activity was observed (using a clock on a computer) and recorded onto a log sheet. A 30 second break was allocated between each activity. Table 25 summarises the sedentary behaviours and LIPA undertaken by the participants.

Table 25 - Experimental study (Laboratory data): Summary of sedentary behaviours and light-intensity physical activities

Posture		Activity
Lying [a]	1	Lying flat on back with legs straight
	2	Lying on back with both legs bent
	3	Lying on side with both legs straight
	4	Lying on side with both legs bent
Sitting [b]	5	Sitting on chair whilst watching TV with both feet on floor (knees at 90 degrees)
	6	Sitting on chair whilst watching TV with legs crossed (right leg over left leg)
	7	Sitting on a chair whilst watching TV with right foot resting on left thigh
	8	Sitting on chair whilst watching TV with legs stretched out forwards (feet touching floor)
	9	Sitting on chair whilst watching TV with legs bent backwards underneath chair
	10	Sitting on a chair with some upper body movement (typing a set statement on a computer)
	11	Sitting whilst playing games on a mobile phone
Upright	12	Standing still
	13	Washing pots
	14	Dusting (set area)
	15	Sweeping floor (set area)
	16	Self-paced free-living walk around the room [c]

[a] *During all lying activities, participants were asked to keep their hands straight by their sides*
[b] *During seated activities 5 to 9, participants were asked to keep their hands on their thighs*
[c] *The velocity range of the self-paced free-living walk (activity 16) was approximately 3km/h to 4km/h with movement in a forward direction*

Data Reduction and Processing: MAD

The raw acceleration data from the two ActiGraph GT3X+ (100 Hz; .gt3x files) and two GENEActiv (100 Hz; .bin files) devices were downloaded using ActiLife V6.10.2 and GENEActiv PC software V2.2, respectively. For the computation of the MAD metric, the four sets of raw acceleration files were converted to time-stamped .csv files, which were then exported into Stata/IC V13.1 (Stata Corporation, College Station, Texas, USA) for processing and analysis. The laboratory log sheets (with the observed start and end times of each activity) were utilised for identifying each activity in the time-stamped .csv files.

MAD is defined as:

$$Mean\ Amplitude\ Deviation\ (MAD) \coloneqq \frac{1}{n} \times \sum_{i=1}^{n} |r_i - \bar{r}|$$

$where$:

$r_i = \sqrt{x_i^2 + y_i^2 + z_i^2} = i^{th}\ vector\ magnitude\ at\ each\ time\ point$

$\bar{r} = mean\ vector\ magnitude\ within\ the\ time\ period\ of\ interest$

$n = \ length\ of\ the\ time\ period$

Each axis (x, y, z) of the raw tri-axial data were first multiplied by 1000 to transform the signals from gravitational units into milligravitational (mg) units. This was implemented in order to ensure that the developed thresholds would be comparable with the prior findings in the literature (254). Research suggests that a 5 second time period can be considered to be adequate for reporting different activities (254, 255). Therefore, since the accelerometers were initialised at their maximum possible frequencies (100 Hz i.e. 100 samples/second), the length of the time period (n) was derived to be 500 (100 Hz x 5 seconds). The vector magnitude (r) was calculated at each time point (i), followed by the mean vector magnitude for the 5 second time

period ($\bar{r}$). This allowed the computation of the MAD metric - which provided a measure of the intensity for every 5 seconds of data.

Data Reduction and Processing: ENMO

For the computation of the ENMO metric, the ActiGraph GT3X+ .gt3x files were converted to time-stamp free .csv files (to avoid computer memory issues). The ActiGraph GT3X+ .csv files and the GENEActiv .bin files were then exported into R statistical software V3.1.2 (R Foundation for Statistical Computing, Vienna, Austria, https://cran.r-project.org/) for processing using the GGIR package V1.2-0 which autocalibrated the raw tri-axial accelerometer signals and computed the ENMO metric (251). The package regenerated the time-stamps and the files were exported into Stata/IC V13.1 for further processing and analysis.

ENMO, described in detail elsewhere (246, 250, 251), is defined as:

$$Euclidean\ Norm\ Minus\ One\ (ENMO) \coloneqq r_i - 1000$$

$where$:

$$r_i = \sqrt{x_i^2 + y_i^2 + z_i^2} = i^{th}\ vector\ magnitude\ at\ each\ time\ point$$

$$1000 = 1000\ milligravitational\ units = 1\ gravitational\ unit$$

The ENMO subtracts a fixed offset value of 1 gravitational unit at each time point to correct for gravity (246, 250, 251). Negative ENMO values are rounded up to zero to reduce any bias and error (250, 251). By design, the ENMO metric is sensitive to poor calibration (251). Therefore, to address these calibration issues, ENMO was calculated using the GGIR package V1.2-0 in R statistical software V3.1.2, which autocalibrates the raw tri-axial accelerometer signal. To ensure that the autocalibration was meaningful and robust, a sparseness criteria of ±300 m*g* were also applied. Further information on the accelerometer calibration technique can be found elsewhere (251). As with MAD,

ENMO was expressed in m*g* and calculated over 5 second epochs. Note, in both ENMO and MAD, the basic idea is similar. ENMO assumes the magnitude of gravity to be one, whereas MAD calculates the mean acceleration, representing the magnitude of gravity, from the measured data. In both metrics, this value is subtracted from the magnitude of the resultant acceleration. Furthermore, if the epoch length (number of samples) is the same and the mean value of the epoch is 1000 m*g*, then at least in theory, ENMO is equivalent to MAD.

To ensure the quality of the findings, the first and last 30 seconds of data of each activity were excluded as it was anticipated these time periods might include transitional movements. Thus, only the central 4 minutes of data of each activity were utilised for analysis.

Statistical Analysis

All statistical analyses were conducted using Stata/IC V13.1. Activities 1 to 11 (any form of lying plus any form of sitting) were combined into one group and classified as 'sedentary behaviours'. For each activity, the means and SEs of the ENMO and MAD values stratified by accelerometer brand (ActiGraph GT3X+ and GENEActiv) and monitor placement (hip and wrist) were calculated and tabulated. T-tests were implemented to compare the mean ENMO and MAD values of each activity between accelerometer brands by monitor placement. Statistical significance was established at p-value<0.05.

Sedentary behaviours were separated from a continuum of LIPA ordered by increasing complexity and movement. To achieve this, the following activity discriminations were considered: discrimination 1 = sedentary behaviours vs. standing still, discrimination 2 = sedentary behaviours vs. washing pots, discrimination 3 = sedentary behaviours vs. dusting, discrimination 4 = sedentary behaviours vs. sweeping floor, and discrimination 5 = sedentary behaviours vs. self-paced free-living walk. Univariate binary logistic regression models were fitted with the discrimination under review as the dependent variable and the hip/wrist ENMO/MAD metric as the independent variable (Stata command: 'logit') (121). Logistic regression analysis was used here since the outcome

of interest was of binary nature; thus, making it the most appropriate statistical technique (121). ROC analyses were implemented to derive the optimum monitor-specific hip and wrist thresholds for activity classification (Stata command: 'lroc') (133). Performances were summarised by calculating the AUROC and the thresholds were examined for validity by conducting a LOOCV (256). The LOOCV is a model validation technique which assesses the generalizability and performance of a developed model on unseen data (256). A training (n - 1 observations) and testing (1 observation) analysis is implemented (n times, with a different observation left out each time) to estimate the predictive performance of a model. The method works as follows: a model is trained on seen data (n - 1 observations) (i.e. the training set) and tested on unseen data i.e. the single observation that was left out (i.e. the testing set). With a different observation left out each time, the model is repeatedly fitted (n times) to predict the performance of the model. The performances between the ENMO and MAD metrics were compared using the AUROC and LOOCV AUROC statistics with their corresponding 95% CIs. The assumptions of logistic regression were assessed (121).

Results

The sample consisted of 33 participants [mean age (SD) = 27.4 (5.9) years; mean BMI (SD) = 23.9 (3.7) kg/m^2; 20 females (60.6%)]. Tables 26 (ENMO) and 27 (MAD) show the mean (SE) raw acceleration metric values of the sedentary behaviours and each LIPA stratified by accelerometer brand and monitor placement. In general, for both hip and wrist monitor placements, the ENMO and MAD values computed from the GENEActiv devices were observed to be slightly higher in comparison to the ActiGraph GT3X+ devices, particularly for the lower-intensity activities. For the monitors positioned on the hip, statistically significant differences (p-value<0.05) in the ENMO metric were detected between the accelerometer brands during the sedentary behaviours (p-value<0.001), standing still (p-value=0.014) and washing pots (p-value=0.020) activities. For the MAD metric, differences were detected during the sedentary behaviours (p-value<0.001) and standing still (p-value<0.001) activities. In comparison, for the monitors positioned on the wrist, differences in the ENMO metric were only detected during the sedentary behaviours (p-value=0.010). For the MAD metric,

differences were detected during the sedentary behaviours (p-value<0.001) and standing still (p-value=0.012) activities. The sensor calibration error was low (<0.01) for all accelerometers (ActiGraph GT3X+ (hip and wrist) and GENEActiv (hip and wrist)).

Table 26 - Experimental study (Laboratory data): Mean (standard error) Euclidean Norm Minus One (ENMO) values for each activity stratified by accelerometer brand and monitor placement

	Mean (standard error) ENMO [a]		
	ActiGraph GT3X+	GENEActiv	
Activity	Hip	Hip	p-value
Sedentary Behaviours [b]	3.6 (0.3)	6.6 (0.3)	**<0.001**
Standing Still	3.6 (0.7)	7.7 (1.4)	**0.014**
Washing Pots	5.9 (0.7)	9.8 (1.5)	**0.020**
Dusting	18.4 (2.2)	19.8 (1.7)	0.626
Sweeping Floor	22.4 (1.8)	25.8 (2.2)	0.228
Self-Paced Free-Living Walk	58.5 (3.7)	64.8 (3.6)	0.225
	Wrist	Wrist	
Sedentary Behaviours [b]	9.3 (0.5)	10.9 (0.4)	**0.010**
Standing Still	10.3 (1.6)	10.8 (0.9)	0.781
Washing Pots	53.8 (5.4)	58.5 (6.6)	0.578
Dusting	67.3 (7.5)	72.3 (7.4)	0.638
Sweeping Floor	107.5 (9.2)	118.0 (7.7)	0.380
Self-Paced Free-Living Walk	103.1 (7.4)	110.9 (5.6)	0.406

[a] *Euclidean Norm Minus One measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Table 27 - Experimental study (Laboratory data): Mean (standard error) Mean Amplitude Deviation (MAD) values for each activity stratified by accelerometer brand and monitor placement

	Mean (standard error) MAD [a]		
	ActiGraph GT3X+	GENEActiv	
Activity	Hip	Hip	p-value
Sedentary Behaviours [b]	1.2 (0.1)	9.1 (0.8)	**<0.001**
Standing Still	1.8 (0.3)	7.3 (0.8)	**<0.001**
Washing Pots	6.9 (0.8)	13.9 (3.7)	0.071
Dusting	29.3 (2.3)	32.8 (2.7)	0.318
Sweeping Floor	37.4 (3.1)	44.2 (4.5)	0.224
Self-Paced Free-Living Walk	119.3 (6.3)	127.3 (6.1)	0.362
	Wrist	Wrist	
Sedentary Behaviours [b]	6.7 (0.5)	12.7 (0.4)	**<0.001**
Standing Still	7.5 (1.1)	11.3 (1.0)	**0.012**
Washing Pots	100.2 (8.3)	102.6 (9.8)	0.855
Dusting	84.2 (6.6)	86.2 (6.5)	0.826
Sweeping Floor	174.3 (10.4)	173.0 (10.1)	0.928
Self-Paced Free-Living Walk	151.5 (6.2)	151.6 (6.3)	0.998

[a] *Mean Amplitude Deviation measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
***Bold** indicates statistical significance (i.e. p-value<0.05).*

Tables 28 (ENMO; hip), 29 (ENMO; wrist), 30 (MAD; hip) and 31 (MAD; wrist) show the monitor-specific hip and wrist raw acceleration metric thresholds (with the corresponding statistics: metric threshold, sensitivity, specificity, AUROC, LOOCV AUROC) for differentiating between the sedentary behaviours and each LIPA. For both hip and wrist monitor placements, poor classification was observed when attempting to isolate standing still from sedentary behaviours (ActiGraph GT3X+ ENMO AUROC [hip: 0.543, wrist: 0.601]; GENEActiv ENMO AUROC [hip: 0.504, wrist: 0.468]; ActiGraph GT3X+ MAD AUROC [hip: 0.638, wrist: 0.603]; GENEActiv MAD AUROC [hip: 0.297, wrist: 0.560]). However, in contrast, sedentary behaviours differentiated well from all motion-based LIPA (washing pots, dusting, sweeping floor and self-paced free-living walk; in general, AUROC >0.95). The LOOCV procedure indicated robustness and stability as the high performance, where observed, was maintained. ENMO and MAD registered similar performances for classifying all motion-based activities for both devices positioned on the hip. However, some small differences between the metrics were observed when distinguishing between sedentary behaviours and standing still. For the accelerometers positioned on the wrist, ENMO and MAD registered comparable performances for both devices (see Tables 28 - 31). Model assumptions were satisfied.

Table 28 - Experimental study (Laboratory data): Monitor-specific hip Euclidean Norm Minus One (ENMO) thresholds to differentiate between sedentary behaviours and light-intensity physical activities

ENMO (hip) [a]		Sedentary behaviours [b] vs.				
		Standing still	Washing pots	Dusting	Sweeping floor	Self-paced free living walk
Threshold	AG [c]	2.6	2.9	7.5	9.4	26.6
	GA [d]	3.9	4.7	8.6	11.2	25.9
Sensitivity (%)	AG [c]	52%	88%	97%	100%	94%
	GA [d]	70%	85%	97%	100%	100%
Specificity (%)	AG [c]	54%	59%	92%	94%	100%
	GA [d]	35%	45%	80%	87%	97%
AUROC [e] (95% CI)	AG [c]	0.543 (0.447, 0.640)	0.779 (0.716, 0.842)	0.965 (0.947, 0.982)	0.979 (0.967, 0.992)	0.994 (0.987, 1.000)
	GA [d]	0.504 (0.402, 0.607)	0.666 (0.578, 0.753)	0.934 (0.906, 0.962)	0.961 (0.943, 0.980)	0.997 (0.993, 1.000)
LOOCV AUROC [f] (95% CI)	AG [c]	0.382 (0.252, 0.491)	0.689 (0.605, 0.773)	0.962 (0.943, 0.981)	0.978 (0.965, 0.991)	0.993 (0.986, 1.000)
	GA [d]	0.332 (0.212, 0.451)	0.600 (0.499, 0.701)	0.930 (0.900, 0.959)	0.958 (0.939, 0.978)	0.996 (0.992, 1.000)

[a] *Euclidean Norm Minus One measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
[c] *ActiGraph GT3X+ accelerometer*
[d] *GENEActiv accelerometer*
[e] *Area under receiver-operating-characteristic curve*
[f] *Leave-one-out-cross-validation area under receiver-operating-characteristic curve*

Table 29 - Experimental study (Laboratory data): Monitor-specific wrist Euclidean Norm Minus One (ENMO) thresholds to differentiate between sedentary behaviours and light-intensity physical activities

ENMO (wrist) [a]		Sedentary behaviours [b] vs.				
		Standing still	Washing pots	Dusting	Sweeping floor	Self-paced free-living walk
Threshold	AG [c]	5.7	25.8	27.9	52.5	41.4
	GA [d]	8.7	30.7	34.4	52.6	47.1
Sensitivity (%)	AG [c]	79%	94%	94%	91%	91%
	GA [d]	70%	97%	100%	100%	100%
Specificity (%)	AG [c]	45%	93%	94%	99%	99%
	GA [d]	43%	99%	99%	100%	100%
AUROC [e] (95% CI)	AG [c]	0.601 (0.520, 0.682)	0.965 (0.928, 1.000)	0.963 (0.913, 1.000)	0.952 (0.887, 1.000)	0.966 (0.920, 1.000)
	GA [d]	0.468 (0.381, 0.555)	0.994 (0.986, 1.000)	0.999 (0.996, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
LOOCV AUROC [f] (95% CI)	AG [c]	0.337 (0.238, 0.436)	0.957 (0.907, 1.000)	0.955 (0.896, 1.000)	0.938 (0.855, 1.000)	0.950 (0.886, 1.000)
	GA [d]	0.383 (0.306, 0.451)	0.992 (0.981, 1.000)	0.998 (0.994, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)

[a] *Euclidean Norm Minus One measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
[c] *ActiGraph GT3X+ accelerometer*
[d] *GENEActiv accelerometer*
[e] *Area under receiver-operating-characteristic curve*
[f] *Leave-one-out-cross-validation area under receiver-operating-characteristic curve*

Table 30 - Experimental study (Laboratory data): Monitor-specific hip Mean Amplitude Deviation (MAD) thresholds to differentiate between sedentary behaviours and light-intensity physical activities

MAD (hip) [a]		Sedentary behaviours [b] vs.				
		Standing still	Washing pots	Dusting	Sweeping floor	Self-paced free-living walk
Threshold	AG [c]	0.8	2.8	7.4	17.8	33.2
	GA [d]	7.2	8.5	16.2	18.4	35.0
Sensitivity (%)	AG [c]	70%	94%	100%	100%	100%
	GA [d]	33%	67%	97%	100%	100%
Specificity (%)	AG [c]	52%	89%	100%	100%	100%
	GA [d]	38%	69%	99%	100%	100%
AUROC [e] (95% CI)	AG [c]	0.638 (0.545, 0.732)	0.958 (0.927, 0.989)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
	GA [d]	0.297 (0.206, 0.387)	0.710 (0.602, 0.818)	0.986 (0.973, 0.999)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
LOOCV AUROC [f] (95% CI)	AG [c]	0.584 (0.479, 0.690)	0.954 (0.917, 0.990)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
	GA [d]	0.278 (0.191, 0.365)	0.653 (0.517, 0.789)	0.975 (0.928, 0.998)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)

[a] *Mean Amplitude Deviation measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
[c] *ActiGraph GT3X+ accelerometer*
[d] *GENEActiv accelerometer*
[e] *Area under receiver-operating-characteristic curve*
[f] *Leave-one-out-cross-validation area under receiver-operating-characteristic curve*

Table 31 - Experimental study (Laboratory data): Monitor-specific wrist Mean Amplitude Deviation (MAD) thresholds to differentiate between sedentary behaviours and light-intensity physical activities

MAD (wrist) [a]		Sedentary behaviours [b] vs.				
		Standing still	Washing pots	Dusting	Sweeping floor	Self-paced free-living walk
Threshold	AG [c]	4.2	33.4	35.9	73.4	66.1
	GA [d]	10.6	39.6	45.2	74.5	67.1
Sensitivity (%)	AG [c]	73%	100%	100%	100%	100%
	GA [d]	45%	100%	100%	100%	100%
Specificity (%)	AG [c]	55%	98%	98%	100%	100%
	GA [d]	58%	98%	99%	100%	100%
AUROC [e] (95% CI)	AG [c]	0.603 (0.512, 0.694)	0.999 (0.998, 1.000)	0.998 (0.996, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
	GA [d]	0.560 (0.447, 0.673)	0.999 (0.998, 1.000)	0.998 (0.996, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
LOOCV AUROC [f] (95% CI)	AG [c]	0.372 (0.264, 0.479)	0.996 (0.990, 1.000)	0.998 (0.995, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)
	GA [d]	0.441 (0.346, 0.535)	0.998 (0.996, 1.000)	0.998 (0.995, 1.000)	1.000 (1.000, 1.000)	1.000 (1.000, 1.000)

[a] *Mean Amplitude Deviation measured in milligravity units*
[b] *Any form of lying plus any form of sitting (activities 1 to 11)*
[c] *ActiGraph GT3X+ accelerometer*
[d] *GENEActiv accelerometer*
[e] *Area under receiver-operating-characteristic curve*
[f] *Leave-one-out-cross-validation area under receiver-operating-characteristic curve*

Discussion

Key Findings

This is the first methodological project to develop and validate ENMO and MAD intensity-based thresholds for differentiating between sedentary behaviours and common LIPA using raw acceleration data collected from both hip- and wrist-worn ActiGraph GT3X+ and GENEActiv tri-axial accelerometers. The monitor-specific hip and wrist ENMO and MAD thresholds showed excellent ability for differentiating between the sedentary behaviours and motion-based LIPA (washing pots, dusting, sweeping floor and self-paced free-living walk). Poor classification was experienced when attempting to isolate standing still from sedentary behaviours. However, these findings are as expected since the magnitude of the acceleration signals is very similar when lying/sitting or standing still, and to accurately discriminate between postures, more features of the acceleration signal (such as the angles between the individual orthogonal axes of acceleration from wrist-worn accelerometers) need to be considered (257-259). Recent experimental and epidemiological research has shown that standing can have beneficial effects on health (19, 28, 61). However, due to their poor performances, the thresholds developed in this project to discriminate between sedentary behaviours and standing would miscalculate the times spent in each characteristic (i.e. they would overestimate sedentary time and underestimate standing time). Whilst taking into consideration that this issue categorically depends on the amount of time individuals actually spend standing still in day-to-day life, adequate caution should be taken if isolating sedentary behaviours from standing is of particular interest using these thresholds. In contrast, the magnitude of the acceleration signals is considerably larger during standing activities which require some light movement (e.g. washing pots) and light-intensity lateral/anteroposterior activities (e.g. dusting, sweeping floor, etc.), and as shown, they can be separated well from sedentary behaviours using both the ENMO and MAD metrics. In comparison to the hip ENMO/MAD values and thresholds, the wrist ENMO/MAD values and thresholds were higher during the LIPA, reflecting the supplementary arm/hand movements whilst performing these particular activities. Findings were robust as the

observed performances were widely sustained. The ENMO and MAD metrics tended to perform similarly across activities and accelerometer brands.

