Neurodegenerative disease

VERSION HISTORY

V1	12/05/2022	Developed by JICC
V2	08/07/2022	Revised by VW
V3	08/09/2023	Updated by JICC
V4	01/10/2023	Updated by JICC
V5	/11/2023	Updated by JICC following RD and VW indications
V6	08/12/2023	Revised by VW to send to LC
V7	04/01/2024	Code lists for any dementia, and Lewy body added by JICC

MAIN PROTOCOL

This document contains the outcome specific elements necessary to implement this protocol: post-covid-events.docx

STUDY POPULATION

Study population defined as per post-covid-events.docx as well as these additional exclusions that are specific to this disease area:
- We will exclude individuals at index if they have a record of the outcome of interest (for example, individuals will be excluded from the analysis of the outcome 'multiple sclerosis' if they have a record of multiple sclerosis prior to index)
- Additionally, for the outcome 'Parkinson's disease', we will exclude individuals if they have a record of any dementia

COHORTS

Use only the collapsed Cox regression time periods from the main protocol, due to rarity of the outcomes.

	Cohort 1: Pre-vaccination	*Cohort 2: Vaccinated*	*Cohort 3: Unvaccinated*
Cox regression time periods, collapsed	[0], [1,28), [28,183), [183, 365), [365,730), [730,1065), [1065, 1582)	[0], [1,28), [28,197) , [28,183), [183, 365), [365,730), [730,1065),	[0], [1,28), [28,183), [183, 365), [365,730), [730,1065),

OUTCOMES

We will study the following outcomes.

Table 1. Outcomes derivation.

Outcome grouping	Outcome	Primary care (SNOMED CT)	Secondary care and deaths (ICD10)
Dementia	Alzheimer's disease	Alzheimer's Disease (SNOMED-CT)	Alzheimer's Disease (ICD10)
	Vascular dementia	Vascular dementia (SNOMED-CT)	Vascular dementia (ICD10)
	Lewy body dementia	Lewy body (dementia) (SNOMED-CT)	N / A*

		Combine: Alzheimer's Disease (SNOMED-CT) Vascular dementia (SNOMED-CT) Lewy body (dementia) (SNOMED-CT) Other dementias (SNOMED-CT) Unspecified dementias (SNOMED-CT)	Combine: Alzheimer's Disease (ICD10) Vascular dementia (ICD10) N / A Other dementias (ICD-10) Unspecified dementias (ICD-10)
	Any dementia		
Dementia risk conditions	Cognitive impairment	Symptoms: cognitive impairment	N / A **
Parkinson's disease	Parkinson's disease	Parkinson's Disease (SNOMED-CT)	Parkinson's Disease (ICD10)
Parkinson's risk conditions	Restless leg syndrome	Restless leg syndrome (SNOMED-CT)	N / A **
	REM sleep disorder	REM sleep disorder (SNOMED-CT)	REM sleep disorder (ICD10)
Other neurodegenerative conditions	Motor neurone disease	Motor neurone disease (SNOMED-CT)	Motor neurone disease (ICD10)
	Multiple sclerosis	Multiple sclerosis (SNOMED-CT)	Multiple sclerosis (ICD10)
Neurological condition	Migraine	Migraine (SNOMED-CT)	Migraine (ICD10)

*HES data only goes up to 4 characters, meaning codes that are longer than that (e.g. G31,83, the ICD10 code for Lewy Body) cannot be included
** As symptoms, we are mainly leaving their definition to primary care

POTENTIAL CONFOUNDERS

We will consider the following potential confounders, which will be defined using the most recent data prior to the study start date:

Table 2. Confounders derivation.

Covariate	Type	Definition	Data sources
Age	Continuous	Modelled as age in years using a restricted cubic spline with 3 knots at the 10th, 50th and 90th percentiles	Primary care
Sex	Categorical	Male, Female	Primary care
Ethnicity	Categorical	1: White 2: Mixed 3: South Asian 4: Black 5: Other	Primary care
Deprivation	Categorical	10 categories from Index of Multiple Deprivation 2019	Index of Multiple Deprivation
Region	Categorical	East of England London Midlands	Primary care