Interpretations

Hildebrand and colleagues recently developed monitor-specific hip and wrist ENMO thresholds for moderate and vigorous physical activities using raw acceleration data from the ActiGraph GT3X+ and GENEActiv devices (250). ENMO was fairly comparable between the two accelerometer brands in adults, but not in children. The MAD thresholds developed by Vähä-Ypyä and colleagues were much larger in comparison to the monitor-specific thresholds in this study as they predominantly focused on classifying higher intensity activities (254). However, until this project, no thresholds to separate sedentary behaviours from LIPA existed for any raw acceleration metric for these two devices under either wear-site. Via using the abundance of high performing thresholds generated here (based on different metrics, accelerometer brands, and wear-sites), researchers now have a reference for distinguishing between sedentary behaviours and common motion-based activities; with all of the thresholds developed for washing pots recommended to be used as potential proxy indicators of entering and engaging in LIPA, irrespective of the metric, accelerometer brand and wear-site used.

For both hip and wrist monitor placements, in comparison to the ActiGraph GT3X+ monitors, the ENMO and MAD values derived from the GENEActiv devices were observed to be slightly higher, particularly for the lower-intensity activities. A greater magnitude of accelerations from the GENEActiv has been previously reported when conducting time domain analyses of raw acceleration data using these two accelerometers (75, 76). Extensive mechanical testing (e.g. shaker diagnostics) has revealed that the differences observed in the magnitude of the raw acceleration signals (e.g. vector magnitude) between the two devices (GENEActiv established to have higher accelerations) could be due to underlying inner structural variances (75, 76), with features such as the MEMS (micro-electro-mechanical systems) sensor affecting the signal processing and digitization of the output. Other potential causal

factors include; the zero-g offset, reference voltage, analog-to-digital bit-rate conversion, any proprietary filtering, and sensitivity of the MEMS sensor (75, 260). Methods for minimising the differences between the devices include the applications of affine conversions (e.g. correction factors) to the raw acceleration signals (76). It appears that features from the frequency domain are comparable between the two accelerometers (76), although these methods are more intricate. In theory, raw acceleration data between different devices should be comparable to each other. However, this chapter further highlights the subtle differences that become apparent when comparing monitors.

Essentially, both the ENMO and MAD metrics offer simple ways of correcting for the gravitational component. Bassett and colleagues recommend that any newly proposed raw acceleration system should be compared to the ones already in use (132). Although Vähä-Ypyä and colleagues compared the performance of MAD to several other raw acceleration traits (where it proved to be the most exemplary method) (254), it was not equated to the ENMO metric. ENMO is emerging as the prototypical trait for analysing raw acceleration data and is being widely-used by accelerometer researchers (246, 250, 251), thus, following recommendations from Bassett and colleagues (132), it is imperative to compare MAD to ENMO. Furthermore, since the ENMO metric is sensitive to poor calibration of the accelerometer (251), it is ideal to implement sensor calibrated ENMO in order to reduce any erroneous findings. This project indicates that in addition to ENMO, MAD provides an alternative, yet a robust and straightforward technique for analysing raw acceleration data.

Strengths and Limitations

This project has several strengths and some limitations. Strengths include utilisation of widely-used accelerometers, comprehensive data analysis of raw acceleration data collected at a high sampling frequency, laboratory-based experimental design with usage of both hip- and wrist-worn devices, robust statistical analysis, and the generation of monitor-specific thresholds that distinguish between sedentary and non-sedentary activities. These thresholds are sample and protocol specific, implying that

the classifications of sedentary behaviours and LIPA should be broadly comparable between studies - irrespective of the metric, accelerometer brand and wear-site used. However, these strengths also have some inherent limitations. The laboratory-based settings may limit generalizability to free-living environments, and these findings may not be applicable or valid externally. For example, in free-living situations, participants are able to engage in several different activities that were not a part of this laboratory study, and it is possible that the accelerations of these different tasks could be similar to the accelerations of the tasks carried out in the laboratory. Therefore, using these thresholds, although it is feasible to discriminate sedentary from non-sedentary tasks, it would be difficult to distinguish or identify specific activities conducted in an external environment. Moreover, it may be more difficult to classify sedentary behaviours in free-living situations using wrist-worn devices since individuals can carry out sedentary tasks involving arm movement as highlighted in this chapter (e.g. using a computer and a mobile phone whilst in a seated position). Thirdly, with the participants instructed to keep their hands on their thighs during the seated activities that involved watching TV (sitting activities 5-9), the real-life positioning and postures of these sedentary behaviours are less likely to be reflected or fully captured. Nevertheless, for both the accelerometer brands, determining the wrist ENMO and MAD thresholds using computer activity as the only sedentary behaviour did not affect the performance or value of the thresholds (in general, AUROC >0.95 with validation indicating robustness and <10% change in threshold values). In addition, as mentioned earlier in the chapter, recruitment was carried out via word of mouth and over email, and this information was not recorded; therefore, no data on the response rates, compliance, etc. of this study were available. Furthermore, the small sample size and limited range of sedentary behaviours and LIPA can also be considered as weaknesses of the project. With 33 individuals in the study, the consequence of a single case was around 3% on the performance of the metrics. The inclusion of additional activities, such as eating, reading a book or using a mobile phone whilst standing in a larger sample, would have added to the strengths. Lastly, although the thresholds in this project were validated, they were only done so internally (using LOOCV). Therefore, it is desirable to cross-validate all available ENMO and MAD thresholds externally; the performance of

algorithms developed in laboratory conditions attenuates when applied in field environments (261).

Conclusion

In conclusion, the ENMO and MAD metrics are accessible and increasingly used approaches for analysing hip- and wrist-worn raw acceleration data; however, well-developed and validated methods utilising outputs from these methods are sparse. This chapter provides comprehensible monitor-specific hip and wrist ENMO and MAD thresholds for analysing raw acceleration data, particularly for researchers interested in sedentary behaviour and light-intensity movement. Users can exploit these robust ENMO and MAD thresholds to accurately separate sedentary behaviours from common motion-based LIPA. However, caution should be taken if separating sedentary behaviours from standing is of specific interest. In terms of making recommendations for future research, due to its' proven competency and continuous use in the field, this project further supports the use of sensor calibrated ENMO, a well-performing metric which is emerging as the prototypical tool for the analysis of raw acceleration data, to help promote comparability between studies. Nevertheless, the MAD metric also offers an alternative, robust and straightforward technique for analysing raw acceleration data; however, more studies further exploring the MAD metric are required.

CHAPTER SEVEN: DISCUSSION

Chapter Overview

Previous chapters critically appraised the three epidemiological databases (2008 HSE, Walking Away From Type 2 Diabetes, and UK Biobank) used within this PhD (Chapter Two), examined the associations between measures of physical activity, sedentary behaviour and health (Chapters Three, Four, and Five), and explored novel approaches for analysing physical activity and sedentary behaviour data more effectively (Chapter Six). Chapters Three, Four, and Five have increased knowledge in Phase 1 of the behaviour epidemiology proposed by Sallis and colleagues (establish links between behaviours and health); whereas Chapter Six has increased knowledge in Phase 2 of the behaviour epidemiology (develop methods for measuring the behaviour). Thus, via using large and multifaceted datasets, this project has helped fill several gaps in the literature. It has advanced our understanding into the measurement of sedentary behaviour and physical activity, and the relationships they share with physical and cognitive health. The findings have been disseminated via conference presentations and publications, with some research articles making a significant impact in the field (e.g. the paper published in BMC Public Health used the 2008 HSE database and has been cited over 35 times till date). In addition, the research presented within this thesis has also gained substantial national and international media interest. This work has also made a significant contribution towards the future aims of the NIHR Leicester BRC, and can also potentially help inform public health policy and guidance. In addition, the presented body of work has contributed to a comprehensive training programme that has allowed me to gain and practice the skills needed to develop into an epidemiologist specialising in lifestyle research. This chapter outlines the main results reported within this thesis, discusses the implications of these findings, and highlights areas for future research. Table S2 (see Appendix Four: Main Findings, Strengths, and Limitations) summarises the main findings, and the strengths and limitations of each chapter that involved statistical analysis of study data (Chapters Three, Four, Five, and Six).

Thesis Summary

Chapter One provided the background and overall rationale for the thesis. It introduced the key definitions of sedentary behaviour and physical activity, discussed a behavioural epidemiology framework that this PhD followed, gave a brief outline of the previous research carried out in this field and highlighted the gaps in knowledge, and stated the main aims and objectives of this programme of work.

Chapter Two summarised and critically appraised the epidemiological databases (2008 HSE, Walking Away from Type 2 Diabetes, and UK Biobank) used within this PhD. In detail, it discussed the strengths and limitations of each database and the implications of having issues such as a low response rate and missing data.

Chapter Three was based on the analysis of epidemiological data and utilised a nationally representative sample of adults with accelerometer data from the 2008 HSE. In this project, the relationships between mutually exclusive categories of objectively measured physical activity and sedentary time with markers of cardiometabolic health were examined. Here, it was observed that being physically active was associated with a better cardiometabolic health profile, even in those with concomitant high sedentary time. By suggesting that being physically active may offset some of the deleterious consequences of a routinely sedentary lifestyle, this analysis further emphasises the importance of physical activity in the promotion and maintenance of health.

Chapter Four was based on the analysis of epidemiological data and used a population of adults at high risk of T2DM recruited from primary care with mortality and accelerometer assessed physical activity and sedentary behaviour data from the Walking Away from Type 2 Diabetes trial. In this analysis, the associations of objectively measured MVPA and sedentary time with all-cause mortality were examined. These data showed that MVPA time was associated with a lower risk of all-cause mortality, whereas sedentary time showed no association with all-cause mortality. This supports the importance of MVPA in adults at high risk of T2DM; however, more research is required to assess whether objectively measured sedentary

time is associated with health outcomes in those at high risk of T2DM independently of MVPA.

Chapter Five was based on the analysis of epidemiological data and utilised the UK Biobank dataset, which consists of a large sample of adults living in the UK with comprehensive data on a broad range of outcomes (e.g. cognitive function, demographic, health, lifestyle, mental, social, etc.). In the first part of this project, the relationships between different sedentary behaviours and cognitive function were examined. The second part of this project explored whether these relationships were modified by cardiorespiratory fitness. Finally, in the third part of this project, the associations between lifestyle factors and cognitive function were investigated. These data showed that TV viewing and driving time were inversely associated with cognitive function. In contrast, computer use time was positively associated with cognitive function. Cardiorespiratory fitness did not modify these associations. The number of healthy lifestyle factors was positively associated with cognitive function. Therefore, some sedentary behaviours, but not all, are associated with poor cognitive function. These results provide robust observational data supporting public health policies designed to reduce TV viewing and driving time in adults, and increase healthy behaviours for cognitive well-being. However, intervention studies are required to test these hypotheses and confirm these findings.

Chapter Six developed and internally-validated ENMO and MAD thresholds for separating sedentary behaviours from common light-intensity physical activities using raw acceleration data collected from both hip- and wrist-worn ActiGraph GT3X+ and GENEActiv tri-axial accelerometers. The data came from an experimental study conducted within a laboratory. This analysis showed that sedentary behaviours can be accurately separated from common motion-based light-intensity physical activities (except standing still) using these intensity-based thresholds derived from raw acceleration data. These are important findings because the derived thresholds are sample and protocol specific, suggesting that the classifications of sedentary behaviours and light-intensity physical activities should be broadly comparable between studies - irrespective of the metric, accelerometer brand and wear-site used.

Implications and Future Directions

Overall, the findings from this thesis have made an important contribution to the physical activity and sedentary behaviour research field (194, 196, 262, 263). The observational data (Chapters Three, Four, and Five) have allowed us to gain a better understanding of the epidemiology (194, 196, 262); whereas the analysis of raw accelerometer data (Chapter Six) has advanced our knowledge around the measurement aspects (263). The epidemiological analyses have highlighted several research areas for experimental investigation; whereas the measurement analysis has pressed for further research with raw acceleration data and metrics.

Some observational studies have suggested that regular MVPA may counteract some of the deleterious consequences of a habitually sedentary lifestyle (33-38). For example, Ekelund and colleagues recently carried out a harmonised meta-analysis using data from more than 1 million adults to examine whether physical activity attenuates the detrimental association of sedentary behaviour and all-cause mortality (38). The authors found that high levels of MVPA (around 60-75 minutes/day) seem to eliminate the increased risk of death associated with high sedentary time. Therefore, supporting the epidemiological findings presented within this thesis, particularly those in Chapter Three (194), one of the key priorities for future interventional research is to investigate, quantify and confirm the extent to which physical activity modifies the associations of sedentary behaviour with cardiometabolic health and physical health at the population level. Based on the results of this thesis and other highlighted studies, the NIHR Leicester BRC have already started to investigate this concept experimentally with one recently published study showing that CRF moderates glycemic responses to sitting and light activity (264). In addition, experimental studies are required to measure the definite impact of sedentary behaviours, CRF, and lifestyle factors on cognitive health in the general population. For example, better understanding is needed on the causative impact of reducing exposures to potentially cognitively harmful sedentary behaviours such as TV viewing.

Other findings from this PhD have also had an important effect in this research field. For example, the results from the mortality analysis presented within this thesis (Chapter Four) have received a lot of attention from wider research groups, in particular, Prof. Ulf Ekelund's group in Norway. Recent literature suggests that the associations between objectively measured sedentary time, physical activity time and mortality are inconsistent (153, 262, 265-270), which may partly be explained by differences in data cleaning, processing and analytical techniques between studies, and in some studies, low power due to a low number of events. Prof. Ekelund's team have established a consortium and have access to the Norwegian surveillance examinations, the Women's Health Study, and the NHANES. As well as these databases, the consortium have requested access to my findings and the mortality data from the Walking Away from Type 2 Diabetes study to further investigate this topic (262). Therefore, the NIHR Leicester BRC are now contributing to this effort via collaborating with this working group to assist them in executing a harmonised meta-analysis to robustly investigate the associations of sedentary time, LIPA time and MVPA time with all-cause mortality. This highlights the significance of the work carried out in this PhD.

Furthermore, it is important to utilise existing observational datasets to explore the epidemiological gaps highlighted in the literature using count accelerometer data (e.g. as carried out with the HSE (Chapter Three) and Walking Away from Type 2 Diabetes (Chapter Four) analyses within this PhD). However, moving forwards and in order to improve the measurement of behaviours, it is essential to refine measurement processing, and in particular, make use of raw acceleration data (e.g. as suggested in Chapter Six) (263). In recent years, the collection and use of raw acceleration data has increased dramatically; nevertheless, there is a major requisite for the analysis of raw acceleration data using methods that can be applied and understood by all; and therefore, this PhD has attempted to help address this need and help inform future sedentary behaviour and physical activity measurement research. These ideas correspond with the behavioural epidemiology framework proposed by Sallis and colleagues (22), and allow for the other phases to slowly evolve. Recall that the aim of my PhD was largely centred on increasing knowledge in Phase 1 and Phase 2 of this

framework (22). Phase 1 is based around forming associations between behaviours and health, an area where this PhD has added considerable knowledge to. For example, supporting the current public health guidelines (5-7), it showed the significance of physical activity as a contributing factor of cardiometabolic health and mortality (194, 262). In addition, this PhD demonstrated the relevance of lifestyle factors, particularly the different sedentary behaviours (196), on cognitive function. As a relatively new research area, this is particularly important and these findings could have public health implications. The epidemiological results from this PhD provide novel evidence (194, 196, 262), and a constant stream of such findings play a part in generating new recommendations or tailoring the current principles (i.e. Phase 5 of the behavioural epidemiology framework) (22). It is yet to be determined to what extent the findings of this PhD will contribute to further guidance. In relation to physical health, this PhD found the role of sedentary behaviour to be somewhat indeterminate, particularly the lack of association it showed with all-cause mortality (262). Although this could be explained by a key limitation in the database used (i.e. the low number of events in the Walking Away from Type 2 Diabetes trial), this area requires further research to cement the function of sedentary behaviour on physical health, and future projects such as the harmonised meta-analysis in this area by Prof. Ekelund's group will help fill some of these gaps in knowledge. Furthermore, via using and analysing raw data collected from hip- and wrist-worn accelerometers, this PhD increased knowledge in Phase 2 of the behavioural epidemiology framework (263), which is based around developing approaches for measuring behaviours. This has value for epidemiological studies that collect physical activity data using objective measurements (e.g. UK Biobank) (23), and these findings can be linked back to Phase 1 of the framework to build robust associations between behaviours and health; and consequently, lead to Phase 5 (22).

The field of physical activity, sedentary behaviour and public health has matured significantly over the last two decades, and via combining the recent technological advancements with the existing scientific foundation, our knowledge on the associations between physical activity and sedentary behaviour with a wide variety of health outcomes will continue to enhance at a healthy pace. In the USA, the

Department of Health and Human Services recently published a report summarising the evidence on physical activity (271). Based on a wide range of studies, the report states that in addition to a reduced risk of death, greater amounts of regular MVPA reduce the risk of heart disease, stroke, hypertension, T2DM, dementia, depression, postpartum depression, excessive weight gain, falls with injuries among the elderly, and breast, colon, endometrial, esophageal, kidney, stomach, and lung cancer are all less common in individuals who are or become more physically active (271). The report also provides evidence that for some of these conditions, individuals who are or become more physically active, in comparison to their peers with the same condition, have a reduced risk of mortality, reduced risk of developing other chronic diseases, and reduced risk of progression of the disease they already have (271). They also have improved physical function and better quality of life (271). As a consequence, there are significant public health implications here since most of these conditions are associated with direct and indirect costs on health care systems (271). However, important gaps in our understanding still remain. The report indicated some key areas that require further research in the near future using both epidemiological and experimental studies (271), and the findings from my PhD fully support these topics. For example, evidence on the extent to which physical activity, during leisure time or at work, can compensate for increases in sedentary time is an important, popular and well-timed research question (38, 194, 271). Due to the benefits, research suggests that physical activity, particularly MVPA, should be a part of everyday lifestyle, especially in individuals who are sedentary for large portions of the day (38, 194, 271). Therefore, with the use of prospective data, it is important to determine the dose-response, independent and interactive effects of physical activity and sedentary behaviour on different health outcomes. In particular, information on the role that physical activity plays in changing the mortality risks associated with sedentary time is rather limited; and a better understanding of these interactive effects will allow for more precise recommendations regarding the duration, frequency and intensity of physical activity required to maximise health benefits in people with different levels of sedentary behaviour (38, 271). It would also be useful to learn how factors such as age, BMI, sex, ethnicity, socioeconomic status, etc. are related to these associations since

few studies have addressed the issues of effect modification. This will help us understand how generalizable the potential benefits of reducing sedentary time and increasing physical activity are in preventing poor physical health, and whether different recommendations are required for different groups of people - again, this could have great public health implications. Furthermore, our understanding on the effects of sedentary behaviour on cognitive health is still in its early stages. Given that recent evidence suggests that sedentary behaviour is distinct from physical inactivity and that different sedentary behaviours may share different relationships with cognitive function (196), more knowledge on the effects of sedentary behaviour on brain health could help inform and target interventions aimed at improving cognitive function across a variety of populations, including middle-aged and older adults who typically spend a significant proportion of their day sitting or engaged in specific sedentary behaviours (15-18). Therefore, it is important to implement randomized controlled trials that improve our understanding of the impact of varying contexts, durations, and patterns of different sedentary behaviours on cognitive health throughout the lifespan (196, 271). Moreover, in the past, it was difficult to collect accurate data on the various elements of physical activity and sedentary behaviour in large cohorts. However, the UK Biobank recently demonstrated that obtaining objectively measured data in sizeable populations (n ~100,000) is in fact possible and practical (99, 213), and some researchers have already started to utilise these data (272-274) (see Chapter Two for a concise discussion on the strengths and limitations of the UK Biobank accelerometer sample). Thus, via using the appropriate metrics, future studies should also make use of such large databases to further examine the associations of physical activity and sedentary behaviour with health outcomes and increase our understanding in this research area.

Adults are recommended to engage in at least 150 minutes of MPA or at least 75 minutes of VPA every week; and these guidelines are clear, well-known and used all over the world (5-7). In contrast, there are no official or transparent guidelines that quantify the maximum amount of time an individual should spend sedentary or in specific sedentary behaviours. Therefore, terminologies such as “low sedentary time” and “high sedentary time” can only be used through data-driven methods.

Nevertheless, based on the limited evidence, some countries have recognised the potential impact of sedentary behaviour on health; and accordingly, they have started to propose that adults reduce their sedentary time (275-279). For example, in 2014, the Norwegian Directorate of Health in Norway recommended that 'sedentary time should be reduced' and 'long periods of sedentary behaviour should be interrupted with activity breaks' (275). Similarly, in 2015, the New Zealand Ministry of Health in New Zealand recommended individuals to 'sit less' and 'break up long periods of sitting' (276). Via the department of health, the four home countries' chief medical officers in the UK also made some recommendations in 2011 (277); however, these too were not measurable. They advised that 'all adults should minimise the amount of time spent being sedentary (sitting) for extended periods' (277). In addition, messages such as 'replacing motorised travel with active travel such cycling and walking; taking regular breaks from extended periods of sedentary behaviour; and reducing total screen time' were also suggested (277). Although these are potentially health promoting messages for the public (the 'reducing total screen time' message is discussed below), they are all quite vague; and without quantification, it is very difficult for an individual to know how much sedentary time is too much or how much they should reduce it by. The challenge here lies in the existing and limited evidence of the associations between sedentary behaviour and health. Sedentary time has previously been shown to be negatively associated with several physical health outcomes, including CVD, T2DM and mortality (8-13). However, particularly relating to the mortality findings presented within this PhD, the role of sedentary behaviour was observed to be somewhat equivocal (262); and as mentioned earlier, the evidence on this is currently vague (153, 265-270). In addition, linking to the screen time message, the analyses with the cognitive function indicated that some sedentary behaviours (TV viewing and driving), but not all (computer use), are related to poor cognitive health (196); and although computer use time is associated with positive cognitive function (57-60, 196), sitting time itself is associated with negative physical health (8-13). Combined all together, this high level of complexity makes it difficult for governing bodies to issue evidence-based guidelines for sedentary time or specific sedentary

behaviours. Inconsistent findings also add to this convolution. Thus, more evidence from both epidemiological and mechanistic studies is required in this field.

On this topic, Stamatakis and colleagues recently conducted a non-systematic narrative review to assess the fundamental evidence relating to the development of guidance on sedentary behaviour for adults (280). They highlighted that although some advancements have been made, we know very little about the independent negative health effects of time spent in sedentary behaviour. Although they mainly considered physical health, and not cognitive health, the authors stated that there are still several areas that require substantial enhancements due to the inconsistencies in how the evidence has been generated and interpreted. Some of the major limitations include discrepancies between epidemiological and experimental studies, reliance on self-reported data, and misinterpretation of epidemiological findings whereby systematically inconsistent associations have been claimed to be strong evidence (280). Therefore, this implies that the evidence on sedentary behaviour is currently ambiguous and still unevolved; and at present, it cannot support quantifiable public health guidelines, which requires a robust and stable evidence base. This PhD has progressed the field and the evidence from it supports these wider conclusions and further highlights the complexities of sedentary behaviour research. Furthermore, whilst the research in this area develops and consistently begins to demonstrate reliable findings, prioritizing a message such as 'move more at any intensity' may be the most practical course of action for the time being (280), but it should not be used to support definitive guidelines. This is particularly important for cognitive health, for example, since the research in this area is still in its infancy, as shown by the analyses in this PhD.

Conclusion

Via these comprehensive epidemiological data analyses, I have highlighted the prominence of physical activity as a key element of cardiometabolic health and all-cause mortality; however, the role of sedentary behaviour was found to be more ambiguous. Further work with cognitive data showed that some sedentary behaviours,

but not all, are associated with poor cognitive function. TV viewing and driving (two of the most common forms of sedentary behaviour) were inversely associated with cognitive function. In contrast, computer use was positively associated with cognitive function. A further analysis of these data demonstrated that CRF does not modify these associations. Additionally, the sedentary behaviours showed the strongest relationships with cognitive function in comparison to all of the other lifestyle factors considered. These findings provide robust observational data supporting public health policies designed to reduce TV viewing and driving time in adults, and increase healthy behaviours for optimum cognitive well-being. However, intervention studies are necessary to test these hypotheses and confirm these findings. Lastly, the experimental data analyses showed that researchers can accurately separate sedentary behaviours from LIPA using robust thresholds derived from raw acceleration data; hence, providing a valuable resource for future studies.

The programme of research carried out in this thesis has made an original contribution to filling the gaps in existing knowledge, and in relation to mental and physical health, the epidemiological work should persuade policy makers to think about the whole band of activity, from sedentary behaviour to MVPA. Nevertheless, until more evidence-based information and guidelines on sedentary behaviour emerge, a simple message for now would be to sit less and move more for optimum overall health.

APPENDICES

Appendix One: Author Contribution to Overall Programme of Work

Kishan Bakrania, the author of this thesis, was responsible for implementing the following key actions (not an exhaustive list) in relation to Chapters Three (Analysis of Epidemiological Data: 2008 HSE Data), Four (Analysis of Epidemiological Data: Walking Away from Type 2 Diabetes: A Cluster Randomized Controlled Trial: Primary Care Data), Five (Analysis of Epidemiological Data: UK Biobank Data), and Six (Analysis of Physical Activity and Sedentary Behaviour Data: Raw Acceleration Data) presented within this thesis:

- Identified the gaps in knowledge
- Conceptualised and developed the research questions
- Obtained the necessary datasets via applications to relevant national health governing bodies and resources where required (e.g. Walking Away from Type 2 Diabetes mortality data (from ONS via HSCIC); and UK Biobank data (from UK Biobank))
- Derived the statistical analysis plans
- Cleaned and managed the study datasets
- Executed the analyses
- Interpreted and wrote-up the findings in a clear and logical manner
- Drafted and submitted abstracts for national and international conferences and meetings
- Drafted and submitted research articles for publications in peer-reviewed academic journals
- Responded to comments from peer-reviewers
- Liaised with the journal editorial team until final publication of findings
- Presented findings and disseminated the research at local, national and international conferences and meetings

In relation to the publications arising from this programme of work, in all instances, the co-authors revised the manuscript and approved the final version of the manuscript before submission to the journal. Dr. Thomas Yates and Dr. Charlotte Edwardson also assisted in identifying the gaps in knowledge as well as conceptualising and developing the research ideas.

Appendix Two: Awards

Collaboration for Leadership in Applied Health Research and Care
East Midlands

NHS
National Institute for Health Research

Institute of Mental Health
University of Nottingham Innovation Park
Triumph Road
Nottingham
NG7 2TU

E: emma.rowley@nottingham.ac.uk
www.clahrc-em.nihr.ac.uk

11 January 2017

NIHR CLAHRC East Midlands - PhD Travel/Research Prize

Dear Kishan

Many thanks for your application for the CLAHRC East Midlands PhD Travel / Research prize. I am pleased to be able to tell you that the scoring panel marked your application highly, and you have been successful in securing the funding, conditional on written confirmation that your paper was accepted.

CLAHRC has awarded you £500 to be used between 1st October 2016 – 31st March 2017.

Next steps:

1. If you have applied for this money to cover the cost of attending a conference, you will need to provide written confirmation that your paper/poster has been accepted for presentation. Please send this to Alice.Phillips@nottingham.ac.uk
2. In order to claim your funding, you will need to email Jothy.Brooks@nottingham.ac.uk (the CLAHRC's Finance Officer) by 31st March 2017 with the following details. Please be aware that any requests received after this date will not be paid.
   - If you are a University of Nottingham student, you will need to send a project code number (your supervisor or your school postgraduate administrator will be able to advise you of this).
   - If you are a student from another University, your Finance Department will need to send an invoice addressed to Jothy Brooks, University of Nottingham, CLAHRC EM, Institute of Mental Health, University of Nottingham Innovation Park, Triumph Road, Nottingham NG7 2TU. (Your school administrator or finance officer will be able to arrange this for you).
3. Once Jothy has either of these she will arrange for the funds to be transferred; you will receive an email confirming that the transfer has been made. You should then liaise with your own department to spend the funds in the way that you described in your application form.
4. One month after you return from the conference, or you finish your data collection, you will need to send your summary report (4 pages maximum) and a copy of all your receipts to the CLAHRC. These should be sent to Alice.Phillips@nottingham.ac.uk
5. The following disclaimer should be included on any publications that result from your research: This research was supported by the National Institute of Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care East Midlands (CLAHRC EM). The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

We will be contacting you periodically for details of any publications, and please feel free to contact us if you feel that CLAHRC EM can be of any further support.

The National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands is a partnership between Nottinghamshire Healthcare and the Universities of Nottingham and Leicester.

Congratulations on your award.

Best wishes

Emma

Dr Emma Rowley
Capacity Development Lead
NIHR CLAHRC EM

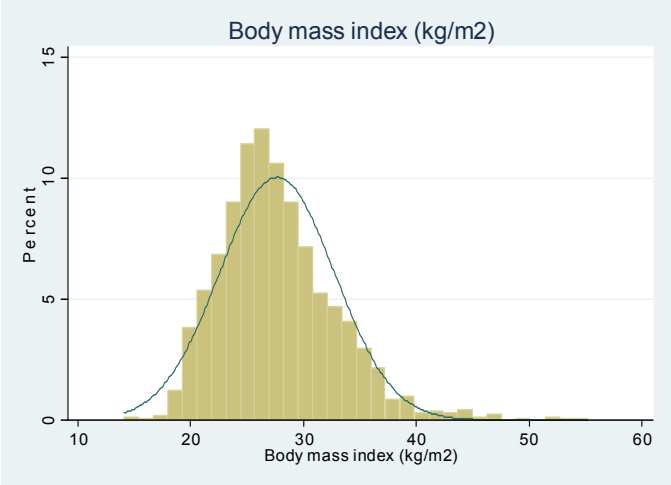
Copied to:
Jothy Brooks – CLAHRC Finance Officer

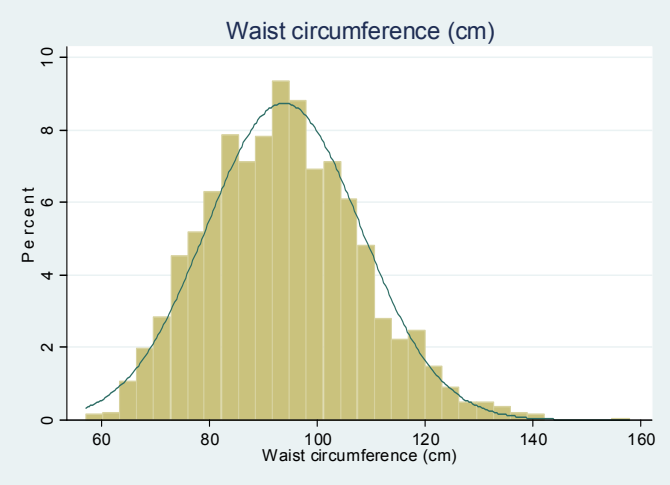
The National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands is a partnership between Nottinghamshire Healthcare and the Universities of Nottingham and Leicester.

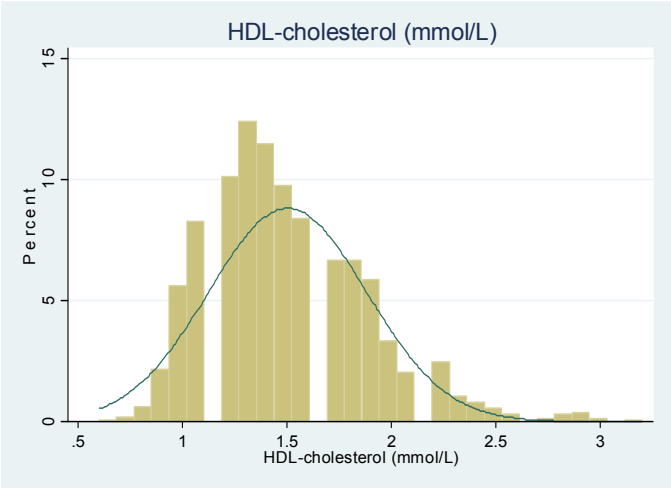
Appendix Three: Supplementary Material

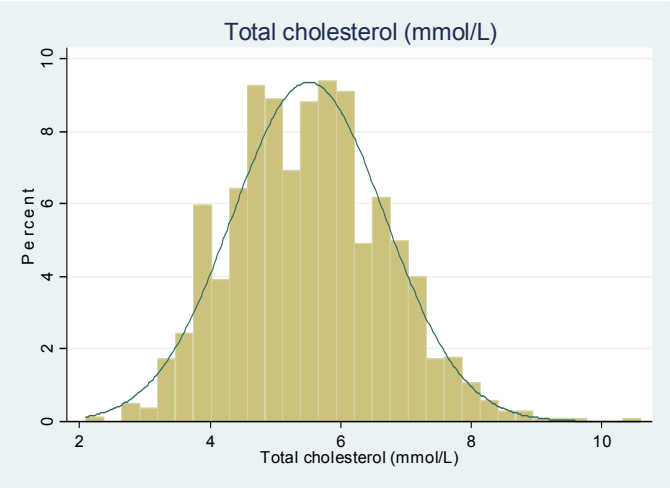
Supplementary Data

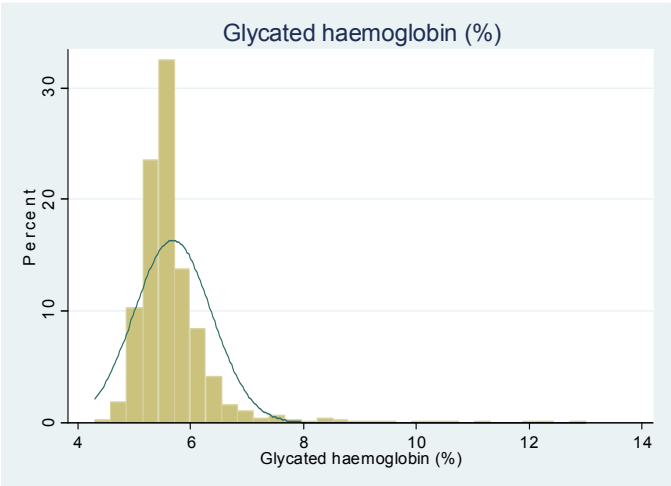
Figure S1 - Observational study (2008 Health Survey for England data): Distributions of the key outcomes and exposures