		North East and Yorkshire North West South East South West Scotland Wales	
Smoking status	Categorical	E: Ever smoker M: Missing N: Never smoker S: Current smoker	Primary care
Care home status	Binary	1 if care home resident; 0 otherwise	Address matching CQC database
Consultation rate	Continuous	Number of GP consultations 12 months prior to the start of the study	Primary care
Health care worker	Binary	1 if healthcare worker; 0 otherwise	NHS England COVID-19 data store
Liver disease	Binary	1 if diagnosis present; 0 otherwise.	Combine: Liver Disease ICD10 Liver Disease SNOMED
Chronic kidney disease	Binary	1 if diagnosis present; 0 otherwise.	Combine: CKD SNOMED CKD ICD10
Cancer	Categorical	1 if diagnosis present; 0 otherwise.	Combine: Cancer SNOMED Cancer ICD10
Hypertension	Binary	1 if diagnosis present; 0 otherwise.	Combine: Hypertension Drugs DMD Hypertension ICD10 Hypertension SNOMED
Diabetes	Binary	1 if diagnosis present; 0 otherwise.	Combine: Diabetes T1 SNOMED Opensafely: Diabetes T1 ICD10 Diabetes T2 SNOMED Diabetes T2 ICD10 Non-diagnostic diabetes SNOMED Other-Nonspecific diabetes SNOMED Gestational Diabetes SNOMED Opensafely: Insulin SNOMED Opensafely: Antidiabetic drugs SNOMED
Obesity	Binary	1 if BMI>=30 or coded diagnosis for obesity; 0 otherwise.	Combine: Obesity SNOMED Obesity ICD10

Chronic obstructive pulmonary disease (COPD)	Binary	1 if diagnosis present; 0 otherwise.	Combine: COPD SNOMED COPD ICD10
Acute myocardial infarction	Binary	1 if diagnosis present; 0 otherwise.	Combine: AMI SNOMED AMI ICD10 AMI Prior ICD10
Ischaemic stroke	Binary	1 if diagnosis present; 0 otherwise.	Combine: Ischeamic Stroke SNOMED Ischeamic Stroke ICD10
Depression	Binary	1 if diagnosis present; 0 otherwise	Combine: Depression SNOMED Depression ICD10
History of cognitive impairment*	Binary	1 if diagnosis present; 0 otherwise	Symptoms: cognitive impairment
History of motor neurone disease*	Binary	1 if diagnosis present; 0 otherwise	Combine: Motor neurone disease (SNOMED-CT) Motor neurone disease (ICD10)
History of migraine*	Binary	1 if diagnosis present; 0 otherwise	Combine: Migraine (SNOMED-CT) Migraine (ICD10)
History of any dementia*	Binary	1 if diagnosis present; 0 otherwise	Combine: Alzheimer's Disease (ICD10) Alzheimer's Disease (SNOMED-CT) Vascular dementia (ICD10) Vascular dementia (ICD10) Lewy body (dementia) (SNOMED-CT) Other dementias (SNOMED-CT) Other dementias (ICD-10) Unspecified dementias (SNOMED-CT) Unspecified dementias (ICD-10)
History of Parkinson's disease*	Binary	1 if diagnosis present; 0 otherwise	Combine: Parkinson's Disease (SNOMED-CT) Parkinson's Disease (ICD10)

History of multiple sclerosis*	Binary	1 if diagnosis present; 0 otherwise	Combine: Multiple sclerosis (SNOMED-CT) Multiple sclerosis (ICD10)
History of Parkinson's risk conditions*	Binary	1 if diagnosis present; 0 otherwise	Combine: Restless leg syndrome (SNOMED-CT) REM sleep disorder (SNOMED-CT) REM sleep disorder (ICD10)

* Where appropriate. For example: when investigating the outcome 'multiple sclerosis', the covariate 'history of multiple sclerosis' will not be included in the model.

SUBGROUP ANALYSES

We will perform the following subgroup analyses:

Table 3. Subgroup analysis derivation

Subgroup	Definition of subgroups	Data source(s) to define subgroup	Outcome(s)
COVID-19 severity	hospitalised / non-hospitalised / history (if not prevax)		All
Age group*	18-39 / 40-64 / 65-84 / 85-110		All
Sex	male / female		All
Ethnicity	White / Asian or Asian British / Black or Black British / Mixed / Other Ethnic Groups		All
High vascular risk	0: No hypertension AND no diabetes 1: Hypertension AND/OR diabetes	Use covariates 'hypertension' and 'diabetes'	Alzheimer's disease Vascular dementia Lewy body Any Dementia Cognitive impairment
Parkinson's risk conditions	0: No prior history of Parkinson's risk conditions 1: Prior history of Parkinson's risk conditions	Use covariate 'history of Parkinson's risk conditions'	Parkinson's disease
Cognitive impairment	0: No history of cognitive impairment 1: Prior history of cognitive impairment	Use covariate 'history of cognitive impairment'	Any dementia
Parkinson's disease	0: No prior history of Parkinson's disease 1: Prior history of Parkinson's disease	Use covariate 'history of Parkinson's disease'	Any dementia

* Age groups will follow clinician suggestion, and these models will use a different year range compared to the other protocols.