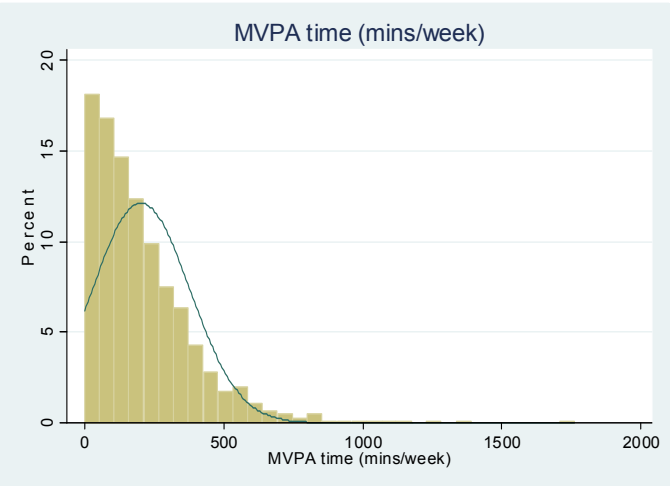


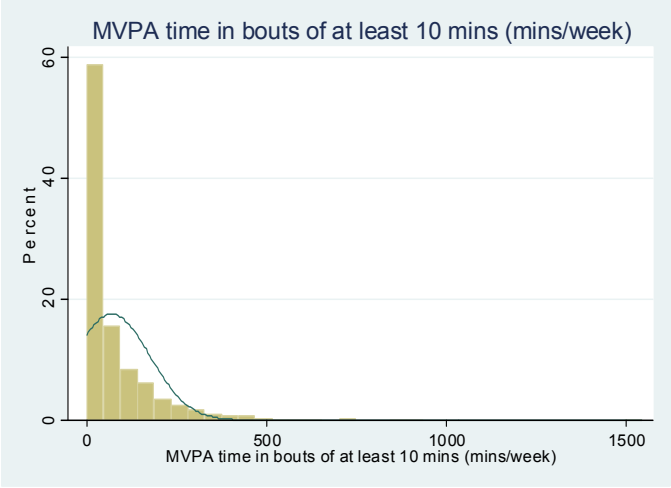


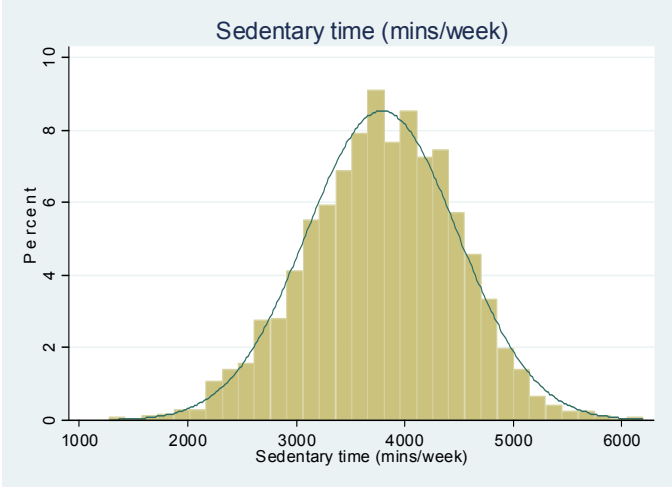


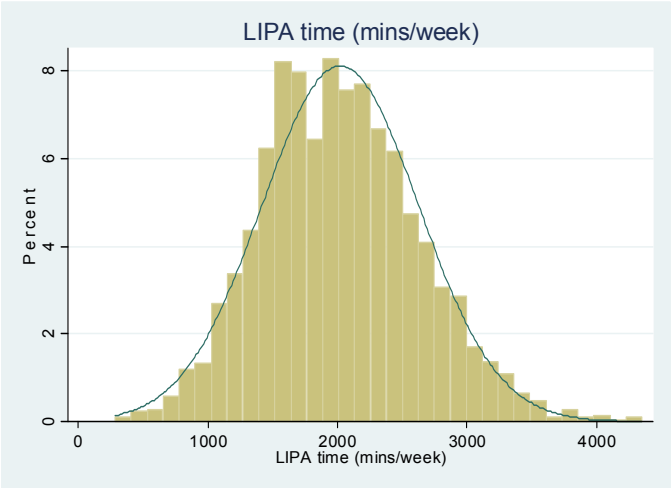







MVPA time in bouts of at least 10 mins (mins/week)
Percent
0
20
40
60
0
500
1000
1500
MVPA time in bouts of at least 10 mins (mins/week)


Sedentary time (mins/week)
Percent
0
2
4
6
8
10
1000
2000
3000
4000
5000
6000
Sedentary time (mins/week)


LIPA time (mins/week)
Percent
0
2
4
6
8
0
1000
2000
3000
4000
LIPA time (mins/week)

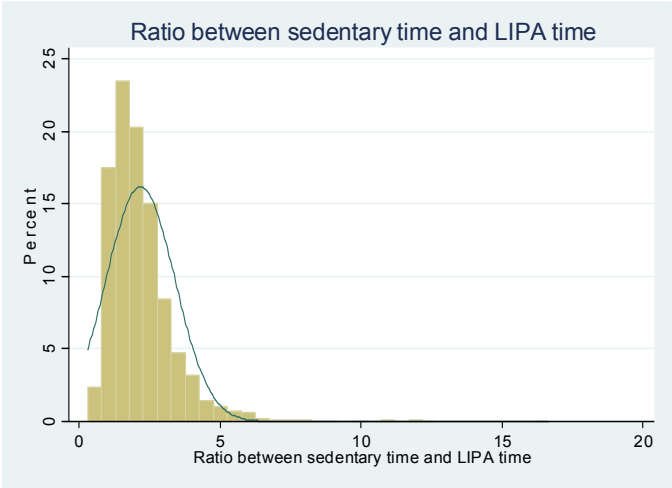
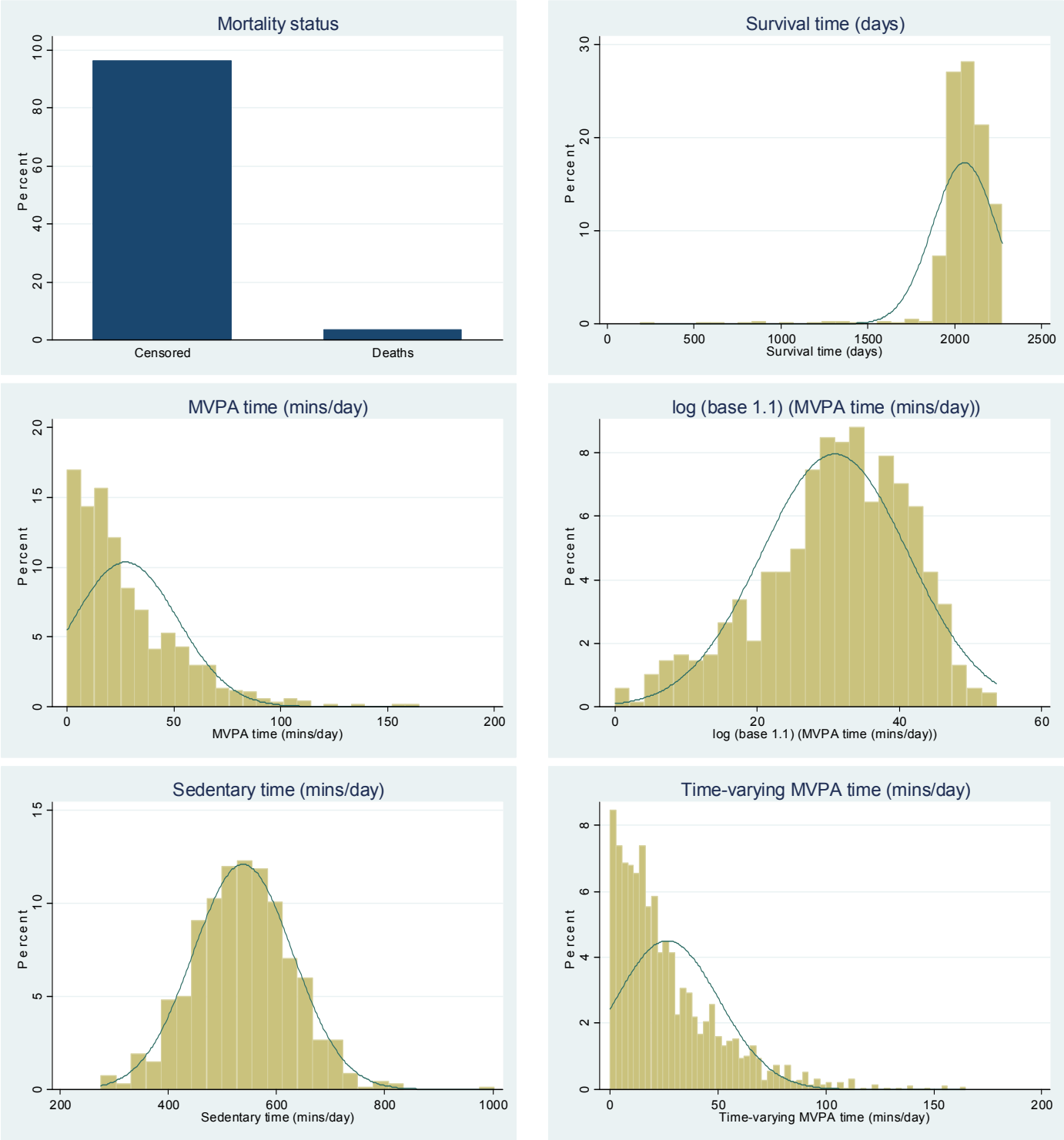
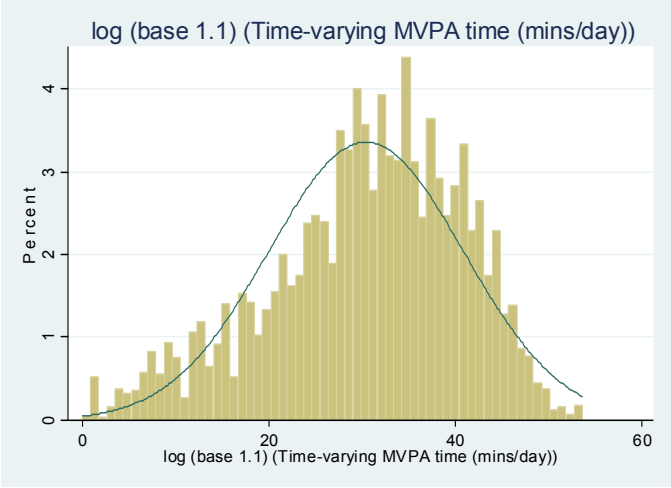

Ratio between sedentary time and LIPA time
Percent
0
5
10
15
20
25
0
5
10
15
20
Ratio between sedentary time and LIPA time

Figure S2 - Observational study (Walking Away from Type 2 Diabetes data): Distributions of the key outcomes and exposures




log (base 1.1) (Time-varying MVPA time (mins/day))
Percent
0
1
2
3
4
0
20
40
60
log (base 1.1) (Time-varying MVPA time (mins/day))

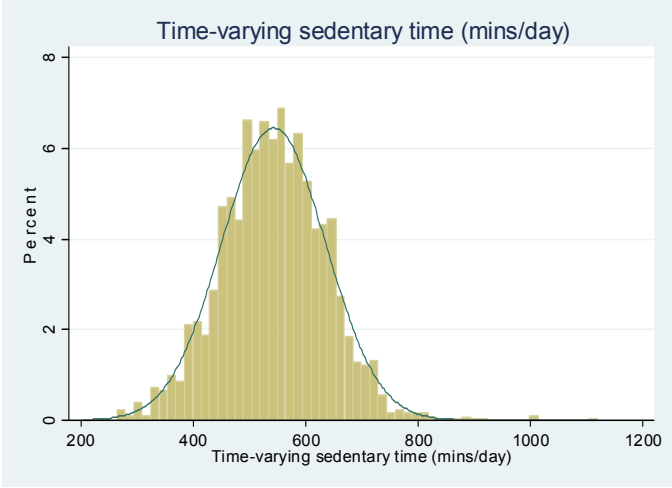
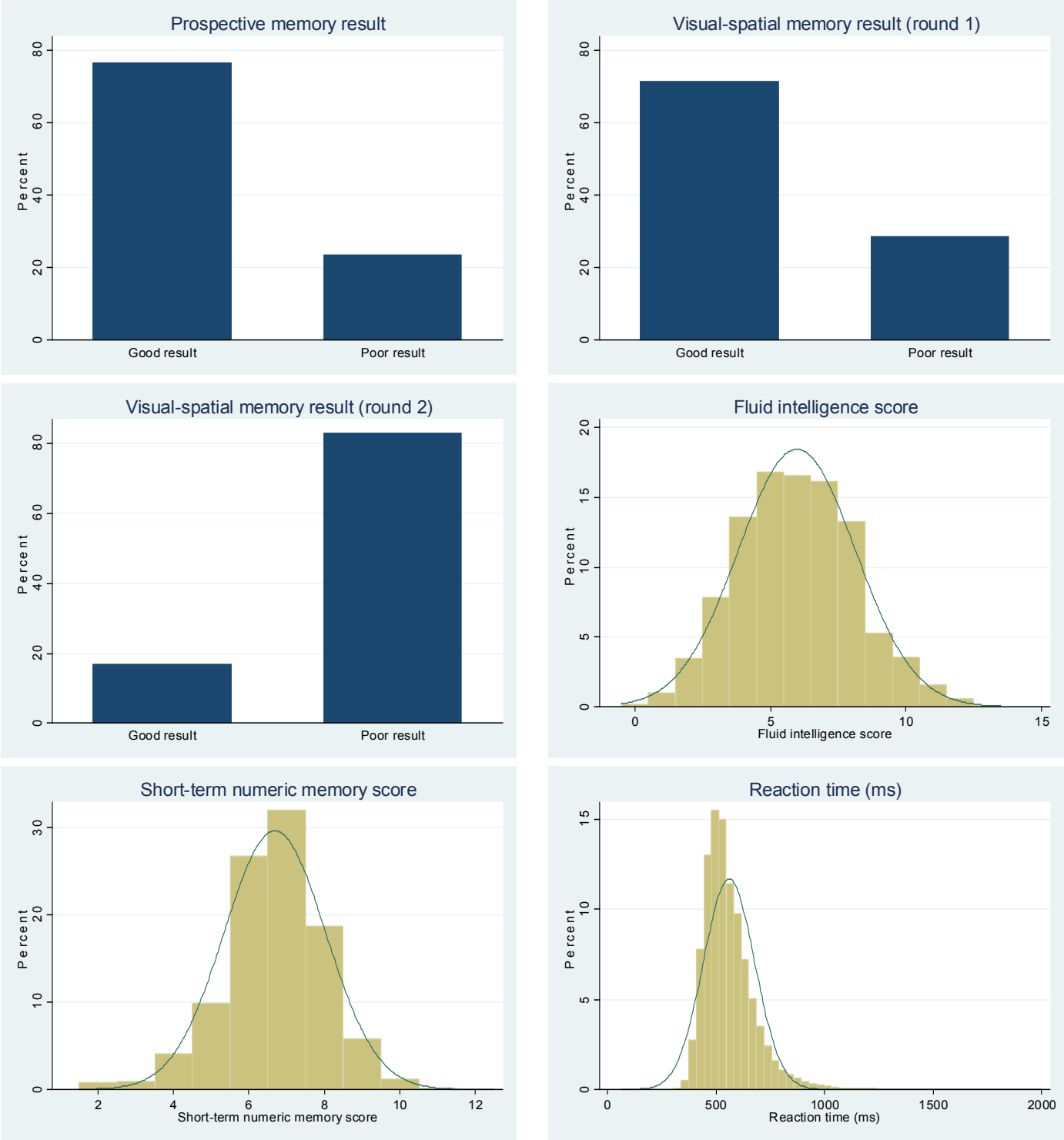
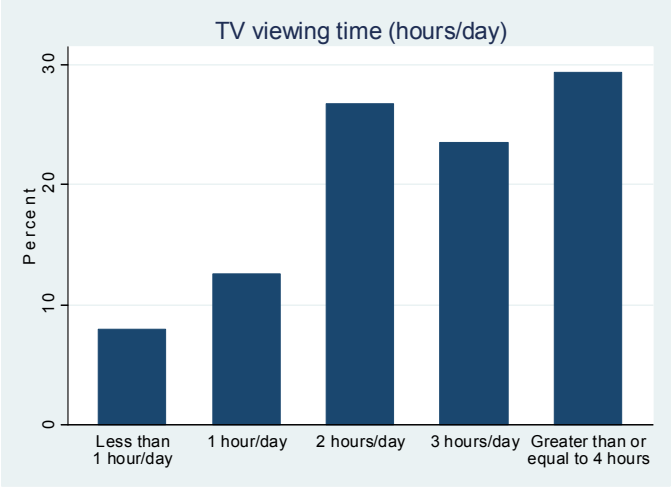
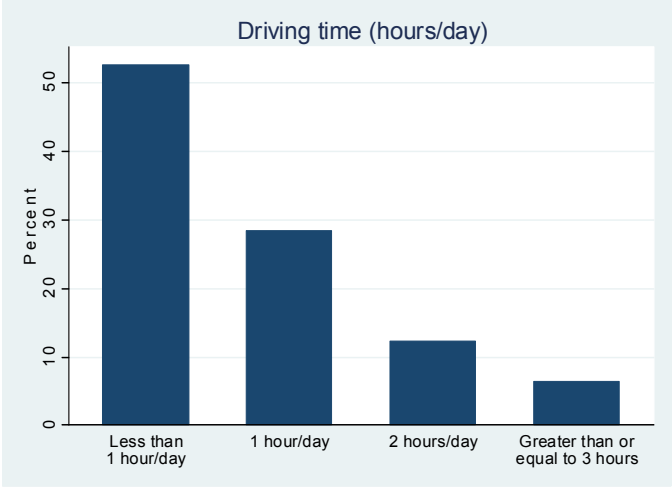
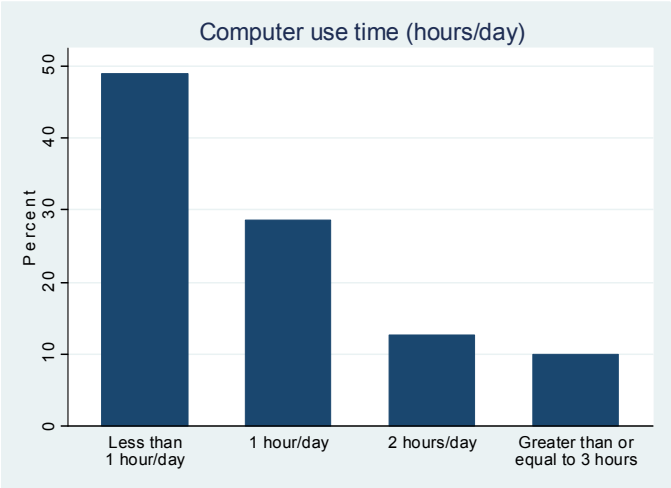

Time-varying sedentary time (mins/day)
Percent
0
2
4
6
8
200
400
600
800
1000
1200
Time-varying sedentary time (mins/day)

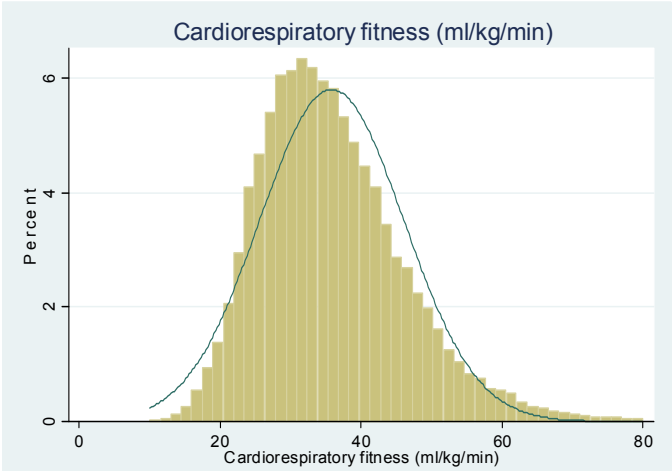
Figure S3 - Observational study (UK Biobank data): Distributions of the key outcomes and exposures

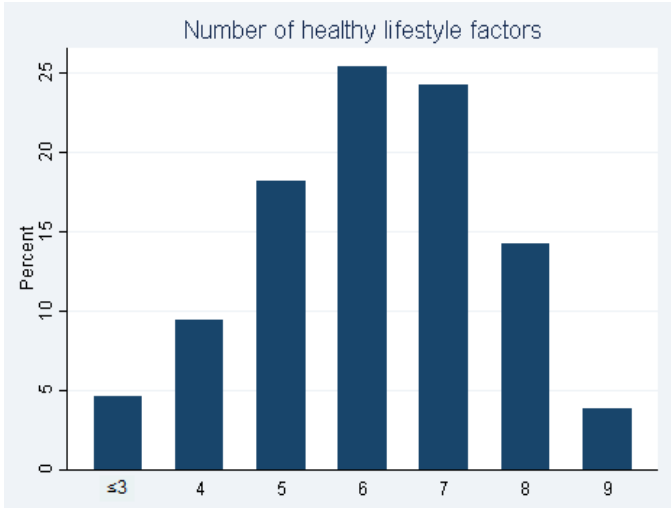


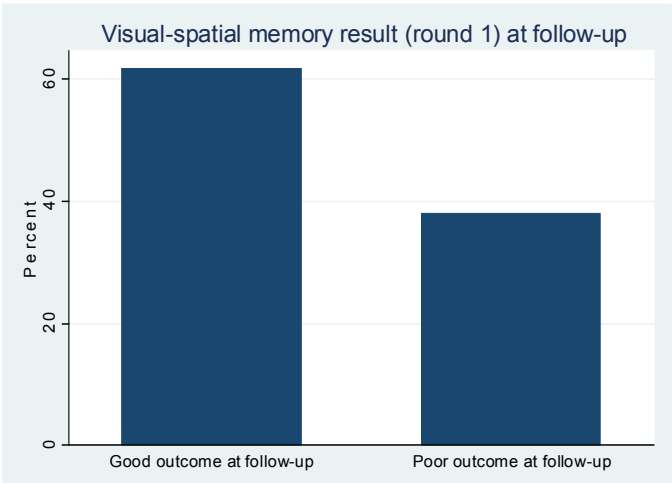

TV viewing time (hours/day)
Percent
0
10
20
30
Less than 1 hour/day
1 hour/day
2 hours/day
3 hours/day
Greater than or equal to 4 hours

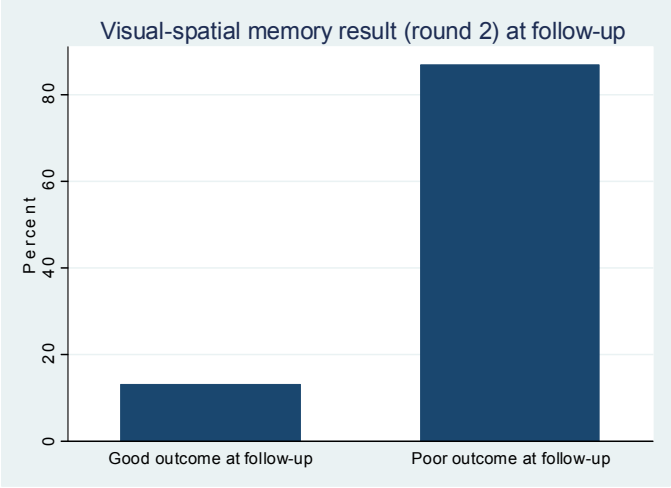

Driving time (hours/day)
Percent
0
10
20
30
40
50
Less than 1 hour/day
1 hour/day
2 hours/day
Greater than or equal to 3 hours

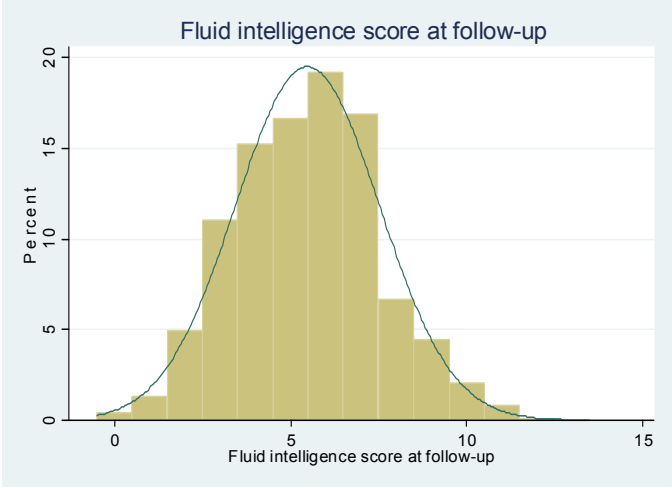

Computer use time (hours/day)
Percent
0
10
20
30
40
50
Less than 1 hour/day
1 hour/day
2 hours/day
Greater than or equal to 3 hours

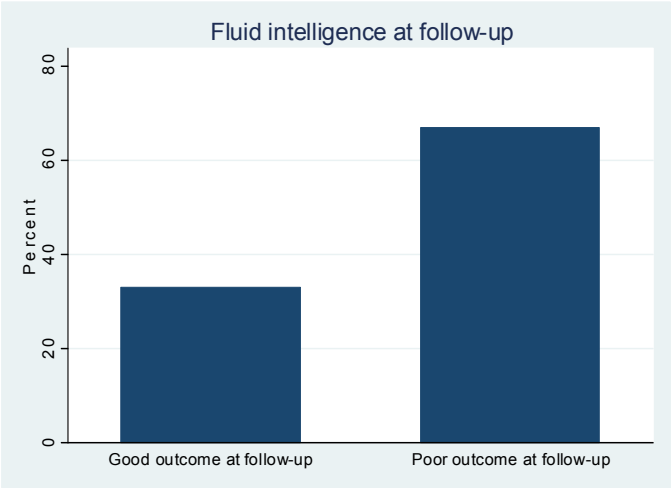

Cardiorespiratory fitness (ml/kg/min)
Percent
0
2
4
6
0
20
40
60
80
Cardiorespiratory fitness (ml/kg/min)

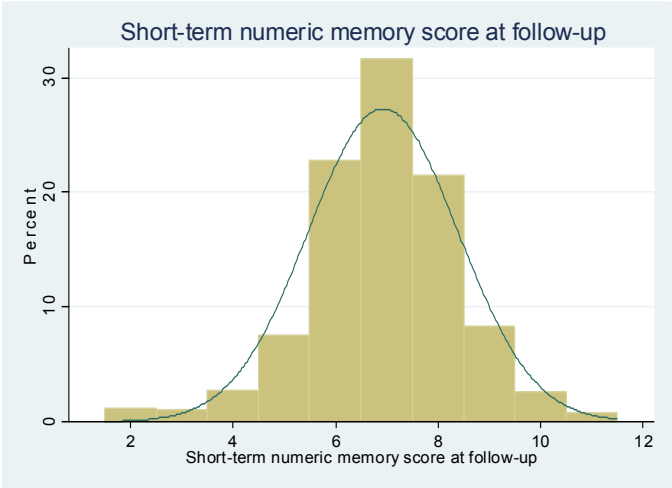

Number of healthy lifestyle factors
Percent
0
5
10
15
20
25
≤3
4
5
6
7
8
9


Visual-spatial memory result (round 1) at follow-up
Percent
0
20
40
60
Good outcome at follow-up
Poor outcome at follow-up


Visual-spatial memory result (round 2) at follow-up
Percent
0
20
40
60
80
Good outcome at follow-up
Poor outcome at follow-up


Fluid intelligence score at follow-up
Percent
0
5
10
15
20
0
5
10
15
Fluid intelligence score at follow-up


Fluid intelligence at follow-up
Percent
0
20
40
60
80
Good outcome at follow-up
Poor outcome at follow-up


Short-term numeric memory score at follow-up
Percent
0
10
20
30
2
4
6
8
10
12
Short-term numeric memory score at follow-up

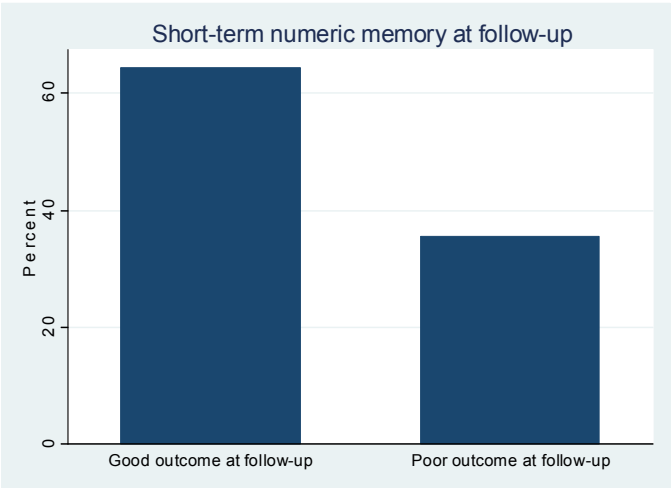
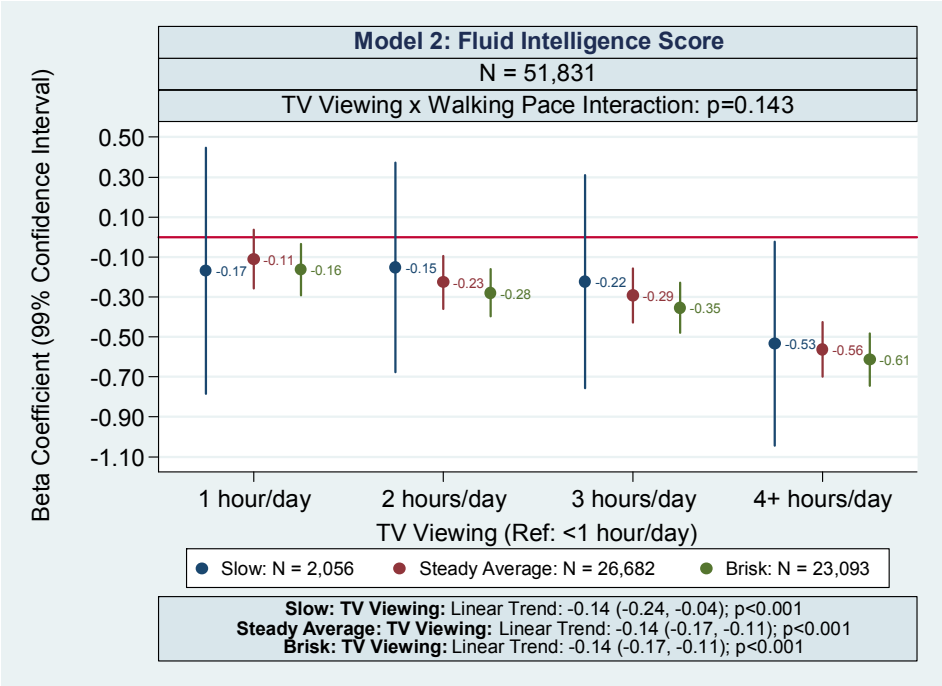

Short-term numeric memory at follow-up
Percent
0
20
40
60
Good outcome at follow-up
Poor outcome at follow-up

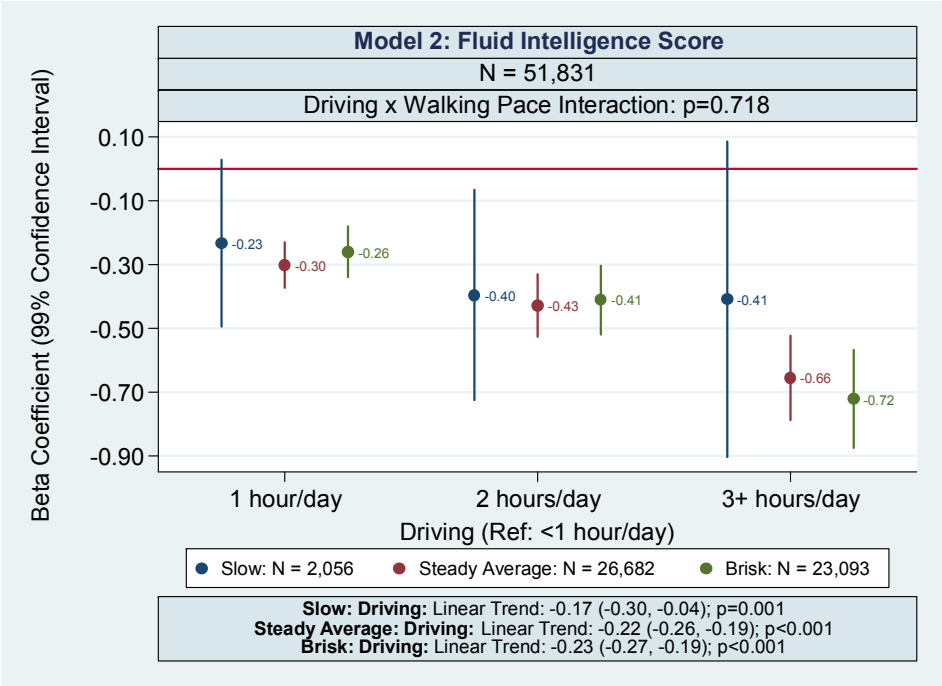
Table S1 - Observational study (UK Biobank data): Correlation coefficients between the different cognitive tests at baseline

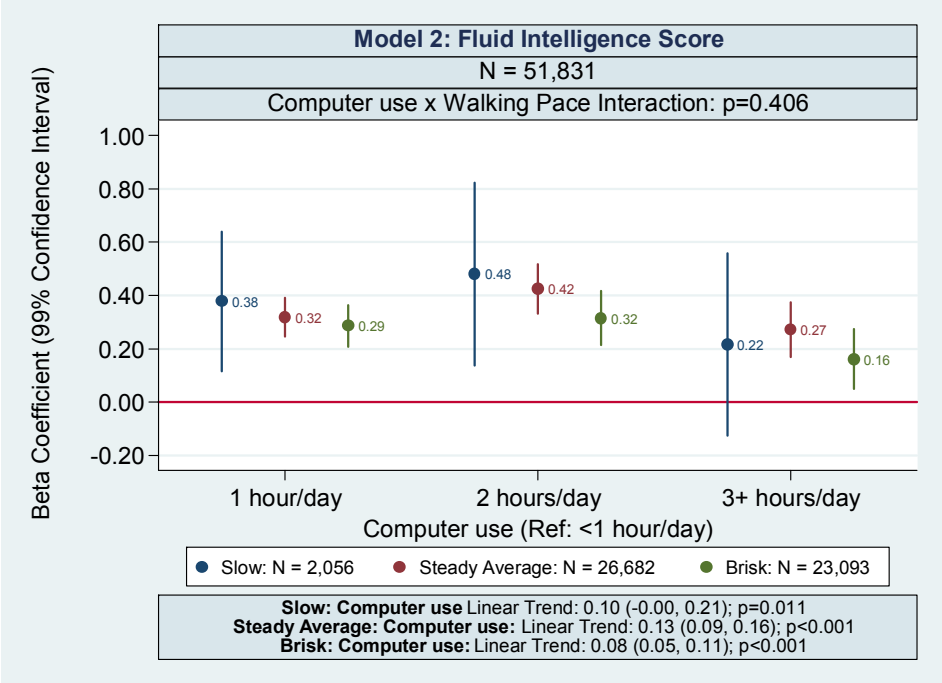
Correlation coefficients	Prospective memory result	Visual-spatial memory result (round 1)	Visual-spatial memory result (round 2)	Fluid intelligence score	Short-term numeric memory score	Reaction time
Prospective memory result	-					
Visual-spatial memory result (round 1)	0.143 †	-				
Visual-spatial memory result (round 2)	0.089 †	0.061 †	-			
Fluid intelligence score	-0.313 ‡	-0.177 ‡	-0.127 ‡	-		
Short-term numeric memory score	-0.216 ‡	-0.137 ‡	-0.086 ‡	0.393 ǂ 0.382 #	-	
Reaction time	0.164 ‡	0.104 ‡	0.083 ‡	-0.181 ǂ -0.176 #	-0.133 ǂ -0.126 #	-

† Phi correlation coefficient (two dichotomous variables)
‡ Point biserial correlation coefficient (one normally distributed continuous variable and one dichotomous variable)
ǂ Pearson correlation coefficient (two normally distributed continuous variables)
Spearman's rank correlation coefficient (two ranked variables)

Figure S4 - Observational study (UK Biobank data): Interactions with walking pace: associations between sedentary behaviours and fluid intelligence







Fluid intelligence score: continuous: total number of correct answers. A beta coefficient of greater than 0 indicates a higher score; and a beta coefficient of less than 0 indicates a lower score.

Interaction between sedentary behaviours and walking pace (statistical significance was established at p-value< 0.05): stratified models (statistical significance was established at p-value<0.01) were mutually adjusted for the other sedentary behaviours and for age, body mass index, sex, ethnicity, social deprivation index, employment status, education level, fruit and vegetable consumption, smoking status, alcohol drinking status, sleep duration, frequency of ≥10 minutes of walking, frequency of ≥10 minutes of moderate physical activity, frequency of ≥10 minutes of vigorous physical activity, number of cancers, number of non-cancer illnesses, and number of medications/treatments.

Supplementary Calculations

Calculation S1

Estimating the clinical significance of the differences observed in fluid intelligence

Cross − sectional associations at baseline beween sedentary behaviours and fluid intelligence

Model 2:

$N = 145{,}124$

SD (fluid intelligence score) $= 2.1$

Linear terms:

β (TV viewing time) $= -0.15$

β (Driving time) $= -0.24$

β (Computer use time) $= 0.12$

Sabia and colleagues (1):

Cox proportional hazards regression model adjusted for age and sex:

A higher fluid intelligence score by 1 SD was significantly associated with a 14% lower risk of all − cause mortality

$\Longrightarrow$ HR $= 0.86$ (95% CI: 0.74, 0.99)

Application to data:

Ratio of β (TV viewing time) to standard deviation $= \dfrac{-0.15}{2.1}$

Calculating the associated HR for a lower fluid intelligence score by 0.15 units:

$\Longrightarrow 0.86^{\frac{-0.15}{2.1}} \cong 1.011$ (3 dp)

$\Longrightarrow$ 1.1% higher risk of all − cause mortality for a lower fluid intelligence score by 0.15 units

Similarly:

Driving time:

$\Longrightarrow$ 1.7% higher risk of all − cause mortality for a lower fluid intelligence score by 0.24 units

Computer use time:

$\Longrightarrow$ 0.9% lower risk of all − cause mortality for a higher fluid intelligence score by 0.12 units

Batterham and colleagues (2):

Cox proportional hazards regression model adjusted for age and sex:

A higher fluid intelligence score by 1 SD was significantly associated with a 24% lower risk of all − cause mortality

$\Longrightarrow$ HR of 0.76 (95% CI: 0.70, 0.82)

Application to data:

Ratio of β (TV viewing time) to standard deviation $= \frac{-0.15}{2.1}$

Calculating the associated HR for a lower fluid intelligence score by 0.15 units:

$\Longrightarrow 0.76^{\frac{-0.15}{2.1}} \cong 1.020$ (3 dp)

$\Longrightarrow$ 2.0% higher risk of all − cause mortality for a lower fluid intelligence score by 0.15 units

Similarly:

Driving time:

$\Longrightarrow$ 3.2% higher risk of all − cause mortality for a lower fluid intelligence score by 0.24 units

Computer use time:

$\Longrightarrow$ 1.6% lower risk of all − cause mortality for a higher fluid intelligence score by 0.12 units

(1) Sabia S, Guéguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. *Neurobiol Aging*. 2010;31(4):688-695.
(2) Batterham PJ, Christensen H, Mackinnon AJ. Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms. *Intelligence*. 2009;37:551-560.

Calculation S2

Estimating the clinical significance of the differences observed in fluid intelligence

Cross – sectional associations at baseline between the number of healthy lifestyle factors and fluid intelligence

Multiple linear regression model:

N = 146,598

SD (fluid intelligence score) = 2.1

Linear trend: β (each additional lifestyle factor > 3) = 0.18

Sabia and colleagues (1):

Cox proportional hazards regression model adjusted for age and sex:

A higher fluid intelligence score by 1 SD was associated with a 14% lower risk of all – cause mortality

⟹ Hazard ratio = 0.86 (95% CI: 0.74, 0.99)

Application to our data:

Ratio of β to standard deviation $= \frac{0.18}{2.1}$

Calculating the associated hazard ratio for a higher fluid intelligence score by 0.18 units:

$\Longrightarrow 0.86^{\frac{0.18}{2.1}} \cong 0.987$ (3 dp)

⟹ 1.3% lower risk of all – cause mortality for a higher fluid intelligence score by 0.18 units

Batterham and colleagues (2):

Cox proportional hazards regression model adjusted for age and sex:

A higher fluid intelligence score by 1 SD was associated with a 24% lower risk of all – cause mortality

⟹ Hazard ratio of 0.76 (95% CI: 0.70, 0.82)

Application to our data:

Ratio of β to standard deviation $= \frac{0.18}{2.1}$

Calculating the associated hazard ratio for a higher fluid intelligence score by 0.18 units:

$\Longrightarrow 0.76^{\frac{0.18}{2.1}} \cong 0.977$ (3 dp)

⟹ 2.3% lower risk of all – cause mortality for a higher fluid intelligence score by 0.18 units

(1) Sabia S, Guéguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. *Neurobiol Aging*. 2010;31(4):688-695.

(2) Batterham PJ, Christensen H, Mackinnon AJ. Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms. *Intelligence*. 2009;37:551-560.

Appendix Four: Main Findings, Strengths, and Limitations

Table S2 - Main findings, strengths, and limitations of each chapter that involved statistical analysis of study data (Chapters Three, Four, Five, and Six)

PhD Thesis Chapter	Main Findings	Strengths	Limitations
Chapter Three: Analysis of Epidemiological Data: 2008 HSE Data	In a large national survey sample of English adults, being physically active was associated with a better cardiometabolic health profile, even in those with concomitant high sedentary time.	• National survey dataset with a multifaceted stratified random sampling procedure • Objectively measured physical activity and sedentary behaviour data • A validated and clinically employed measure of glycaemic status was included (HbA1c) • Wide range of sensitivity analyses	• Sedentary status classified using a data-driven approach • Non-fasting measures of HDL-cholesterol and total cholesterol • Moderately high proportions of missing data in the blood analytes (HDL-cholesterol, total cholesterol, and HbA1c) • Although HbA1c is an established clinical measure of glycaemia that imitates average glucose concentrations over the previous 2-3 months, it is not a perfect index of blood glucose for all individuals, and it does not adequately reflect the glycaemic control status in some diseases that change the lifespan of erythrocytes, such as chronic liver disease • Cross-sectional design prohibits the possibility of establishing causality (reverse-causality remains open)

			• Unmeasured variables may have confounded the observed associations • Relatively small sample for a national survey (only a small fraction of the total participants was asked to wear an accelerometer) • Accelerometer data were based on classifying horizontal movement intensity; and cannot differentiate between different postures (i.e. sitting and standing) • Ethnically heterogeneous White population
Chapter Four: Analysis of Epidemiological Data: Walking Away from Type 2 Diabetes: A Cluster Randomized Controlled Trial: Primary Care Data	In a regional sample of adults at high risk of T2DM recruited from primary care, MVPA time was associated with a lower risk of all-cause mortality. Conversely, sedentary time showed no association with all-cause mortality.	• Objectively measured MVPA and sedentary behaviour data • High risk sample • Robust statistical analysis plan	• Low number of events • Only a small number of key covariates were adjusted for; thus, it is possible that other factors were confounding the associations or that reverse causation was contributing to the observed association between MVPA and all-cause mortality • The non-significant association with sedentary time could be due to a type II error arising from a lack of statistical power

Chapter Five: Analysis of Epidemiological Data: UK Biobank Data	In a large sample of adults living in the UK, TV viewing and driving time were inversely associated with cognitive function. In contrast, computer use time was positively associated with cognitive function (first part of project). A further analysis of these data demonstrated that cardiorespiratory fitness does not modify these associations (second part of project). Lastly, a final analysis of these data demonstrated that the number of healthy lifestyle factors was positively associated with cognitive function (third part of project).	• Large sample of UK adults • Evaluation of dose-response and linear relationships between mutually adjusted and time quantified sedentary behaviours and a wide range of comprehensive cognitive outcomes • Detailed covariate data enabling several important and relevant factors to be controlled for • Interactions analyses by age and sex (first and third parts of project only) • Follow-up cognitive function data allowing for prospective associations to be investigated (first and third parts of project only) • Robust sensitivity analyses • The cognitive data from the UK Biobank study have been shown to be a significant and valid resource for investigating predictors and modifiers of cognitive abilities and associated health outcomes in the general population • Objectively measured BMI, CRF, and hand grip strength data • Evaluation of dose-response and additive relationships between an extensive range of lifestyle factors and cognitive function (third part of project only)	• Although the UK Biobank is representative of the general population with respect to age, sex, ethnicity, and deprivation within the age range recruited, it may not be representative in other regards • Only three sedentary behaviours included; thus, the findings cannot be generalized to other types of sedentary behaviour • Self-reported assessments of sedentary behaviour are subjective and are influenced by recall and response issues • Not possible to accurately classify or infer the type of computer use undertaken; and it may have involved crossover into cognitively inert tasks • Only those who provided an email address at baseline (~300,000) were contacted to participate in the online follow-up of cognitive function; therefore, these participants all had computer access and presumably, some computer use experience. Consequently, the prospective analysis may be biased and lack generalizability (first and third parts of project only)

	• The difference in the mode of administration of the cognitive tests at baseline and follow-up (baseline: touchscreen interface vs. follow-up: mouse interface) could possibly account for some of the variability in cognitive performance and change over time (first and third parts of project only) • Unmeasured factors (e.g. type of employment/occupation) may have further confounded the reported associations; thus, the results may be subject to residual confounding or reverse causality • Due to large variations between the numbers of individuals who completed each cognitive assessment at both baseline and follow-up, analyses were based on different sample sizes (first and third parts of project only) • Individuals with better cognitive function are more likely to engage in healthy behaviours and abstain from unhealthy ones, a concept known as neuroselection • Besides the BMI, CRF, and hand grip strength data, all of the other exposure variables in this study were self-reported

Chapter Six: Analysis of Physical Activity and Sedentary Behaviour Data: Raw Acceleration Data	Sedentary behaviours can be accurately separated from common motion-based LIPA (except standing still) using the developed and validated intensity-based thresholds derived from raw acceleration data.	• Widely-used accelerometers employed • Comprehensive data analysis of raw acceleration data collected at a high sampling frequency (100 Hz) • Laboratory-based experimental design with usage of both hip- and wrist-worn devices • Robust statistical analysis plan • Derived a generation of monitor-specific thresholds • Thresholds are sample and protocol specific; implying that the classifications of sedentary behaviours and LIPA should be broadly comparable between studies - irrespective of the metric, accelerometer brand and wear-site used	• Laboratory-based settings may limit generalizability to free-living environments • Difficult to classify sedentary behaviours in free-living situations using wrist-worn devices since individuals can carry out sedentary tasks involving arm movement • Study participants were instructed to keep their hands on their thighs during the seated activities that involved watching TV; thus, the real-life positioning and postures of these sedentary behaviours are less likely to be reflected or fully captured • Small range of sedentary behaviours and LIPA • Thresholds were only validated internally

BIBLIOGRAPHY

1. Sedentary Behaviour Research Network. Letter to the Editor: Standardized use of the terms “sedentary” and “sedentary behaviours”. Applied Physiology, Nutrition, and Metabolism. 2012;37(3):540-2.

2. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN) - Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act. 2017;14(1):75.

3. Jette M, Sidney K, Blumchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol. 1990;13(8):555-65.

4. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Medicine and science in sports and exercise. 2000;32(9 Suppl):S498-504.

5. World Health Organisation. Global recommendations on physical activity for health. 2010. [Available from: http://whqlibdoc.who.int/publications/2010/9789241599979_eng.pdf. Accessed: 1 August 2017].

6. Department of Health. Physical Activity Guidelines in the UK: Review and Recommendations. 2011. [Available from: https://www.gov.uk/government/publications/uk-physical-activity-guidelines. Accessed: 1 August 2017].

7. US Department of Health and Human Services. Physical activity guidelines for Americans. 2008. [Available from: http://www.health.gov/paguidelines/guidelines/. Accessed: 1 August 2017].

8. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, et al. Sedentary Time and Its Association With Risk for Disease Incidence, Mortality, and Hospitalization in Adults: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2015;162(2):123-32.

9. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily Sitting Time and All-Cause Mortality: A Meta-Analysis. PLoS ONE. 2013;8(11):e80000.

10. Edwardson CL, Gorely T, Davies MJ, Gray LJ, Khunti K, Wilmot EG, et al. Association of sedentary behaviour with metabolic syndrome: a meta-analysis. PLoS One. 2012;7(4):e34916.

11. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A meta-analysis. JAMA. 2011;305(23):2448-55.

12. Thorp AA, Owen N, Neuhaus M, Dunstan DW. Sedentary Behaviors and Subsequent Health Outcomes in Adults: A Systematic Review of Longitudinal Studies, 1996–2011. American Journal of Preventive Medicine. 2011;41(2):207-15.

13. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia. 2012;55(11):2895-905.

14. Zhai L, Zhang Y, Zhang D. Sedentary behaviour and the risk of depression: a meta-analysis. Br J Sports Med. 2015;49(11):705-9.

15. Colley RC, Garriguet D, Janssen I, Craig CL, Clarke J, Tremblay MS. Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. Health reports. 2011;22(1):7-14.

16. Hagströmer M, Troiano RP, Sjöström M, Berrigan D. Levels and Patterns of Objectively Assessed Physical Activity—A Comparison Between Sweden and the United States. American journal of epidemiology. 2010;171(10):1055-64.

17. Joint Health Surveys Unit. Health Survey for England 2008: Volume 1. Leeds (UK): The Health and Social Care Information Centre. 2008. [Available from: http://www.hscic.gov.uk/catalogue/PUB00430/heal-surv-phys-acti-fitn-eng-2008-rep-v2.pdf. Accessed: 1 August 2017].

18. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. American journal of epidemiology. 2008;167(7):875-81.

19. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes care. 2008;31(2):369-71.

20. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Medicine and science in sports and exercise. 2009;41(5):998-1005.

21. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. Exerc Sport Sci Rev. 2010;38(3):105-13.

22. Sallis JF, Owen N, Fotheringham MJ. Behavioral epidemiology: a systematic framework to classify phases of research on health promotion and disease prevention. Ann Behav Med. 2000;22(4):294-8.

23. UK Biobank. Stockport (UK): UK Biobank. 2017. [Available from: http://www.ukbiobank.ac.uk/. Accessed: 1 August 2017].

24. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. Eur Heart J. 2011;32(5):590-7.

25. Henson J, Yates T, Biddle SJ, Edwardson CL, Khunti K, Wilmot EG, et al. Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. Diabetologia. 2013;56(5):1012-20.

26. Howard A, Joint M. Fatigue and Stress in Driving. Employee Counselling Today. 1994;6(6):3-7.

27. Howard B, Winkler EA, Sethi P, Carson V, Ridgers ND, Salmon JO, et al. Associations of Low- and High-Intensity Light Activity with Cardiometabolic Biomarkers. Medicine and science in sports and exercise. 2015;47(10):2093-101.

28. Loprinzi PD, Pariser G. Physical activity intensity and biological markers among adults with diabetes: considerations by age and gender. Journal of Diabetes and its Complications. 2013;27(2):134-40.

29. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006;174(6):801-9.

30. O'Donovan G, Hillsdon M, Ukoumunne OC, Stamatakis E, Hamer M. Objectively measured physical activity, cardiorespiratory fitness and cardiometabolic risk factors in the Health Survey for England. Prev Med. 2013;57(3):201-5.

31. Stamatakis E, Davis M, Stathi A, Hamer M. Associations between multiple indicators of objectively-measured and self-reported sedentary behaviour and cardiometabolic risk in older adults. Prev Med. 2012;54(1):82-7.

32. Stamatakis E, Hamer M, Tilling K, Lawlor DA. Sedentary time in relation to cardio-metabolic risk factors: differential associations for self-report vs accelerometry in working age adults. Int J Epidemiol. 2012;41(5):1328-37.

33. Cooper AJ, Brage S, Ekelund U, Wareham NJ, Griffin SJ, Simmons RK. Association between objectively assessed sedentary time and physical activity with metabolic risk factors among people with recently diagnosed type 2 diabetes. Diabetologia. 2014;57(1):73-82.

34. Henson J, Yates T, Edwardson CL, Khunti K, Talbot D, Gray LJ, et al. Sedentary time and markers of chronic low-grade inflammation in a high risk population. PLoS One. 2013;8(10):e78350.

35. Loprinzi PD, Lee H, Cardinal BJ. Daily movement patterns and biological markers among adults in the United States. Preventive Medicine. 2014;60(0):128-30.

36. Peterson MD, Snih SA, Stoddard J, McClain J, Lee I. Adiposity and Insufficient MVPA Predict Cardiometabolic Abnormalities in Adults. Medicine and science in sports and exercise. 2014;46(6):1133-9.

37. Shuval K, Finley CE, Barlow CE, Gabriel KP, Leonard D, Kohl HW, 3rd. Sedentary behavior, cardiorespiratory fitness, physical activity, and cardiometabolic risk in men: the cooper center longitudinal study. Mayo Clin Proc. 2014;89(8):1052-62.

38. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet. 2016;388(10051):1302-10.

39. Joint Health Surveys Unit. Health Survey for England 2008: Volume 2. Leeds (UK): The Health and Social Care Information Centre. 2008. [Available from: http://www.hscic.gov.uk/catalogue/PUB00430/heal-surv-phys-acti-fitn-eng-2008-rep-v3.pdf. Accessed: 1 August 2017].

40. Mindell J, Biddulph JP, Hirani V, Stamatakis E, Craig R, Nunn S, et al. Cohort profile: the health survey for England. Int J Epidemiol. 2012;41(6):1585-93.

41. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ. 2007;334(7588):299.

42. Yates T, Haffner SM, Schulte PJ, Thomas L, Huffman KM, Bales CW, et al. Association between change in daily ambulatory activity and cardiovascular events in people with impaired glucose tolerance (NAVIGATOR trial): a cohort analysis. Lancet. 2014;383(9922):1059-66.

43. Henson J, Dunstan DW, Davies MJ, Yates T. Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. Diabetes Metab Res Rev. 2016;32 Suppl 1:213-20.

44. Yates T, Davies MJ, Henson J, Troughton J, Edwardson C, Gray LJ, et al. Walking away from type 2 diabetes: trial protocol of a cluster randomised controlled trial evaluating a structured education programme in those at high risk of developing type 2 diabetes. BMC Fam Pract. 2012;13:46.

45. Geldmacher DS, Whitehouse PJ. Evaluation of dementia. N Engl J Med. 1996;335(5):330-6.

46. Leritz EC, McGlinchey RE, Kellison I, Rudolph JL, Milberg WP. Cardiovascular Disease Risk Factors and Cognition in the Elderly. Curr Cardiovasc Risk Rep. 2011;5(5):407-12.

47. World Health Organisation. Dementia. 2016. [Available from: http://www.who.int/mediacentre/factsheets/fs362/en/. Accessed: 1 August 2017].

48. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001;58(3):498-504.

49. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA. 2008;300(9):1027-37.

50. Chapman SB, Aslan S, Spence JS, Defina LF, Keebler MW, Didehbani N, et al. Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. Front Aging Neurosci. 2013;5:75.

51. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. J Gerontol A Biol Sci Med Sci. 2006;61(11):1166-70.
52. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A. 2004;101(9):3316-21.
53. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, et al. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108(7):3017-22.
54. Smith JC, Nielson KA, Antuono P, Lyons JA, Hanson RJ, Butts AM, et al. Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. J Alzheimers Dis. 2013;37(1):197-215.
55. Falck RS, Davis JC, Liu-Ambrose T. What is the association between sedentary behaviour and cognitive function? A systematic review. Br J Sports Med. 2017;51(10):800-11.
56. Hoang TD, Reis J, Zhu N, Jacobs DR, Jr., Launer LJ, Whitmer RA, et al. Effect of Early Adult Patterns of Physical Activity and Television Viewing on Midlife Cognitive Function. JAMA Psychiatry. 2016;73(1):73-9.
57. Wang JY, Zhou DH, Li J, Zhang M, Deng J, Tang M, et al. Leisure activity and risk of cognitive impairment: the Chongqing aging study. Neurology. 2006;66(6):911-3.
58. Hamer M, Stamatakis E. Prospective study of sedentary behavior, risk of depression, and cognitive impairment. Medicine and science in sports and exercise. 2014;46(4):718-23.
59. Kesse-Guyot E, Charreire H, Andreeva VA, Touvier M, Hercberg S, Galan P, et al. Cross-sectional and longitudinal associations of different sedentary behaviors with cognitive performance in older adults. PLoS One. 2012;7(10):e47831.
60. Tun PA, Lachman ME. The association between computer use and cognition across adulthood: use it so you won't lose it? Psychol Aging. 2010;25(3):560-8.
61. Henson J, Davies MJ, Bodicoat DH, Edwardson CL, Gill JM, Stensel DJ, et al. Breaking Up Prolonged Sitting With Standing or Walking Attenuates the Postprandial

Metabolic Response in Postmenopausal Women: A Randomized Acute Study. Diabetes care. 2016;39(1):130-8.

62. Prince SA, Adamo KB, Hamel ME, Hardt J, Connor Gorber S, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. Int J Behav Nutr Phys Act. 2008;5:56.

63. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Medicine and science in sports and exercise. 2008;40(1):181-8.

64. Freedson P, Bowles HR, Troiano R, Haskell W. Assessment of physical activity using wearable monitors: recommendations for monitor calibration and use in the field. Medicine and science in sports and exercise. 2012;44(1 Suppl 1):S1-4.

65. Godfrey A, Conway R, Meagher D, OLaighin G. Direct measurement of human movement by accelerometry. Medical engineering & physics. 2008;30(10):1364-86.

66. Straker L, Campbell A. Translation equations to compare ActiGraph GT3X and Actical accelerometers activity counts. BMC medical research methodology. 2012;12:54.

67. Crouter S, Churilla J, Bassett D, Jr. Estimating energy expenditure using accelerometers. Eur J Appl Physiol. 2006;98(6):601-12.

68. Marschollek M. A Semi-Quantitative Method to Denote Generic Physical Activity Phenotypes from Long-Term Accelerometer Data – The ATLAS Index. PLoS ONE. 2013;8(5):e63522.

69. Chen KY, Bassett DR, Jr. The technology of accelerometry-based activity monitors: current and future. Medicine and science in sports and exercise. 2005;37(11 Suppl):S490-500.

70. Brage S, van Hees VT, Brage N. Intergeneration accelerometer differences and correction for on-board frequency-based filtering. J Appl Physiol (1985). 2009;106(4):1473; author reply 4.

71. Brage S, Wedderkopp N, Andersen LB, Froberg K. Influence of Step Frequency on Movement Intensity Predictions with the CSA Accelerometer: A Field Validation Study in Children. Pediatric Exercise Science. 2003;15(3):277-87.

72. Brage S, Brage N, Wedderkopp N, Froberg K. Reliability and Validity of the Computer Science and Applications Accelerometer in a Mechanical Setting. Measurement in Physical Education and Exercise Science. 2003;7(2):101-19.

73. Esliger DW, Rowlands AV, Hurst TL, Catt M, Murray P, Eston RG. Validation of the GENEA Accelerometer. Medicine and science in sports and exercise. 2011;43(6):1085-93.

74. Figo D, Diniz P, Ferreira D, Cardoso JP. Preprocessing techniques for context recognition from accelerometer data. Pers Ubiquit Comput. 2010;14(7):645-62.

75. John D, Sasaki J, Staudenmayer J, Mavilia M, Freedson PS. Comparison of raw acceleration from the GENEA and ActiGraph GT3X+ activity monitors. Sensors (Basel, Switzerland). 2013;13(11):14754-63.

76. Rowlands AV, Fraysse F, Catt M, Stiles VH, Stanley RM, Eston RG, et al. Comparability of measured acceleration from accelerometry-based activity monitors. Medicine and science in sports and exercise. 2015;47(1):201-10.

77. Zhang S, Rowlands AV, Murray P, Hurst TL. Physical activity classification using the GENEA wrist-worn accelerometer. Medicine and science in sports and exercise. 2012;44(4):742-8.

78. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey. Hyattsville (MD): Centers for Disease Control and Prevention (CDC). 2016. [Available from: http://www.cdc.gov/nchs/nhanes.htm. Accessed: 1 August 2017].

79. Gordon-Dseagu VL, Shelton N, Mindell J. Diabetes mellitus and mortality from all-causes, cancer, cardiovascular and respiratory disease: evidence from the Health Survey for England and Scottish Health Survey cohorts. J Diabetes Complications. 2014;28(6):791-7.

80. Oyebode O, Gordon-Dseagu V, Walker A, Mindell JS. Fruit and vegetable consumption and all-cause, cancer and CVD mortality: analysis of Health Survey for England data. J Epidemiol Community Health. 2014;68(9):856-62.

81. Perreault K, Bauman A, Johnson N, Britton A, Rangul V, Stamatakis E. Does physical activity moderate the association between alcohol drinking and all-cause,

cancer and cardiovascular diseases mortality? A pooled analysis of eight British population cohorts. Br J Sports Med. 2017;51(8):651-7.

82. Stamatakis E, Kelly P, Strain T, Murtagh EM, Ding D, Murphy MH. Self-rated walking pace and all-cause, cardiovascular disease and cancer mortality: individual participant pooled analysis of 50 225 walkers from 11 population British cohorts. Br J Sports Med. 2018;52(12):761-8.

83. Evans SJ. Good surveys guide. Bmj. 1991;302(6772):302-3.

84. Yates T, Edwardson CL, Henson J, Gray LJ, Ashra NB, Troughton J, et al. Walking Away from Type 2 diabetes: a cluster randomized controlled trial. Diabet Med. 2017;34(5):698-707.

85. Gray LJ, Davies MJ, Hiles S, Taub NA, Webb DR, Srinivasan BT, et al. Detection of impaired glucose regulation and/or type 2 diabetes mellitus, using primary care electronic data, in a multiethnic UK community setting. Diabetologia. 2012;55(4):959-66.

86. Gray LJ, Khunti K, Edwardson C, Goldby S, Henson J, Morris DH, et al. Implementation of the automated Leicester Practice Risk Score in two diabetes prevention trials provides a high yield of people with abnormal glucose tolerance. Diabetologia. 2012;55(12):3238-44.

87. Leicester City Council. Diversity and migration. 2012. [Available from: https://www.leicester.gov.uk/media/177367/2011-census-findings-diversity-and-migration.pdf. Accessed: 1 April 2018].

88. Gray LJ, Tringham JR, Davies MJ, Webb DR, Jarvis J, Skinner TC, et al. Screening for type 2 diabetes in a multiethnic setting using known risk factors to identify those at high risk: a cross-sectional study. Vascular health and risk management. 2010;6:837-42.

89. Webb DR, Gray LJ, Khunti K, Srinivasan B, Taub N, Campbell S, et al. Screening for diabetes using an oral glucose tolerance test within a western multi-ethnic population identifies modifiable cardiovascular risk: the ADDITION-Leicester study. Diabetologia. 2011;54(9):2237-46.

90. Chatterton H, Younger T, Fischer A, Khunti K. Risk identification and interventions to prevent type 2 diabetes in adults at high risk: summary of NICE guidance. Bmj. 2012;345:e4624.

91. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. American journal of epidemiology. 2007;165(6):710-8.

92. Allen N, Sudlow C, Downey P, Peakman T, Danesh J, Elliott P, et al. UK Biobank: Current status and what it means for epidemiology. Health Policy and Technology. 2012;1(3):123-6.

93. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.

94. UK Biobank. UK Biobank: Protocol for a large-scale prospective epidemiological resource. 2016. [Available from: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/11/UK-Biobank-Protocol.pdf. Accessed: 1 August 2017].

95. UK Biobank. Repeat Assessment Data. 2013. [Available from: https://biobank.ctsu.ox.ac.uk/~bbdatan/Repeat_assessment_doc_v1.0.pdf. Accessed: 1 April 2018].

96. UK Biobank. UK Biobank Showcase User Guide. 2017. [Available from: http://biobank.ctsu.ox.ac.uk/~bbdatan/ShowcaseUserGuide.pdf. Accessed: 1 April 2018].

97. UK Biobank. Death register. 2018. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100093. Accessed: 1 April 2018].

98. UK Biobank. FAQs. 2018. [Available from: http://www.ukbiobank.ac.uk/all-faqs/. Accessed: 1 April 2018].

99. Doherty A, Jackson D, Hammerla N, Plotz T, Olivier P, Granat MH, et al. Large Scale Population Assessment of Physical Activity Using Wrist Worn Accelerometers: The UK Biobank Study. PLoS One. 2017;12(2):e0169649.

100. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population. American journal of epidemiology. 2017;186(9):1026-34.

101. UK Biobank. Cognitive function follow-up - Online follow-up. 2017. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=116. Accessed: 1 August 2017].
102. Bradbury KE, Young HJ, Guo W, Key TJ. Dietary assessment in UK Biobank: an evaluation of the performance of the touchscreen dietary questionnaire. Journal of nutritional science. 2018;7:e6.
103. Galante J, Adamska L, Young A, Young H, Littlejohns TJ, Gallacher J, et al. The acceptability of repeat Internet-based hybrid diet assessment of previous 24-h dietary intake: administration of the Oxford WebQ in UK Biobank. The British journal of nutrition. 2016;115(4):681-6.
104. Swanson JM. The UK Biobank and selection bias. Lancet. 2012;380(9837):110.
105. Macfarlane GJ, Beasley M, Smith BH, Jones GT, Macfarlane TV. Can large surveys conducted on highly selected populations provide valid information on the epidemiology of common health conditions? An analysis of UK Biobank data on musculoskeletal pain. British journal of pain. 2015;9(4):203-12.
106. Friedman HS, Martin LR, Tucker JS, Criqui MH, Kern ML, Reynolds CA. Stability of physical activity across the lifespan. Journal of health psychology. 2008;13(8):1092-104.
107. Mertens E, Clarys P, Mullie P, Lefevre J, Charlier R, Knaeps S, et al. Stability of physical activity, fitness components and diet quality indices. European journal of clinical nutrition. 2017;71(4):519-24.
108. Milanovic Z, Pantelic S, Trajkovic N, Sporis G, Kostic R, James N. Age-related decrease in physical activity and functional fitness among elderly men and women. Clinical interventions in aging. 2013;8:549-56.
109. Sallis JF. Age-related decline in physical activity: a synthesis of human and animal studies. Medicine and science in sports and exercise. 2000;32(9):1598-600.
110. UK Biobank. Cognitive function - UK Biobank Assessment Centre. 2017. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100026. Accessed: 1 August 2017].
111. UK Biobank. Touchscreen questionnaire. 2012. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=100025. Accessed: 1 April 2018].

112. Evenson KR, Wen F, Metzger JS, Herring AH. Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. Int J Behav Nutr Phys Act. 2015;12:20.
113. Omorou AY, Coste J, Escalon H, Vuillemin A. Patterns of physical activity and sedentary behaviour in the general population in France: cluster analysis with personal and socioeconomic correlates. J Public Health (Oxf). 2015.
114. Chomistek AK, Manson JE, Stefanick ML, Lu B, Sands-Lincoln M, Going SB, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. J Am Coll Cardiol. 2013;61(23):2346-54.
115. Matthews CE, George SM, Moore SC, Bowles HR, Blair A, Park Y, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. Am J Clin Nutr. 2012;95(2):437-45.
116. Maddison R, Jiang Y, Foley L, Scragg R, Direito A, Olds T. The association between the activity profile and cardiovascular risk. J Sci Med Sport. 2015.
117. Schmid D, Ricci C, Leitzmann MF. Associations of Objectively Assessed Physical Activity and Sedentary Time with All-Cause Mortality in US Adults: The NHANES Study. PLoS ONE. 2015;10(3):e0119591.
118. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Medicine and science in sports and exercise. 1998;30(5):777-81.
119. Orme M, Wijndaele K, Sharp SJ, Westgate K, Ekelund U, Brage S. Combined influence of epoch length, cut-point and bout duration on accelerometry-derived physical activity. Int J Behav Nutr Phys Act. 2014;11(1):34.
120. Kozakova M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Balkau B. Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population. Eur Heart J. 2010;31(12):1511-9.
121. Kutner MH, Nachtsheim CJ, Neter J, Li W. Applied linear statistical models: McGraw-Hill/Irwin New York; 2005.

122. Cooper AR, Sebire S, Montgomery AA, Peters TJ, Sharp DJ, Jackson N, et al. Sedentary time, breaks in sedentary time and metabolic variables in people with newly diagnosed type 2 diabetes. Diabetologia. 2012;55(3):589-99.
123. Maher C, Olds T, Mire E, Katzmarzyk PT. Reconsidering the sedentary behaviour paradigm. PLoS One. 2014;9(1):e86403.
124. Yates T, Henson J, Edwardson C, Dunstan D, Bodicoat DH, Khunti K, et al. Objectively measured sedentary time and associations with insulin sensitivity: Importance of reallocating sedentary time to physical activity. Prev Med. 2015;76:79-83.
125. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes. 2007;56(11):2655-67.
126. Ahmed HM, Blaha MJ, Nasir K, Rivera JJ, Blumenthal RS. Effects of Physical Activity on Cardiovascular Disease. The American Journal of Cardiology. 2012;109(2):288-95.
127. Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. Diabetes Metab Res Rev. 2004;20(5):383-93.
128. Hawley JA, Gibala MJ. Exercise intensity and insulin sensitivity: how low can you go? Diabetologia. 2009;52(9):1709-13.
129. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J. 2007;28(19):2375-414.
130. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.

131. World Health Organisation. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. 2011. [Available from: http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Accessed: 1 April 2018].

132. Bassett DR, Jr., Rowlands A, Trost SG. Calibration and validation of wearable monitors. Medicine and science in sports and exercise. 2012;44(1 Suppl 1):S32-8.

133. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Caspian journal of internal medicine. 2013;4(2):627-35.

134. Matthews CE, Keadle SK, Berrigan D, Staudenmayer J, Maurice PS, Troiano RP, et al. Influence of Accelerometer Calibration Approach on MVPA Estimates for Adults. Medicine and science in sports and exercise. 2018.

135. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. Medicine and science in sports and exercise. 2011;43(8):1561-7.

136. Silva P, Mota J, Esliger D, Welk G. Technical Reliability Assessment of the Actigraph GT1M Accelerometer. Measurement in Physical Education and Exercise Science. 2010;14(2):79-91.

137. Herman Hansen B, Bortnes I, Hildebrand M, Holme I, Kolle E, Anderssen SA. Validity of the ActiGraph GT1M during walking and cycling. Journal of sports sciences. 2014;32(6):510-6.

138. Kelly LA, McMillan DG, Anderson A, Fippinger M, Fillerup G, Rider J. Validity of actigraphs uniaxial and triaxial accelerometers for assessment of physical activity in adults in laboratory conditions. BMC medical physics. 2013;13(1):5.

139. Jimmy G, Seiler R, Mäder U. Comparing the Validity and Output of the GT1M and GT3X Accelerometer in 5- to 9-Year-Old Children. Measurement in Physical Education and Exercise Science. 2013;17(3):236-48.

140. Brage S, Wedderkopp N, Franks PW, Andersen LB, Froberg K. Reexamination of validity and reliability of the CSA monitor in walking and running. Medicine and science in sports and exercise. 2003;35(8):1447-54.

141. Rothney MP, Apker GA, Song Y, Chen KY. Comparing the performance of three generations of ActiGraph accelerometers. J Appl Physiol (1985). 2008;105(4):1091-7.
142. Rowlands AV, Stone MR, Eston RG. Influence of speed and step frequency during walking and running on motion sensor output. Medicine and science in sports and exercise. 2007;39(4):716-27.
143. NCD Risk Factor Collaboration N-R. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30.
144. Webb DR, Khunti K, Srinivasan B, Gray LJ, Taub N, Campbell S, et al. Rationale and design of the ADDITION-Leicester study, a systematic screening programme and randomised controlled trial of multi-factorial cardiovascular risk intervention in people with type 2 diabetes mellitus detected by screening. Trials. 2010;11:16.
145. Cox DR. Regression Models and Life-Tables. Journal of the Royal Statistical Society Series B (Methodological). 1972;34(2):187-220.
146. Stata. stsplit. 2018. [Available from: https://www.stata.com/manuals13/ststsplit.pdf. Accessed: 1 April 2018].
147. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol. 2011;40(5):1382-400.
148. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239-46.
149. Loprinzi PD, Loenneke JP, Ahmed HM, Blaha MJ. Joint effects of objectively-measured sedentary time and physical activity on all-cause mortality. Prev Med. 2016;90:47-51.
150. Fishman EI, Steeves JA, Zipunnikov V, Koster A, Berrigan D, Harris TA, et al. Association between Objectively Measured Physical Activity and Mortality in NHANES. Medicine and science in sports and exercise. 2016;48(7):1303-11.

151. Loprinzi PD, Sng E. The effects of objectively measured sedentary behavior on all-cause mortality in a national sample of adults with diabetes. Prev Med. 2016;86:55-7.

152. Lyerly GW, Sui X, Lavie CJ, Church TS, Hand GA, Blair SN. The association between cardiorespiratory fitness and risk of all-cause mortality among women with impaired fasting glucose or undiagnosed diabetes mellitus. Mayo Clin Proc. 2009;84(9):780-6.

153. Lee IM, Shiroma EJ, Evenson KR, Kamada M, LaCroix AZ, Buring JE. Accelerometer-Measured Physical Activity and Sedentary Behavior in Relation to All-Cause Mortality: The Women's Health Study. Circulation. 2018;137(2):203-5.

154. Office for National Statistics. Methodology: User guide to mortality statistics: July 2017. 2017. [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017. Accessed: 1 April 2018].

155. Office for National Statistics. Quality in official statistics. 2018. [Available from: https://www.ons.gov.uk/methodology/methodologytopicsandstatisticalconcepts/qualityinofficialstatistics. Accessed: 1 April 2018].

156. Santos-Lozano A, Marín PJ, Torres-Luque G, Ruiz JR, Lucía A, Garatachea N. Technical variability of the GT3X accelerometer. Medical engineering & physics. 2012;34(6):787-90.

157. Courvoisier DS, Combescure C, Agoritsas T, Gayet-Ageron A, Perneger TV. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. J Clin Epidemiol. 2011;64(9):993-1000.

158. UK Biobank. Non-cancer illness code. 2018. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002. Accessed: 1 April 2018].

159. Aggio D, Smith L, Fisher A, Hamer M. Context-Specific Associations of Physical Activity and Sedentary Behavior With Cognition in Children. Am J Epidemiol. 2016;183(12):1075-82.

160. Akbaraly TN, Portet F, Fustinoni S, Dartigues JF, Artero S, Rouaud O, et al. Leisure activities and the risk of dementia in the elderly: results from the Three-City Study. Neurology. 2009;73(11):854-61.

161. Iwasa H, Yoshida Y, Kai I, Suzuki T, Kim H, Yoshida H. Leisure activities and cognitive function in elderly community-dwelling individuals in Japan: a 5-year prospective cohort study. J Psychosom Res. 2012;72(2):159-64.
162. Verghese J, Lipton RB, Katz MJ, Hall CB, Derby CA, Kuslansky G, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003;348(25):2508-16.
163. Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA. 2002;287(6):742-8.
164. Elias MF, Sullivan LM, D'Agostino RB, Elias PK, Beiser A, Au R, et al. Framingham stroke risk profile and lowered cognitive performance. Stroke. 2004;35(2):404-9.
165. Kaffashian S, Dugravot A, Nabi H, Batty GD, Brunner E, Kivimaki M, et al. Predictive utility of the Framingham general cardiovascular disease risk profile for cognitive function: evidence from the Whitehall II study. Eur Heart J. 2011;32(18):2326-32.
166. Belkic K, Savic C, Theorell T, Rakic L, Ercegovac D, Djordjevic M. Mechanisms of cardiac risk among professional drivers. Scand J Work Environ Health. 1994;20(2):73-86.
167. Morris JN, Heady JA, Raffle PAB, Roberts CG, Parks JW. Coronary heart-disease and physical activity of work. The Lancet. 1953;262(6796):1111-20.
168. Robinson CF, Burnett CA. Truck drivers and heart disease in the United States, 1979-1990. Am J Ind Med. 2005;47(2):113-9.
169. Abd-Elfattah HM, Abdelazeim FH, Elshennawy S. Physical and cognitive consequences of fatigue: A review. J Adv Res. 2015;6(3):351-8.
170. van der Linden D, Frese M, Meijman TF. Mental fatigue and the control of cognitive processes: effects on perseveration and planning. Acta Psychol (Amst). 2003;113(1):45-65.
171. Scott SB, Graham-Engeland JE, Engeland CG, Smyth JM, Almeida DM, Katz MJ, et al. The Effects of Stress on Cognitive Aging, Physiology and Emotion (ESCAPE) Project. BMC Psychiatry. 2015;15:146.
172. Bassuk SS, Glass TA, Berkman LF. Social disengagement and incident cognitive decline in community-dwelling elderly persons. Ann Intern Med. 1999;131(3):165-73.

173. Golden J, Conroy RM, Bruce I, Denihan A, Greene E, Kirby M, et al. Loneliness, social support networks, mood and wellbeing in community-dwelling elderly. Int J Geriatr Psychiatry. 2009;24(7):694-700.

174. Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. Psychosom Med. 2013;75(2):161-70.

175. McCarrey AC, An Y, Kitner-Triolo MH, Ferrucci L, Resnick SM. Sex differences in cognitive trajectories in clinically normal older adults. Psychol Aging. 2016;31(2):166-75.

176. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation. 2011;124(19):2145-54.

177. Sabia S, Guéguen A, Marmot MG, Shipley MJ, Ankri J, Singh-Manoux A. Does cognition predict mortality in midlife? Results from the Whitehall II cohort study. Neurobiol Aging. 2010;31(4):688-95.

178. Batterham PJ, Christensen H, Mackinnon AJ. Fluid intelligence is independently associated with all-cause mortality over 17 years in an elderly community sample: An investigation of potential mechanisms. Intelligence. 2009;37(6):551-60.

179. Basterra-Gortari FJ, Bes-Rastrollo M, Gea A, Nunez-Cordoba JM, Toledo E, Martinez-Gonzalez MA. Television viewing, computer use, time driving and all-cause mortality: the SUN cohort. Journal of the American Heart Association. 2014;3(3):e000864.

180. Collins R. What makes UK Biobank special? Lancet. 2012;379(9822):1173-4.

181. Manolio TA, Collins R. Enhancing the feasibility of large cohort studies. JAMA. 2010;304(20):2290-1.

182. Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, et al. Cognitive Test Scores in UK Biobank: Data Reduction in 480,416 Participants and Longitudinal Stability in 20,346 Participants. PLoS One. 2016;11(4):e0154222.

183. Alzheimer's Association. What Is Dementia? 2018. [Available from: https://www.alz.org/alzheimers-dementia/what-is-dementia. Accessed: 1 April 2018].

184. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. Malawi medical journal : the journal of Medical Association of Malawi. 2012;24(3):69-71.
185. Hutcheon JA, Chiolero A, Hanley JA. Random measurement error and regression dilution bias. BMJ. 2010;340:c2289.
186. Atkin AJ, Gorely T, Clemes SA, Yates T, Edwardson C, Brage S, et al. Methods of Measurement in epidemiology: sedentary Behaviour. Int J Epidemiol. 2012;41(5):1460-71.
187. Marshall AL, Miller YD, Burton NW, Brown WJ. Measuring total and domain-specific sitting: a study of reliability and validity. Medicine and science in sports and exercise. 2010;42(6):1094-102.
188. Rosenberg DE, Norman GJ, Wagner N, Patrick K, Calfas KJ, Sallis JF. Reliability and validity of the Sedentary Behavior Questionnaire (SBQ) for adults. Journal of physical activity & health. 2010;7(6):697-705.
189. Pettee KK, Ham SA, Macera CA, Ainsworth BE. The reliability of a survey question on television viewing and associations with health risk factors in US adults. Obesity (Silver Spring, Md). 2009;17(3):487-93.
190. Clark BK, Sugiyama T, Healy GN, Salmon J, Dunstan DW, Owen N. Validity and reliability of measures of television viewing time and other non-occupational sedentary behaviour of adults: a review. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2009;10(1):7-16.
191. Van Cauwenberg J, Van Holle V, De Bourdeaudhuij I, Owen N, Deforche B. Older adults' reporting of specific sedentary behaviors: validity and reliability. BMC Public Health. 2014;14:734.
192. Aggio D, Smith L, Fisher A, Hamer M. Aggio et al. Respond to "Lessons for Research on Cognitive Aging". Am J Epidemiol. 2016;183(12):1086-7.
193. Belsky DW. Invited Commentary: Lessons for Research on Cognitive Aging From a Study of Children. Am J Epidemiol. 2016;183(12):1083-5.
194. Bakrania K, Edwardson CL, Bodicoat DH, Esliger DW, Gill JM, Kazi A, et al. Associations of mutually exclusive categories of physical activity and sedentary time

with markers of cardiometabolic health in English adults: a cross-sectional analysis of the Health Survey for England. BMC Public Health. 2016;16:25.

195. Yates T, Bakrania K, Zaccardi F, Dhalwani NN, Hamer M, Davies MJ, et al. Reaction time, cardiorespiratory fitness and mortality in UK Biobank: An observational study. Intelligence. 2017:Under Revision.

196. Bakrania K, Edwardson CL, Khunti K, Bandelow S, Davies MJ, Yates T. Associations Between Sedentary Behaviors and Cognitive Function: Cross-Sectional and Prospective Findings From the UK Biobank. American journal of epidemiology. 2018;187(3):441-54.

197. Edwards MK, Loprinzi PD. Combined associations of sedentary behavior and cardiorespiratory fitness on cognitive function among older adults. Int J Cardiol. 2017;229:71-4.

198. Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J Am Geriatr Soc. 2003;51(4):459-65.

199. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci. 2003;14(2):125-30.

200. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev. 2008(3):CD005381.

201. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, et al. Ageing, fitness and neurocognitive function. Nature. 1999;400(6743):418-9.

202. Chodzko-Zajko WJ, Moore KA. Physical fitness and cognitive functioning in aging. Exerc Sport Sci Rev. 1994;22:195-220.

203. Loprinzi PD, Kane CJ. Exercise and cognitive function: a randomized controlled trial examining acute exercise and free-living physical activity and sedentary effects. Mayo Clin Proc. 2015;90(4):450-60.

204. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA. 2004;292(12):1454-61.

205. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. Neurobiol Aging. 2014;35 Suppl 2:S20-8.

206. Erickson KI, Prakash RS, Voss MW, Chaddock L, Hu L, Morris KS, et al. Aerobic fitness is associated with hippocampal volume in elderly humans. Hippocampus. 2009;19(10):1030-9.

207. Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci. 2003;58(2):176-80.

208. Davenport MH, Hogan DB, Eskes GA, Longman RS, Poulin MJ. Cerebrovascular reserve: the link between fitness and cognitive function? Exerc Sport Sci Rev. 2012;40(3):153-8.

209. Powell RR, Pohndorf RH. Comparison of adult exercisers and nonexercisers on fluid intelligence and selected physiological variables. Res Q. 1971;42(1):70-7.

210. Singh-Manoux A, Richards M, Marmot M. Leisure activities and cognitive function in middle age: evidence from the Whitehall II study. J Epidemiol Community Health. 2003;57(11):907-13.

211. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, et al. Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. J Intern Med. 2011;269(1):107-17.

212. UK Biobank. Cardio Assessment. 2011. [Available from: https://biobank.ctsu.ox.ac.uk/showcase/docs/Cardio.pdf. Accessed: 1 April 2018].

213. UK Biobank. Enhancement data. 2009. [Available from: https://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Protocol_addendum_2.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6. Accessed: 1 April 2018].

214. PhysioNet. Physio Toolkit. 2018. [Available from: https://www.physionet.org/. Accessed: 1 April 2018].

215. Processing of Electrocardiographic Signals analysis of UK Biobank data and arrhythmia detection. 2015. [Available from: http://www.robots.ox.ac.uk/~davidc/pubs/HT2015_jo.pdf. Accessed: 1 April 2018].

216. Kim Y, White T, Wijndaele K, Westgate K, Sharp SJ, Helge JW, et al. The combination of cardiorespiratory fitness and muscle strength, and mortality risk. European journal of epidemiology. 2018.

217. Engelse W, Zeelenberg C. A single scan algorithm for QRS-detection and feature extraction. Computers in cardiology. 1979;6(1979):37-42.

218. PhysioNet. sqrs. 2018. [Available from: https://www.physionet.org/physiotools/wag/sqrs-1.htm. Accessed: 1 April 2018].

219. PhysioNet. ihr. 2018. [Available from: https://physionet.org/physiotools/wag/ihr-1.htm. Accessed: 1 April 2018].

220. Celis-Morales CA, Lyall DM, Anderson J, Iliodromiti S, Fan Y, Ntuk UE, et al. The association between physical activity and risk of mortality is modulated by grip strength and cardiorespiratory fitness: evidence from 498 135 UK-Biobank participants. Eur Heart J. 2017;38(2):116-22.

221. UK Biobank. Touch-screen Fluid intelligence test. 2012. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/docs/Fluidintelligence.pdf. Accessed: 1 August 2017].

222. Blair SN, Kampert JB, Kohl HW, 3rd, Barlow CE, Macera CA, Paffenbarger RS, Jr., et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. Jama. 1996;276(3):205-10.

223. The University of Nottingham. Cardiology Teaching Package. 2018. [Available from: https://www.nottingham.ac.uk/nursing/practice/resources/cardiology/function/limb_leads.php. Accessed: 1 April 2018].

224. Yates T, Zaccardi F, Dhalwani NN, Davies MJ, Bakrania K, Celis-Morales CA, et al. Association of walking pace and handgrip strength with all-cause, cardiovascular, and cancer mortality: a UK Biobank observational study. Eur Heart J. 2017;38(43):3232-40.

225. UK Biobank. Usual walking pace. 2017. [Available from: http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=924. Accessed: 1 April 2018].

226. Ferrie JE, Shipley MJ, Akbaraly TN, Marmot MG, Kivimaki M, Singh-Manoux A. Change in sleep duration and cognitive function: findings from the Whitehall II Study. Sleep. 2011;34(5):565-73.

227. Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunner EJ. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. Clin Nutr. 2016.

228. Clouston SA, Brewster P, Kuh D, Richards M, Cooper R, Hardy R, et al. The dynamic relationship between physical function and cognition in longitudinal aging cohorts. Epidemiol Rev. 2013;35:33-50.

229. Gale CR, Allerhand M, Sayer AA, Cooper C, Deary IJ. The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing. Age (Dordr). 2014;36(4):9682.

230. North TL, Palmer TM, Lewis SJ, Cooper R, Power C, Pattie A, et al. Effect of smoking on physical and cognitive capability in later life: a multicohort study using observational and genetic approaches. BMJ Open. 2015;5(12):e008393.

231. Anstey KJ, von Sanden C, Salim A, O'Kearney R. Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies. American journal of epidemiology. 2007;166(4):367-78.

232. Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. Am J Public Health. 2005;95(12):2252-8.

233. Agrigoroaei S, Lachman ME. Cognitive functioning in midlife and old age: combined effects of psychosocial and behavioral factors. J Gerontol B Psychol Sci Soc Sci. 2011;66 Suppl 1:i130-40.

234. Cadar D, Pikhart H, Mishra G, Stephen A, Kuh D, Richards M. The role of lifestyle behaviors on 20-year cognitive decline. J Aging Res. 2012;2012:304014.

235. Elwood P, Galante J, Pickering J, Palmer S, Bayer A, Ben-Shlomo Y, et al. Healthy lifestyles reduce the incidence of chronic diseases and dementia: evidence from the Caerphilly cohort study. PLoS One. 2013;8(12):e81877.

236. Kesse-Guyot E, Andreeva VA, Lassale C, Hercberg S, Galan P. Clustering of midlife lifestyle behaviors and subsequent cognitive function: a longitudinal study. Am J Public Health. 2014;104(11):e170-7.

237. Sabia S, Nabi H, Kivimaki M, Shipley MJ, Marmot MG, Singh-Manoux A. Health Behaviors From Early to Late Midlife as Predictors of Cognitive Function: The Whitehall II Study. American journal of epidemiology. 2009;170(4):428-37.

238. Lee Y, Kim J, Back JH. The influence of multiple lifestyle behaviors on cognitive function in older persons living in the community. Prev Med. 2009;48(1):86-90.

239. Marioni RE, Valenzuela MJ, van den Hout A, Brayne C, Matthews FE, Stud MCFA. Active Cognitive Lifestyle Is Associated with Positive Cognitive Health Transitions and Compression of Morbidity from Age Sixty-Five. Plos One. 2012;7(12).

240. NHS. Eat well. 2016. [Available from: https://www.nhs.uk/live-well/eat-well/. Accessed: 1 April 2018].

241. Office of Disease Prevention and Health Promotion. Food and Nutrition. 2018. [Available from: https://health.gov/dietaryguidelines/. Accessed: 1 April 2018].

242. IPAQ scoring protocol. 2016. [Available from: https://sites.google.com/site/theipaq/scoring-protocol. Accessed: 1 April 2018].

243. Jang JY, Kim J. Association between handgrip strength and cognitive impairment in elderly Koreans: a population-based cross-sectional study. J Phys Ther Sci. 2015;27(12):3911-5.

244. Cho H, Kim C, Kim HJ, Ye BS, Kim YJ, Jung NY, et al. Impact of smoking on neurodegeneration and cerebrovascular disease markers in cognitively normal men. Eur J Neurol. 2016;23(1):110-9.

245. Durazzo TC, Mattsson N, Weiner MW, Alzheimer's Disease Neuroimaging I. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement. 2014;10(3 Suppl):S122-45.

246. van Hees VT, Gorzelniak L, Dean Leon EC, Eder M, Pias M, Taherian S, et al. Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. PLoS One. 2013;8(4):e61691.

247. Chung WY, Purwar A, Sharma A, editors. Frequency domain approach for activity classification using accelerometer. Conf Proc IEEE Eng Med Biol Soc; 2008.

248. Karantonis DM, Narayanan MR, Mathie M, Lovell NH, Celler BG. Implementation of a real-time human movement classifier using a triaxial

accelerometer for ambulatory monitoring. Information Technology in Biomedicine, IEEE Transactions on. 2006;10(1):156-67.

249. Khusainov R, Azzi D, Achumba I, Bersch S. Real-Time Human Ambulation, Activity, and Physiological Monitoring: Taxonomy of Issues, Techniques, Applications, Challenges and Limitations. Sensors. 2013;13(10):12852.

250. Hildebrand M, van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Medicine and science in sports and exercise. 2014;46(9):1816-24.

251. van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva ICM, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. Journal of Applied Physiology. 2014;117(7):738-44.

252. Aittasalo M, Vaha-Ypya H, Vasankari T, Husu P, Jussila AM, Sievanen H. Mean amplitude deviation calculated from raw acceleration data: a novel method for classifying the intensity of adolescents' physical activity irrespective of accelerometer brand. BMC sports science, medicine and rehabilitation. 2015;7:18.

253. Vaha-Ypya H, Vasankari T, Husu P, Manttari A, Vuorimaa T, Suni J, et al. Validation of Cut-Points for Evaluating the Intensity of Physical Activity with Accelerometry-Based Mean Amplitude Deviation (MAD). PLoS One. 2015;10(8):e0134813.

254. Vaha-Ypya H, Vasankari T, Husu P, Suni J, Sievanen H. A universal, accurate intensity-based classification of different physical activities using raw data of accelerometer. Clinical physiology and functional imaging. 2015;35(1):64-70.

255. Matthews CE, Hagstromer M, Pober DM, Bowles HR. Best practices for using physical activity monitors in population-based research. Medicine and science in sports and exercise. 2012;44(1 Suppl 1):S68-76.

256. Efron B, Tibshirani RJ. An introduction to the bootstrap: CRC press; 1994. p. 240-1.

257. Rowlands AV, Olds TS, Hillsdon M, Pulsford R, Hurst TL, Eston RG, et al. Assessing sedentary behavior with the GENEActiv: introducing the sedentary sphere. Medicine and science in sports and exercise. 2014;46(6):1235-47.

258. Trost SG, Zheng Y, Wong WK. Machine learning for activity recognition: hip versus wrist data. Physiol Meas. 2014;35(11):2183-9.
259. Husu P, Suni J, Vaha-Ypya H, Sievanen H, Tokola K, Valkeinen H, et al. Objectively measured sedentary behavior and physical activity in a sample of Finnish adults: a cross-sectional study. BMC Public Health. 2016;16:920.
260. Brond JC, Arvidsson D. Sampling frequency affects the processing of Actigraph raw acceleration data to activity counts. J Appl Physiol (1985). 2016;120(3):362-9.
261. Bastian T, Maire A, Dugas J, Ataya A, Villars C, Gris F, et al. Automatic identification of physical activity types and sedentary behaviors from triaxial accelerometer: laboratory-based calibrations are not enough. Journal of applied physiology (Bethesda, Md : 1985). 2015;118(6):716-22.
262. Bakrania K, Edwardson CL, Khunti K, Henson J, Stamatakis E, Hamer M, et al. Associations of objectively measured moderate-to-vigorous-intensity physical activity and sedentary time with all-cause mortality in a population of adults at high risk of type 2 diabetes mellitus. Preventive medicine reports. 2017;5:285-8.
263. Bakrania K, Yates T, Rowlands AV, Esliger DW, Bunnewell S, Sanders J, et al. Intensity Thresholds on Raw Acceleration Data: Euclidean Norm Minus One (ENMO) and Mean Amplitude Deviation (MAD) Approaches. PLoS One. 2016;11(10):e0164045.
264. McCarthy M, Edwardson CL, Davies MJ, Henson J, Bodicoat DH, Khunti K, et al. Fitness Moderates Glycemic Responses to Sitting and Light Activity Breaks. Medicine and science in sports and exercise. 2017;49(11):2216-22.
265. Matthews CE, Keadle SK, Troiano RP, Kahle L, Koster A, Brychta R, et al. Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in US adults. Am J Clin Nutr. 2016;104(5):1424-32.
266. LaMonte MJ, Buchner DM, Rillamas-Sun E, Di C, Evenson KR, Bellettiere J, et al. Accelerometer-Measured Physical Activity and Mortality in Women Aged 63 to 99. J Am Geriatr Soc. 2018;66(5):886-94.
267. Koolhaas CM, Dhana K, van Rooij FJ, Kocevska D, Hofman A, Franco OH, et al. Sedentary time assessed by actigraphy and mortality: The Rotterdam Study. Prev Med. 2017;95:59-65.

268. Ensrud KE, Blackwell TL, Cauley JA, Dam TT, Cawthon PM, Schousboe JT, et al. Objective measures of activity level and mortality in older men. J Am Geriatr Soc. 2014;62(11):2079-87.

269. Dohrn IM, Sjostrom M, Kwak L, Oja P, Hagstromer M. Accelerometer-measured sedentary time and physical activity-A 15 year follow-up of mortality in a Swedish population-based cohort. J Sci Med Sport. 2018;21(7):702-7.

270. Diaz KM, Howard VJ, Hutto B, Colabianchi N, Vena JE, Safford MM, et al. Patterns of Sedentary Behavior and Mortality in U.S. Middle-Aged and Older Adults: A National Cohort Study. Ann Intern Med. 2017;167(7):465-75.

271. Department of Health and Human Services. 2018 Physical Activity Guidelines Advisory Committee Scientific Report. 2018. [Available from: https://health.gov/paguidelines/second-edition/report/pdf/PAG_Advisory_Committee_Report.pdf. Accessed: 1 June 2018].

272. Cassidy S, Fuller H, Chau J, Catt M, Bauman A, Trenell MI. Accelerometer-derived physical activity in those with cardio-metabolic disease compared to healthy adults: a UK Biobank study of 52,556 participants. Acta diabetologica. 2018.

273. Hamer M, Sharma N, Batty GD. Association of objectively measured physical activity with brain structure: UK Biobank study. J Intern Med. 2018.

274. Kim Y, White T, Wijndaele K, Sharp SJ, Wareham NJ, Brage S. Adiposity and grip strength as long-term predictors of objectively measured physical activity in 93 015 adults: the UK Biobank study. International journal of obesity (2005). 2017;41(9):1361-8.

275. Norwegian Directorate of Health. Recommendations to reduce sedentary behaviour. 2016. [Available from: https://helsedirektoratet.no/folkehelse/fysisk-aktivitet/anbefalinger-om-a-redusere-stillesitting. Accessed: 1 April 2018].

276. Ministry of Health. Eating and Activity Guidelines for New Zealand Adults. 2015. [Available from: https://www.health.govt.nz/system/files/documents/publications/eating-activity-guidelines-for-new-zealand-adults-oct15_0.pdf. Accessed: 1 April 2018].

277. Department of Health. Start Active - Stay Active. A report on physical activity for health from the four home countries' Chief Medical Officers. 2011. [Available from:

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/216370/dh_128210.pdf. Accessed: 1 April 2018].

278. Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines. 2017. [Available from: http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines#apaadult. Accessed: 1 April 2018].

279. Fuzeki E, Vogt L, Banzer W. [German National Physical Activity Recommendations for Adults and Older Adults: Methods, Database and Rationale]. Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)). 2017;79(S 01):S20-s8.

280. Stamatakis E, Ekelund U, Ding D, Hamer M, Bauman AE, Lee IM. Is the time right for quantitative public health guidelines on sitting? A narrative review of sedentary behaviour research paradigms and findings. Br J Sports Med. 2018.